i supplementi di tumori

a Journal of Experimental and Clinical Oncology

XIV Congresso Nazionale

Roma, 27-29 ottobre 2012

Marriott Park Hotel

AIOM

Associazione Italiana di Oncologia Medica
XIV NATIONAL CONGRESS OF MEDICAL ONCOLOGY

October 27-29, 2012: Rome, Italy

Guest Editor

Stefano Cascinu
Medical Oncology, Università Politecnica delle Marche, Ancona
President, Italian Association of Medical Oncology (AIOM)
The Scientific Committee has chosen the papers on the basis of the originality of the research and the originality of the results. The authors are responsible for the text and the translation.
XIV NATIONAL CONGRESS OF MEDICAL ONCOLOGY

October 27-29, 2012: Rome, Italy

Abstracts

S1    Plenary session

S3    Session A
      Gastrointestinal tumours (colorectal excluded)

S23   Session B
      Colorectal cancers

S51   Session C
      Supportive and palliative care

S76   Session D
      Thoracic and lung cancers, head and neck tumours

S105  Session E
      Breast cancers

S138  Session F
      Genitourinary tumours

S153  Session G
      Sarcoma, lymphoma, melanoma, brain tumours

S165  Session H
      Gynaecological tumours

S170  Session L
      Health Technology Assessment

S176  Session N
      Oncology nursing

S185  Author index

Please, note that abstracts marked with an asterisk (*) are Oral communications.
Dear Colleagues,

on behalf of the Board of Directors and of the Scientific Committee, it is a great pleasure for me to introduce the proceedings of the XIV National Congress of our Association.

As usually, the abstracts have been published in a special issue of Tumori, the official Journal of AIOM. By reading them, there are at least two aspects of satisfaction.

The first one is the increasing number of abstracts. It seems to suggest not only the interest for the Congress but also a diffuse research activity in Italy. This is not limited to a specific geographic area but it involves all the country.

The second aspect is the role of young oncologists. Many and many young oncologists are coauthors of the abstracts and several are first authors. This is probably the most relevant indication at least in my mind: there is a present for AIOM but there will be also a future.

As you can realize by reading this issue, all topics of medical oncology has been covered. These topics, including prevention, screening, translational research, simultaneous care, ethics and multidisciplinary approaches, will be debated in several educational and scientific sessions. We would like to highlight as simultaneous care and multidisciplinary approach are relevant parts of the program of the meeting. As medical oncologists, clinicians involved in the care of the patients, we have to keep in our mind that ‘research’ does not mean to forget the daily activity in the ward as well as the ability to answer the patients’ daily needs. Nevertheless, at the same way, we must remember that a research activity improves the care of cancer patients in our Units. The ability to conjugate these two aspects is the only way to improve the chance of cure for our patients.

Finally, I’d like to thank the Scientific Committee and all the reviewers for the invaluable work along last months and I hope that all of you can enjoy the meeting and it could be the occasion of sharing knowledge, and experiences by providing an enrichment in our skills.
The Board of Directors for the years 2011-2013 includes:

- Stefano Cascinu (President)
- Carmine Pinto (Secretary)
- Stefania Gori (Treasurer)
- Massimo Aglietta
- Giuseppe Altavilla
- Editta Baldini
- Giovanni Bernardo
- Saverio Cinieri
- Fabio Puglisi
- Pierosandro Tagliaferri
- Giuseppe Tonini

We are looking forward to seeing you in Rome.

Prof. Stefano Cascinu
(President of the Congress)

This abstracts book will be available on-line and will also be freely available to all visitors to the following website from October 30th, 2012 (http://www.aiom.it/default.asp)
**EDITORIAL BOARD**

**Editor-in-Chief:** Franco Zunino (*Milano*)

**Associate Editors:** Emilio Bajetta (*Milano*), Adriana Albinì (*Milano*), Renzo Corvò (*Genova*), Antonio Mussa (*Torino*)

<table>
<thead>
<tr>
<th>Epidemiology and Biometry</th>
<th>Medical Oncology</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Franco Berrino (<em>Milano</em>)</td>
<td>Giovanni Bernardo (<em>Pavia</em>)</td>
<td>Carlo Capella (<em>Varese</em>)</td>
</tr>
<tr>
<td>Patrizia Boracchi (<em>Milano</em>)</td>
<td>Francesco Boccardo (<em>Genova</em>)</td>
<td>Vincenzo Eusebi (<em>Bologna</em>)</td>
</tr>
<tr>
<td>Paolo Bruzzi (<em>Genova</em>)</td>
<td>Sergio Bracarda (<em>Arezzo</em>)</td>
<td>Tumor Markers</td>
</tr>
<tr>
<td>Andrea Micheli (<em>Milano</em>)</td>
<td>Roberto Buzzoni (<em>Milano</em>)</td>
<td>Emilio Bombardieri (<em>Milano</em>)</td>
</tr>
<tr>
<td>Ilaria Panzini (<em>Rimini</em>)</td>
<td>Diego Cortinovis (<em>Monza</em>)</td>
<td>Stefano Ciatti (<em>Firenze</em>)</td>
</tr>
<tr>
<td>Paolo Vineis (<em>Torino</em>)</td>
<td>Maria Teresa Ionta (<em>Monseratt, CA</em>)</td>
<td>Aldo Bono (<em>Milano</em>)</td>
</tr>
<tr>
<td>Evaristo Maiello (<em>San Giovanni Rotondo, PG</em>)</td>
<td>Basic Research</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Surgery Oncology</th>
<th>Radiation Oncology</th>
<th>Palliative/Supportive Care &amp; Cancer in the Elderly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maurizio D’Incalci (<em>Milano</em>)</td>
<td>Filippo Alongi (<em>Milano</em>)</td>
<td>Enrico Aitini (<em>Mantova</em>)</td>
</tr>
<tr>
<td>Cristiana Sessa (<em>Bellinzona</em>)</td>
<td>Stefano Magrini (<em>Brescia</em>)</td>
<td>Gianni Beretta (<em>Milano</em>)</td>
</tr>
<tr>
<td>Vittorio A Bedini (<em>Milano</em>)</td>
<td>Mauro Palazzi (<em>Milano</em>)</td>
<td>Oscar Bertetto (<em>Torino</em>)</td>
</tr>
<tr>
<td>Luca Cozzaglio (<em>Milano</em>)</td>
<td>Umberto Ricardi (<em>Torino</em>)</td>
<td>Carla Ripamonti (<em>Milano</em>)</td>
</tr>
<tr>
<td>Luciano Di Martino (<em>Cagliari</em>)</td>
<td>Elvio Russi (<em>Cuneo</em>)</td>
<td>Fausto Roila (<em>Perugia</em>)</td>
</tr>
<tr>
<td>Roberto Doci (<em>Milano</em>)</td>
<td>Vincenzo Valentini (<em>Roma</em>)</td>
<td></td>
</tr>
<tr>
<td>Gabriella Ferrandina (<em>Campobasso</em>)</td>
<td>Andrea Anichini (<em>Milano</em>)</td>
<td></td>
</tr>
<tr>
<td>Nicola Mozzillo (<em>Napoli</em>)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**ADVISORY BOARD**

<table>
<thead>
<tr>
<th>Alan Balmain (<em>Glasgow</em>)</th>
<th>Suzanne Eccles (<em>Belmont</em>)</th>
<th>Pier Giorgio Natali (<em>Roma</em>)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mariano Barbacid (<em>Princeton</em>)</td>
<td>Silvio Garattini (<em>Milano</em>)</td>
<td>Lloyd J Old (<em>New York</em>)</td>
</tr>
<tr>
<td>Robert C Bast (<em>Houston</em>)</td>
<td>Giuseppe Giaccone (<em>Amsterdam</em>)</td>
<td>Marie Overgaard (<em>Aarhus</em>)</td>
</tr>
<tr>
<td>Jacques Bernier (<em>Bellinzona</em>)</td>
<td>Geoffrey W Hanks (<em>Bristol</em>)</td>
<td>Pier Giuseppe Pellicci (<em>Perugia</em>)</td>
</tr>
<tr>
<td>Gianni Bonadonna (<em>Milano</em>)</td>
<td>Curtis Harris (<em>Bethesda</em>)</td>
<td>Herbert M Pinedo (<em>Amsterdam</em>)</td>
</tr>
<tr>
<td>Vincent Castronovo (<em>Liegi</em>)</td>
<td>Stephen B Howell (<em>La Jolla</em>)</td>
<td>Bruce Ponder (<em>Cambridge</em>)</td>
</tr>
<tr>
<td>Franco Cavalli (<em>Bellinzona</em>)</td>
<td>David Kerr (<em>Oxford</em>)</td>
<td>Vito Quaranta (<em>La Jolla</em>)</td>
</tr>
<tr>
<td>Susan PC Cole (<em>Kingston</em>)</td>
<td>John M Kirkwood (<em>Pittsburgh</em>)</td>
<td>Davide Schiffer (<em>Torino</em>)</td>
</tr>
<tr>
<td>Maria Ines Colnaghi (<em>Milano</em>)</td>
<td>Carlo La Vecchia (<em>Milano</em>)</td>
<td>Gilberto Schwartsmann (<em>Porto Alegre</em>)</td>
</tr>
<tr>
<td>Paolo Comoglio (<em>Torino</em>)</td>
<td>Ferdy J Lejeune (<em>Lausanne</em>)</td>
<td>Rosella Silvestrini (<em>Milano</em>)</td>
</tr>
<tr>
<td>Carlo M Croce (<em>Philadelphia</em>)</td>
<td>Alberto Mantovani (<em>Milano</em>)</td>
<td>Paul Sugarbaker (<em>Washington</em>)</td>
</tr>
<tr>
<td>Riccardo Dalla Fava (<em>New York</em>)</td>
<td>Ettore Marubini (<em>Milano</em>)</td>
<td>Giovanni Tallini (<em>New Haven</em>)</td>
</tr>
<tr>
<td>Mario De Lena (<em>Bari</em>)</td>
<td>Gordon J McVie (<em>London</em>)</td>
<td>Giancarlo Vecchio (<em>Napoli</em>)</td>
</tr>
<tr>
<td>Giuseppe Della Porta (<em>Milano</em>)</td>
<td>Francesco M Marincola (<em>Bethesda</em>)</td>
<td>Umberto Veronesi (<em>Milano</em>)</td>
</tr>
<tr>
<td>Tommaso Dragani (<em>Milano</em>)</td>
<td>Franco M Muggia (<em>Los Angeles</em>)</td>
<td>Michael Zelefsky (<em>New York</em>)</td>
</tr>
</tbody>
</table>

Tumori is published for the “Fondazione IRCCS Istituto Nazionale dei Tumori” by Il Pensiero Scientifico Editore, via San Giovanni Valdarno 8, 00138 Roma. E-mail: pensiero@pensiero.it

Internet: www.tumorionline.it

*Tumori* is a publication of Fondazione IRCCS Istituto Nazionale dei Tumori, Milan (Marco A. Pierotti, Director)

Associazione Italiana di Oncologia Medica (Stefano Cascini, President)

Società Italiana di Chirurgia Oncologica (Alfredo Garofalo, President)

and Associazione Italiana di Radioterapia Oncologica (Giovanni Mandoliti, President)
Plenary session

1st ITACA-S (INTERGROUP TRIAL OF ADJUVANT CHEMOTHERAPY IN ADENOCARCINOMA OF THE STOMACH) TRIAL: COMPARISON OF A SEQUENTIAL TREATMENT WITH IRINOTECAN (CPT-11) + 5-FLUOROURACIL (5FU)/FOLINIC ACID (LV) FOLLOWED BY DOCETAXEL AND CISPLATIN VERSUS A 5-FU/LV REGIMEN AS POSTOPERATIVE TREATMENT FOR RADICALLY RESECTED GASTRIC CANCER


1Istituto di Oncologia del Policlinico di Monza, Monza; 2Istituto di Ricerche Farmacologiche “Mario Negri”, Milano; 3Fondazione IRCCS Istituto Nazionale dei Tumori, Milano; 4Ospedali Riuniti, Bergamo; 5Azienda Ospedaliero-Universitaria Pisana, Pisa; 6Azienda Ospedaliero-Universitarria Careggi, Firenze; 7IRCCS Studio Nazionale dei Tumori-Fondazione G. Pascale, Napoli; 8IRCCS-Istituto Scientifico Romagnolo per lo Studio e la Cura del Tumori-IRST, Meldola; 9Policlinico Sant’Orsola Malpighi, Bologna; 10Azienda Ospedaliera Universitaria Integrata, Verona; 11Azienda Ospedaliera, Padova; 12Azienda Ospedaliera G. Rummo, Benevento; 13Istituto Clinico Humanitas, Rozzano; 14Arcispedale Santa Maria Nuova-IRCCS, Reggio Emilia; 15Azienda Ospedaliera San Gerardo di Monza, Monza; 16Azienda Ospedaliera San Carlo, Potenza; 17Ospedale Infermi, Rimini; 18Ospedale Civico, Carrara

Background. Following radical resection of gastric or gastro-esophageal junction (GEJ) adenocarcinoma, a meta-analysis of individual data demonstrated better survival in patients treated with fluoropyrimidine regimens compared to surgery alone. ITACA-S trial is an Italian, non-profit, multicenter, randomized, open-label, superiority phase III study aimed at evaluating whether a more intensive postoperative chemotherapy has a better efficacy, when replaces fluoropyrimidine.

Methods. Patients radically resected for gastric or GEJ adenocarcinoma, with ≥D1-lymphadenectomy, node involvement (pN+) or pN0 with pT2b-3-4 within 3-8 weeks after surgery were eligible.

Treatment consisted in CPT-11 180 mg/m² on d1, LV 100 mg/m² d1-2, 5-FU 400-600 mg/m² d1-2, q14; for 4 cycles (FOLFIRI regimen) followed by docetaxel 75 mg/m² d1, cisplatin 75 mg/m² d1, q21; for 3 cycles (arm A) vs LV 100 mg/m² d1-2, 5-FU 400-600 mg/m² d1-2, q14 for 9 cycles (arm B). The primary hypothesis on disease-free survival (DFS) requires 636 events (first recurrence or death for any cause) to detect an hazard ratio (HR) of 0.80, with 2-sided 5% significance level for the log-rank test and a power of 80%.

Results. From February 2005 to August 2009, 1106 pts were randomized and 1100 were included in the analysis (562 arm A, 538 arm B; 6 major violations) by 104 Italian centers. By April 2012, with a median follow-up of 49 months ( quartile range: 36-62) we observed 562 events for DFS (HR 0.99; 95% CI 0.84-1.17; p = 0.91) accounting for 88% of the target number and 444 deaths (HR 1.00; 95% CI 0.83-1.20; p = 0.99). Toxicity was consistent with literature. Given the data observed, both under the original hypothesis and the current trend, the probability to reach statistically significant results at the target events is <0.0001.

Conclusions. The results of this study suggest that a postoperative chemotherapy in gastric cancer with more intensive regimen does not result in a significant prolongation of both DFS and OS when compared to bolus/infusion FU/LV regimen.

2nd PARAMOUNT: FINAL OVERALL SURVIVAL (OS) RESULTS OF THE PHASE III STUDY OF MAINTENANCE PEMETREXED (Pem) PLUS BEST SUPPORTIVE CARE (BSC) VERSUS PLACEBO (PLB) PLUS BSC IMMEDIATELY FOLLOWING INDUCTION TREATMENT WITH PEM PLUS CISPLATIN (CIS) FOR ADVANCED NON-SQUAMOUS (NS) NON-SMALL CELL LUNG CANCER (NSCLC)


1SG Moscati Hospital, Avellino; 2San Camillo-Forlanini Hospital, Roma; 3Institute of Oncology, Bucharest, Romania; 4ThauraxKlinik, University of Heidelberg, Germany; 5Montpellier Academic Hospital, Montpellier, France; 6San Gerardo Hospital, Monza; 7Le Mans Regional Hospital, France; 8University Hospital, Hamburg Eppendorf, Germany; 9Hospital Grosshansdorf, Germany; 10Cisanello Hospital, Pisa; 11Lido di Camaiore Hospital, Viareggio; 12Santa Maria della Misericordia Hospital, Udine; 13CRO, Aviano; 14Arcispedale S. Maria Nuova, Reggio Emilia; 15IST, Genova; 16Vrangel del Rocio University Hospital, Seville, Spain; 17Eli Lilly and Company, Indianapolis, USA; 18Eli Lilly and Company, Suresnes, Hauts de Seine, France; 19Eli Lilly and Company, Sesto Fiorentino, Italy

Background. As previously reported, the PARAMOUNT trial showed that pem continuation maintenance therapy after pemcisplatin induction therapy significantly reduced the risk of disease progression over placebo (HR 0.62; 95% CI 0.49-0.79; p = 0.00007) in patients with advanced non-squamous NSCLC. Here we present the final OS data.

Methods. In a double-blind, placebo-controlled study, 939 pts were treated with induction therapy [four cycles of induction pem (500 mg/m²) and cisplatin (75 mg/m²) on day 1 of a 21-day cycle], after which 539 pts who had not progressed and had an Eastern Cooperative Oncology Group performance status (PS) of 0/1 were randomized (2:1; stratified for PS, induction response, disease stage) to maintenance pem (500 mg/m², day 1 of a 21-day cycle) plus BSC (n = 359) or placebo plus BSC (n = 180) until disease progression. All pts received vitamin B12, folic acid, and dexamethasone. After 390 deaths, the final analysis of OS was done on randomized patients and was based on a nominal alpha level of 0.0498.

Results. Patients characteristics were balanced between arms; median age = 61 years; 58% male; 32% PS 0; 91% stage IV; 95% Caucasian; 86% adenocarcinoma; and 45% complete/partial response (CR/PR) to induction. Median number of cycles was 4 for pem (range 1-44) and 4 for placebo (range 1-38), with 37% of pts completing >6 cycles on pem vs 18% on placebo. Among the 359 pts randomized to continuation maintenance with pemetrexed, there was a statistically significant increase in OS over the placebo arm (hazard...
ratio 0.78; 95% CI 0.64-0.96; p = 0.0195), with a median OS of 13.9 mos for pem and 11.0 mos for placebo. Measured from start of the induction treatment, median OS was 16.9 mos for pem and 14.0 mos for placebo. Postdiscontinuation therapy (PDT) was administered for 64% of pem-treated pts and 72% of placebo patients.

Conclusions. Pem continuation maintenance therapy offers superior OS compared with placebo. These final results confirm that pem-cis induction followed by continuation pem further benefits pts compared with induction therapy alone, offering a change in the treatment paradigm for advanced NS NSCLC.

3º GIOGTO STUDY: AN ITALIAN PROSPECTIVE, MULTICENTER, OBSERVATIONAL STUDY ON GIST IN COLLABORATION WITH THE ITALIAN RARE CANCER NETWORK

Fumagalli E.1, Sanfilippo R.1, Frustaci S.2, Aglietta M.3, Comandone A.4, Apice G.5, Santoro A.6, Labianca R.7, Fasola G.8, Ciuffreda L.9, Gnochi C.10, Amore P.10, Casali P.1

Background. GIST are a rare disease which was completely redefined at the end of the ’90s and then was revolutionized by the introduction of effective targeted therapies. This opened a new scenario that changed dramatically the clinical practice. The Italian Network of Rare Cancers is a collaborative group aimed to improve quality of health care for rare adult solid cancer patients in Italy, through a national network between reference and peripheral centers.

Methods. From April 2004 to June 2009, the observational GIOTTO study was carried out, involving 69 Italian centers, to collect all consecutive GIST cases observed in terms of diagnosis, treatment, disease evolution.

Results. Seven hundred and eighty-eight pts were included, M/F: 420/368, median age 61 years. 100 pts (13%) had a pathologic diagnosis other than GIST, including leiomyosarcoma (45 pts, 45%), and leiomyoma (11 pts, 11%). For most pts (73%) the disease was localized at diagnosis. Primary tumour site was stomach and small intestine, respectively, in 383 (49%) and 208 (27%) patients. Metastatic sites were liver and peritoneum, respectively, in 113 (14%) and 99 (13%) patients. Unusual sites recorded in <4%. Median FU was 39 months; median OS was 190 months. RFS and OS were also analyzed based on risk classification. The correct pathologic diagnosis in rare cancers is an issue and thus a priority for collaborative networks.

4º TAILOR: PHASE III TRIAL COMPARING ERLOTINIB VERSUS DOCETAXEL AS SECOND-LINE TREATMENT OF ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS WITH WILD TYPE EGFR (WT)


1Oncologia Aziendale Ospedaliera San Giovanni-Addolorata, Roma; 2Dipartimento di Oncologia, Ospedale Fatebenefratelli e Oftalmico, Milano; 3Oncologia A Policlinico Umberto I, Università “La Sapienza”, Roma; 4UOC Oncologia, Presidio Ospedaliero Centrale del Vomero, Napoli; 5Dipartimento di Oncologia ed Ematologia Ospedali Riuniti Bergamo; 6UO Oncologia Medica Fondazione IRCCS Ca’ Granda, Ospedale Maggiore Policlinico, Milano; 7UOC Oncologia, Ospedale San Pietro Fatebenefratelli, Roma; 8Oncologia Medica, Azienda Ospedaliera “Maggiore dell’Aquilla”, Novara; 9Azienda Ospedaliera Universitaria di Sassari; 10Oncologia Medica, Dipartimento di Oncologia, Policlinico Universitario “P. Giaccone”, Palermo; 11SC Oncologia Medica, Azienda Ospedaliera Valtellina e Valchiavenna, Presidio San Martino, Tirano; 12Oncologia Medica, Ospedale Centrale di Bolzano; 13Azienda Ospedale Civile, Brescia; 14SC di Oncologia Medica AO della Provincia di Lecco; 15Dipartimento Oncologia Medica, Ospedale S. Camillo-Forlanini Roma; 16Dipartimento di Medicina Sperimentale “Università La Sapienza”, Roma; 17Ospedale di Piacenza; 18Ospedale Civile SS Annunziata, Sassari; 19Stuttura Complessa di Anatomo Patologica, Azienda Ospedaliera Niguarda-Ca’ Granda, Milano; 20Laboratory of Molecular Pharmacology, Oncology Department, Istituto di Ricerche Farmacologiche “Mario Negri”, Milano; 21Dipartimento di Anatomia Patologica, Ospedale Fatebenefratelli e Oftalmico, Milano; 22Laboratorio di Clinical Trials, Oncology Department, Istituto Ricerche Farmacologiche “Mario Negri”, Milano; 23Istituto per la Ricerca e la Curatela del Cancro (IRCC), Torino

Background. While the benefit of EGFR tyrosine kinase inhibitors in the treatment of patients with NSCLC harbouring EGFR mutation has been widely assessed, their role in treating patients with wt EGFR is still ambiguous. To assess the role of erlotinib in these patients, we performed a multicenter, independent, superiority phase III trial (TAILOR NCT00637910), comparing erlotinib versus docetaxel in second-line having overall (OS) and progression-free survival (PFS) as endpoints.

Methods. EGFR and KRAS mutational status was assessed by direct sequencing in all NSCLC eligible patients; only patients with wt EGFR (exons 19, 21) at progression and previously treated with a first-line platinum-based chemotherpay were randomized to receive either erlotinib 150 mg daily or docetaxel 75 mg/m2 (3-weekly) or 35 mg/m2 (weekly) until disease progression or unacceptable toxicity occurred. To detect an hazard ratio of 0.67 (2-sided 5% significance level for the log-rank test and a power of 80%), 199 events were required for both OS and PFS.

Results. At the planned analysis date (March 30th, 2012), 221 eligible patients were randomized and 218 were evaluable (docetaxel 110, erlotinib 111; three major protocol violations). At a median follow-up of 20 months, 193 relapses and 157 deaths were observed. The Kaplan-Meier PFS curves showed a highly significant increase in favouring docetaxel (HR 0.70 with 95% CI of 0.53-0.94, p = .016). The HR translates into an estimated absolute difference in 6-month PFS of 12% (16% vs 28%). Toxicity was similar with literature.

Conclusions. These results clearly indicate a superiority of docetaxel over erlotinib in second-line in patients with absence of EGFR mutations in exons 19 or 21.
**Session A** • Gastrointestinal tumours (colorectal excluded)

### A1* THE ROLE OF MET AND TIVANTINIB (ARQ 197) IN PRETREATED HEPATOCELLULAR CARCINOMA (HCC): FINAL RESULTS OF A RANDOMIZED CONTROLLED PHASE 2 TRIAL (RCT)


1Humanitas Cancer Center, Istituto Clinico Humanitas IRCCS, Rozzano (Milano), Italy; 2Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; 3Cliniques Universitaires Saint-Luc, Brussels, Belgium; 4G. Rummo Hospital, Benevento, Italy; 5Azienda Ospedaliera Parma, Parma, Italy; 6Erasmus University Hospital, Brussels, Belgium; 7University Hospital Gent, Gent, Belgium; 8JW Goethe-University Hospital, Frankfurt, Germany; 9Klinikum der Universität München-Großhadern, Munich, Germany; 10Van- couver General Hospital, British Columbia Cancer Clinic, Vancouver, Canada; 11Cedar Sinai, Los Angeles, CA, USA; 12Policlinico Universitario Agostino Gemelli, Roma, Italy; 13Azienda Ospedaliero Universitaria di Pisa, Pisa, Italy; 14University of Texas, Galveston, TX, USA; 15Toronto General Hospital, Toronto, Ontario, Canada; 16Osp S. Giuseppe Moscati, Avellino, Italy; 17Arcispedale S. Maria Nuova - IRCCS, Reggio Emilia, Italy; 18Daichi Sankyo, Edison, NJ, USA; 19ArQule, Inc, Woburn, MA, USA

#### Background.
Tivantinib is a selective, oral inhibitor of MET, the hepatocyte growth factor (HGF) receptor involved in tumour cell migration, invasion, proliferation and angiogenesis. Tivantinib has shown previous promising results in HCC as monotherapy and in combination with sorafenib.

#### Methods.
This multi-center RCT enrolled patients with inoperable HCC. 1 failed systemic therapy, ECOG PS <2, excluding Child-Pugh B-C. Patients were randomized 2:1 to oral tivantinib [starting dose: 360 mg bid (A), then 240 mg bid (B) in all patients due to G ≥3 neutropenia] or placebo, stratifying by PS and performance status. 2 patients due to G ≥3 neutropenia or placebo, stratifying by PS and performance status. 2 patients due to G ≥3 neutropenia or placebo, stratifying by PS and performance status.

#### Results.
Characteristics of the 107 enrolled HCC patients were generally well balanced. The study met its primary endpoint (TTP in the ITT). Major OS, TTP, PFS, DCR benefits were generally well balanced. The study met its primary endpoint (TTP in the ITT). Major OS, TTP, PFS, DCR benefits were generally well balanced. The study met its primary endpoint (TTP in the ITT). Major OS, TTP, PFS, DCR benefits were generally well balanced. The study met its primary endpoint (TTP in the ITT). Major OS, TTP, PFS, DCR benefits were generally well balanced. The study met its primary endpoint (TTP in the ITT). Major OS, TTP, PFS, DCR benefits were generally well balanced. The study met its primary endpoint (TTP in the ITT).

#### Conclusions.
MET was prognostic in the enrolled 2nd-line HCC population. Compared to placebo, tivantinib provided a significant advantage, especially in MET High patients, with manageable safety profile at 240 mg BID.

#### Table 1 - Efficacy results (medians)

<table>
<thead>
<tr>
<th>Tivantinib Placebo</th>
<th>HR</th>
<th>CI</th>
<th>Log-rank p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Endpoint (in ITT, 90% CI):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTP (mos)</td>
<td>1.6</td>
<td>1.4</td>
<td>0.64</td>
</tr>
<tr>
<td>Secondary Endpoints (in MET High patients, 95% CI):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTP (mos)</td>
<td>2.7</td>
<td>1.4</td>
<td>0.43</td>
</tr>
<tr>
<td>OS (mos)</td>
<td>7.2</td>
<td>3.8</td>
<td>0.38</td>
</tr>
<tr>
<td>DCR (CI)</td>
<td>50%</td>
<td>20%</td>
<td>(28-72%)</td>
</tr>
</tbody>
</table>

#### Table 2 - Efficacy results from the placebo arm (medians)

<table>
<thead>
<tr>
<th>MET High MET Low</th>
<th>HR</th>
<th>95% CI</th>
<th>Log-rank p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS (mos)</td>
<td>3.8</td>
<td>9.0</td>
<td>2.94</td>
</tr>
<tr>
<td>TTP (mos)</td>
<td>1.4</td>
<td>1.4</td>
<td>1.6</td>
</tr>
</tbody>
</table>

### A2* TRANSLATIONAL RESEARCH ON MOLECULAR MARKERS IN GASTRIC CANCER PATIENTS TREATED WITH ADJUVANT THERAPY.

ANCILLARY STUDY OF ITACA-S (INTERGROUP TRIAL OF ADJUVANT CHEMOTHERAPY OF ADENOCARCINOMA OF THE STOMACH)

Di Bartolomeo M.1, Miceli R.2, Mariani L.2, Pietrantonio F.1, Martinetti A.1, Sottotetti E.1, Dotti K.F.1, Buzzoni R.3, Scuro M.4, Pellegrinelli A.4

1S.C. Oncologia Medica, 2Unità di Epidemiologia Clinica e Organizzazione Trial, 3S.C. Day Hospital e Ambulatorio, 4Unità di Anatomia Patologica, Fondazione IRCCS, Istituto Nazionale dei Tumori, Milano

#### Background.
The ITACA-S is an open-label randomized superiority study that compares DFS and OS in radically resected gastric or gastroesophageal junction pts, randomized to receive 5-FU/LV for 9 cycles (control arm) or FOLFIRI regimen for 4 cycles followed by cisplatin/docetaxel for 3 cycles (experimental arm). Inclusion criteria consisted of nodal involvement pN+ or depth of invasion pT3-4 without distant metastases. The aim of this project was to evaluate different biological molecular factors, on formalin-fixed, paraffin-embedded (FFPE) primary gastric tumour tissue as osteopontin (OPN), cyclooxygenase-2 (COX-2), beta-catenin, E-cadherin (CDH1) and correlate them to pathological stage, node involvement, histological type, tumour site and relapse-free survival (RFS) in ITACA-S patients.

#### Methods.
Since 7/2011, 371 tumour samples of primary gastric cancer have been collected. This is a preliminary analysis on the first 100 evaluable patients. Disease relapse was documented...
in 64 pts, whereas 13 died without any previous relapse, and the overall number of deaths was 71. The immunohistochemistry expression of OPN, COX-2, beta-catenin and CDH1 was evaluated. Univariable analyses for evaluating the association between RFS and OPN, COX-2, beta-catenin and CDH1 were performed by stratifying each marker in two groups. The RFS curves were estimated using the Kaplan-Meier method; the Cox model was used for estimating the HRs and the corresponding 95% confidence intervals.

**Results.** No significant difference in terms of RFS according to selected biomarkers was observed, although a trend was documented for OPN, beta-catenin and CDH1.

**Conclusions.** We have planned to complete the analysis for all samples collected.

**This study is supported by AIRC (Associazione Italiana per la Ricerca sul Cancro) grant.**

**A3* EFFICACY AND SAFETY OF DOSE-DENSE CHEMOTHERAPY WITH MODIFIED TCF REGIMEN (TCF-DD) IN ELDERLY PATIENTS WITH METASTATIC GASTRIC CANCER (MGC)**

Tomasello G., Liguigli W., Lazzarelli S., Poli R., Negri F., Brighenti M., Curti A., Donini M., Toppo L., Maltese M., Ratti M., Panniti S., Perrucci B., Rossi V., Colombi C., Passalacqua R.

**Unità Operativa di Oncologia, Azienda Istituti Ospitalieri di Cremona**

**Background.** Gastric cancer is more common in elderly patients with its highest incidence around the seventh decade of life.
Most oncologists are reluctant to treat this pts population with the most active poli-chemotherapy combinations because of safety concerns. Subgroup analysis of elderly pts enrolled in European studies (Trumper 2006, Van Cutsem 2006, Al Batran 2008) show limited and conflicting data. We previously reported on the feasibility and high activity of a dose-dense TCF regimen (TCF-dd) (Tomasetto 2010). This study aims to evaluate the efficacy and safety of this schema in the elderly pts subgroup (≥65 years).

Methods. From November 2004 to May 2012, 111 consecutive pts with histologically confirmed measurable MGC, ECOG PS 0-2, not previously treated for the advanced disease, were enrolled in a single-center phase II study. Patients received docetaxel 70 mg/m² d1, cisplatin 60 mg/m² d1, 1-folinic acid 100 mg/m² d1-2, followed by 5-fluorouracil 400 mg/m² bolus d1-2, and then 600 mg/m² as a 22 hour continuous infusion d1-2, every 14 days, plus pegfilgrastim 6 mg on day 3. Patients aged ≥65 years (56) received the same schedule with a dose reduction by 30%.

Results. Overall pts characteristics: 84% male, 27% female; median age 65, range 31-81. A median of 4 cycles was administered. Ninety-six pts were evaluable for response (87%) and all for toxicity. In pts aged ≥65 years, we observed 4 CR (7%), 25 PR (45%), 10 SD (18%) and 7 PD (13%); in younger pts: 2 CR (4%), 30 PR (55%), 9 SD (16%) and 9 PD (17%); ORR by ITT was 56% (95% CI 45-64). Median OS was 11.9 months (CI 9.4-14.8); in elderly and younger pts was 11.2 (CI 8.4-11.1) and 12.7 (CI 9-16.5), respectively. Out of 48 evaluable pts aged ≥65 years, 26 (54%) were treated at full doses without any delay, thus respecting the dose-dense criterion. In the elderly most frequent grade 3-4 toxicities were: neutropenia (14%), leucopenia (7%), thrombocytopenia (15%), anemia (4%), febrile neutropenia (7%), ashenia (27%), diarrhea (9%), nausea/vomiting (9%) and hypokalemia (17%); in the younger: neutropenia (56%), leucopenia (31%), thrombocytopenia (21%), anemia (15%), febrile neutropenia (16%), asthenia (43%), diarrhea (15%), nausea/vomiting (22%) and hypokalemia (21%).

Conclusions. This study shows that elderly pts can be safely treated with a TCF-dd regimen with a 30% dose reduction achieving similar efficacy results of younger patients with lesser toxicity.

A5* A PANEL OF FOUR GENE POLYMORPHISMS INVOLVED IN DNA REPAIR AND PLATINUM METABOLISM IDENTIFIED SUBSETS OF PATIENTS WITH UNFAVOURABLE SURVIVAL IN LOCALLY ADVANCED ESOPHAGEAL CANCER (LAEC) TREATED WITH PREOPERATIVE CHEMORADIATION

Pasini F.1, de Manzoni G.2, Bertoloso L.1, Paganin P.1, Zanoni A.2, Cestari L.1, Bononi A.1, Modena Y.1, Menon D.1, Crepaldi G.1, Barile C.1, Gusella M.1

1Oncologia Medica, ULSS-18, Rovigo; 2Chirurgia dell’esofago e dello stomaco, Università di Verona

Background. Preoperative chemoradiation is now the standard of care in LAEC; however a not negligible number of patients fails to respond or relapses and ultimately dies of the disease. This study investigated the association between survival and some gene polymorphisms involved in pathways of drugs metabolism and DNA repair in order to identify subsets of patients with different prognosis.

Methods. One hundred and five patients were treated with weekly docetaxel (35 mg/m²) and CDDP (25 mg/m²), continuous venous infusion of 5-FU (150 mg/m²/die) and concomitant radiotherapy (50 Gy) followed by surgery; median follow-up was 5 years. Genomic DNA was extracted from peripheral blood lymphocytes and gene variants were determined for 5-FU metabolism (TYMS, MTHFR), docetaxel cellular efflux (MDR1), CD- DP processing (GSTP1, MPO) and DNA repair (XPA, XRCC1, ERCC1, XRC3), through DHPLC or RFLP analysis.

Results. Forty-five patients presented pathologic complete remission (pCR), 17 microfoci of residual disease at the primary (mrd), 43 patients were considered as non-responders. Univariate analysis showed that mutated XPA 23AA (p <0.07), GSTP1 114CC (p <0.04), MDR1 267GT (p <0.05) and MPO -463GG (p <0.1) affected long-term PFS and/or survival. These genotypes were then combined to set up a gene panel. The number
of involved genotypes identified subgroups with statistically significant different prognosis. 5-year survival rate was significantly reduced in patients with ≥3 high risk genotypes: 30% compared with 70% of patients with 2 or less gene variations (p = 0.019).

**Conclusions.** In our series single gene polymorphisms (XPA 23AA, GSTP1 114CC, MDR1 2677GT and MPO -463GG), involved in DNA repair and platinum processing, predicted long-term survival in LAEC treated with neoadjuvant docetaxel-cisplatin-fluorouracil and concomitant radiotherapy. A model including the 4 variant genomic predictors was able to identify subgroups with unfavorable outcome and may be proposed to tailor treatment.

<table>
<thead>
<tr>
<th>Genetic variations and survival in 105 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Pts with high risk genotypes</td>
</tr>
<tr>
<td>4 genotypes 6* vs 99 1.65 vs NR 0.044</td>
</tr>
<tr>
<td>3 genotypes 5* vs 70 2.04 vs NR 0.003</td>
</tr>
<tr>
<td>2 genotypes 74* vs 31 2.40 vs NR 0.007</td>
</tr>
<tr>
<td>NR = not reached.</td>
</tr>
</tbody>
</table>

**A6** CLINICAL AND TRANSLATIONAL RESULTS OF A PHASE II RANDOMIZED TRIAL OF MAINTENANCE SUNITINIB (MS) OR OBSERVATION (O) IN METASTATIC PANCREATIC ADENOCARCINOMA (MPA)

Renzi M.1, Cereda S.1, Novarino A.2, Milella M.3, Passardi A.4, Belli C.3, Di Lucca G.3, Mambrini A.6, Ferrari L.7, Danova M.8, Bergamo F.9, Franceschi E.10, Giovannetti E.11, Rovati B.8, Gallà V.11, Villa E.1

1S. Raaffaele Scientific Institute, Milano; 2Centro Oncomatologico Subalpino Molinette Hospital, Torino; 3Regina Elena National Cancer Institute, Roma; 4Istituto Scientifico Romagnolo per lo Studio e la Curia dei Tumori, Meldola; 5Saronno Hospital; 6Carrara Civic Hospital; 7University Hospital, Udine; 8IRCCS Fondazione San Matteo, Pavia; 9Istituto Oncologico Veneto - IRCCS, Padova; 10Bellaria Hospital, Bologna; 11VU University Medical Center, Amsterdam, The Netherlands

**Background.** To prolong chemotherapy over 6 months in MPA has unproven benefit and is hampered by cumulative toxicity. This phase II trial explored the role of MS, using an O group as calibration arm. The predictive role of circulating endothelial cells (CEC) and of functional polymorphisms (SNPs) of genes involved in tumour activation, metabolism and transport (VEGFA, VEGFR-2, CYP3A5, CYP1A1, ABCB1, ABCG2) was explored.

**Methods.** Patients with pathologic diagnosis of MPA, PS >50%, no PD after 6 months of chemotherapy were randomized to O (arm A) or MS (37.5 mg daily) for 6 months (arm B). Primary endpoint was PFS-6. The target enrolment was 26 patients among whom >5 PFS-6 were necessary to declare MS of interest. CEC and SNPs were evaluated on baseline blood samples.

**Results.** Twenty-eight patients were assigned to arm A and 28 to arm B, one of whom was ineligible (kidney cancer). Baseline characteristics were balanced; previous chemotherapy was (A/B): gemcitabine 2/3; combination chemotherapy 25/25. Median duration of MS was 2.8 months. Grade 3-4 toxicity (arm B) was 15% neutropenia, 12% thrombocytopenia and hand-foot syndrome, 8% diarrhoea. PFS-6 was 4% and 22%; median PFS was 2.0 and 3.2 months (p = .01); 2 yrs OS was 5% and 22% (p = .12). CEC analysis (N = 46; 84%) showed a longer median PFS in untreated patients with CEC <30 when compared to >30 (2.9 versus 1.9 months; p = .08); a significantly increased PFS in patients with CEC >30 treated by MS versus O (3.4 months; p = .02); no PFS difference between arms in patients with CEC <30. Genotyping analysis (N = 43; 78%) showed a longer median OS among arm B patients with ABCB1 3435TT genotype as compared to 3435CC/CT genotype (26 versus 7 months; p = .01); and with VEGFA -634GC-CC genotype as compared to -634GG genotype (11 versus 6 months; p = 0.013).

**Conclusions.** MS fulfilled the primary endpoint of the trial and yielded remarkable OS figures. CEC and SNPs may be useful to predict benefit from MS.

**A7 THE ROLE OF VASCULAR ENDOTHELIAL GROWTH FACTORS (VEGFs) AND VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTORS (VEGFRs) POLYMORPHISMS IN THE PREDICTION OF CLINICAL OUTCOME FOR ADVANCED HEPATOCELLULAR CARCINOMA RECEIVING SORAFENIB**

Scartozzi M.1, Faloppi L.2, Loretelli C.1, Svegliati Baroni G.3, De Minics S.3, Bianconi M.4, Giampieri R.1, Mandolesi A.4, Biagetti S.4, Alfonsi S.4, Del Prete M.2, Bittoni A.1, Francoetti M.1, Bearzi I.1, Causi A.1

1Clinica di Oncologia, 2Scuola di Specializzazione in Oncologia, 3Clinica di Gastroenterologia, 4Anatomia Patologica, AO Spedali Riuniti, Università Politecnica delle Marche, Ancona

Although the introduction of new treatment possibilities has radically changed the medical approach to hepatocellular carcinoma (HCC), this disease still represents a medical challenge in cancer therapy. Currently the therapeutic stronghold is represented by the TKIs directed against the VEGF family, sorafenib. Polymorphisms of the VEGF and VEGFRs genes are involved in regulating angiogenesis and lymphangiogenesis and consequently in control of tumour growth. The aim of our study is to evaluate the potential predictive and prognostic role of VEGF and VEGFRs polymorphisms in determining the clinical outcome of HCC patients receiving sorafenib.

Fifty-four histologic samples (biopsies and surgical specimens) of HCC patients receiving sorafenib were tested for VEGF-A, VEGF-C and VEGFR-1,2,3 single nucleotide polymorphisms (SNPs). Patients time to progression (TTP) and overall survival (OS) were analysed.

VEGF-AI rs25648 C >T polymorphism was statistically significant in OS (15.0 months for C vs 9.4 months for T; p = 0.025). VEGF-AI rs10434 G >A was statistically significant for TTP (4.1 months for G vs 1.2 months for A; p = 0.0076) and OS (14.2 months for G vs 1.7 for A; p <0.0001). VEGF-CHR rs7664413 C >T was significant in TTP (13.4 months for C vs 2.0 for T; p = 0.0125) and OS (14.7 months for C vs 5.6 for T; p = 0.0007). VEGFR-2 rs1870377 A >T was significant in TTP (19.9 months for A vs 3.0 for T; p = 0.0271) and OS (29.6 months for A vs 11.9 for T; p = 0.0096).

In our analysis patients with G polymorphism at rs10434, C polymorphism at rs7664413 and A polymorphism at rs1870377 have a better response (PFS and OS) during treatment with sorafenib. Patients with C polymorphism of rs7664413 and A polymorphism of rs1870377 show a favourable impact in this setting. Notably, VEGFR polymorphism results closely related to the treatment response and the specific signalling of sorafenib. Thus analysis of VEGF and VEGFRs polymorphisms may represent a crucial selection tool in order to identify patients with a possible favourable response to sorafenib.
A8 A PROPOSAL OF A NEW STAGING CLASSIFICATION FOR PATIENTS WITH GASTRIC CANCER RECEIVING D2 GASTRECTOMY

Graziano F.1, Catalano V.1, Sisti V.2, Spada D.3, Giordani P.1, Alessandroni P.1, Baldelli A.M.1, Casadei V.1, Rossi D.1, D’Emidio S.1, Luzi Fedeli S.1, De Nicolis M.4, Rocchi M.5, Testa E.3, Fiorentini G.1, Zingaretti C.2

1Department of Medical Oncology, Surgery, Pathology, Azienda Ospedaliera “Ospedali Riuniti Marche Nord”, Pesaro; 2Department of Medical Oncology, Urbino Hospital, Urbino; 3Institute of Biomathematics, University of Urbino, Urbino

Background. Studies on Asian, US, and German patients have moved some criticisms on the validity of the 7th edition of the AJCC classification to discriminate outcome of gastric cancer stages. We investigated the effect of this AJCC classification in a high-quality surgical populations of patients receiving D2 lymphadenectomy and proposed a new staging system.

Methods. From the prospective database at San Salvatore Hospital, Pesaro, we identified 515 patients with gastrointestinal sphageal junction (GEJ, Siewert II and III) or stomach adenocarcinoma who underwent gastrectomy with curative intent from 1998 to 2010. Lymphadenectomy extended to the 3rd level (D2/D3) was performed in all patients. Overall survival (OS) probabilities, calculated from the date of surgery to the date of death, from any cause, were estimated using the Kaplan-Meier method and compared using the log-rank test.

Results. 58% of patients were male, median age was 73 years (range 36-96); 75 patients (15%) had GEJ tumors. According to the Lauren’s classification, 313 (61%) patients had intestinal type tumors, 159 (31%) diffuse and 43 (8%) mixed type tumors. According to the Lauren’s classification, 313 (61%) patients had intestinal type tumors, 159 (31%) diffuse and 43 (8%) mixed type tumors. Median number of examined lymph nodes was 32 (range 1-89), and only 8.9% of patients had less than 15 examined lymph nodes; 94 patients received adjuvant chemotherapy and 3 patients chemoradiotherapy. As shown in the table, the 7th edition of AJCC classification did not differentiate outcome significantly between stages IA and IB, IIA and IIB, IIB and IIIA, IIIC and IV.

Conclusions. This study confirms once again that the 7th edition of the AJCC classification does not discriminate adequately the outcome from stage to stage. In a European population of patients undergoing gastrectomy plus at least D2 lymphadenectomy, the revised PSS better defines patient prognosis.

Table A8

<table>
<thead>
<tr>
<th>Stage</th>
<th>Groupings</th>
<th>N</th>
<th>5-yr OS (%)</th>
<th>p*</th>
<th>Stage</th>
<th>Groupings</th>
<th>N</th>
<th>5-yr OS (%)</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>T1N0</td>
<td>106</td>
<td>86.6</td>
<td>.9926</td>
<td>I</td>
<td>T1N0-2, T2N0</td>
<td>165</td>
<td>85.7</td>
<td>.0018</td>
</tr>
<tr>
<td>IB</td>
<td>T2N0, T1N1</td>
<td>55</td>
<td>83.3</td>
<td>.0407</td>
<td>II</td>
<td>T3-4aN0, T2N1-2</td>
<td>84</td>
<td>68.4</td>
<td>.0376</td>
</tr>
<tr>
<td>IIA</td>
<td>T3N0, T2N1, T1N2</td>
<td>61</td>
<td>67.6</td>
<td>.7468</td>
<td>IIIA</td>
<td>T3-4aN1-2</td>
<td>105</td>
<td>53.8</td>
<td>.0023</td>
</tr>
<tr>
<td>IIB</td>
<td>T4aN0, T3N1, T2N2, T1N3</td>
<td>65</td>
<td>64.8</td>
<td>.3845</td>
<td>IIB</td>
<td>TxN3, T4bNx</td>
<td>117</td>
<td>28.1</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>IIIA</td>
<td>T4aN1, T3N2, T2N2</td>
<td>58</td>
<td>56.3</td>
<td>.0016</td>
<td>IV</td>
<td>TxNxM1</td>
<td>44</td>
<td>4.6</td>
<td>.0741</td>
</tr>
<tr>
<td>IIIB</td>
<td>T4bN0-1, T4aN2, T3N3</td>
<td>87</td>
<td>35.6</td>
<td>.0376</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IIIC</td>
<td>T4bN2-3, T4aN3</td>
<td>39</td>
<td>8.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>TxNxM1</td>
<td>44</td>
<td>4.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*a compared with row above.
CP-675,206 15 mg/kg-group. Seven patients had stable disease >10 weeks.

Conclusions. CP-675,206 plus gemcitabine was well tolerated and may have antitumor activity in patients with metastatic pancreatic cancer. Additional studies with CP-675,206 are required in this disease.

A10 FHIT, APC, AND HER-2 STATUS AS SURVIVAL PREDICTORS FOR RESECTED GASTRIC CANCER (GC) PATIENTS: A CLINICAL, PATHOLOGICAL AND MOLECULAR RISK STRATIFICATION MODEL

Bria E.1,2, de Manzoni G.3, Beghelli S.4, Tomazzoli A.1, Barbì S.1, Frizziero M.2, Sperduti I.5, Bersani S.1,4, Tortora G.2, Scarpa A.1,4

1Department of Pathology and Diagnostics, 2Medical Oncology, 31st Division of General Surgery, University of Verona, Verona; 4ARC-NET Applied Research on Cancer Center; 5Regina Elena National Cancer Institute, Rome

Background. The disappointing prognosis of GC strongly calls for the identification of prognostic nomograms to better address patients to adjuvant treatment. With this intent, the potential prognostic role of a series of biomarkers was analyzed in a retrospective series (208 pts) of resected GC.

Methods. Clinical, pathological and molecular data were correlated to cancer-specific/overall survival (CSS/OS) using a Cox model. Microsatellite instability, CDX2, APC, β-catenin, E-Cadherin, FHIT, P53, p21, HER-2 (IHC/FISH), TOP2A amplification (FISH) e PIK3CA mutation (exons 9/20) were determined. ROC analysis was adopted for model validation and cut-offs. The individual pts probability (IPP) of death was constructed with a logistic equation with regression analysis coefficients. Cox's ratios were adopted to derive a continuous prognostic score for risk class generation. Internal cross-validation (100 simulations, 80% of the dataset) was accomplished.

Results. With a median follow-up of 20 months, at the multivariate analysis, 8 CSS predictors were identified: sex (HR 1.53, p = 0.04), R (HR 2.69, p = 0.0001), stage (HR 5.40, p < 0.0001), LN (HR 1.55, p = 0.02), localization (HR 1.64, p = 0.008), APC (HR 1.91, p = 0.001), FHIT (HR 1.54, p = 0.05) and HER-2 (HR 1.92, p = 0.08). Sex, age, stage, R, localization, LN, APC and HER-2 were predictors for OS. At the cross-validation analysis APC, FHIT and HER-2 significantly correlated with CSS (replication rate 98%, 51%, 31%). 2-yr IPP of CSS/OS was predicted by the model with a prognostic accuracy of 0.87 (SE 0.02)/0.91 (SE 0.02). On the basis of the ROC generated cut-off prognostic score (AUC 0.87; sensitivity 85.3%, specificity 78.9%), a 2-class risk model was developed, significantly dichotomizing low/high risk pts (CSS: 16.4% vs 82.5%; OS: 15.6% vs 79.7%, p < 0.0001), with a prognostic performance of 0.820/81 (CSS/OS). The 3-class model was developed:

<table>
<thead>
<tr>
<th></th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSS</td>
<td>89.7%</td>
<td>37.3%</td>
<td>7.3%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>OS</td>
<td>84.8%</td>
<td>23.3%</td>
<td>0%</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Conclusions. The expression of FHIT, APC and HER-2 may powerfully complement clinical factors for surgically removed GC, in order to reliably predict outcome risk at the individual level.

A11 PANCREATIC DUCTAL ADENOCARCINOMA: A HOMOGENEOUS MORPHOLOGICALLY BUT MOLECULARLY HETEROGENEOUS TUMOUR. IMPLICATIONS FOR ITS MANAGEMENT

Faloppi L.1, Mandolesi A.2, Scartozzi M.1, Loretelli C.1, Bianconi M.1, Bittoni A.1, Giampieri R.1, Del Prete M.1, Bearzi I.2, Cascini S.3

1Clinica di Oncologia Medica, 2Anatomia Patologica, AOU Ospedali Riuniti, Università Politecnica delle Marche, Ancona

Pancreatic cancer has not achieved significant improvements in therapeutic results, probably due to a poor comprehension of the underlying molecular mechanisms.

The aim of our study was to classify pancreatic tumours in categories from a molecular point of view, in order to better identify the main pathogenetic molecular alterations potentially useful as targets for new drugs.

In 110 histological samples of pancreatic duct adenocarcinoma were performed immunohistochemical examinations of K-ras, stromal IL-6 (IL-6s), tumoral IL-6 (IL-6t), Cox-2, EGFR, Her2, Her3, MLH1, MSH2, MSH3 and molecular biology assessment of CD24, MUC6, HGF, MET, SMAD4, CDKN2A, PIGF, VEGF-A/B, VEGFR-1/2, PGDFRβ, WNT1, BMP4, stemness (ALCAM, PROM1, OCT3/4, CD44, LGR5), Hedgehog (SHH, DHH, IHH, SMO, PTCH1, PTCH2), SPARC, NOTCH1, BRCA1, BRCA2.

A preliminary analysis showed that the positivity of the inflammation mediators stromal IL-6, tumoral IL-6, Cox-2 allowed to differentiate two categories of pancreatic tumours: inflammatory tumours, associated with an intense desmoplastic reaction and alteration of EGFR and MLH1, and on the contrary tumours not associated with inflammation.

Within these two groups statistical significant differences were found for EGFR and MLH1. An overexpression of EGFR was found in triple (97%) and double (88%) positive tumours, compared to negative or single positive (52%) (p = 0.0002). A higher rate of loss of MLH1 expression was found in triple positive tumours (69%), compared to double positive (40%) and negative or single positive (27%) (p = 0.02).

Inflammation has been identified as a significant factor in the development of other malignancies. Mediators of the inflammatory pathway have been shown to be involved in proliferation, loss of tumour suppressor function, oncogene overexpression, all of which may lead to malignancy.

Although definitive results concerning all the molecular factors analyzed will be presented during the AIOM 2012 congress, inflammation and its related molecular alterations may be specific targets for novel agents potentially useful for the treatment of these malignancies.

A12 NATURAL HISTORY OF BONE METASTASES IN GASTRIC CANCER: RESULTS OF AN ITALIAN MULTICENTER SURVEY

Silvestris N.1, De Vita F.2, Giampaolo M.A.3, Maiello E.4, Berardi R.5, Di Costanzo F.6, Angelini F.7, Cinieri S.8, Vasile E.9, Santini D.10

1Medical and Experimental Oncology Unit, National Cancer Institute of Bari; 2Medical Oncology Unit, II University of Naples; 3Medical Oncology Unit, Hospital of Frosinone; 4Medical Oncology Unit, Hospital Casa Sollievo della Sofferenza; 5Medical Oncology Unit, Hospital of Ancona; 6Medical Oncology Unit, Hospital of
A13 FIRST-LINE TREATMENT WITH FOLFIRINOX IN ADVANCED, INOPERABLE PANCREATIC CANCER (APDAC) PATIENTS: SUPPORTIVE MEASURES OPTIMIZATION FOR A SAFE ADMINISTRATION IN ROUTINE CLINICAL PRACTICE

Vaccaro V.1, Bria E.2, Sperduti I.3, Massari F.2, Pino M.S.4, Lucchini E.2, Gelibter A.1, Cognetti F.1, Tortora G.2, Milella M.1

1Oncologia Medica A, Istituto Nazionale Tumori Regina Elena, Roma; 2Oncologia Medica, Azienda Ospedaliera Universitaria Integrata, Verona; 3Dipartimento di Biostatistica, Istituto Nazionale Tumori Regina Elena, Roma; 4SC Oncologia Medica, Azienda Sanitaria di Firenze, Firenze

Purpose. Although FOLFIRINOX has become one of the standard options for the treatment of aPDAC, tolerability and safety issues, with particular regard to hematologic toxicity and increased risk of AE in pts carrying biliary stents, may represent a barrier for the routinely adoption in clinical practice.

Methods. The clinical reports of 36 aPDAC pts undergone 1st-line FOLFIRINOX in 2 different institutions were reviewed. Toxicities, activity and efficacy were determined according to 1) primary G-CSF prophylaxis (dd 7-9-11; yes/no 21/15 pts), and 2) presence/absence biliary stent.

Results. Patients characteristics: N: 36; cycles: 241, M/F: 22/14; median age: 57 yrs (range 37-70); ECOG PS 0/1: 33/3; stage III/IV: 10/26, G3/4 toxicity occurred in <1% of cycles, with the exception of G3/4 neutropenia (16.6% of pts, 3.7% of cycles); 25%-dose reduction occurred in 48/205 cycles (23%), with 3 pts stopping after 1 cycle for G3 GI toxicity in 1 pt and early PD in 2 patients. No differences according to presence/absence of biliary stent were found, in terms of G3/4 toxicities. Prophylactic G-CSF administration did not significantly change G3/4 neutropenia (5/155 [3.2%], versus 4/86 [4.6%]). Patients receiving G-CSF significantly experienced more anemia (p < 0.001) and thrombocytopenia (p = 0.009). Given the administration of PALO/aprepitant/dexamethasone, complete control of nausea/vomiting was achieved at cycle 1 in 72% (95% CI 58-87%) and 86% (95% CI 75-97%) of patients. Partial response and stable disease occurred in 25% and 43% of 28 evaluable pts, with a disease control rate of 68% (95% CI 51-85%). Median PFS was 8 mos (95% CI 6-9 mos). 61% of pts experienced a >50% reduction in CA19.9.

Conclusions. These data indicate that FOLFIRINOX seems to be well tolerated and easily manageable in young (<70 yrs) and fit (PS 0-1) aPDAC pts on an outpatient basis, and may be employed in pts with biliary stents. Although the routine G-CSF prophylaxis is not currently recommended, it can be considered for older/less fit/comorbid pts with aPDAC.

A14 NEOADJUVANT GEMOX FOLLOWED BY GEM-BASED CHEMORADIATION FOR LOCALLY ADVANCED UNRESECTABLE PANCREATIC CANCER

Vaccaro V.1, Sperduti I.2, Bria E.3, Saracino B.4, Pino M.S.5, Grazi G.6, Gelibter A.1, Vallati G.7, Cognetti F.1, Milella M.1

1Oncologia Medica A, 2Dipartimento di Biostatistica, Istituto Nazionale Tumori Regina Elena, Roma; 3Oncologia Medica, Azienda Ospedaliera Universitaria Integrata, Verona; 4Radioterapia Oncologica, Istituto Nazionale Tumori Regina Elena, Roma; 5SC Oncologia Medica, Azienda Sanitaria di Firenze, Firenze; 6Radiologia e Diagnostica per Immagini, 7Dipartimento di Chirurgia, Istituto Nazionale Tumori Regina Elena, Roma

Purpose. To assess activity, safety and secondary resectability in unresectable locally advanced pancreatic cancer (LAPC) patients.

Methods. Unresectable LAPC pts were eligible for this phase II study. Primary endpoint was clinical benefit (CB = CR + PR + SD). A sample size of 37 pts was considered sufficient to give an 80% probability of rejecting a baseline clinical benefit rate of 55%, with an exact 5% one-sided significance test when the true disease control rate was 75%. The drug regimen would have been considered of interest if at least 26 patients showed clinical benefit. Neoadjvant induction chemotherapy (CHT) encompassed gemcitabine (GEM) 1000 mg/m² (100-min infusion on d1) and oxaliplatin 100 mg/m² (2-hr infusion on d2) every 2 wks, for 6 cycles. After CHT pts were restaged for surgery and/or chemoradiation (CRT) consolidation (EBRT up to a total dose of 50.4 Gy plus concomitant GEM 300 mg/m²/week). After CRT completion, pts were restaged to evaluate secondary surgery.

Results. From January 2005 to January 2012, 35 pts (M/F: 17/18; median age 68 yrs, range 46-78; ECOG PS 0-1/2; 28/7) entered the study. A median of 5 (range 1-7) CHT induction cycles were delivered. Toxicity was mild, with G3-4 neutropenia in 2 pts (6%), G3 thrombocytopenia in 1 pt (3%), G3 transaminase elevation in 5 pts (14%), and G3 diarrhea in 2 pts (6%). CHT dose was reduced or delayed in 8 and 7 pts, respectively. Nine...
confirmed PR and 17 SD were observed for a CB of 74% (95% CI 56.7-87.5%). A decrease in serum CA 19.9 ≥50% of the baseline was observed in 14 of 23 evaluable patients. Nineteen pts completed CRT, including 5 pts who subsequently underwent surgery; 1 pt underwent surgery without CRT. Toxicity for the CRT phase was mild, with G3 thrombocytopenia in 1 pt (3%) and G3 neutropenia in 3 pts (8%). Median overall survival (OS) and progression-free survival (PFS) for all 35 patients were 10 (95% CI 8-12) and 9 mos (95% CI 6-12), respectively. One-yr OS and PFS rates were 26% and 30%, respectively.

Conclusions. The regimen under study is active and well tolerated. Although an encouraging response rate was reported, OS remains poor, calling for a better selection strategy for LAPC pts who are candidates to neoadjuvant treatment.

A15 METASTATIC SITE IN PANCREATIC ADENOCARCINOMA (PA) CORRELATES WITH PROGNOSIS

Cereda S.1, Belli C.1, Rognone A.1, Passoni P.2, Slim N.2, Carvello M.3, Balzano G.3, Reni M.1

Department of Medical Oncology1, Radiotherapy2 and Surgery3, San Raffaele Scientific Institute, Milan

Introduction. PA is mostly metastatic at time of diagnosis and is associated with a poor prognosis.

We explored whether metastatic site correlates with prognosis.

Patients and methods. Patients with pathologic diagnosis of metastatic PA, treated at our Institution with upfront combination chemotherapy between April 1997 and August 2010 were eligible for this analysis. Baseline tumour assessment consisted of contrast enhanced computed tomography scan of the abdomen and the thorax which was repeated every two months during treatment and follow-up.

Results. 265 patients with metastatic PA were eligible: median age 60 years; median PS 90; median CA19.9 1048 U/mL; 19 (7.2%) had prior pancreatic surgery. Metastases were located: in a single organ (N = 150; 56.6%); liver (N = 227; 85.3%); peritoneum (N = 52; 12.1%); lung (N = 53; 19.9%). Lung was the only metastatic site in 15 cases (5.6%). Median and 1y overall survival (OS) was 9.0 months and 32.2%. Prior surgery correlated with better OS (11.7 and 51.0% versus 8.9 and 30.8%; p = 0.006); liver metastases with worse OS (median and 1y OS: 8.8 months and 29.7% versus 11.1 and 47.4%; p = 0.005); while no difference in OS was observed based on number of metastatic sites (p = 0.37); peritoneal (p = 0.50) or lung metastases (p = 0.10). Patients with lung as isolated metastatic site lived longer (17.3 and 66.7%) with respect both to the whole population (9.0 and 30.1%; p = 0.01) and to patients with lung metastases associated to other metastatic sites (8.8 and 34.2%; p = 0.07).

Conclusion. Prior surgery and metastatic site correlate with prognosis and should be used as a stratification criterion in prospective trials. Patients with lung as isolated metastatic site have a particularly good prognosis.

A16 CLINICAL OUTCOME OF ADVANCED GASTRIC CANCER (GC) PATIENTS RECEIVING FIRST-LINE CHEMOTHERAPY ACCORDING TO TUMOUR HISTOLOGY AND LOCATION

Bittoni A.1, Scartozzi M.1, Giampieri R.1, Faloppi L.2, Bianconi M.2, Mandolesi A.2, Del Prete M.2, Pistelli M.1, Bearzi I.3, Cascinu S.1

1Clinica di Oncologia Medica, AOI Ospedali Riuniti-Università Politecnica delle Marche, Ancona; 2Scuola di Specializzazione in Oncologia Medica, Università Politecnica delle Marche, Ancona; 3Anatomia Patologica, AOI Ospedali Riuniti-Università Politecnica delle Marche, Ancona

Background. In daily clinical practice GC is considered as a single disease. However, preliminary data identified distinct subtypes characterized by relevant differences in epidemiology, carcinogenesis and gene expression profiles. Recently three subtypes have been identified: type 1 (proximal non diffuse GC), type 2 (diffuse GC) and type 3 (distal non diffuse GC). Aim of our analysis was to compare clinical outcome (in terms of response rate, RR, progression-free survival, PFS and overall survival (OS) according to different GC subtypes (1, 2, 3) in patients receiving first-line chemotherapy.

Patients and methods. Advanced GC pts treated with a first-line combination chemotherapy were included in our analysis. Patients were divided in three subgroups (type 1, type 2 and type 3) as previously defined.

Results. A total of 202 advanced GC pts were included: most of pts belonged to type 2 (50.5%) and type 3 (40.6%); type 1 included 18 pts (8.9%). The majority of pts (62%) received a three-drugs chemotherapy combination including a platinum derivate, a fluoropyrimidine with the addition of an anthracycline, a taxane or mytomicin C; the remaining patients received a platinum and fluoropyrimidine combination. The three pts subgroups resulted comparable for relevant clinical factors such as ECOG PS, tumour stage, number of metastatic sites, previous surgical resecion, first-line combination and use of second-line treatments; as expected peritoneal carcinosis was more common in type 2 patients. RR was found to be higher in type 3 pts (RR = 45.1%) than in type 1 (27.8%) and type 2 (25.5%) (p = 0.017). Type 2 pts presented a shorter PFS (median PFS 5.7 months) compared to type 1, median PFS = 6.9 months, and type 3, median PFS = 7.8 months (p = 0.0069). These differences did not translate in statistically significant differences in OS.

Conclusions. Our results suggest that GC subtypes may be important predictors of benefit from chemotherapy in advanced GC patients. Future clinical trials should take in account these differences for a better stratification of patients.

A17 INDUCTION GEMOX THERAPY FOLLOWED BY A TWICE-WEEKLY INFUSION OF GEMCITABINE AND CONCURRENT EXTERNAL BEAM RADIATION FOR NEOADJUVANT TREATMENT OF LOCALLY ADVANCED PANCREATIC CANCER: A SINGLE INSTITUTIONAL EXPERIENCE

Colombi F.1, Massucco P.2, Gatti M.3, Sperti E.1,4, Campanella D.5, Regge D.5, Gabriele P.3, Capussotti L.2,4, Aglietta M.1, Leone F.1

1University of Turin, Medical Oncology Department, Institute for Cancer Research and Treatment (IRCC), Candriolo; 2Surgical Oncology Department, 3Radiation Oncology Department, IRCCS, Candriolo; 4Ordine Mauriziano, Umberto I Hospital, Torino; 5Radiology Department, IRCCS, Candriolo
Background. Optimal therapy for patients with locally advanced pancreatic carcinoma (LAPC) is still controversial. Combined modality therapies have been proposed to achieve better local tumour control or tumour down-staging with a subsequent potentially curative resection. We have previously demonstrated the achievement of significant disease control, and a median overall survival (OS) of 14 months by chemoradiotherapy (CRT) in LAPC patients. We evaluated the use of induction chemotherapy followed by a CRT neoadjuvant protocol.

Materials and methods. Patients firstly received 4 cycles of induction GEMOX (gemcitabine 1000 mg/m² and oxaliplatin 100 mg/m²). Patients without disease progression then received gemcitabine twice weekly (50 mg/m²/day) concurrent with radiotherapy (50.4 Gy) and were re-evaluated for resectability.

Results. Between June 2003 and December 2009, 39 patients (15 borderline resectable and 24 unresectable) entered the study. Toxicities were acceptable with minimal life-threatening side effects and no treatment-related deaths. Disease control was obtained in 29/39 of patients. Only 2 patients progressed after GEMOX. After a median follow-up of 13 months, the median progression-free survival (PFS) was 10.2 months (16.6 months for borderline resectable, 9.1 months for unresectable, p = 0.056). The first pattern of failure was local in 18% of patients and systemic in 82% of patients. For the whole group the median OS was 16.7 months (27.8 months for borderline resectable, 13.3 months for unresectable, p = 0.045). Eleven patients (nine borderline resectable and two unresectable at diagnosis) were successfully resected. Resected patients had a significantly higher median PFS (19.7 versus 7.6 months, p <0.001) and higher median OS (31.5 versus 12.3 months, p <0.001) compared to non-resected patients.

Conclusions. Induction GEMOX followed by CRT was found to be feasible and safe in LAPC patients. Both borderline resectable and unresectable patients could receive clinical benefits, a chance to obtain resectability, and survival improvement. A high local disease control rate is achievable in most patients. Since distant recurrence remains the principal reason for treatment failure, future trials should focus on systemic disease control.

A18 FOLFIRINOX IN METASTATIC PANCREATIC ADENOCARCINOMA: PRELIMINARY RESULTS OF A SINGLE CENTER PHASE 2 STUDY


Divisione di Oncologia Medica, Università Cattolica del Sacro Cuore, Roma

Background. In the pivotal phase 2-3 trial by Conroy et al., FOLFIRINOX was associated with a meaningful survival advantage compared with gemcitabine as first-line treatment for pts with metastatic pancreatic adenocarcinoma. The pts accrued in that study, however, were certainly fitter than the average patient with pancreatic cancer treated in the daily clinical practice, and probably FOLFIRINOX should be further investigated before being considered as the new standard of care. We report the preliminary result from a phase 2 study.

Methods. From January 2011, 25 pts with previously untreated metastatic pancreatic adenocarcinoma have been enrolled in the study. All pts were treated with FOLFIRINOX until disease progression or unacceptable toxicity.

Results. Median age was 60, 60% of pts were male and 48% had carcinoma of the pancreatic head. Performance status (PS) score was 0-1 for 22 pts, only 3 pts with PS 2 were included in the study. Response rate was 52% with a disease control rate of 84%. Median PFS and OS were 9 and 12 months, respectively. The most common G3/4 toxicities were diarrhoea (20%), nausea/vomiting (20%), neutropenia (16%), neuropathy (16%), thrombocytopenia (8%) and cholangitis (8%). G-CSF was administered as primary prophylaxis for neutropenia in pts with high risk of biliary sepsis. 28% of pts required a dose reduction for toxicity. No toxic deaths were observed. The 3 pts with PS 2 had a worse outcome compared with PS 0-1 pts: 2 of them experienced disease progression within only 3 months of treatment and 1 of them within 5 months.

Conclusion. Preliminary results of our study add to the already available evidence that FOLFIRINOX is a highly effective and reasonably tolerated regimen for selected pts with MPA, but it has probably a limited benefit for pts with a poor PS. A good supportive care environment would be advisable in order to minimize the treatment-related toxicity.

A19 SORAFENIB (SFB) REDUCED DOSE (rD) IN ADVANCED HEPATOCELLULAR CARCINOMA (aHCC) ELDERLY PATIENTS WITH COMORBIDITY: EVALUATION OF rD EFFICACY VS STANDARD DOSE (sD)


*University Dept, Oncogeriatric Unit, Palermo; **Oncology Unit, Novi Ligure General Hospital; ^Unit of Medical Oncology, ASP Reggio Calabria; #Chair of Geriatrics, Federico 2nd University, Napoli; **Oncology Clinical Dept, S. Paolo Hospital, Milan; ^University Medical Oncology Dept, University of Cagliari

Background. HCC accounts for approximately 90% of all primary liver cancers, is the sixth common cancer in the world, the third cancer-related cause of death and is more often correlate to hepatic cyrosis. So far prognosis of aHCC is very poor, particularly in stage C according to BCLC classification, no therapy strategy till now demonstrates significant outcome. Sorafenib, a multikinase inhibitor active also against Vegf activity, shows significant improvement of clinical benefit and it is to become the current standard drug for the first-line systemic treatment in patients with aHCC stage C. The other side of coin is that the most elderly patients are affected by one or more co-morbidities, that determine worsening in the outcomes of treatment.

Aim. Aim of the study is to investigate if SFB delivered at rD is efficient as SFB delivered at sD in aHCC elderly pts with comorbidity.

Methods. Fifty-seven patients were enrolled, mean age 72.6 with aHCC histologically proven.

Main inclusion criteria: pts with aHCC, Child-Pugh A or B, BCLC C, adequate liver, hematological and renal function; written informed consent acquired. Every pt received SFB 400 mg once a day until unbearable AADRs or progression disease. Serum CgA, VEGF and αFP were evaluated at baseline and
every four months of observation. Response evaluation according to RECIST, Comprehensive Geriatric Assessment (CGA) according to Balducci’s classification and PFS (ECOG) not greater then 2 were considered as well.

**Results.** Patients received 400 mg p.o. once a day until intolerable ADRs or progression disease.

No discontinuation of treatment was needed for 48 out of 57 pts and treatment is still ongoing. Nine pts experienced severe ADRs (grade IV diarrhea and fatigue). Treatment was definitively stopped after a fifteen days discontinuation tentative with the intent of an amelioration of general conditions. Patients with better clinical response showed also lower values of serum CgA, VEGF and AFP.

**Conclusions.** In elderly pts one or more comorbidities. Although the increased age is poor prognostic factor for tolerability, the reduction of dose doesn’t seem to reduce the efficacy of treatment in this group of patients. On the other hand the minimization of ADRs positively affects the quality of life and clinical benefit. Finally further data were needed to assess how the lower values of serum CgA and VEGF levels could play a role as novel prognostic factors in clinical management of aHCC elderly patients.

**A20 MODIFIED FOLFOXIRI IN ADVANCED PANCREATIC CANCER**

**Methods.** The objective of this study was to prospectively evaluate the tolerability and activity of a modified (m)FOLFOXIRI regimen in metastatic or locally advanced PC. The regimen included a lower dose of irinotecan (150 mg/m2 on day 1 every 14 days) and of infusional 5-fluorouracil (2800 mg/m2 in 48-hour continuous infusion on days 1 to 3 every 14 days). Folinic acid and oxaliplatin remained unchanged.

**Results.** From August 2010 onwards, 39 patients with cytological or histological diagnosis of PC received mFOLFOXIRI (a total of 260 cycles administered). Seventeen had metastatic disease, 22 had locally advanced disease. The grade 3-4 toxicities reported were: neutropenia in 35.9% of patients; thrombocytopenia 2.6%; liver toxicity 5.1%; nausea/vomiting 5.1%; stomatitis 7.7%; diarrhea 5.1%; sensory neuropathy 5.1%; fatigue 2.6%. No toxic deaths, febrile neutropenia and grade 3-4 anemia have occurred. G-CSF has been used in seven patients (17.9%). An administration of chemotherapy delay was required in 12 patients (30.8%) and a doses reduction in 7 cases (41%).

Among 30 evaluable patients we observed 11 partial responses (36.7%) and 14 stable disease (46.7%). Median progression-free survival (PFS) was 11.5 months and median overall survival (OS) 25.5 months. For metastatic patients only, response rate resulted 33% with a PFS and OS of 8.4 and 14.8 months, respectively.

**Conclusions.** The mFOLFOXIRI regimen as we used resulted feasible and quite well tolerated, maintaining its activity in metastatic PC.

**A21 PHASE II STUDY OF NEOADJUVANT MODIFIED FOLFOXIRI IN LOCALLY ADVANCED PANCREATIC CANCER**

**Background.** Considering the high activity of FOLFIRINOX in metastatic pancreatic cancer (PC), the regimen could be of interest also for patients with inoperable locally advanced (LA) disease. Our group developed a very similar schedule in colorectal cancer named FOLFOXIRI containing no bolus 5-fluorouracil and a slight lower dose of irinotecan.

**Methods.** FOLFOXIRI was modified with a lower dose of irinotecan (150 mg/m2) and of infusional 5-fluorouracil (2800 mg/m2 as a 48-hour continuous infusion on days 1 to 3). Folinic acid and oxaliplatin remained unchanged.

The study enrolled patients with diagnosis of pancreatic adenocarcinoma, stage III locally advanced disease without evidence of metastatic disease (cT4,cN0-1), ECOG performance status (PS) 0-1, age 18-75. The primary endpoint of the study was the percent of patients who undergo radical surgical resection after chemotherapy; the trial was designed with a percentage of low activity p0 = 30% and a percentage of interest p1 = 50% with an α and β error of 0.05 and 0.20.

**Results.** Twenty-two patients have been enrolled; M/F = 8/14; PS 0/1 = 10/12. Median age was 60 years (range 44-75). Celiac axis was involved in 7 patients, superior mesenteric artery in 10 cases, both arteries in 5 patients. Baseline computer tomography showed pathological nodes in 19 patients.

Fifteen patients have been so far evaluated, with 6 partial responses (40%) and 9 stable disease (60%). A local treatment after chemotherapy was received by 9 patients until now: 5 (55.5%) underwent radical surgical; 1 underwent an explorative laparotomy with evidence of liver metastases; 3 received concomitant chemo-radiotherapy with gemcitabine.

Median progression-free survival was 24.5 months and median overall survival was 30.1 months.

**Conclusions.** Chemotherapy with mFOLFOXIRI seems active in LAPC and may allow to obtain a downstaging of disease in some patients leading to achieve a curative surgical resection. Longer follow-up is needed to better evaluate long-term outcome of this strategy.
A22 A RETROSPECTIVE ANALYSIS OF HER-2 HYPEREXPRESSION IN GASTRIC AND GASTROESOPHAGEAL JUNCTION (GEJ)

Lencioni M.1, Vasile E.1, Ginocchi L.1, Di Maso L.1, Caparello C.1, Caponi S.1, Barette M.1, Lucchesi M.1, Da Prat V.1, Bellumoini L.1, Ricci S.1, Falcone A.1, Ugolini C.1, Fontanini G.2, Solito B.3, Santi S.3, Fabrini M.G.4

1Polo Oncologico, Azienda Ospedaliero-Universitaria Pisana, Istituto Toscano Tumori, Pisa; 2Anatomia Patologica Sperimentale, Università di Pisa, Istituto Toscano Tumori, Pisa; 3Department of Gastroenterology, Esophageal Surgery Unit, Tuscany Regional Referral Center for the Diagnosis and Treatment of Esophageal Disease, Pisa; 4Division of Radiation Oncology, S. Chiara Pisa Hospital, Pisa

Background. Gastric and GEJ adenocarcinoma Her-2 hyperexpression is reported in 20% of cases; its prognostic relevance is controversial.

Methods. We retrospectively analyzed gastric and GEJ adenocarcinoma clinical data and tumour specimens.

Results. 114 patients (75M/39F) were included into the analysis, divided in two groups: localized disease (LD) (72) and metastatic disease (MD) (42). Median age was 54 years (33-85), 65 patients had ECOG performance status (PS) 0, 37 PS 1, 12 PS 2. Tumour involved GEJ in 45 patients and stomach in 69; 25 patients had intestinal histological subtype, 42 diffuse and 47 mixed. Twenty-two patients had stage I disease, 25 stage II, 35 stage III, 42 stage IV. Forty-two LD patients received perioperative chemotherapy. MD patients underwent first-line treatment with mono or polichemotherapy (regimens including fluoropyrimidine, taxane, platin, anthracyclines); HER-2 positive patients received also trastuzumab. HER-2 was scored 3+ in 10 patients (6 LD, 4 MD), 2+ in 53 patients (43 LD, 10 MD). HER-2 positivity was found in 16% of gastric adenocarcinoma and in 32% of GEJ adenocarcinoma. At univariate analysis CA19-9 represented a prognostic factor (median overall survival (OS) if CA19-9 ≤37 U/mL vs >37 U/mL was 18.49 vs 9.21 months, respectively, p = 0.0004); while surprisingly the presence of vascular and perineural invasion was found to be a favorable prognostic factor (median OS in patients with invasion vs without invasion was 27.5 vs 9.6 months, respectively, p = 0.0002). At multivariate analysis the presence of invasion was found to be an independent favorable prognostic factor, while the high level of CA19-9 resulted an independent unfavorable prognostic factor.

Conclusions. Levels of CA19-9 at the beginning of the first-line chemotherapy represent an independent prognostic factor, therefore it should be considered in deciding the treatment. Surprisingly the presence of invasion appeared as an independent favorable prognostic factor in advanced pancreatic cancer and this result may impact therapy decisions and stratification of future clinical trials.

A24 FOLFIRI AS THIRD-LINE TREATMENT IN METASTATIC GASTRIC CANCER

Santi S.1, Caparello C.2, Vasile E.2, Lencioni M.2, Caponi S.2, Ginocchi L.2, Lucchesi M.2, Belluomini L.2, Fabrini M.G.3, Da Prat V.2, Barette M.2, Ricci S.2, Falcone A.2

1Department of Gastroenterology, Esophageal Surgery Unit, Tuscany Regional Referral Center for the Diagnosis and Treatment of Esophageal Disease, Pisa; 2Polo Oncologico, Azienda Ospedaliero-Universitaria Pisana, Istituto Toscano Tumori, Pisa; 3Division of Radiation Oncology, S. Chiara Pisa Hospital, Pisa

Background. In metastatic gastric cancer, besides the use of fluoropyrimidines and platinum compounds, also the availability of different active agents, such as docetaxel and irinotecan, has given the opportunity to administer further lines of treatment in this setting of patients. There are many patients progressed after two lines of chemotherapy who maintain a good performance status and are fit for a third-line treatment.

Methods. The objective of this retrospective analysis was to evaluate the activity of the combination of 5-fluorouracil/folinic acid and irinotecan (FOLFIRI) as third-line treatment for metastatic gastric adenocarcinoma patients.

Results. A total of twenty-one patients (M/F 16/5; ECOG Performance Status 0/1: 3/18) treated between 2009 and 2011 were included in the analysis; median age was 64 years (range 38-77). All patients received first-line chemotherapy with fluoropyrimidine plus platinum compounds; in 7 of them a triple-drug combi-
nation with epirubicin was used; one patient with HER-2 positive disease received trastuzumab in addition to chemotherapy. All patients received second-line taxane-based chemotherapy (docetaxel in 18 and paclitaxel in 3 patients), in association with 5-fluorouracil in 5 cases.

A total of 151 cycles of third-line FOLFIRI were administered (median number 7; range 2-18). Treatment was well tolerated; grade 3 or 4 toxicities included diarrhea in 3 patients, neutropenia in 3 patients, asthenia and vomiting in 1 patient each; 9 patients needed a delay of treatment and 3 patients a reduction of doses. Among the twenty evaluable patients, 2 (10%) partial responses, 10 (50%) stable disease and 8 (40%) stable disease were observed, thus obtaining a disease control rate of 50%. Median duration of response was 7 months.

Median progression-free survival was 3.8 months and median overall survival was 9.1 months from the start of third-line treatment.

Conclusions. FOLFIRI was feasible and showed an encouraging activity also in third-line setting of largely pretreated selected metastatic gastric cancer patients.

A25 WHOLE GENOME DISCOVERY OF GENETIC ALTERATIONS IN RESECTABLE AND ADVANCED PANCREATIC CANCER

Macchini M.1, Astolfi A.2, Casadei R.3, Ricci C.3, Indio V.2, Vecchiarelli S.1, D’Ambra M.3, Grassi E.1, Santini D.4, Minini F.4, Biasco G.1, Di Marco M.1

1Department of Hematology and Oncology “L. e A. Seràgnoli”; 2“G. Prodi” Cancer Research Center, University of Bologna; 3Department of Surgery; 4Department of Pathology, Sant’Orsola-Malpighi Hospital, Bologna

Background. Pancreatic cancer (PC) is the fourth leading cause of cancer deaths, with a 5-year survival rate of 4%. To date no medical treatment has significantly increased patients’ survival. The molecular mechanisms involved in the high tumorigenicity of PC are not yet well known. A better knowledge of pancreatic biology is currently very important and could have many implications in clinical practice.

Methods. Pancreatic tumour samples from 14 patients were collected by ultrasound-guided biopsy and used for RNA and DNA extraction. Whole transcriptome massively parallel sequencing was performed on an Illumina HiScanSQ platform, at 75bp read length. Single Nucleotide Variants (SNVs) were identified by alignment to the Reference Genome hg19 with TopHat/Bowtie pipeline and SNV calling with SamTools and SNVmix2. Novel SNVs were highlighted by comparison with dbSNP and 1000Genomes databases and disease-related variants were predicted with SNPs&GO. High resolution copy number analysis was performed on Affymetrix SNP array 6.0 and analyzed with segmentation algorithm against a reference of 270 Ceu HapMap individuals (Partek Genomic Suite).

Results. Whole transcriptome sequencing was performed in three patients, identifying an average of 24 non synonymous SNV/patient. Prediction of the functional effect of the putative mutations identified genes harbouring disease-related variants, in particular those regulating apoptosis (PDCD4), Unfolded Protein Response (ATF6B) and proliferation (LCP1). 9/14 patients exhibited both macroscopic and cryptic cytogenetic alterations, with a mean of 10 copy number alteration per patient, while 5 patients did not show any copy number gain or loss. Deletions out-numbered amplifications by more than 2-fold. The chromosomes showing more copy number gains were chr 12, 18, 19, while chromosomes 6, 9, 17 and 18 were most frequently deleted. In particular, deletions on 9p21 encompassed CDKN2A and 2B tumour suppressor genes, that on chromosome 18q overlapped with SMAD4, the one on chromosome 6 included RUNX2, while TP53 was the target gene deleted on chr 17p. Amplified regions on chromosome 12p encompassed KRAS and ETV6 genes, while on 19q included PAK4. We observed that the number of alterations correlates with clinical course, and in particular that patients with none to few alterations show a time to disease progression significantly longer than those that have a high number (>10) of abnormalities (10.4 vs 4.4 months respectively, p = 0.031).

Conclusions. SNV detection through next generation sequencing, combined with high resolution cytogenetic analysis by SNP-array, has the potential to uncover all the genetic alterations carried by pancreatic tumours.

A26 ROLE OF ADJUVANT CHEMOTHERAPY IN THE TREATMENT OF RADICALLY RESECTED BILIARY TRACT CANCER: A SINGLE INSTITUTION EXPERIENCE

Lucchesi M.1, Vasile E.1, Ginocchi L.1, Caponi S.1, Da Prat V.1, Caparell C.1, Baretta M.1, Lencioni M.2, Lombardi I.1, Ricci S.2, Falcone A.1

1Oncologia Medica 2 Universitaria, 2Oncologia Medica 1 Ospedaliera, Polo Oncologico, Azienda Ospedaliero-Universitaria Pisana, Istituto Toscano Tumori, Pisa

Background. The benefit of adjuvant chemotherapy for resected biliary tract cancers is unclear and there is no current standard in this setting, despite the majority of patients suffers from recurrent disease after surgery.

Methods. We retrospectively reviewed the outcome of patients who underwent radical surgical resection for biliary tract cancer from 2007 to 2011 and who received adjuvant treatment or only observation at our institution.

The aim of this study was to evaluate prognostic factors associated with disease-free survival (DFS) and to analyze the role of adjuvant chemotherapy for these patients.

Results. One hundred and ten evaluable patients were identified, 59 women and 51 men. The site of biliary cancer was intrahepatic in 26 patients (24%), perihilar in 14 (13%), distal in 25 (23%), gallbladder in 16 (14%), and ampullary carcinoma in 29 cases (26%). Sixty-nine patients (63%) had T3 or T4 tumours and 47 (43%) had positive nodes; poor differentiation (grade 3 or 4) was in 48 (44%) cases.

Median DFS was 22.4 months. Ampullary carcinoma showed longer DFS compared to other cancers (median DFS 73.6 months versus 20 months; p = 0.04). At univariate analysis with log-rank test, the presence of node metastases (p = 0.001) and a higher grade of differentiation (p = 0.01) resulted negative prognostic factors associated with shorter DFS.

At multivariate analysis according to Cox proportional hazards model adjusting for these prognostic factors, adjuvant chemotherapy resulted associated with longer DFS (hazard ratio 1.93; 95% confidence interval 1.05-3.55; p = 0.034).

Node positivity and grading maintained their prognostic role also in multivariate analysis (p = 0.003 and p = 0.009, respectively).
Conclusions. Our study supports the use of adjuvant chemotherapy for high risk resected biliary tract cancer patients. Prospective randomized trials are needed to provide higher level of evidence for this strategy but, on the basis of recent literature data, in line with our experience, future trials should have an active comparator arm rather than a surgery-alone arm especially for patients with node positive disease.

A27 FIXED-DOSE RATE GEMCITABINE PLUS CAPECITABINE: A SECOND-LINE OPTION FOR METASTATIC PANCREATIC CANCER PATIENTS PRETREATED WITH OXALIPLATIN

Masi G.1, Lucchesi M.1, Caparelli C.1, Vasile E.1, Ginocchi L.1, Caponi S.1, Da Prat V.1, Baretti M.1, Lencioni M.2, Ricci S.2, Falcone A.1

1Oncologia Medica 2 Universitaria, 2Oncologia Medica 1 Ospedaliera, Polo Oncologico, Azienda Ospedaliere-Universitaria Pisana, Istituto Toscana Tumori, Pisa

Background. There is no consensus about second-line chemotherapy for pancreatic cancer. First-line options are changing and combination chemotherapy containing oxaliplatin such as FOLFIRINOX is frequently used. Therefore, we performed a phase II trial to evaluate the activity of a regimen with fixed-dose rate gemcitabine and capecitabine (FDR GEM-CAP) as second-line treatment for metastatic pancreatic cancer patients pretreated with oxaliplatin.

Methods. Patients with pathological diagnosis of pancreatic adenocarcinoma, with ECOG performance status (PS) 0 or 1, who progressed after first-line chemotherapy including oxaliplatin were enrolled and treated with capecitabine 650 mg/m2 bid on days 1 to 14 plus FDR gemcitabine 800 mg/m2 infused in 80 minutes on days 1 and 8, with cycles repeated every 21 days.

The primary endpoint of the study was the percentage of patients free of progression at 2 months after beginning of chemotherapy; with $p = 0.50$ and $p1 = 0.70$, an $\alpha = 0.10$ and $\beta = 0.20$, a total of 20 patients should be necessary for the analysis.

Results. Twenty patients were enrolled; M/F = 9/11; PS 0/1 = 13/7. Median age was 60 years (range 42-75). First-line treatment was gemcitabine plus oxaliplatin (GEMOX) in 13 patients and FOLFIRINOX in 7.

The median number of cycles of second-line FDR GEM-CAP was 4 (range 2-14), with a total of 108 cycles administered. The only grade 3 toxicity recorded was anemia in 1 patient. Only 9 cycle delays (8.3%) were needed for toxicity. Among 18 patients so far evaluable for response, 2 partial responses (11.1%) and 7 stable diseases (38.9%) have been observed.

The trial met its primary endpoint; median progression-free survival was 4.3 months with a percentage of patients free of progression at 2 months of 79%. Median overall survival from the beginning of second-line was 12 months.

Conclusions. The combination of FDR GEM-CAP as we used is well tolerated and active in metastatic pancreatic cancer patients and could be an interesting second-line option for selected patients treated with first-line FOLFIRINOX.

A28 A PHASE II TRIAL OF SECOND-LINE THERAPY WITH TRABECTEDIN IN METASTATIC PANCREATIC ADENOCARCINOMA (mPA)

Bellì C.1, Cereda S.1, Piemonti L.2, D’Incalci M.3, Allavena P.4, Miggiano C.1, Rognone A.1, Fugazza C.1, Longoni S.1, Reni M.1

1Department of Medical Oncology, 2Diabetes Research Institute, San Raffaele Scientific Institute, Milan; 3Department of Oncology, Mario Negri Institute, Milan; 4Department of Immunology and Inflammation, Clinical Institute Humanitas, Rozzano, Milan

Background. No standard second-line chemotherapy exists for mPA albeit a randomized trial suggested that salvage chemotherapy may improve overall survival (OS) compared to best supportive care. This study evaluates the activity and safety of trabectedin as second-line therapy in mPA.

Methods. Patients with mPA progressing after gemcitabine-based chemotherapy, age <76 yrs, Karnofsky performance status (KPS) >50 and adequate renal, hepatic and bone marrow function were treated with i.v. trabectedin at 1.3 mg/m2 every 3 weeks until PD, unacceptable toxicity, patient’s refusal, or for a maximum of 6 months. The primary endpoint of this study was the progression-free survival rate at 6 months (PFS-6). The maximum PFS-6 rate of low interest was 10% and the PFS-6 rate of interest was set to 30%. Twenty five pts were required ($\alpha$ and $\beta :10$, one sided). If at least 5 out of 25 pts were PFS-6, the treatment will be considered of interest.

Results. Between February 2011 and February 2012, 25 pts with mPA, median age 58 yrs (range 48-73); median KPS 90 (range 80-100) received trabectedin. Prior therapy consisted of adjuvant gemcitabine (N = 3); adjuvant PEXG (cisplatin, epirubicin, capecitabine, gemcitabine; N = 2); PEXG (N = 19) or gemcitabine (N = 1) for mPA. Median prior PFS was 9 months; maximum response to prior chemotherapy in 20 mPA pts was partial response (PR) in 14 (70%) and stable disease (SD) in 6 (30%). Only 1 pt completed all the planned 9 cycles; 23 interrupted trabectedin due to PD, and 1 due to toxicity. Only 2 pts (8%) were PFS-6. Median PFS was 1.9 months (range 0.7-7.4). Median OS was 4.7 months (range 1.1-13.9) and 1-yr OS was 24%. No PR and 6 SD (24%) were observed. Grade 3-4 toxicity consisted of neutropenia (44% of pts); fatigue (16%), anemia, thrombocytopenia and transaminis (8% each); febrile neutropenia (4%).

Conclusions. This study showed that trabectedin has a limited activity compared to other drugs used as salvage therapy in mPA.

A29 THE ROLE OF MACROPHAGES POLARIZATION IN PREDICTING PROGNOSIS IN RADICALLY RESECTED GASTRIC CANCER

Pantano F.1, Berti P.1, Guida F.M.1, Intagliata S.1, Graziano F.2, Perrone G.3, Onetti Muda A.3, Vincenzi B.1, Tonini G.1, Santini D.1

1Department of Medical Oncology, Campus Bio-Medico University, Rome; 2Unit of Medical Oncology, Hospital of Pesaro, Pesaro; 3Department of Anatomical Pathology, Campus Bio-Medico University, Rome

Introduction. Macrophages are one of the major populations of tumour-infiltrating immune cells. Tumour associated macrophages (TAM) present two different phenotypes or polarizations: classical (M1) characterized by immunostimulation activity and tumour suppression; alternative (M2) characterized by angiogenesis, tumour promotion, and immune suppression. De-
A30 COMPARING RECIST AND CHOI’S CRITERIA TO EVALUATE RADIOLOGICAL RESPONSE TO CHEMOTHERAPY IN PATIENTS WITH RESECTABLE AND ADVANCED PANCREATIC CANCER

Macchini M.1, Ricci C.2, Vecchiarelli S.1, D’Ambra M.2, Casadei R.2, Calculi L.1, Pezzilli R.2, Grassi E.1, Minni F.2, Biasco G.1, Di Marco M.1

1Department of Hematology and Oncology “L. e A. Seràgnoli”, University of Bologna, Bologna; 2Department of surgery, 3Department of Radiology, 4Department of Internal Medicine, Sant’Orsola-Malpighi Hospital, Bologna

Background. Assessment of response after chemotherapy for pancreatic cancer is currently based on RECIST criteria. In 2007 Choi et al. published a new classification system.

Objectives. To evaluate the accuracy of the two classification systems for radiological response to chemotherapy in patients affected by resectable and advanced pancreatic cancer.

Methods. From January 2008 to December 2011, 41 untreated patients affected by pancreatic adenocarcinoma underwent neoadjuvant or palliative chemotherapy. There were 24 (58.5%) male and 17 (41.5%) female, with mean age of 62 ± 10 years. Ten (24.4%) patients with a resectable disease (stage II according UICC-TNM) underwent neoadjuvant therapy with gemcitabine and radiotherapy. Thirty-one (75.7%) with unresectable disease underwent neoadjuvant therapy with gemcitabine (GEM)-based.

We assessed radiological response after three months of neoadjuvant or first-line therapy applying both RECIST criteria, that evaluate differences in CT size, than Choi’s criteria, that consider changes both in size and in density at CT. We compared the accuracy in restaging the class of response with overall survival. The survival was calculated with Kaplan-Meier method. The concordance test with two classification systems was evaluated with Kendall’s concordance test. The accuracy in restaging was made with log-rank test.

Results. At restaging, using RECIST criteria, we registered 3 (7.3%) patients with partial response, 28 (68.3%) patients with stable disease, and 10 (24.4%) cases of disease progression. Instead Choi’s criteria assessed 15 (36.6%) partial responses, 14 (34.1%) stable diseases and 12 (29.3%) progressive diseases. One third of partial responses was observed in patients who underwent neoadjuvant therapy.

Conclusions. In our experience, Choi’s criteria seem to better assess radiological response after neoadjuvant or first-line chemotherapy in pancreatic cancer patients than RECIST criteria. Due to the small number of patients, larger prospective studies are needed.

A31 CREATION OF A PATHOLOGY SPECIALIZED REGISTRY OF THE GASTRIC CANCER CASES INCIDENT IN THE CREMONA PROVINCE AREA. STUDY OF THE RISK FACTORS AND CLINICAL, HISTOLOGICAL AND BIOMOLECULAR FEATURES

Donida B.M.1, Gnocchi E1., Bizzoco S.2, Brambilla G.3, Buffoli F.1, Lazzarelli S.1, Colombi C.1, Mainardi E.3, Marchetti G.1, Panni A.1, Pergola L.1, Poli R.1, Rovatti M.1, Tommassello G.1, Villa M.2, Passalacqua R.1

1Istituti Ospitalieri of Cremona, Cremona; 2Azienda Sanitaria Locale, ASL of Cremona; 3Ospedale Maggiore of Crema, Crema, CR

Background. Gastric cancer (GC) remains one of the leading causes of cancer-related deaths worldwide. There is difference between different countries in the world in the incidence and outcome. Also Italy on its inside shows a variability between regions and Lombardy holds the most incidence and mortality Italian rate, with the province of Cremona as one of the leading area with its GC mortality rate (http://www.aslcremona.it/html/at-lante/introduzione.htm).

Aim. To define the incidence of GC in the province of Cremona and the correlation with environmental, familiar, genetic and social factors. Then, we could adopt prevention strategies to reduce the impact of the disease. Moreover, a GC Bio-Bank, including blood and tissue samples, will be created for collaborative research projects regarding molecular and cellular aspects of GC.

Methods. The study has been approved by the Ethical Committee of Cremona and Crema. It will be conducted in collabora-
tion with the ASL (Azienda Sanitaria Locale) of Cremona and all the public and private hospitals of the DIPO (Dipartimento Inter-aziendale Provinciale Oncologico). The study was designed to assess the registration of a cohort of patients, which are living in the Cremona province and which have a primary GC diagnosis since January 1st 2010. For each registered case will be collected social demographic data, morphology, topography, grading tumour classification and instrumental clinical investigations, details on type of surgery and on other treatments, Helicobacter pylori infection and HER-2 staining. Host genetic background and biomolecular characteristics, so as social and environmental factors will be also registered.

**Conclusions.** Tumour specialized registry can be viewed as one of the main strategies for studying and monitoring the impact of an important cancer diagnosis. In addition the information obtained from it can be translated into preventive measures and health surveillance that might lead to a better control of this tumour in a province with a so high mortality rate.

### A32 OPTIMAL PREOPERATIVE STAGING AND EARLY DETECTION OF LUNG METASTASES FOR PATIENTS AFFECTED BY INVASIVE INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS (IPMNs) OF THE PANCREAS

Caponi S., Vasile E., Caparelo C., Ginocchi L., Lucchesi M., Baretto M., Da Prat V., Lencioni M., Ricci S., Falcone A.

Polo Oncologico, Azienda Ospedaliero-Universitaria Pisana, Istituto Toscano Tumori, Pisa

**Background.** The incidence of IPMNs (intraductal mucin-producing cystic neoplasms) of the pancreas is rising and nowadays IPMNs account for approximately 25% of resected pancreatic neoplasms. It has been described that 26-65% of patients experience disease progression. Recurrence is usually observed within 3 years after surgery and often in form of distant disease. However, in clinical trials of adjuvant chemotherapy for pancreatic cancer patients with disease-free survival as primary endpoint, the postoperative work-up included only abdominal evaluation.

**Materials and methods.** We retrospectively reviewed clinical data of patients radically resected for invasive IPMN at University Hospital of Pisa, who were adequately followed up at our institution; for these patients, total body computer tomography (CT) was repeated every 3-6 months for the first three years after surgical resection. The main aim of our study was to evaluate the pattern of recurrence in order to better understand the natural history of disease and to optimize the follow-up procedures.

**Results.** Twenty-nine patients (M/F 16/13) progressed after resection for invasive IPMN were identified. Median age was 70 years (range 61-86). Disease progression occurred in form of liver metastases for 12 (41%) of them (with liver-only disease in 5 patients), lymph node involvement in 8 (28%), peritoneal carcinosis in 4 (14%), local recurrence in 5 (17%) and finally lung metastases in 14 (48%) patients; for 7 (24%) of these patients lung was the only site of progression. Median overall survival from evidence of metastases was 13.0 months.

**Conclusions.** We observed a high percentage of lung metastases as first and unique site of progression in patients resected for invasive IPMN. These data suggest the importance to perform CT including chest for an optimal preoperative staging and an early detection of lung metastases in these patients.

### A33 DOCETAXEL AS SECOND-LINE TREATMENT IN METASTATIC GASTRIC CANCER

Caparelo C.1, Lencioni M.1, Vasile E.1, Caponi S.1, Fabrini M.G.2, Ginocchi L.1, Lucchesi M.1, Baretto M.1, Belluomini L.1, Da Prat V.1, Santi S.1, Pallabazzer G.3, Ricci S.1, Falcone A.1

1Polo Oncologico, Azienda Ospedaliero-Universitaria Pisana, Istituto Toscano Tumori, Pisa; 2Division of Radiation Oncology, S. Chiara Pisa Hospital, Pisa; 3Department of Gastroenterology, Esophageal Surgery Unit, Tuscany Regional Referral Center for the Diagnosis and Treatment of Esophageal Disease, Pisa

**Background.** Second-line chemotherapy with docetaxel or irinotecan seemed to confer improved overall survival over best supportive care, nevertheless at today no standard treatment is approved in second-line setting in metastatic gastric cancer (MGC).

**Methods.** The objective of our retrospective analysis was to evaluate the activity of a second-line taxane-based treatment in MGC patients.

**Results.** A total of forty-eight patients (M/F 40/8; ECOG PS at second-line treatment 0/1/2: 23/22/3) were included into the analysis; median age was 67 years (range 38-86). All patients received a first-line fluoropyrimidine-based chemotherapy: 6 in monochemotherapy and 42 in combination with platinum compounds (9 received a triplet with anthracyclines and 2 with trastuzumab). Among the forty-six patients evaluable for analysis 37 patients received a docetaxel monotherapy (16 weekly, 5 biweekly and 16 three-weekly schedule), 10 a combination of docetaxel with fluorouracil, 1 with cisplatin. Grade 3 or 4 toxicities included: neutropenia in 6 patients, diarrhea in 1 patient, anemia in 3 patients, fatigue, vomiting and neurotoxicity in 1 patient each, stomatitis in 2 patients; a delay of treatment was needed in 13 patients and a reduction of doses in 5 patients. In a total of 46 evaluable patients, 7 (15.2%) experienced a partial response, 13 (28.3%) a stable disease, 26 (56.5%) a progression of disease. Twenty-four patients received a third-line treatment, 21 of whom an irinotecan-based chemotherapy. Median progression-free survival (mPFS) from the start of second-line treatment was 4.3 months and median overall survival was 8.6 months. No significant differences were found in mPFS, response rate (RR) and toxicity profile between different treatment schedules. mPFS seemed to be longer in patients with PS 0 than in patients with PS 1 or 2 (5.4 months versus 2.1 and 0.95 respectively; p = 0.046). No difference in mPFS emerged according to RR at first-line therapy.

**Conclusions.** Docetaxel as second-line setting in MGC seems to have a promising activity with an acceptable toxicity profile.

### A34 EVEROLIMUS TREATMENT IN METASTATIC PANCREATIC NEUROENDOCRINE CARCINOMAS AND METASTATIC GASTROINTESTINAL NEUROENDOCRINE CARCINOMA

Marconcini R.1, Galli L.1, Antonuzzo A.1, Derosa L.1, Biasco E.1, Farnesi A.1, Baldi G.G.2, Ricci S.1, Falcone A.1

1U.O. Oncologia medica, Ospedale S. Chiara, Pisa; 2U.O. Oncologia Medica, Ospedale Misericordia e Dolce, Prato
**Rationale.** Everolimus treatment has been adopted for advanced pancreatic neuroendocrine tumours (PNET). Gastrointestinal neuroendocrine tumours (GNET) have the same biology. This retrospective study wants to show the efficacy of everolimus in both groups in our experience.

**Methods.** We reviewed the medical records of 16 patients (8 with PNET, 8 with GNET) who were treated using everolimus for advanced disease between January 2007 and May 2012 at our hospital.

**Results.** All 16 patients experienced progression after almost 1 line of somatostatine analog treatment, or even chemotherapy. The primary site of the GNET was: colon 3 patients, small bowel 4 patients, and stomach 1 patient. All patient performed somatostatine analog treatment during everolimus treatment. Everolimus was first administered at 10 mg/die. Best response to everolimus treatment was stable disease for all patients in both groups. Four patients in both groups are still in treatment. The estimated PFS was 5.16 months (1.9-9.2) in the PNET group, 8.13 months (2.46-16.7) in the GNET group. The most frequent grade 1-2 adverse events in the both groups were mucositis, asthenia. The grade 3-4 adverse events observed were mucositis, asthenia, thrombocytopenia: respectively 2, 1, 1 patients in GNET and 1, 2, 0 in PNET group.

**Conclusions.** In our experience, everolimus treatment may have comparable efficacy both in PNET and GNET. Toxicities were similar in the two groups as expected by everolimus treatment.

---

**A35 SAFETY AND EFFICACY OF SORAFENIB IN PATIENTS WITH ADVANCED HEPATOCELLULAR CARCINOMA AND CHILD-PUGH A OR B CIRRHOSIS**


*Gastroenterology, **Medical Oncology, Department of Clinical and Experimental Medicine “Magrassi-Lanzara”, Second University of Naples

**Background.** Sorafenib provides survival benefit for pts with advanced hepatocellular carcinoma (HCC) and liver cirrhosis Child-Pugh (CP) A. Few data are available in regard to safety and efficacy of sorafenib in CPB HCC patients. Here we report our experience of using sorafenib in pts with HCC and CPA and CPB cirrhosis.

**Patients and methods.** Clinical data from patients with HCC treated with sorafenib at our Department were analyzed retrospectively, in terms of their tumour response, tolerance, and survival. Treatment outcomes were analyzed according to their respective CP status. Adverse events were graded using CTC, version 3.0; tumour response was assessed according to RECIST, version 1.2.

**Results.** Twenty-six pts started sorafenib at 400 mg twice daily. Median age was 69 years (range 58-81), males/females: 18/8; 15 had HCV infection, 8 had HBV infection and 3 had a co-infection HCV/HBV; 20 (77%) pts had underlying Child-Pugh A cirrhosis and 6 (23%) Child-Pugh B (until a score of 7). Previous treatments were the following: surgery 4; TACE 5; PEI/RFA 12. We observed a PR in 3 pts (11%), a SD lasting at least 12 weeks in 13 pts (50%) and a PD in 10 pts (38.9%). The median OS was 7.4 months (95% CI 3.2-11.6), while the median PFS was 3.7 months (95% CI 1.9-5.5). The median OS and PFS were different among CPA and CPB pts with a statistically not significant trend (p = 0.06) toward a worse outcome in CPB patients. Patients without extrahepatic spread, particularly without lung metastases, were more likely to benefit from sorafenib treatment. The most common G3 toxicities were hand-foot-skin reaction (23%), malaise (15%), diarrhea (7%) and mucositis (4%); furthermore 12 pts (46%) had transient liver function derangement. Overall, the two groups of pts (CPA and CPB) experienced similar incidence of most of these adverse events. A dose reduction was required in 59% of the patients. Patients with and without underlying portal vein thrombosis had similar therapeutic benefits and toxicity with sorafenib treatment.

**Conclusions.** Sorafenib demonstrated good efficacy and acceptable tolerability in our advanced HCC pts population. CPA and CPB (until 7 score) pts tolerated sorafenib similarly and derived similar clinical and survival benefit.

---

**A36 LACTATE DEHYDROGENASE (LDH): A SIMPLE TOOL TO ASSESS PROGNOSIS IN ADVANCED PANCREATIC CANCER?**


Clinica di Oncologia Medica, AO Ospedali Riuniti, Università Politecnica delle Marche, Ancona

High LDH level, an indirect marker of hypoxia and angiogenesis, characterizes a worse prognosis in several tumours. In pancreatic cancer its role is not clearly defined although these biological features play a key role in cancer progression. While in several tumours, serum LDH level, an indirect marker of hypoxia and angiogenesis, characterizes a worse prognosis, in pancreatic cancer its role is not clearly defined although these biological features play a key role.

Aim of our analysis was to evaluate the potential prognostic role of LDH in pancreatic cancer patients. We retrospectively assessed 71 patients included in phase II MAPS trial treated with sorafenib plus chemotherapy (cisplatin and gemcitabine) or chemotherapy alone. For all patients LDH values were collected within one month before the procedure. We divided patients according to serum LDH levels (group A: LDH ≤1.25 UNR vs group B: LDH >1.25 UNR, CART method). A statistically significant difference (p = 0.0017; Figure 1) was found in progression-free survival (PFS) between patients with LDH values under or above the cut-off (group A: 5.2 months; group B: 1.9 months).

No differences were found according to the treatment administered.

The two patients groups proved homogeneous for all the clinical assessed variables.

Moreover, this difference was confirmed in a common practice population of 131 advanced pancreatic cancer patients (98 pts with LDH >UNR vs 33 pts LDH <UNR; PFS 4.3 vs 2.3 months respectively; p = 0.012; Figure 2).

LDH seemed able to reliably predict outcome for pancreatic cancer patients. Patients with high LDH levels, according to their worse prognosis, could be candidate to receive only supportive care. On the contrary, patients with low LDH levels could be the most suitable for an active treatment and for enrollment in clinical trials. Otherwise, this parameter should represent a crucial factor for stratification of patients in the clinical trials.

---

**S18 SESSION A XIV NATIONAL CONGRESS MEDICAL ONCOLOGY**
Results. Thirteen patients (M/F 8/5) affected by metastatic inva-
sive IPMN were identified. Median age was 69 years (range
64-81). Most patients (12, 92%) had a recurrence after radical re-
section while 1 patient had synchronous metastases. All patients
were treated with first-line gemcitabine based chemotherapy;
seven (54%) patients received gemcitabine monotherapy; six
(46%) received the combination of gemcitabine and oxaliplatin.
All patients except one experienced disease progression and 6
died. Two (15%) patients experienced partial response with first-
line chemotherapy; 6 (46%) had stable disease while 5 (38%)
showed disease progression. The estimated median progression-
free survival was 9.6 months. Eight patient received also further
lines of chemotherapy. Median overall survival was 15.4 months.

Conclusions. Our results confirm that metastatic invasive
IPMNs have a dismal prognosis. The outcome of these patients is
similar to patients affected by pancreatic ductal adenocarcinoma.
In the absence of prospective clinical trials conducted in patients
with this histology, the choice of chemotherapy should be based
on data about pancreatic ductal adenocarcinoma.

A38 THROMBOTIC THROMBOCYTOPENIC PURPURA
( TTP) AS FIRST MANIFESTATION OF METASTATIC
GASTRIC CANCER: A MONOINSTITUTIONAL
EXPERIENCE

Di Cicilia R., Mordenti P., Anselmi E., Nobili E., Cavanna L.

Dipartimento Oncologia, Ematologia, Ospedale Guglielmo da
Saliceto, Piacenza

Solid tumours can be associated with hematological disorders
and TTP has been observed rarely as a paraneoplastic syndrome
in many different types of cancer. Most patients die within a few
weeks after the diagnosis. Although TTP is mainly caused by au-
to-antibodies to a protease called ADAMTS-13, several authors
have suggested that fibrinoid necrosis of the bone marrow (BM)
and tumour cell emboli of the small vessels are the causes of the
paraneoplastic syndrome, but the exact pathogenesis remains un-
clear.

From 2006 to 2012, five pts were diagnosed with secondary
TTP. There were 2 males and 3 females with a median age of 61
years (range 39-71 years). Median ECOG PS was 2 (1-3). Mi-
croangiopathic hemolytic anemia (MAHA), decreased haptoglo-
bin levels, elevated serum levels of ALP, LDH, indirect bilirubin,
CEA, CA 19.9, thrombocytopenia and hemorrhagic manifesta-
tions were observed in all patients. All pts had a neoplastic cells
infiltration of the BM with positivity for CK 20 while CK 7 and
TTP has been observed rarely as a paraneoplastic syndrome
in many different types of cancer. Most patients die within a few
weeks after the diagnosis. Although TTP is mainly caused by au-
to-antibodies to a protease called ADAMTS-13, several authors
have suggested that fibrinoid necrosis of the bone marrow (BM)
and tumour cell emboli of the small vessels are the causes of the
paraneoplastic syndrome, but the exact pathogenesis remains un-
clear.

From 2006 to 2012, five pts were diagnosed with secondary
TTP. There were 2 males and 3 females with a median age of 61
years (range 39-71 years). Median ECOG PS was 2 (1-3). Mi-
croangiopathic hemolytic anemia (MAHA), decreased haptoglo-
bin levels, elevated serum levels of ALP, LDH, indirect bilirubin,
CEA, CA 19.9, thrombocytopenia and hemorrhagic manifesta-
tions were observed in all patients. All pts had a neoplastic cells
infiltration of the BM with positivity for CK 20 while CK 7 and
TTP-1 stained negative. In 1 case c-erb-B2 and CK 7 also stained
positive. Endoscopic examinations of the gastrointestinal tract re-
vealed gastric cancer with signet ring cells in 3 pts and one squa-
mous carcinoma of the esophagogastric junction. Contrast en-
hanced CT scan revealed multiple sites of metastasis in 4 pa-
tients. All pts received 5-fluorouracil (5-FU) 200 mg/m² by con-
tinuous infusion. Platelet and red blood transfusions were made.
Only 2 pts received plasmapheresis. Four pts obtained a clinical
and laboratoristic improvement in few days hence 2 pts contin-
ued with 5-FU plus oxaliplatin, 2 pts started cisplatin, 5-FU,
epirubicin and the last one cisplatin plus trastuzumab. Three pts
had a median overall survival of 9 months (range 7-12 months)
and 2 pts are still alive after 12 months and 1 month from the be-
tinning of the chemotherapy.

In conclusion, in patients suffering from MAHA and thrombo-
cytopenia, malignancy should be considered as a possible cause
and the early diagnosis may avoid unnecessary overtreatment.

A37 CHEMOTHERAPY FOR METASTATIC INVASIVE
INTRADUCTAL PAPILLARY MUCINOUS NEOPLASMS
(IPMNs) OF THE PANCREAS

Ricci S., Caponi S., Baretti M., Vasile E., Ginocchi L.,
Caparello C., Da Prat V., Lucchesi M., Lencioni M.,
Falcone A.

Polo Oncologico, Azienda Ospedaliero-Universitaria Pisana,
Istituto Toscano Tumori, Pisa

Background. IPMNs are intraductal mucin-producing cystic
neoplasms of the pancreas; the incidence of these neoplasms is
rising and it has been reported in recent works that IPMNs ac-
count for approximately 25% of resected pancreatic neoplasms.
It has been described that recurrence of disease is observed in 26-
65% of patients resected for invasive IPMN (also named papil-
lary mucinous carcinoma), usually within 3 years from surgery
and often in form of distant disease. The natural history of
metastatic invasive IPMNs is not clear and few data regarding
the role of palliative treatments are available.

Materials and methods. We retrospectively collected data
about patients with diagnosis of metastatic invasive IPMN who
were treated with palliative chemotherapy at our institution from
2008 to 2012 in order to evaluate the clinical outcome of this dis-
ease and the response to medical treatment.
A39 TEMOZOLOMIDE-BASED CHEMOTHERAPY IN PATIENTS WITH METASTATIC NEUROENDOCRINE TUMOURS: EXPERIENCE IN NINE CASES

Fontana A.1, Gelsomino F.1, Zunarelli E.2, Bertolini F.1, Zironi S.1, Depanni R.1, Spallanzani A.1, Luppi G.1, Conte P.F.1

1Department of Oncology, Hematology and Respiratory Diseases, 2Pathology Section, Azienda Ospedaliero-Universitaria, Policlinico di Modena

Background. Systemic chemotherapy regimens for neuroendocrine tumours (NETs) are associated with limited response rates and significant toxicity. Streptozocin is the only US Food and Drug Administration approved therapy for patients with advanced pancreatic NETs. Traditional streptozocin-based regimens used for pancreatic NETs include streptozocin/fluorouracil, streptozocin/doxorubicin and a three drugs combination of streptozocin/doxorubicin/fluorouracil. Temozolomide (TMZ), an oral second-generation alkyating agent, has also been successfully used in monotherapy or in association with capecitabine.

Patients and methods. Nine patients (pts), seven males/two females, median age 58 years (range 39-79), with metastatic NETs (eight well differentiated pancreatic endocrine tumours with liver metastases in five pts, also bone and lymphnodal metastases in two patients; lung metastases in another patient; one well differentiated with probable pulmonary origin and liver metastases) were treated with TMZ at doses of 200 mg/m² daily for 5 days every 4 weeks. In two pts capecitabine was used in association with TMZ at doses of 750 mg/m² twice daily, days 1-14. All pts were treated with somatostatin analogs and have received previous treatments: median previous anti tumoral medical regimens were 3 (range 1-6). Tumour response was assessed according to RECIST criteria every 3 months.

Results. Median number of treatment cycles of TMZ was 6 (range 2-17). Radiologic response was seen in 33% of pts (3 pts) and stable disease in 33% (3 pts); one patient is not yet evaluable for response because submitted only to two cycles of treatment. Median time to progression was 6 months (range 2-20). Grade 3-4 toxicities were not found: we have reported only one case of grade 2 thrombocytopenia and grade 2 nausea. We also tested the expression of O (6)-methylguanine-DNA methyltransferase (MGMT), but so far in all our patients was unmethylated.

Conclusions. TMZ as single agent or in association with capecitabine is a well tolerated oral chemotherapy in pts with metastatic neuroendocrine tumours who have already received other treatments and had an acceptable antitumor effect in this small sample of patients. According to ongoing new trial, TMZ will have the opportunity to be associated with capecitabine or antiangiogenic drugs and we could optimize TMZ-based treatment using MGMT expression as a predictive marker in future studies of advanced neuroendocrine tumours.

A40 LONG LASTING COMPLETE PATHOLOGICAL RESPONSE AFTER TREATMENT WITH FOLFOX IN A METASTATIC GASTRIC CANCER PATIENT

Pagano M., Panebianco M., Asensio Sierra N.M., Bisagni G., Boni C.

Introduction. Gastric cancer is the fourth most commonly diagnosed cancer and the second most common cause of cancer related death worldwide. Most patients are diagnosed at an advanced or metastatic stage and, therefore, the prognosis is poor. In metastatic gastric cancer, chemotherapy is the standard treatment because it prolongs survival when compared to best supportive care alone. However, even after the use of the most effective regimens, the overall survival remains disappointing, justifying the need for new treatment options.

Case report. We report the case of a 73-years-old male patient who came to our hospital with metastatic gastric cancer. Esophagogastroduodenoscopy study showed a lesion of the gastric body of 40 mm diameter; the biopsy revealed an undifferentiated adenocarcinoma.

A staging workup, including total body computed tomography (CT) scan, detected the presence of hepatomegaly with diffuse metastatic liver replacement. Ca19/9 value was 4703 ng/mL and LDH was 1762 UI/L.

From April to September 2009 the patient was treated with 12 cycles of FOLFOX (5-fluorouracil 400 mg/m² bolus followed by 3000 mg/m² i.v. 46 hours, folinic acid 200 mg total and oxaliplatin 80 mg/m² both intravenously on day 1, every 15 days). After the eighth cycle, an excellent clinical response was reported, with a partial response of liver metastases and reduction of Ca19/9 (from 4703 ng/mL to 62).

In October 2009, the post-treatment CT of chest showed persistence of partial response, and the patient entered follow-up.

In August 2010 an abdominal CT scan showed a complete remission of liver metastases that persists until now after 31 months (last negative CT in March 2012).

In March 2012, a gastroduodenoscopy with biopsy indicated presence of chronic gastritis.

Conclusions. To our knowledge, no cases of a long lasting pathological complete response with FOLFOX in patients with recurrent metastatic gastric cancer are reported in literature. Because of this unexpected result we have subsequently evaluated the HER2 status; the immunohistochemistry of the tumour cells revealed HER2 overexpression, with an intensity of 3 + at IHC; and a gene amplification at FISH. This results could suggest that FOLFOX + trastuzumab is a valid combination to be tested in HER2 positive metastatic gastric cancer, and that the role of HER2 is still not clearly defined.

A41 SUBMANDIBULAR SALIVARY GLAND METASTASES FROM HEPATOCELLULAR CARCINOMA(HCC): A CASE REPORT


ColoRectal Cancer Unit, Medical Oncology 1, AOU S. Giovanni Battista, Turin

Introduction. Hepatocellular carcinoma (HCC) induces distant metastases in approximatively 50% of cases. Metastases to the head and neck region and the salivary glands are an even more unusual site.

Case report. We describe the case of a 65-year-old man, with no reported history of liver diseases. His medical history includ-
ed diabetes mellitus and atrial fibrillation in medical therapy. A liver lesion occupying nearly all the right hepatic segments was discovered during radiological exams performed for weight loss and asthenia in April 2011. Baseline alphafetoprotein (AFP) was 70 ng/mL. Biopsy of the liver lesion was performed and it was diagnosed as HCC (grade 2 according to Edmonsons-Steiner patterns). The disease recurred after selective portal vein embolization and the patient began systemic therapy with sorafenib 800 mg/die. In September 2011 a firm mass, painless on palpation, located in the submandibular right side appeared. A fine-needle biopsy lesion revealed a metastasis from HCC. After salivary gland biopsy AFP rapidly increased until 460 ng/mL and a CT scan showed also a liver disease progression; for this reason sorafenib was discontinued. The patient died 6 months after the diagnosis.

Discussion. This is the third known reported case in which HCC spread to major salivary glands. Similarly to the two cases reported by Romanas et al. in 2004, our patient did not have lung metastases and a possible role of Batson’s plexus can be advocated in the pathogenesis of this type of neoplastic spread.

Conclusions. Although the metastases to the salivary glands are very rare, these should be included in the differential diagnosis of patients with HCC and submandibular lesion.

A final note of caution should be sent to clinicians caring for patients with HCC. All extrahepatic masses should be investigated, taking into account the possibility of HCC metastatic spread.

A42 FIRST-LINE POLYCHEMOTHERAPY IS MORE EFFECTIVE THAN GEMCITABINE IN UNSELECTED PATIENTS AFFECTED BY ADVANCED PANCREATIC CARCINOMA


Dipartimento di Scienze Radiologiche, Oncologiche e Anatomopatologiche, DH Oncologico, Sapienza Università di Roma

Background. Metastatic pancreatic cancer (mPC) patients have poor prognosis. Clinical trials showed increased activity of polychemotherapy compared to monochemotherapy in selected patients. We analyzed unselected mPC patients treated at our Institution to evaluate the clinical benefit derived from polychemotherapy.

Methods. All patients with mPC who received a first-line chemotherapy (FLC) from January 2008 to March 2012 were included in the analysis. We collected general patients characteristics and history of disease. CT scan was performed for all patients at baseline and every two months. The overall response rate (ORR) was evaluated according to RECIST Criteria (v1.1). Type of chemotherapy (polychemotherapy vs monochemotherapy) was collected. PFS was defined as time from the beginning of FLC to radiological progression of disease. The relationship between type of chemotherapy and ORR and PFS was evaluated with one-sided Spearman test.

Results. Twenty-nine pts were included in the final analysis: 44.4% were male, the median age was 63.5 yrs. Most of these (55.6%) received polychemotherapy with two drugs in 36.6% or three drugs in 19% of cases, 44.4% of patients received monotherapy with gemcitabine. In the overall population median PFS was 4 months (95% CI 2.5-5.5) and median overall survival was 8.6 months (95% CI 5.3-11.8). The ORR stratified for type of treatment was PR in 0% and 33%, SD in 33% and 33% and PD in 67% and 34% of pts treated with monochemotherapy and polychemotherapy, respectively. A positive relationship was found between type of therapy and the best response rate (rs = 0.416; p = 0.015) and a PFS above the median value (rs = 0.481; p = 0.006).

Conclusions. We report a higher ORR and a longer PFS in patients treated with upfront polychemotherapy for advanced disease. Finally, this study confirms that polychemotherapy is more effective than monochemotherapy also in unselected group of patients. Due to the lower number of cases and its retrospective nature the use of polychemotherapy should be further evaluated in this subset of patients.

A43 CERVICAL SPINAL METASTASES OF CHOLANGIOCARCINOMA: CASE REPORT


°SC Oncology, Presidio Sanitario Gradenigo, Torino; *FARO Foundation, Turin

The spinal cord compression is one of the most feared complications of SRE (skeletal related event) and it's considered an oncologic emergency. The primary liver malignancy may make up as few as 0.32% of the cases and cases described of metastatic invasion of the cervical spine are infrequent. Here we describe a case of cervical spine metastases of cholangiocarcinoma. A 39-years-old man. August 2009: obstructive jaundice due to a lesion of the right epatic of 9.8.7 cm associated with two nodules of the sixth segment. Performed biopsy: cholangiocarcinoma. Ptioned biliary drainage and subjected to neoadjuvant chemotherapy with gemcitabine and oxaliplatin (GEMOX) for eight cycles (October 2009-February 2010), at doses reduced for neutropenia G2. March 2010 submitted to surgery of liver dx-caudatectomia resection and biliodigestive anastomosis (pT3N1). May 2010 at TC: focal liver metastases and subsequent termoablation. TC June 2010: epatic progression with multiple adenopathic lesions and new line of chemotherapy with carboplatin-fluorofolates. Af- ter the first cycle appearance of intense pain of the cervical spine with radiological finding of morfostructural rearrangement interesting extensively the soma of C5, with slight misalignment of the posterior wall. Admission of the Division of Spine Surgery CTO Hospital of Turin and surgery for resection of pathologic tissue at the level of C5 and C4-C6 spinal arthrosis. Next radiotherapy 3000 eGy with benefit. Continued chemotherapy until April 2011 when it was suspended for deterioration of general condition and started to palliative care in Hospice. To our knowledge this is one of the few published report of cervical spinal metastases of cholangiocarcinoma.

A44 RAPID-ONSET SEVERE ORAL MUCOSITIS INDUCED BY SORAFENIB. A CASE REPORT


ColoRectal Cancer Unit, Medical Oncology 1, AOU S. Giovanni Battista, Turin
Case report. We report the case of a 50-year-old man with chronic viral B and C hepatitis and multifocal hepatocellular carcinoma that started a three-month course of sorafenib before pre-OLT staging according to a clinical trial. After only 3 days of 800 mg of sorafenib he developed an ulcerative mucositis grade 3 (according to Common Terminology Criteria for Adverse Events version 3.0) with overlapping mycosis (Figure 1), asthenia and iporexia G2. Sorafenib was immediately stopped and antifungal therapy with fluconazole and topical mouthwash were started. Mucositis decreased in about ten days but a hospital admission was needed due to persisting G2-3 asthenia. Patient refused to resume sorafenib.

Discussion. Up to 38% of patients receiving sorafenib develops oral mucositis, the majority in the first four weeks of treatment. It can be graded as G3 or G4 in up to 9% of patients.

The information about the clinical appearance and the pathogenesis of oral mucositis induced by tyrosine kinase inhibitors (TKI) is limited while oral mucosal injury induced by chemotherapy and radiotherapy has been better understood. It is a multi-step-process characterized by injury to submucosal and mucosal tissues mediated by reactive oxygen species (ROS), the ceramide pathway, proinflammatory cytokines and a number of transcription factors, including nuclear factor-kappa B (NF-kB). The ulcerative phase is exacerbated by local microbial colonization. There are evidences that sorafenib inhibits NF-Kb and a possible role of this transcription factors can be advocated.

Conclusions. Even if rare, severe mucositis can rapidly develop in patients treated with sorafenib. Individual predisposing factors and effective management strategies need to be further elucidated.
Session B * Colorectal cancers

B1* A MULTICENTER, RANDOMIZED PHASE III STUDY OF SECOND-LINE CHEMOTHERAPY (CT) WITH OR WITHOUT BEVACIZUMAB (BV) IN METASTATIC COLORECTAL CANCER (MCRC) PATIENTS WHO PROCEEDED TO A FIRST-LINE TREATMENT CONTAINING BV: RESULTS FROM THE BEBYP TRIAL BY THE GRUPPO ONCOLOGICO NORD OVEST (GONO)

Salvatore L.1, Masi G.1, Loupakis F.1, Cremolini C.1, Schirripa M.1, Fornaro L.1, Antoniotti C.1, Vivaldi C.1, Granetto C.2, Fea E.2, Antonuzzo L.3, Giommoni E.3, Boni C.4, Banzi M.4, Chiara S.5, Sonaglio C.5, Allegrini G.6, Marcucci L.6, Valsuani C.7, Greco F.7, Salina V.7, Boni L.8, Falcone A.9,10


Introduction. Retrospective data suggested that the continuation of BV with second-line CT beyond the first progression in pts who received the anti-VEGF monoclonal antibody (moAb) as part of the first-line treatment can improve the outcome.

Objectives. The objective of the BEBYP trial, a multicenter randomized phase III study, was to evaluate the outcome of mCRC pts receiving a second-line CT with or without BV after a first-line treatment containing the anti-VEGF moAb. Primary endpoint was progression-free survival (PFS).

Methods. Patients with measurable mCRC as per RECIST criteria, treated in first-line with BV plus fluoropyrimidine, FOLFIRI, FOLFOX or FOLFOXIRI, were randomized to receive a second-line CT with FOLFOX or FOLFIRI (depending on first-line CT) with or without BV. Patients were evaluated with CT scans every 8 weeks until progression.

To detect a HR for PFS of 0.70 in favor of the experimental arm, with an α and β error of 0.05 and 0.20 respectively, the study required 249 events. Assuming an accrual time of 24 months and a follow-up of 12 months we planned to randomize 262 patients.

Anticipated data. The enrollment started on April 2008. Seventeen Italian centers were involved in the trial. In consideration of recent results of the AIO/AMG ML1847 study that showed an improved overall survival (OS) with continuing BV beyond progression, the accrual was stopped prematurely on May 11th 2012. A total of 185 mCRC pts were randomized. The study data cut-off for analysis is set at June 30th 2012. Considering the number of registered events at the time of accrual closure (142) and the minimum length of follow-up that will be available for each pt, we estimate to reach approximately 170 events with a power of 63% to detect a HR for PFS ≤0.70. Data on the primary and other secondary endpoints will be presented at the congress.

This study was supported by AIFA.

B2* EVALUATION OF RELAPSE-FREE SURVIVAL IN T3N0 COLON CANCER: THE ROLE OF CHEMOTHERAPY. A MULTICENTRIC RETROSPECTIVE ANALYSIS

Grandi R.1, Cosimelli M.2, Gemma D.1, Ciancola F.3, Corsi D.4, Rossi L.4, Sperduti I.5, Fabbri A.6, Mancini R.2, Ruggeri E.6, Longo F.3, Quadroni S.1, Zampa G.7, Bianchetti S.8, Gamucci T.1

1Medical Oncology Unit, ASL Froxinone; 2Department of Surgery, Regina Elena National Cancer Institute, Rome; 3Medical Oncology Unit, “La Sapienza University”, Rome; 4Medical Oncology Unit S. Giovanni Calibita, Fatebenefratelli Hospital, Rome; 5Bio-Statistics Unit, Regina Elena National Cancer Institute, Rome; 6Medical Oncology Unit, Belcolle Hospital, Viterbo; 7Medical Oncology Unit, ASL RM/A, Rome; 8Medical Oncology Unit, Regina Apostolorum, Albano Laziale, Rome

Background. Use of adjuvant chemotherapy (AC) in stage II colon cancer (CC) is still under debate. Choice should be based on patients and disease characteristics. According to worldwide guidelines AC should be considered in high-risk (H) T3N0 pts. No data are available for better option in low-risk (L) patients. Aim of the study is to evaluate relapse-free survival (RFS) and disease-free survival (DFS) retrospectively in T3N0 CC pts related to treatment.

Methods. RFS and DFS are evaluated with Kaplan-Meier method. In order to find the optimal cut-off for node number the receiver operating characteristics curve analysis and Maximally Selected Rank Statistics were performed. Multivariate Cox proportional hazard model was developed using stepwise regression, enter limit and remove limit were p = 0.10 and p = 0.15 respectively.

Results. 1,000 pts with T3N0 CC were recruited. To date, data of 926 pts are available. Median age was 69 (29-93), M/F 513/413, grading 1/2/3 46/668/158; 360 L (39%), 155 unknown (17%); 137 (15%) pts showed symptoms (S) at diagnosis: 51 pts had perforation (P) or bowel obstruction (BO). Median sampled lymph nodes (LN) were 15 (1-76); 383 (41%) pts were treated with AC. Median follow-up (fu) was 5 years (ys) (range 3-24). Survival analysis was performed only for pts with a minimum fu of 3 yrs and younger than 80 (80%). Five yrs RFS was 78% and 5 yrs DFS was 76%. At multivariate analysis S and AC were prognostic factors for RFS. AC is prognostic factor for all endpoints (data are shown in Table). In L group 5 yrs RFS was 88% in treated pts and 75% in non-treated pts (p = 0.03); in H group was respectively 82% and 72% (p = 0.006).

Conclusions. Preliminary data confirmed the role of known prognostic factors and suggest the relevance of AC also in L stage II T3N0 CC patients. However, the highest risk in L subgroup should be identified to be submitted to AC. Data collection is ongoing, update results will be presented.
B3* MICRONORNA SIGNATURE PREDICTS SENSITIVITY TO ANTI-EGFR MONOCLONAL ANTIBODIES IN METASTATIC COLORECTAL CANCER

Landi L.1, Cappuzzo F.1, Sacconi A.2, Biagioni F.2, Ludovini V.3, Sensi E.4, Salvini J.1, D’Arcangelo M.1, Minuti G.1, Lani E.1, D’Incecco A.1, Fontanini G.4, Blandino G.2, Crinò L.3
1 Istituto Toscano Tumori, Oncologia Medica, Ospedale Civile, Livorno; 2 Translational Oncogenetic Unit, Regina Elena Cancer Institute, Roma; 3 S.C. Oncologia Medica, Ospedale S. Maria della Misericordia, Perugia; 4 Azienda Ospedaliera Universitaria Pisana, Pisa

Background. MicroRNAs (miRNAs) are a class of non-coding RNAs that bind to complementary sequences on target messenger RNA transcripts, causing either degradation or inhibition of translation, silencing their mRNA target. Available data indicated that miRNA levels could modulate sensitivity to targeted agents, including anti-EGFR compounds. In the present study we aimed to investigate whether miRNA signature was predictive for sensitivity to anti-EGFR monoclonal antibodies in metastatic colorectal cancer (mCRC) patients.

Methods. A total of 183 mCRC from two independent cohorts (cohort 1: 74 cases; validation cohort: 109 cases) treated with cetuximab/panitumumab either alone (N = 19) or in combination with chemotherapy (N = 164) were included in the study. MiRNA arrays were analysed using Agilent’s MiRNA platform.

Results. MiRNA array analyses identified the cluster miR-99a/Let7c/miR-125b located on 21p11.1 as associated with differential outcome to anti-EGFR therapies. In the first cohort, patients with high signature (N = 25, 33.8%) had a significantly longer progression-free survival (PFS 6.1 versus 2.3 months, p = 0.02, HR = 0.42) and overall survival (OS, 29.8 versus 7.0 months, p = 0.02, HR = 0.65). To further assess the potential confounding effect of KRAS and BRAF mutations, we analyzed the outcome of patients with high and low signature in the 75 cases with KRAS or BRAF mutation and in 98 cases KRAS and BRAF wild-type. In the wild-type population, high signature patients (N = 31, 31.6%) had a significantly longer PFS (8.2 versus 4.4 months, p = 0.02, HR = 0.54) and longer OS (16.9 versus 10.9 months, p = 0.1, HR = 0.68) than low signature individuals, with no difference in the KRAS or BRAF mutated patients.

Conclusions. MiR-99a/Let7c/miR-125b signature is useful for improving selection of KRAS/BRAF wild-type mCRC patients candidate for anti-EGFR strategies.

B4* HIGH ACTIVITY AND RESECTION RATE IN MOLECULARLY SELECTED PATIENTS WITH UNRESECTABLE METASTATIC COLORECTAL CANCER (mCRC) TREATED WITH PANITUMUMAB (P) AND FOLFOXIRI AS FIRST-LINE THERAPY: A PHASE II STUDY

Aprile G.1, Loupakis F.2, Bergamo F.3, Masi G.2, Fornaro L.2, Lonardi S.3, Schirripa M.2, Morvillo M.2, Cremoni C.2, Salvatore L.2, Mioranza E.3, Zaniboni A.4, Zagone V.5, Falcone A.2
1 Azienda Ospedaliero-Universitaria di Udine, Udine; 2 UO Oncologia Medica 2, Azienda Ospedaliero-Universitaria Pisana, Istituto Toscano Tumori, Pisa; 3 Oncologia Medica 1, Istituto Oncologico Veneto-IRCCS, Padova; 4 UO Oncologia Medica, Casa di Cura Poliambulanza, Brescia

Background. GONO-FOLFOXIRI demonstrated higher efficacy compared to FOLFIRI. P with oxaliplatin- or irinotecan-based doublets is feasible and associated with improved activity in KRAS codon 12-13 wild-type patients. BRAF and other RAS rare mutations have been suggested as additional potential biomarkers for anti-EGFR agents.

Methods. Patients with untreated unresectable mCRC and wt BRAF-RAS genes were enrolled in this GONO multicenter phase II trial of biweekly P 6 mg/kg d1 with a modified FOLFOXIRI regimen (IRI 150 mg/m2 d1, OXA 85 mg/m2 d1, 1-LV 200 mg/m2 d1 and 5FU 3000 mg/m2 48-h continuous infusion d1, reduced to 2400 mg/m2 due to grade 3-4 toxicity in 2 of the first 3 patients). Primary endpoint was response rate (RR). Based on a two stage Simon’s Minimax design (p0 = 60%, p1 = 80%; α = 0.05, β = 0.2) at least 26 responses on 36 evaluable pts are needed to satisfy primary endpoint.

Results. 37/87 screened pts were enrolled (M/F: 57/43%; median age 63 years, range 33-72; ECOG PS 0/1-2, 76/24%; primary colon/rectum 70/30%; primary on site 42%; sites of disease single/multiple 54/46%; liver only 35%). Among the first 3 pts treated with 5FU 3000 mg/m2, 2 experienced SAEs (1 grade 4 diarrhoea and neutropenia; 1 grade 3 diarrhoea). Grade 3-4 toxicities observed among 34 pts treated at amended dose were: neutropenia 53% (2 febrile neutropenia); diarrhea 35%; stomatitis 18%; neurotoxicity (grade 2-3) 35%; skin rash 24%. Delays or dose reductions were needed only in 9% and 10% of 337 cycles. Two SAE resulting in pt death occurred after amendment. 34 partial
responses, 2 disease stabilizations and 1 progression were observed, with a RR of 92%. Fifteen pts underwent local procedures on metastases (R0 in 12) with pathologic complete response in 3 of them. At a median follow-up of 12.2 months mPFS was 10.8 months while mOS has not been reached.

Conclusions. The regimen appears feasible. In molecularly selected unresectable pts P and FOLFOXIRI resulted in high activity and interesting resection rate.

B5-KSR1 GENE POLYMORPHISM IN MCRC PATIENTS TREATED WITH FIRST-LINE FOLFIRI AND BEVACIZUMAB


1 U.O. Oncologia Medica 2, Azienda Ospedaliero-Universitaria Pisana, Istituto Toscano Tumori Pisa; 2 University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; 3 Policlinico Universitario, Oncologia Medica, Udine; 4 Response Genetics Inc., Los Angeles, CA; 5 U.O. Oncologia Medica Azienda USL-5, Istituto Toscano Tumori, Pontedera; 6 Medical Oncology Division, Second University of Naples, Napoli; 7 Imperial College Healthcare NHS Trust, London, United Kingdom

Background. Kinase suppressor of Ras (KSR) 1 is a scaffolding protein regulating the Raf/Mek/ERK cascade. Preclinical data showed that KSR1 could increase estrogen receptor transcriptional activity after exposure to estrogens. Recent retrospective analyses suggested a possible role for KSR1 in predicting the outcome of mCRC patients with mCRC.

Methods. MCRC patients receiving first-line FOLFIRI + bevacizumab prospectively enrolled in a translational research program were selected on the basis of KRAS and BRAF mutational status availability. KSR1 rs2241906 polymorphism was analyzed on DNA extracted from peripheral blood by means of PCR and direct sequencing. Taking into account the connection between estrogen pathway and KSR1, subgroup analyses according to gender were pre-planned.

Results. 287 patients were included. Main patients’ characteristics were the following: M/F: 175/112; median age 62 (range 26-79); ECOG-PS 0/1-2 = 240/47; synchronous/metachronous disease = 213/74; Köhne score (low/intermediate/high/data missing) = 122/129/22/14; KRAS-BRAF mutational status (wt-wt/mut-wt/wt-mut) = 123/146/18. In the overall KRAS-BRAF wt population, KSR1 polymorphism did not affect the outcome. The analysis performed according to gender showed that in the KRAS-BRAF wt population females with KSR1 rs2241906 T- achieved a significantly better PFS (median 15.9 mos) in comparison to C/C variant carriers (median 8.8 mos) (HR = 0.44 [95% CI 0.21-0.91], p = 0.010); meanwhile males with T- showed a worse PFS in comparison to those carrying the C/C variant (HR = 1.92 [95%CI 1.05-3.53], p = 0.021). These results were significant also in a multivariate model and a significant interaction of gender with PFS according to KSR1 allelic variants was demonstrated (p = 0.004).

Conclusions. This prospectively conceived pharmacogenetic study confirms the role of KSR1 polymorphisms in affecting the outcome of mCRC KRAS-BRAF wt patients. In particular, these results indirectly indicate that estrogen stimulation could affect the proliferation of KRAS-BRAF wt CRC cells through an interaction with KSR1. Preclinical investigations to further explore this preliminary hypothesis are ongoing.

B6 PROSPECTIVE EVALUATION OF CANDIDATE SNPS OF VEGF/VEGFR PATHWAY IN METASTATIC COLORECTAL CANCER (mCRC) PATIENTS TREATED WITH FIRST-LINE FOLFIRI PLUS BEVACIZUMAB (BV)

Cremolini C.1, Loupakis F.1, Yang D.2, Salvatore L.1, Zhang W.2, Wakatsuki T.2, Schirripa M.1, Lonardi S.3, Antoniotti C.1, Casagrande M.4, Aprille G.3, Masi G.1, Graziano F.3, Russo A.4, Lucchesi S.7, Ronzoni M.8, Maus M.K.H.4, Bocci G.10, Tonini G.11, Lenz H.J.2, Falcone A.1,12

1 University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA; 2 Istituto Oncologico Veneto, IRCCS, Padova; 3 Azienda Ospedaliero-Universitaria di Udine, Udine; 4 UOC Oncologia, AO, Pescara; 5 Section of Biochemistry and Molecular Biology, Department of Biomolecular Sciences, University of Urbino, Urbino; 6 UO Oncologia Medica, Ospedale Pontedera; 7 Dipartimento di Oncologia, Istituto Scientifico San Raffaele, Milano; 8 Response Genetics Inc., Los Angeles, CA; 9 Division of Chemotherapy and Pharmacology, Department of Internal Medicine, University of Pisa, Pisa; 10 Università Campus Bio-Medico, Roma; 11 University of Pisa, Department of Oncology, Transplants and New Technologies in Medicine, Pisa

Background. Despite several attempts, no predictors of benefit from BV have been so far identified. We reported the association of VEGF rs833061 T/T to a worse outcome in mCRC pts treated with first-line FOLFIRI+BV, but not in a historical cohort treated with FOLFIRI. Recent post-hoc analyses on randomized trials suggested the potential prognostic and/or predictive role of other VEGF and VEGFR1/2 SNPs.

Methods. Moving from our retrospective finding, we designed a prospective validation trial in mCRC pts treated with first-line FOLFIRI+BV to detect a HR for PFS of 1.7 for VEGF rs833061 T/T compared to C- variants. With two-sided α = 0.05 and β = 0.20, 199 events were required. Accrual was faster than expected and in the meanwhile promising results about other SNPs were reported and we therefore included a confirmatory analysis of VEGF rs699946 A/G, VEGFR1 rs9582036 A/C and rs7993418 A/G, VEGFR2 rs11133360 C/T, rs12505758 C/T and rs2305948 C/T and EPAS rs4154836 A/G SNPs. Germ-line DNA was extracted from peripheral blood. SNPs were analyzed by PCR and sequencing.

Results. Four hundred and twenty-four pts were included. At a median follow-up of 24 months, median PFS was 10.5 months. At the univariate analysis, no differences in PFS according to VEGF rs833061 C/T variants were observed (p = 0.38). Among analyzed SNPs, only VEGFR2 rs12505758 C- variants (N = 118) were associated to shorter PFS compared to TT (N = 306) (HR = 1.40 [95% CI 1.07-1.84], p = 0.015). In the multivariate model, this association retained significance (HR = 1.402 [95% CI 1.07-1.82], p = 0.012), that was lost by applying multiple testing correction.
Conclusions. This prospective experience failed to validate the hypothesized predictive impact of VEGF rs833061 variants. Also other previous retrospective findings on different candidate SNPs were not confirmed. Only VEGFR2 rs12505758 variants, whose prognostic rather than predictive impact was previously reported, correlated with PFS. We suggest that future studies on biomarkers of benefit from BV should look at the complexity of tumoral angiogenesis at different levels and not only from the genetic perspective.

B7 PHARMACOGENETIC PROFILING FOR TOXICITY OF OXALIPLATIN AND FLUOROPYRIMIDINES. AN ANCILLARY PROTOCOL TO THE TOSCA TRIAL.


Background. Functional germline polymorphisms may contribute to inter-individual differences in response/toxicity to anti-cancer chemotherapy, allowing for the adoption of tailored treatments in clinical practice. Current evidence is often limited to retrospective and not adequately powered studies. Within the frame of the TOSCA (Three Or Six Colon Adjuvant) trial, an ancillary pharmacogenetic study was conducted giving an unique opportunity for a prospective assessment of pharmacogenetic associations for toxicity.

Methods. TOSCA is a no-profit, Italian, multicenter, randomized, phase III study conducted in radically resected high risk stage II and III colorectal cancer patients treated with 6 or 3 months of either FOLFOX-4 or XELOX. Patients eligible for the main study were asked to give a further written informed consent for blood sampling and DNA extraction. DNA was used for genotyping 17 polymorphisms in 11 genes related to 5-fluorouracil/oxaliplatin pathways, detoxification, transport and DNA repair (TS, MTHFR, ERCC1, EXRC1, XRCC3, XPD, GSTT, GSTP, GSTM, ABCC1, ABCC2). The sample size was calculated assuming a 20% risk of grade 3-4 toxicity and a prevalence of unfavorable genotypes ≥30%. With 531 patients (106 events) the study had a power of 90% to detect an odd ratio = 2 with an alpha error of 5% (two-sided) for the Wald test using the logistic regression analysis.

Results. From July 2007 to October 2011, 531 patients were enrolled in 26 experimental centers (194 patients in the 6-month FOLFOX-4 arm, 194 patients in the 3-month FOLFOX-4 arm, 74 patients in the 6-month XELOX arm, 69 patients in the 3-month XELOX arm). The proportion of stage II-III patients was balanced according to the two options of adjuvant chemotherapy and treatment duration (three versus six months). Polymorphisms have been already analyzed in 185 patients and the complete data set will be available for October 2012.

Conclusions. The results of this study may supply a definitive indication on the role of pharmacogenetic analyses for toxicity in this setting.

B8 RASH IN COLORECTAL CANCER PATIENTS TREATED WITH ANTI-EGFR MONOCLONAL ANTIBODIES: A PREDICTIVE ROLE?

Ghildardi M., Borgonovo K., Petrelli F., Cabiddu M., Cremonesi M., Maspere F., Barni S.

Medical Oncology Division, A.O. Treviglio-Caravaggio, Treviglio

Introduction. Skin rash is an early and frequent phenomenon during treatment with anti-epidermal growth factor receptor (EGFR) monoclonal antibodies. It predominantly affects visible areas of the body, which can cause distress and anxiety in many patients and negatively affect self-image and self-esteem. It has been observed that EGFR-targeted therapy is associated with a clinical benefit when this form of skin rash appears. We performed a review to assess the predictive value of skin rash in patients with advanced colorectal cancer (CRC) treated with cetuximab (C) and panitumumab (P).

Materials and methods. We searched PubMed and ASCO Meetings for publications reporting the correlation of skin rash with survival and/or response rate. Hazard ratios (HRs) with 95% confidence intervals for progression (PFS) and/or survival (OS), and/or risk ratios (RRs) for response rate in patients with rash were obtained from publications and pooled in a meta-analysis.

Results. Fourteen publications (for a total of 3,833 patients) were included in this meta-analysis. All included studies enrolled patients with advanced disease. The occurrence of skin toxicity represents a predictive factor for survival (HR = 0.51; p < 0.00001) (Table 1) and for progression (HR = 0.58; p < 0.00001) (Table 2). Patients who developed moderate or severe rash had an increased chance of response (35 vs 13%; RR 2.23, p < 0.00001). The results appear similar for C and P trials for all the endpoints.

Conclusions. The occurrence of skin rash during treatment with C and P is associated with better progression-free and overall survival. Skin rash represents an early predictive biomarker of response. The prognostic value of this event must be better studied.
Background. Preoperative chemo-radiotherapy (CRT) in locally advanced rectal cancer (LARC) has achieved growing importance, most of all in light of its impact on local disease control and sphincter preserving surgery (SPS). Aim of this work is to carry out a systematic review of literature and a meta-analysis of controlled and randomized clinical trials (RCTs) to evaluate the impact of CRT in LARC.

Methods. A systematic review of literature from 1966 to May 2012 was performed independently by two Authors (ET and VP) using EMBASE, MEDLINE and Cochrane Central Register of Controlled Trials search engines. The outcomes evaluated were 5-year disease-free survival (DFS), 5-year overall survival (OS), 5-year local relapse (LR), and SPS. The quality of the studies was evaluated by two Authors using Jadad scores.

Table 1 B8 - Meta-analysis of correlation between skin rash and OS

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>IV, Random, 95% CI</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berlin 2007</td>
<td>-0.755</td>
<td>0.108</td>
<td>19.8%</td>
<td>0.47 [0.38, 0.58]</td>
<td></td>
</tr>
<tr>
<td>Gamucci 2008</td>
<td>-1.542</td>
<td>0.509</td>
<td>4.6%</td>
<td>0.21 [0.08, 0.58]</td>
<td></td>
</tr>
<tr>
<td>Jonker 2007</td>
<td>-1.109</td>
<td>0.209</td>
<td>13.8%</td>
<td>0.33 [0.22, 0.50]</td>
<td></td>
</tr>
<tr>
<td>Koza CECOG 2009</td>
<td>-0.755</td>
<td>0.274</td>
<td>10.7%</td>
<td>0.47 [0.27, 0.80]</td>
<td></td>
</tr>
<tr>
<td>Paez 2010</td>
<td>-0.315</td>
<td>0.162</td>
<td>16.5%</td>
<td>0.73 [0.53, 1.00]</td>
<td></td>
</tr>
<tr>
<td>Sborro 2012</td>
<td>-0.693</td>
<td>0.141</td>
<td>17.8%</td>
<td>0.50 [0.38, 0.66]</td>
<td></td>
</tr>
<tr>
<td>Stintzing 2012</td>
<td>-0.288</td>
<td>0.158</td>
<td>16.8%</td>
<td>0.75 [0.55, 1.02]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>100.0%</td>
<td>0.51 [0.40, 0.64]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.06; Chi² = 18.60, df = 6 (p = 0.005); I² = 68%
Test for overall effect: Z = 5.58 (p <0.00001)

Table 2 B8 - Meta-analysis of correlation between skin rash and PFS

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>IV, Fixed, 95% CI</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gamucci 2008</td>
<td>-0.896</td>
<td>0.39</td>
<td>4.6%</td>
<td>0.41 [0.19, 0.88]</td>
<td></td>
</tr>
<tr>
<td>Paez 2010</td>
<td>-0.693</td>
<td>0.151</td>
<td>30.5%</td>
<td>0.50 [0.37, 0.67]</td>
<td></td>
</tr>
<tr>
<td>Park 2011</td>
<td>-0.774</td>
<td>0.302</td>
<td>7.6%</td>
<td>0.46 [0.26, 0.83]</td>
<td></td>
</tr>
<tr>
<td>Sborro 2012</td>
<td>-0.511</td>
<td>0.141</td>
<td>35.0%</td>
<td>0.60 [0.46, 0.79]</td>
<td></td>
</tr>
<tr>
<td>Stintzing 2012</td>
<td>-0.248</td>
<td>0.177</td>
<td>22.2%</td>
<td>0.78 [0.55, 1.10]</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>100.0%</td>
<td>0.58 [0.49, 0.68]</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi² = 5.22, df = 4 (p = 0.27); I² = 23%
Test for overall effect: Z = 6.54 (p <0.00001)

Results. 1348 patients of 4 randomized trials comparing preoperative vs postoperative CRT in LARC were considered and included into the analysis. Thirty-eight preoperative patients and 63 postoperative patients developed a LR (5.7% vs 9.5%, OR 0.58; CI 0.38-0.88; p = 0.01). No significant differences were observed for DFS (27.2% vs 24.9%, OR 0.82; CI 0.64-1.04; p = 0.11), OS (21.8% vs 24.9%, OR 0.85; CI 0.65-1.11; p = 0.23), and SPS (33.1% vs 35%, OR 0.93; CI 0.73-1.18; p = 0.54).

Conclusions. Our data confirm the role of preoperative CRT in improving the local activity of radiotherapy with 5 years LR reduction. However, lack of properly designed trials, difficulties and limitations in enrolling patients and the limits in surgical standardization do not allow any definitive conclusion about the impact of preoperative CRT treatment on limiting the need for sphincter preserving surgery. The future strategy should evaluate the effectiveness of biological agents in increasing the systemic control of disease and elucidate the role of preoperative CRT in modifying the surgical strategy in rectal cancer.

B9 PREOPERATIVE VS POSTOPERATIVE CHEMORADIOThERAPY IN LOCALLy ADVANCED RECTAL CANCER (LARC): SYSTEMATIC REVIEW OF LITERATURE AND META-ANALYSIS OF RANDOMIZED CLINICAL TRIALS

Polli V.1, Tamburini E.1, Affatato A.1, Papi M.1, Gianni L.1, Drudi F.1, Santelmo C.1, Venturi A.2, Francioni G.3, Veneroni L.3, Arcangeli V.1, Ravaoli A.1

1Department of Oncology, 2Department of Radiotherapy, 3Department of Surgery, Rimini Infermi City Hospital
B11 PROSPECTIVE STUDY OF EGFR INTRON 1 CA TANDEM REPEATS AS PREDICTIVE FACTOR OF BENEFIT FROM CETUXIMAB AND IRINOTECAN

Antoniotti C.1,2, Loupakis F.3, Cremolini C.1,2, Zhang W.3, Yang D.3, Wakatsuki T.3, Schirripa M.1,2, Salvatore L.1,2, Ricci V.4, Graziano F.5, Masl G.1,2, Ruzzo A.1, Lutrin S.E.7, Labonte M.J.3, Ning Y.3, El-Khoueiry R.3, Falcone A.1,2, Lenz H.J.3

1U.O. Oncologia Medica 2 Universitaria, Azienda Ospedaliare Universitaria Pisana, Pisa; 2Istituto Toscano Tumori (ITT); 3Department of Medical Oncology, University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, CA; 4Unità di Oncologia, Istituto Sciintifico San Raffaele, Milano; 5Medical Oncology Unit, Hospital of Pesaro, Pesaro; 6Section of Biochemistry and Molecular Biology, Department of Biomolecular Sciences, University of Urbino, Urbino; 7Department of Medical Oncology, University Hospital of Udine

Background. Retrospective experiences have investigated the potential influence of EGFR intron 1 CA repeats on the efficacy of cetuximab-containing treatments. Different series, adopting different criteria to define short (S) and long (L) variants, have provided contrasting results.

Methods. We designed a prospective confirmatory study, to detect a HR for PFS of 1.75 for L- compared to SS genotypes in a population of KRAS and BRAF wild-type irinotecan-resistant mCRC pts treated with cetuximab and irinotecan. Estimating a prevalence of 60% of the SS variant and setting a two-sided alpha = 0.05 with a power of 80%, 104 events were required. We defined S and L allelic variants those presenting < and ≥20 repeats, respectively. EGFR (CA), repeat polymorphism was assessed following a 5'-end [γ-33P] ATP-labeled PCR protocol.

Results. One hundred and fifteen pts were included. At a median follow-up of 21.9 months, PFS and OS were 5.2 and 13.4 months, respectively. Thirty-three (29%) out of 114 evaluable pts achieved response. EGFR (CA), repeat genotype was L- and SS in 45 (40%) and 68 (60%) out of 113 evaluable cases. No differences in PFS or OS were observed between L- and SS genotypes (median PFS 4.4 vs 5.3 months, HR = 1.00 [95% CI 0.67-1.51], p = 0.991; median OS 11.3 vs 14.2 months, HR = 1.30 [95% CI 0.80-2.22], p = 0.261). Ten (22%) out of 45 L- pts achieved response compared to 22 (33%) out of 67 SS pts (Fisher’s Exact test: p = 0.617). Other exploratory analyses adopting different cut-off values reported in literature led to similar results.

Conclusions. This prospective study, including a clinically homogenous and molecularly selected population, does not confirm any predictive or prognostic effect for EGFR (CA), repeat allelic variants with respect to the efficacy of cetuximab and irinotecan in advanced lines of treatment. The present experience strengthens the need of prospectively challenging retrospective findings, as an essential step on biomarkers’ way toward clinical practice.

B12 EFFECT OF MYC GENE COPY NUMBER (GCN) IN METASTATIC COLORECTAL CANCER (mCRC) PATIENTS TREATED WITH ANTI-EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) THERAPY

D’Incecco A.1, Landi L.1, D’Arcangelo M.1, Kalogeras K.T.2, Geva R.3, Minuti G.1, Lani E.1, Frattini M.1,2, Rossi E.1, Salvinì J.1, Ludovini V.5, Cinò L.5, Varella-Garcia M.1,2, Cappuzzo F.1

1Istituto Toscano Tumori, Oncologia Medica, Ospedale Civile, Livorno; 2Hellenic Cooperative Oncology Group (HeCOG), Athens, Aristotle University of Thessaloniki School of Medicine,
Background. Monoclonal antibodies against EGFR demonstrated efficacy in mCRC patients without mutations in the KRAS gene. Nevertheless, clinical data indicate that a consistent proportion of KRAS wild type patients have no benefit from cetuximab or panitumumab therapy, suggesting that other mechanisms, such as MYC GCN, could be involved in anti-EGFR sensitivity.

Methods. This retrospective study was conducted in a cohort of 303 mCRC patients treated with cetuximab/panitumumab, either alone (N = 24) or in combination with chemotherapy (N = 279). MYC GCN was assessed by fluorescence in situ hybridization (FISH) in primary colorectal cancer tissue samples.

Results. In the study population response rate (RR) was 28%, median progression-free survival (PFS) 5.6 months and median overall survival (OS) 11.8 months. MYC was successfully evaluated in 298 cases and resulted amplified in 17 patients (5.7%). In individuals with MYC amplification showed a trend for a lower RR (7.7% versus 28.9%, p = 0.12), shorter PFS (3.0 months versus 5.8 months, p = 0.22) and shorter OS (11.3 months versus 12.6 months, p = 0.15) than non-amplified patients. A Receiver Operating Characteristic (ROC) analysis was also performed in order to identify the cut-off for MYC GCN best discriminating anti-EGFR sensitive and resistant cases. In this analysis, MYC FISH positive patients (mean GCN ≥2.53; N = 199, 66.8%) had a significantly higher RR (32.2% versus 19.1%, p = 0.02), a longer PFS (5.6 months versus 4.5 months, p = 0.06) and a longer OS (12.3 months versus 11.4 months, p = 0.59) than MYC FISH negative patients (mean <2.53; N = 99, 33.2%). In order to assess the potential confounding effect of KRAS and BRAF status, we further analyzed the outcome of the 81 KRAS/BRAF wild-type patients according to MYC GCN. In this subset, a trend for improved RR (42% versus 20%, p = 0.05), PFS (8.6 months versus 4.2 months, p = 0.16) and OS (13.5 months versus 9.7 months, p = 0.51) favored MYC FISH GCN ≥2.73 patients.

Conclusions. MYC amplification is a rare event in mCRC, not significantly reducing sensitivity to anti-EGFR agents.

B13 DIFFERENT CLINICAL OUTCOME OF METASTATIC COLORECTAL CANCER (MCRC) PATIENTS TREATED WITH INTENSIVE TRIPLET CHEMOTHERAPY PLUS BEVACIZUMAB (FIR-B/FOX) ACCORDING TO KRAS GENOTYPE AND DISEASE EXTENSION

Bruera G.1, Cannita K.1, Di Giacomo D.2, Lamy A.3, Dal Mas A.4, Frébourg T.5, Sabourin J.C.6, Tosi M.5, Rojas Llimpe F.L.1, Di Fabio F.1, Pini S.1, Iacopino B.2, Leccè F.3, Ugolini G.3, Varrese F.3, Giaguinta S.1, Di Tullio P.G.1, Cola B.3, Mazzarotto R.2, Martoni A.1, Pinto C.1

1Medical Oncology Unit, 2Radiotherapy Unit, 3Surgery Unit, S. Orsola-Malpighi Hospital, Bologna

Background. Bevacizumab (BEV) plus triplet chemotherapy can increase efficacy of first-line treatment of MCRC (Bruera G et al., BMC Cancer, 10: 567, 2010), particularly if integrated with secondary liver surgery in liver-limited (L-L) patients (Bruera G et al., Clin Colorectal Cancer, 2012). Clinical outcome of Fir-B/FOX regimen was evaluated according to KRAS genotype in L-L and other MCRC patients.

Methods. Tumoral and metastatic samples were screened for KRAS codon 12 and 13, and BRAF mutations by SNAPSHOT and/or direct sequencing. MCRC pts were classified as L-L and other or multiple metastatic (O/MM). Activity and efficacy were evaluated and compared using log-rank test.

Results. Fifty-nine pts were evaluated: 31 KRAS wild-type, 53%; 28 KRAS mutant, 47%. At 21.5 months median follow-up, objective response rate (ORR), progression-free survival (PFS) and overall survival (OS) were, respectively: KRAS wild-type 90%, 14 months, 38 months; KRAS mutant 67%, 11 months, 20 months. PFS and OS were, respectively: overall in 25 L-L compared to 32 O/MM evaluable pts, 17 and 12 months, 47 and 21 months, significantly different; in KRAS wild-type, 12 L-L compared to 18 O/MM, 21 and 12 months, 47 and 28 months, significantly different; in KRAS mutant, 13 L-L compared to 14 O/MM, 11 months equivalently, 39 and 19 months, not significantly different.

Conclusions. First-line Fir-B/FOX regimen can increase activity and efficacy of KRAS wild-type and mutant MCRC pts; integration with secondary liver surgery significantly discriminates increased clinical outcome in KRAS wild-type L-L compared to O/MM pts while not in KRAS mutant patients.

B14 NEOADJUVANT CHEMORADIOThERAPY (CRT) IN ELDERLY AND YOUNG PATIENTS WITH LOCALLy ADVANCED RECTal CANCer (LARC) BOLOGNA MULTIDISCIPLINARY RECtAL CANCer GROUP STUDY (BMrg-C01)

Rojas Llimpe F.1, Di Fabio F.1, Pini S.1, Iacopino B.2, Leccè F.3, Ugolini G.3, Varrese F.3, Giaguinta S.1, Di Tullio P.G.1, Cola B.3, Mazzarotto R.2, Martoni A.1, Pinto C.1

1Medical Oncology Unit, 2Radiotherapy Unit, 3Surgery Unit, S. Orsola-Malpighi Hospital, Bologna

Background. Currently preoperative CRT is the standard treatment in LARC, but the treatment strategy in elderly patients is less well defined.

Methods. The aim of this study is to assess the tolerability, compliance and efficacy of neoadjuvant CRT in elderly (E) (age ≥70 years) compared to younger (Y) patients with rectal cancer. We prospectively evaluated patients with rectal adenocarcinoma cT3-T4 N-/+ located ≤12 cm from the anal margin or uT2N+- with closer location (<5 cm from the anal margin). Preoperative CRT consisted of radiotherapy 50.4 Gy in 28 daily fractions in combination with 5-fluorouracil (5-FU) continuous infusion or capecitabine (CAPE) ± oxaliplatin (OXA). Rectal surgery with total mesorectal excision (TME) was performed 6-8 weeks after the end of neoadjuvant treatment. Data were consecutively collected in a dedicated BMrg database.

Results. Between December 2001 and April 2012 we evaluated 152 patients, 68 (45%) E (age ≥75 years 59%) and 84 (55%)
CHEMORADIOTHERAPY (CRT): BOLOGNA

PATIENTS TREATED WITH NEOADJUVANT LOCALLY ADVANCED RECTAL CANCER (LARC)

CLINICAL AND PATHOLOGICAL FACTORS IN B15 PREDICTIVE AND PROGNOSTIC VALUE OF

csignificantly reduced.

Despite this down-treatment, the efficacy was not significantly reduced.

Pts had more CRT modifications than Y pts (35% vs 17%, p = 0.014); despite this down-treatment, the efficacy was not significantly reduced.

Table 1

<table>
<thead>
<tr>
<th>Pts characteristics</th>
<th>&lt;70 years</th>
<th>≥70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>84/152 (55%)</td>
<td>68/152 (45%)</td>
</tr>
<tr>
<td>Male</td>
<td>54 (64%)</td>
<td>45 (66%)</td>
</tr>
<tr>
<td>Female</td>
<td>30 (36%)</td>
<td>23 (34%)</td>
</tr>
<tr>
<td>Median age (range)</td>
<td>61 (34-69)</td>
<td>75 (70-84)</td>
</tr>
<tr>
<td>Median KPS (range)</td>
<td>100 (80-100)</td>
<td>100 (80-100)</td>
</tr>
</tbody>
</table>

Stage at diagnosis

<table>
<thead>
<tr>
<th>cT2N-1 (1.2%)</th>
<th>1 (1.5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cT2N+</td>
<td>2 (2.4%)</td>
</tr>
<tr>
<td>cT3N-</td>
<td>22 (26.2%)</td>
</tr>
<tr>
<td>cT3N+</td>
<td>41 (48.8%)</td>
</tr>
<tr>
<td>cT4N-</td>
<td>7 (8.3%)</td>
</tr>
<tr>
<td>cT4N+</td>
<td>11 (13.1%)</td>
</tr>
</tbody>
</table>

Neoadjuvant CRT

<table>
<thead>
<tr>
<th>5-FU</th>
<th>35 (41.6%)</th>
<th>18 (26.5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPE</td>
<td>8 (9.6%)</td>
<td>17 (25%)</td>
</tr>
<tr>
<td>5-FU+OXA</td>
<td>41 (48.8%)</td>
<td>31 (45.5%)</td>
</tr>
<tr>
<td>OXA</td>
<td>0</td>
<td>2 (3%)</td>
</tr>
</tbody>
</table>

Compliance to treatment

<table>
<thead>
<tr>
<th>Completed planned crt</th>
<th>&lt;70 years</th>
<th>≥70 years</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>70 (83.3%)</td>
<td>41 (60.3%)</td>
<td>ns</td>
<td></td>
</tr>
</tbody>
</table>

Reduced or interrupted cht

<table>
<thead>
<tr>
<th>Reduced or interrupted cht and rt</th>
<th>&lt;70 years</th>
<th>≥70 years</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 (16.6%)</td>
<td>24 (35.2%)</td>
<td>0.014</td>
<td></td>
</tr>
<tr>
<td>Reduced or interrupted cht</td>
<td>1 (1.2%)</td>
<td>2 (3%)</td>
<td></td>
</tr>
<tr>
<td>Ongoing</td>
<td>0</td>
<td>1 (1.5%)</td>
<td></td>
</tr>
</tbody>
</table>

Grade 3-4 toxicity

<table>
<thead>
<tr>
<th>Grade 3-4 toxicity</th>
<th>&lt;70 years</th>
<th>≥70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>13 (15%)</td>
<td>16 (23%)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Surgery

<table>
<thead>
<tr>
<th>Low-anterior resections</th>
<th>&lt;70 years</th>
<th>≥70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>63 (75%)</td>
<td>39 (57.3%)</td>
<td></td>
</tr>
</tbody>
</table>

Abdominal-perineal amputation

<table>
<thead>
<tr>
<th>Anus excision</th>
<th>&lt;70 years</th>
<th>≥70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 (21.4%)</td>
<td>19 (28%)</td>
<td></td>
</tr>
</tbody>
</table>

Trans-anal excision

<table>
<thead>
<tr>
<th>Refuse surgery</th>
<th>&lt;70 years</th>
<th>≥70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (2.4%)</td>
<td>7 (10.2%)</td>
<td></td>
</tr>
</tbody>
</table>

Ongoing

<table>
<thead>
<tr>
<th>Ongoing</th>
<th>&lt;70 years</th>
<th>≥70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (1.2%)</td>
<td>2 (3%)</td>
<td></td>
</tr>
</tbody>
</table>

Pathological complete response

<table>
<thead>
<tr>
<th>Pathological complete response</th>
<th>&lt;70 years</th>
<th>≥70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>14 (17%)</td>
<td>8 (12%)</td>
<td>ns</td>
</tr>
</tbody>
</table>

Adjuvant cht performed

<table>
<thead>
<tr>
<th>Adjuvant cht performed</th>
<th>&lt;70 years</th>
<th>≥70 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>66 (79%)</td>
<td>39 (57%)</td>
<td></td>
</tr>
</tbody>
</table>

The main causes of treatment modification were similar in both patient groups. Major toxicities (grade 3-4) were: diarrhea (E 16%, Y 9%), leukopenia (E 4%, Y 2%), cardiac events (E 1.5%, Y 1.2%), epitheliolysis and haematuria (E 4%, Y 0%). No perioperative mortality or deaths due to toxicity were recorded in either patient group. 3-year-DFS rate was 82% in E pts and 86% in Y pts (p = ns).

Conclusions. The results of our analysis show that neoadjuvant CRT is feasible in elderly pts with acceptable toxicity. These pts had more CRT modifications than Y pts (35% vs 17%, p = 0.014); despite this down-treatment, the efficacy was not significantly reduced.

MULTIDISCIPLINARY RECTAL CANCER GROUP STUDY (BMRG-B01-STUDY)

Pini S.1, Di Fabio F.1, Ceccarelli C.2, Iacopino B.3, Lecce F.4, Ugolini G.4, Varrese F.5, Rojas Limpe F.1, Giaquinta S.1, Martoni A.1, Pinto C.1

1Medical Oncology Unit, 2Pathology Unit, 3Radiotherapy Unit, 4Surgery Unit, S. Orsola-Malpighi Hospital, Bologna

Methods. Between December 2001 and January 2012 we evaluated 149 pts with cT3-T4 N-/+ rectal adenocarcinoma located ≤12 cm from the anal margin. Preoperative CRT consisted of radiotherapy 50.4 Gy in 28 daily fractions in combination with 5-fluorouracil continuous infusion or capecitabine ± oxaliplatin. Rectal surgery with total mesorectal excision (TME) was performed 6-8 weeks after the end of neoadjuvant treatment. Pathological examination of surgical specimens included TRG according to the Dworak criteria (TRG 0 = no regression, TRG 1 = minor regression, TRG 2 = moderate regression, TRG 3 = good regression, TRG 4 = complete regression). TS, EGFR, Ki-67, p53, Bcl-2, MLH1 and MSH2 were immunohistochemically determined in pre-treatment biopsies and surgical specimens. For immunohistochemistry evaluation serial sections of formalin-fixed, paraffin-embedded tissues were stained with specific antibodies using a biotin-free ready-to-use amplification system.

Results. After a median follow-up of 60 months (2-122) we observed 4.7% local recurrences, 12.7% distant recurrences, and 13.4% deaths. In surgical specimens TRG 1, 2, 3 and 4 were observed respectively in 22.5%, 35.3%, 25.6% and 16.6% of patients. ypN and TRG were independent prognostic factors of DFS with p = 0.020 and p = 0.027 respectively. CRM and TRG were independent prognostic factors of OS with p = 0.016 and p = 0.010 respectively. High pre-treatment biopsy expression of TS was associated with poor TRG (0-1) (p = 0.007); high biopsy expression of Ki-67 was associated with good TRG (2-4) (p = 0.039); decrease between pre-treatment biopsy and surgical specimen of Ki-67 (ΔKi-67 ≥0) was associated with good TRG (2-4) (p = 0.02). Decrease in Ki-67 (ΔKi-67 ≥0) was associated with good DFS (p = 0.011) and confirmed by multivariate analysis as an independent prognostic factor (p = 0.035).

Conclusions. In our analysis ypN, CRM and TRG were independent prognostic factors; baseline expression of TS, Ki-67 and decrease in Ki-67 were predictive of TRG; decrease in Ki-67 was an independent prognostic factor of DFS.

B16 BODY MASS INDEX AND IMPAIRED FASTING BLOOD GLUCOSE AS PREDICTIVE FACTOR OF EFFICACY IN CETUXIMAB-BASED COLORECTAL CANCER TREATMENT

Guida F.M.1, Pantano F.1, Vasile E.2, Rodriguez Garrote M.3, Grande E.3, Silvestris N.4, Vincenzi B.1, Santini D.1, Falcone A.2, Tonini G.1

1Università Campus Bio-Medico, Roma; 2Division of Medical Oncology, Department of Oncology, Livorno; 3Medical Oncology...
**Introduction.** Cetuximab is an anti-EGFR monoclonal antibody with antitumor efficacy in metastatic colorectal cancer harboring wild-type K-Ras gene. However, not all patients K-Ras wild-type benefit from cetuximab, underscoring the need for additional markers to help in patient selection. Preclinical evidences suggest that the EGFR and insulin-like growth factor-I receptor (IGF-1R) pathways interact to drive tumour growth and survival. It’s well known that in hyperinsulimic state, higher insulin levels upregulate IGF-1 production, leading this state a potential biomarker for cetuximab efficacy. The aim of our study was to evaluate the feasibility to stratify patients more likely to benefit from cetuximab treatment using two well known signs of hyperinsulimic state such as the high body mass index (BMI) and impaired fasting blood glucose (FBG).

**Methods.** We retrospectively collected 250 K-Ras wild-type metastatic colorectal cancer patients treated with cetuximab containing regimens in first to fifth-line setting. From this cohort we selected 76 patients treated with cetuximab+CPT11 after failure of first-line CPT11 based containing regimen. We divided this population into two groups according to the presence of both elevated BMI (cut-off 24.99 according to WHO Criteria) and high FBG (cut-off 100 mg/dL according to American Diabetes Association) and we evaluated the time to progression (TTP) of these two groups.

**Results.** We found a statistically significant lower TTP in patients with both elevated BMI and FBG compared to patients with presence of none or only one of the two parameters (median TTP 4.3 months, CI 95% 2.5-5.4 vs 5.6 months, CI 95% 2.5-5.8; p = 0.034).

**Conclusions.** The statistically significant poorer outcome in patients with both BMI and FBG treated with cetuximab+CPT11 after CPT11 failure could be explained by the reduction of cetuximab efficacy due to the probable presence of upregulation of vasc pathways such as IGF-1R linked to hyperinsulimic state.

**B18 PHASE II TRIAL OF PANITUMUMAB IN COMBINATION WITH INFUSIONAL OXALIPLATIN AND ORAL CAPECITABINE (XELOX) CHEMOTHERAPY AS FIRST-LINE THERAPY IN PATIENTS WITH COLORECTAL CANCER AND ADVANCED LIVER METASTASES: THE METAPAN STUDY**

Leone F.1, Marino D.1, Artale S.2, Cagnazzo C.1, Gioeni L.1, Cascini S.3, Martoni A.4, Sobrero A.5, Tampellini M.6, Siena S.2, Aglietta M.1

1 Dipartimento di Oncologia Medica IRCC, Candiolo; 2 Struttura Complessa di Oncologia Falck AO Ospedale Niguarda Ca’ Granda, Milano; 3 Oncologia Medica Azienda Ospedaliero Universitaria, Ospedali Riuniti Umberto I, Ancona; 4 UOC di Oncologia Medica, Azienda Ospedaliero Universitaria, Ospedale S. Orsola-Malpighi, Bologna; 5 Unità Operativa di Oncologia Medica, A.O.U. Ospedale San Martino, Genova; 6 Oncologia Medica, Azienda Ospedaliera San Luigi, Orbassano

**Background.** Preoperative chemotherapy improves outcome in potentially resectable colorectal cancer with liver metastases. We evaluated the activity of a neoadjuvant treatment with capecitabine-oxaliplatin (XELOX) associated with the anti-EGFR antibody panitumumab in patients with unresectable, liver-only, metastatic colorectal cancer (CRC).

**Patients and methods.** Chemotherapy-naïve patients with unresectable liver metastases of CRC and no other metastatic sites were enrolled. Criteria of unresectability were defined as: more than 3 liver metastases including >50% hepatic involvement and requiring a major hepatectomy with contralateral wedge resection or any metastases requiring a resection that does not preserve two contiguous hepatic segments. Since November 2008 only patients bearing wild type KRAS were included. All patients re-
ceived neoadjuvant XELOX plus panitumumab (P-XELOX) and were reevaluated for resectability every four cycles. Primary endpoint was radiological objective response rate (ORR). Secondary endpoints were overall survival (OS), progression-free survival (PFS), percentage of patients whose disease became radically resectable, and safety of the P-XELOX combination.

**Results.** Forty-nine patients were recruited, of which 35 were KRAS wild type, and 14 (enrolled before study amendment), were unknown (9 patients or mutated 5 patients). Forty-six were evaluable for response. Following neoadjuvant P-XELOX, the ORR in the general population was 54%, with 3 CR, 22 PR, 14 SD. In wild type KRAS patients ORR reached 65% (3 CR, 18 PR, 7 SD), and this allowed 15 patients with initial unresectable liver metastases to be converted to resectability. As per the policy of our treating institutions, 3 patients with radiological CR did not proceed to liver resection. Survival analysis showed median PFS and OS of 8.5 months and 22.1 months, respectively. Resected patients had significantly better OS if compared to unresected (p = 0.00014). The most common toxicities were cutaneous, gastrointestinal, and neurological. Overall toxicities were predictable and manageable.

**Conclusions.** Neoadjuvant P-XELOX yields high response rates for patients with metastatic CRC and extensive liver involvement, and leads to remarkable conversion to resectability of liver metastases.

**B19 FUNCTIONAL CHARACTERIZATION OF EZH2 SINGLE NUCLEOTIDE POLYMORPHISM AND CORRELATION OF EZH2 EXPRESSION WITH CLINICO-PATHOLOGICAL AND MOLECULAR PARAMETERS IN COLORECTAL (CRC) CANCER SAMPLES**

Vivaldi C.1, Crea F.2, Fornaro L.1, Faviana P.3, Masì G.1, De Gregorio V.1, Paolicchi E.2, Sensi E.3, Lupi C.3, Fontanini G.3, Danesi R.2, Falcone A.1

1Azienda Ospedaliero-Universitaria Pisana, U.O. Oncologia Medica 2 Universitaria, Pisa; 2Divisione di Farmacologia, Dipartimento di Medicina Interna, Università di Pisa, Pisa; 3Anatomia Patologica Sperimentale, Università di Pisa, Istituto Toscano Tumori, Pisa

**Background.** EZH2, a histone methyltransferase, is a cancer stem cell-related gene involved in cancer development through gene silencing. The EZH2 polymorphism rs3757441 was shown to be associated with mRNA expression in lymphocytes and may predict clinical outcome in metastatic CRC patients treated with first-line FOLFIRI and bevacizumab.

**Materials and methods.** In order to investigate the correlation between EZH2 expression and other biologic parameters, a total of 129 formaline-fixed paraffin-embedded tissue of primary tumours were collected. EZH2 expression was evaluated by immunohistochemistry. **KRAS** codon 12-13 and **BRAF** V600E mutational status were assessed by pyrosequencing analysis of DNA extracted from tumour rich regions and the EZH2 rs3757441 SNP variants were identified by real-time PCR from colonic healthy tissue. Student T test and ANOVA were used to evaluate the association between EZH2 expression and other parameters.

**Results.** Characteristics of the samples assessed up to now are summarized in Table 1.

Neither stage, grading or site nor **KRAS-BRAF** mutational status correlate with the percentage of EZH2-positive cells. The rs3757441-CC genotype is associated with higher EZH2 expression, even if this correlation does not reach statistical significance (p = 0.1). The percentage of EZH2-positive cells is significantly higher in mucinous than in non-mucinous tumours (p = 0.022).

**Conclusions.** CRC tumours characterized by mucinous histology show higher levels of EZH2 expression, which seems to be independent from other investigated parameters. As mucinous adenocarcinoma is characterized by negative prognosis and poor response to treatment, increased EZH2 expression may contribute to this aggressive tumour behavior. EZH2 deserves further investigation as prognostic indicator and therapeutic target in CRC.

| Feature | N = 129 (%)
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage, I/II/III/IV</td>
<td>5/47/54/23 4/36/42/18</td>
</tr>
<tr>
<td>Grade, 1/2/3</td>
<td>0/81/48 0/63/37</td>
</tr>
<tr>
<td>Site, right colon/left colon/rectum</td>
<td>56/49/24 43/38/19</td>
</tr>
<tr>
<td>Mucinous histology, yes/no</td>
<td>40/89 31/69</td>
</tr>
<tr>
<td><strong>KRAS</strong>, wild-type/mutant</td>
<td>74/55 57/43</td>
</tr>
<tr>
<td><strong>BRAF</strong>, wild-type/mutant</td>
<td>115/14 89/11</td>
</tr>
<tr>
<td>EZH2 rs3757441 genotype, CC/CT/TT (not tested)</td>
<td>5/36/59 (29) 4/28/46 (22)</td>
</tr>
</tbody>
</table>

**B20 BRAF MUTATION IN COLON CANCER PATIENTS WITH MICROSATELITE INSTABILITY (MSI): A MONOINSTITUTIONAL ANALYSIS**


*Department of Medical Oncology, ‘Unit of Surgical Pathology, Laboratory of Molecular Pathology, Santa Chiara Hospital, Trento

**Background.** Molecular markers in colon cancer are needed for a precise classification and personalized treatment. Almost 20% of sporadic colon cancer pts present MSI, due to defects in the mismatch repair (MMR) system which is associated with a better prognosis. **BRAF** mutation is observed approximately in 10% of the colonic tumours and its correlation with prognosis is recently being studied.

**Results.** MSI-H was observed in 136 cases (~10%); they were 35 stage I disease (26%), 70 stage II (51%), and 31 stage III (23%). Braf was determined in 100 of these pts and was mutated in 55 cases (55%): 17/35 stage I, 24/70 stage II and 14/31 stage III; moreover, BRAF mutation was observed in 63% of well-differentiated tumours, in 90% of right side tumours, in 74% of lymph node negative and in 18% of T4 tumours. The median DFS was 28.8 months (range 0.4-71 months) in the BRAF mutated patients and 28 months in the wild type group (range 0.5-69.6 months). At a median follow-up of 29 months (range 0.4-72
months), 9 patients (16%) died due to disease in the BRAF mutated group and 7 patients (15%) in the BRAF wild type group.

Conclusions. It appears from our results that BRAF mutation is a quite frequent event in MSI-H colorectal tumours, but it does not seem related to a higher frequency of recurrence and death. These data could suggest that the good prognosis of patients with MSI-H tumours may not be affected by BRAF mutation.

**B21 KRAS MUTATIONAL STATUS, ERCC1 AND OXALIPLATIN SENSITIVITY: IN VITRO VERITAS**


Unit of Medical Oncology, Catholic University of Sacred Heart, Rome

Background. Oxaliplatin is a milestone of colorectal cancer therapy, but is still lacking of a validated biomarker of response. In order to evaluate the possible role of KRAS mutations as biomarker of response to oxaliplatin, we conducted a retrospective analysis and investigated the molecular basis of the association between RAS and ERCC1.

Methods. We evaluated the efficacy of FOLFOX6 in 90 metastatic colorectal cancer patients according to KRAS mutational status and to IHC ERCC1 expression. We selected four colorectal cancer cell lines, two KRAS wild type (HCT-8, HT-29) and two KRAS mutated (SW620, SW480). The sensitivity of these cell lines to oxaliplatin was evaluated by MTT-test. ERCC1 levels before and after exposure to oxaliplatin were determined by RealTime-PCR. KRAS was silenced in SW620 cells in order to evaluate the effect on oxaliplatin sensitivity and on ERCC1 levels. ERCC1 was silenced in all cell lines.

Results. Retrospective analysis showed a statistically significant benefit from oxaliplatin in term of RR (56% vs 26%; p = 0.006) and PFS (10 vs 8 months; HR 1.64, p = 0.0069) for KRAS mut patients. We did not observe any statistical significant correlation between ERCC1 tissue levels and oxaliplatin efficacy. In vitro study showed that mt KRAS cell lines were more sensitive to oxaliplatin (OR 2.68; p <0.001). KRAS mt and wt cell lines did not show differences in ERCC1 basal levels. After exposure to oxaliplatin, only KRAS wt cell lines showed a statistically significant upregulation of ERCC1, XPF and AP1 (OR 42.9; p <0.0005). Silencing of KRAS reduced oxaliplatin sensitivity restoring the ability to induce ERCC1 in KRAS mt cell lines. Silencing of ERCC1 increased oxaliplatin citotoxicity only in those cells able to upregulate ERCC1 after exposure to oxaliplatin (KRAS wt and KRAS mt/silenced colorectal cancer cell lines).

Conclusions. Tissue ERCC1 levels do not seem to correlate with oxaliplatin efficacy. Based on our in vitro findings KRAS mutational status could represent a predictor of response to oxaliplatin, as a surrogate for ERCC1 modulation.

**B22 NEOADJUVANT MULTIDISCIPLINARY PHASE II STUDY (BRANCH) OF AN EARLY BEVACIZUMAB SCHEDULE PLUS CHEMO-RADIATION THERAPY IN RECTAL CANCER: EFFICACY, SAFETY, AND BIOMARKERS**


Istituto Nazionale Tumori, Fondazione G. Pascale, Napoli

Background. The benefits of combining bevacizumab (BEV) plus chemotherapy have thus far been rather modest, stimulating interest in developing novel effective combination schedule as well as valid predictive biomarkers. Several evidences support the hypothesis that BEV can normalize the abnormal tumour vasculature, resulting in more efficient delivery of drugs and oxygen to cancer cells and that this effect seems to be transient and with a relatively narrow therapeutic window.

In BRANCH study (NCT01481545) we assess the safety and efficacy of an experimental schedule of early (4 days before) BEV added to neoadjuvant chemotherapy (CT) and radiotherapy (RT) in poor-risk locally advanced rectal cancer (pLARC) patients and explore the potential of circulating endothelial cells (CECs) and tumour lesion glycolysis (TLG) as surrogate markers of pathological response.

Patients and methods. Forty-six pts (cT4, cN+, cT3 ≤5 cm from the anal verge and/or positive circumferential margin, M1 resectable) received 3 biweekly courses of oxaliplatin (100 mg/m²)/ralitrexed (2.5 mg/m²) on day 1, and 5-FU (800 mg/m²)/folinic acid (250 mg/m²) on day 2 during pelvic RT (45 Gy). BEV (5 mg/kg) was given biweekly 4 days before beginning of CT/RT for 2 courses. Toxicity was graded with NCI-CTC v.3. Pathological response was defined using a modified Mandard tumour regression grade (TRG). According to the Simon’s two-stage design, assuming an hypothesis of a 50% TRG1 (complete tumour regression) (α error = 0.05, β error = 0.20), at least 6/16 TRG1 should be obtained to continue accrual to 46 pts. CECs were quantified at baseline (BL) before BEV, at several time points thereafter during treatment and before surgery, by flow cytometry. TLG was evaluated at BL, on day 10 and before surgery, by FDG-PET. Statistical analysis was by Mann-Whitney test.

Results. TRG1 required by statistical design was reached in the first 16 pts and in the final 46 pts: 23 TRG1 (50%), 14 TRG2 (30%) and 8 TRG3-4 (17%). One pt refused surgery. Grade 3-4 neutropenia was the most common adverse event (13/46 pts, 28%). TLG reduction on day 10 vs BL was significantly higher in responders TRG1-2 compared to non-responders TRG3-4 pts (median -2%, range -90%+31% vs -38%, range -45%+25%; p <0.05). Preoperative PET CT studies, on the other hand, were not predictive of pathologic response (responders TLG change median -92%, range -400% +4%, non-responders median 86%, range -94%-76%, p = ns). Median CECs at BL were higher in TRG1-2 vs TRG3-4 pts (median 0.22/µL, range 0-3.98 vs 0/µL, range 0-0.174; p = 0.009). Moreover, in TRG1-2 pts CECs were significantly reduced on day 10 vs BL (median 0.014/µL, range 0-2.29; p = 0.002). This pattern was not seen in TRG3-4 pts with a tendency toward increased levels (median 0.316/µL, range 0-2.64; p = 0.997). In both TRG 1-2 and TRG 3-4 preoperative CECs were not predictive of pathologic response.

Conclusions. Our findings indicate that the current scheme of BEV plus CT and RT appears safe and active, yielding high rate of TRG1 and TRG2 responses in pLARC. Early FDG-PET and CECs evaluation emerged as potential biomarkers for treatment selection to be incorporated in design of future studies with this regimen.
Background. BRAF V600E mutation plays a negative prognostic role in metastatic colorectal cancer (mCRC) patients, leading to a median PFS of 4–6 months with first-line conventional treatments. Recently, results from a retrospective exploratory analysis suggested that an up-front intensive treatment with FOLFOXIRI plus bevacizumab could improve the outcome of BRAF mutant mCRC.

Methods. Fifteen consecutive BRAF mutant mCRC patients treated with first-line FOLFOXIRI plus bevacizumab were included in a validation set. The primary endpoint was 6-month progression-free rate (6m-PFR). Secondary endpoints were: overall survival, response rate and the pooled analysis of all main outcome parameters in both the exploratory and validation set.

Results. In the validation set, 11 out of 15 patients included were progression-free at 6 months, for a 6m-PFR of 73.3%. Primary endpoint was met. At a median follow-up of 21.6 months, median progression-free survival was 9.2 months while median OS has not yet been reached. In the pooled data analysis of the validation set and the initial retrospective cohort 24 out of 25 total patients were evaluable for response: partial or complete response was obtained in 17 (68%) and in 1 (4%) patient, respectively, for an overall response rate of 72%. At a median follow-up of 34.1 months, the pooled set of patients showed a median PFS of 11.8 months and a median OS of 23.8 months.

Conclusions. These data suggest that FOLFOXIRI plus bevacizumab could be a reasonable option for the first-line treatment of BRAF mutant metastatic colorectal cancer patients.

B24 CORRELATION BETWEEN BEVACIZUMAB EFFECTIVENESS, KRAS MUTATION AND METASTATIC SITES IN FIRST-LINE TREATMENT OF METASTATIC COLORECTAL CANCER (mCRC)

Zoratto F.1, Velti E.2, Zullo A.3, Rossi L.1, Colonna M.4, Mottolese M.5, Giannarelli D.5, Ruco L.7, Romiti A.8, Barucca V.8, Adua D.9, Arcangeli G.10, Cianni R.11, Giannini G.12, Sacchi M.13, Tomao S.1

Background. Bevacizumab plus chemotherapy prolongs PFS and OS in mCRC independently of KRAS status. This study investigated the role of anti-vascular endothelial growth factor therapy on clinical response, mean progression-free survival (mPFS) and mean overall survival (mOS) according to KRAS status and metastatic sites.

Methods. From September 2008 to March 2011, 108 patients were treated with first-line FOLFIRI or FOLFOX chemotherapy in combination with bevacizumab. Tissue samples were analyzed for DNA sequencing to identify KRAS mutations. Statistical association was evaluated by chi-square test and logistic regression analysis to objective response rate (RR), mPFS and mOS.

Results. RR was available in 108 pts while mPFS and mOS in 106 pts. Overall, RR was 43.5%. mPFS was 11.3 months and mOS was 26.9 months. Fifty-three pts presented only hepatic metastases. RR in pts with only hepatic metastases was higher than in extra-hepatic or multiple metastases patients (49% vs 39%; p = 0.36), mPFS was 12 months vs 11 months respectively (p = 0.59) and mOS was 24.8 months vs 27.1 months (p = 0.72). KRAS mutations were investigated in 108 patients. Sixty-nine patients were wild-type (wt 64%) while 39 patients were mutated (mut 36%). RR was 49.3% in wt group vs 33.3% in mut group (p = 0.11), mPFS was 12.8 months in KRAS wt group vs 10 months in KRAS mut group (p = 0.75) and mOS was 28.8 months vs 23.9 months respectively (p = 0.70).

Conclusions. RR, mPFS and mOS tended to be higher in KRAS wt pts but these results were not statistically significant. Despite RR and mPFS positive trend in patients with only hepatic metastases, an increase mOS compared to pts with extra-hepatic metastases or multiple metastatic sites was not shown.

B25 IMPACT OF KRAS AND BRAF MUTATION STATUS ON BEVACIZUMAB EFFICACY OUTCOMES IN 1ST-LINE TREATMENT OF METASTATIC COLORECTAL CANCER (mCRC)

Rossi L.1, Velti E.2, Zullo A.3, Zoratto F.1, Colonna M.4, Longo F.5, Mottolese M.6, Ruco L.7, Romiti A.8, Barucca V.8, Adua D.9, Baiano G.9, Giannini G.10, Nardi S.11, Tomao S.1

Background. Several analyses showed that bevacizumab benefit occurs irrespective from KRAS and BRAF status. This retrospective study describes correlation between oncogenes mutation and bevacizumab efficacy outcomes like objective response rate (RR), mean progression-free survival (mPFS) and mean overall survival (mOS).

Methods. Eighty-two mCRC patients were treated with first-line FOLFIRI or FOLFOX chemotherapy plus bevacizumab. Their tissue samples were analyzed for DNA sequencing to identify KRAS and BRAF mutations.
Results. KRAS and BRAF mutations were observed in 34.1% and 13.4% respectively. RR in KRAS wild-type (wt) group was 50% vs 32.1% in KRAS mutated (mut) group. mPFS was 12 months vs 11.6 months respectively and mOS was 27.5 months vs 28.8 months. In BRAF wt group RR was 45% vs 36.4% BRAF mut group, mPFS was 12.2 months vs 8.8 months respectively and mOS was 28.2 months vs 25.6 months. By analyzing bevacizumab efficacy outcomes in the following subpopulations (48 patients KRAS wt/BRAF wt; 23 patients KRAS mut/BRAF wt; 6 patients KRAS wt/BRAF mut and 5 patients KRAS mut/BRAF mut) we obtained these results: in the first group RR was 52%, mPFS 12.4 months and mOS 28 months; in the second group RR 30.4%, mPFS 12.9 months and mOS 27.5 months; in KRAS wt/BRAF mut subpopulation RR 33.3%, mPFS 9.5% months and mOS 19.8 months and in the last group RR 40%, mPFS 8 months and mOS 32.6 months. Finally we evaluated the difference in RR, mPFS and mOS between KRAS wt/BRAF wt group and patients with a single or both oncogenes mutation. RR in KRAS/BRAF wt patients was 52% vs 32.3% in KRAS mut ± BRAF mut patients, mPFS was 12.4 months vs 11.6 months respectively and mOS was 28 months vs 26.9 months.

Conclusions. RR in KRAS groups was different with advantage in wt patients. RR, mPFS and mOS values were better in BRAF wt patients than BRAF mut patients. Bevacizumab efficacy outcomes tended to be higher in KRAS wt/BRAF wt group than in pts with only one or both oncogenes mutation.

B26 HETEROGENEOUS PREVALENCE OF KRAS, BRAF, AND PIK3CA MUTATIONS IN PATIENTS WITH COLORECTAL CARCINOMA FROM SARDINIA

Palomba G.1, Colombino M.1, Contu A.2, Massidda B.3, Baldino G.2, Pazzola A.2, Ionta M.T.3, Capelli F.4, Trova V.5, Sedda T.6, Sanna G.7, Tanda F.8, Budroni M.9, Palmieri G.1, Cosso A.10 on behalf of the Sardinian Translational Oncology Group (STOG)

1Istituto di Chimica Biomolecolare, CNR, Sassari; 2Servizio Oncologia, ASL1, Sassari; 3Oncologia Medica, Università di Cagliari; 4Oncologia, Ospedale di Nuoro; 5Oncologia, Ospedale di Alghero; 6Oncologia, Ospedale di Oristano; 7Oncologia Medica, AOU, Sassari; 8Anatomia Patologica, Università di Sassari; 9Servizio Epidemiologia, ASL1, Sassari; 10Anatomia Patologica, AOU, Sassari

Background. Role of KRAS, BRAF, and PIK3CA mutations in pathogenesis of colorectal cancer (CRC) has been recently investigated worldwide. In this population-based study, we evaluated the incidence rates and distribution of such somatic mutations in genetically isolated population of Sardinia.

Methods. From April 2009 to July 2011, formalin-fixed paraffin-embedded tissues (N = 478) were prospectively collected from Sardinian CRC patients at clinics across the entire island. Genomic DNA was isolated from tissue sections and screened for mutations in KRAS, BRAF, and PIK3CA genes by automated DNA sequencing.

Results. Overall, KRAS tumour mutation rate was 30% (145/478 positive cases). Distribution of mutation carriers was surprisingly different within the island: 87/204 (43%) in North Sardinia vs 58/274 (21%) in Middle-South Sardinia (p = 0.023). Among 384 CRC cases whose DNA was available, only one (0.3%) mutation in BRAF gene was observed; conversely, PIK3CA was found mutated in 158/384 (41%) patients. An inverse distribution of PIK3CA mutation rates was then observed within Sardinian population: 60/181 (33%) cases from northern vs 98/203 (48%) cases from central-southern island. This heterogeneity in frequencies of KRAS/PIK3CA somatic mutations is consistent with the already reported discrepancies in distribution of germline mutations for other malignancies within Sardinian population. Preliminary clinical evaluation of 118 KRAS wild-type patients undergoing anti-EGFR-based treatment indicated lack of role for PIK3CA in predicting response to therapy.

Conclusions. Our findings support the hypothesis that differences in patients origins and related genetic backgrounds may contribute to even determine the incidence rate of somatic mutations in candidate cancer genes.

B27 BETA 4 INTEGRIN POLYMORPHISM MEDIATES AN ALTERNATIVE RESISTANCE PATHWAY IN HER-3 NEGATIVE, K-RAS WILD-TYPE METASTATIC COLORECTAL CANCER PATIENTS RECEIVING IRINOTECAN CETUXIMAB

Del Prete M.1, Scartozzi M.2, Giampieri R.2, Loretelli C.2, Mandolesi A.2, Biagetti S.3, Alfonsi S.3, Fallopi L.1, Bianconi M.1, Bittoni A.2, Francoletti M.2, Bearzi I.3, Cascinu S.2

1Scuola di Specializzazione in Oncologia, Università Politecnica delle Marche, Ancona; 2Clinica di Oncologia, 3Anatomia Patologica, AO Ospedali Riuniti, Università Politecnica delle Marche, Ancona

Previous data suggested that HER-3 positive, K-RAS wild-type colorectal tumours are resistant to anti-EGFR monoclonal antibodies. However a not negligible proportion of HER-3 negative colorectal cancer patients still does not seem to benefit from such a treatment.

Integrins up-regulation may mediate an alternative survival pathway in HER-3 negative tumour cells by activation of PI3K-Akt. In particular an alpha-6 and beta-4 integrin altered expression has been demonstrated in HER-3 negative tumours and may be responsible of anti-HER treatment resistance. Our study evaluated the interaction between polymorphisms (SNPs) of alpha-6 and beta-4 integrins and clinical outcome in HER-3 negative, K-RAS wild type colorectal cancer patients receiving third-line irinotecan cetuximab.

HER-3 expression was evaluated by immunohistochemistry, whereas genotyping of alpha-6 (rs17664 G>A, rs2293649, A>G) and beta-4 (rs743554, C>T, rs8669, C>G, rs871443, T>C, rs9367, T>C) integrins was performed by real-time PCR. Among 128 K-RAS wild type metastatic colorectal cancer patients treated with third-line irinotecan cetuximab, 62 (48%) were HER-3 negative and were included in the present study. At univariate analysis the beta-4 rs8669, rs871443 and rs9367 polymorphisms correlated with both median progression-free survival and overall survival, whereas only the beta-4 rs8669 genotype showed a trend for a statistically significant correlation with response (partial remission rate for genotype G vs C/G/C = 20% vs 48%, p = 0.059). At multivariate analysis the only the same allelic variant of beta-4 (rs8669 G vs C/G/C) maintained an independent role in negatively influencing median PFS (HR = 0.13, 95% CI 0.051-0.35, p <0.0001) and OS (HR = 0.29, 95% CI 0.10-0.81, p <0.0001).

We believe that beta-4 rs8669 genotyping may help identifying a sub-group of HER-3 negative, K-RAS wild-type colorectal cancer patients less likely to benefit from anti-EGFR treatment. Our findings could be also relevant in planning future trials test-
ing treatment strategies against the integrins-activated molecular pathway.

B28 HIGH RESOLUTION MELTING ANALYSIS (HRMA) FOR KRAS MUTATIONAL STUDY IN METASTATIC COLORECTAL CANCER (mCRC) PATIENTS


“Department of Molecular and Clinical Endocrinology and Oncology, ᵇDepartment of Biomorphologic and Functional Sciences, University of Naples Federico II, Naples; ᵆCEINGE Biotechnologie Avanzate, Napoli

Background. Anti-EGFR monoclonal antibodies are restricted to KRAS wild-type (WT) metastatic colorectal cancer (mCRC) patients. Standard method for KRAS testing is direct sequencing that may yield false negative results because of genetic heterogeneity within the tumour sample. To overcome this limit, novel methods were developed. We evaluated the efficiency of high resolution melting analysis (HRMA) in identifying KRAS-mutant (MUT) tumours. HRMA is a highly sensitive and cost-effective screening method that identifies KRAS mutations even in a small fraction of alleles in a background of wild-type DNA. We analysed the therapeutic effects of cetuximab in direct sequencing tested WT patients, according to their HRMA mutational status.

Methods. We retrospectively considered 50 KRAS-WT mCRC patients (35 males, 15 females) at direct sequencing and treated with cetuximab containing chemotherapy. Median age was 61 years (range 29-77). Most (40%) patients had liver metastases and 24% had multi-organ disease. They received second or third-line cetuximab containing chemotherapy, with irinotecan (N = 25) or with combination regimen (22FOLFIRI and 3FOLFOX). Twenty-eight patients were treated in second-line and 22 in third-line. KRAS mutation status was reassessed in all patients using HRMA and these results were correlated with response rate (RR), progression-free (PFS) and overall survival (OS).

Results. Four (8%) patients were identified as KRAS mutated only by HRMA. RR of HRMA KRAS-WT patients was 28.3%. There was no response in HRMA KRAS-MUT patients. Disease control rate (responsive plus stable disease) was 58.7% in HRMA KRAS-WT patients and 25% in HRMA KRAS-MUT patients. No significant correlation was found between HRMA KRAS status and RR (p = 0.287) or disease control (p = 0.219). Median PFS (5.1 versus 2.5 months; HR = 0.34, p = 0.04) and OS (11.3 versus 3.2 months; HR = 0.11, p = 0.03) were significantly longer for HRMA KRAS-WT than for HRMA KRAS-MUT patients.

Conclusions. HRMA identified 8% more KRAS-MUT patients not responding to cetuximab-containing regimens, suggesting that HRMA may be more effective than direct sequencing in selecting patients for anti-EGFR antibodies.

B29 SAFETY AND RELATIVE DOSE INTENSITY IN STAGE III COLON CANCER PATIENTS TREATED WITH ADJUVANT FOLFOX4 REGIMEN

Sciaccia V.¹, Pistillucci G.¹, Ciorra A.¹, Cirino C.¹, Di Palma T.¹, Calabretta F.¹, Lugini A.², Rossi R.¹, Veltri E.¹

¹U.O. Oncologia Medica, Ospedale Santa Maria Goretti, Latina; ²U.O. Oncologia Medica, Ospedale San Camillo de Lellis, Rieti

Background and aims. Adjuvant FOLFOX-4 chemotherapy is a standard regimen for stage III and high risk stage II colon cancer. We have evaluated the safety of this regimen and how frequently chemotherapy is reduced or discontinued for toxicity in routine clinical practice.

Materials and methods. From January 2008 to December 2011 we treated 92 stage III colon cancer patients with adjuvant FOLFOX-4 regimen. Median age was 63 years (range 36-78), 60 pts were males and 32 females; all pts had ECOG PS 0-1. We assessed the completion of the prescribed adjuvant chemotherapy, dose reduction and oxaliplatin and fluorouracil dose intensity.

Results. All the pts were evaluable. Neuro- and hematotoxicity were the main causes of dose reduction or stop of only oxaliplatin or 5-fluorouracil and oxaliplatin. The main haematological side effects were: neutropenia grade 3 in 19 pts (20.6%) and grade 4 in 6 pts (6.5%), grade 3-4 thrombocytopenia in nine pts (10%). Oxaliplatin induced peripheral neurotoxicity was evaluated by subjective assessment according to National Cancer Institute Common Toxicity Criteria scale (clinician-rated): grade 2 and 3 toxicity was reported in 12 and 8 pts respectively (22%). Forty-three pts (46.7%) completed the 12 planned cycles without dose modification. The median number of FOLFOX4 cycles received at 100% of dose was ten; the median dosage of oxaliplatin was 36.1 mg per square meter per week across all cycles received. Median relative dose intensities of oxaliplatin and fluorouracil were 85% (range 31-100%) and 100% (range 66-100%) respectively with no differences by gender and age. Two pts interrupted oxaliplatin treatment for severe hypersensibility reaction after 9 and 10 cycles respectively and have continued with only De Gramont schedule.

Conclusions. Our retrospective study in unselected patients showed that in clinical practice the oxaliplatin planned dose intensity is less frequently administered for significant related toxicities, so a different schedule could be explored in colon cancer adjuvant treatment. Ongoing trials (ie TOSCA trial) to test whether 3 months of oxaliplatin-based adjuvant therapy are not inferior to 6 months of the identical therapy could show a new and less toxic standard treatment.

B30 BRAF VERSUS KRAS G12V MUTATION FOR PREDICTION OF OUTCOME TO CHEMOTHERAPY AND PROGNOSIS IN METASTATIC COLORECTAL CANCER (mCRC): A MULTICENTER, MATCHED-PAIR, CASE-CONTROL STUDY

Pietrantonio F.¹, Biondani P.¹, Venturini F.², Giacobbe F.², Perrone F.³, Villa F.², Ricci V.⁵, Di Bartolomeo M.¹, Cassingena A.², Pietrogiavanna L.², Amoroso V.⁶, Petrella M.C.⁷, Tessani A.¹, Nonnis D.⁶, de Braud F.¹

¹Medical Oncology Unit 1, Fondazione IRCCS, Istituto Nazionale dei tumori, Milano; ²Falck Division of Medical Oncology, Ospedale Niguarda Ca’ Granda, Milano; ³Pathology Unit, Fondazione IRCCS, Istituto Nazionale dei Tumori, Milano; ²Medical Oncology Unit, AO San Gerardo, Monza; ³Medical Oncology Unit, San Raffaele Scientific Institute, Milano; ⁵Medical Oncology Unit, Azienda Spedali Civili, Brescia; ⁶Medical Oncology Unit, Versilia Hospital, Lido di Camaiore
Background. In colorectal cancer (CRC), codon 12, 13 and 61 KRAS mutations are negative predictors of cetuximab or panitumumab efficacy in stage IV (Siena et al., J Natl Cancer Inst, 2009) and the G12V mutation is associated with worse prognosis in stage III (Andreyev et al., Br J Cancer, 2001). In the metastatic setting, the prognostic role of KRAS is still controversial and it has not been stratified by mutation subtypes, while BRAF mutation is consistently associated with poorer survival (Tran et al., Cancer, 2011). A matched-pair, case-control study was carried out to evaluate the prognostic role of BRAF versus KRAS G12V.

Methods. A total of 68 metastatic CRCs were treated with first-line chemotherapy at 5 Italian Institutions from 2002 to 2012 and included in this observational study. Patients were matched according to: Köhne prognostic score (Köhne et al., Ann Oncol, 2002), synchronous/metachronous disease and radical surgery of metastatic sites. All matched subjects were divided into two groups with the same clinical characteristics: 34 BRAF versus 34 KRAS G12V mutated. OS of the two groups was calculated from the date of start of first-line chemotherapy to death/last follow-up and compared with two-sided log-rank test.

Results. BRAF mutations were V600E in 30/34 (88%) cases, K601E in 2 (6%), K601N and D594A in 1 (both 3%). Matched subjects were classified according to Köhne prognostic score as good 42/68 (62%), intermediate 20/68 (19%) or poor 6/68 (9%); as synchronous 42/68 (62%) or metachronous 26/68 (38%); surgery of metastases was performed in 14/68 (21%). In 32 BRAF-mutated evaluable for response, 9 PR and 1 CR were observed (response rate 10/32, 31%). All three patients treated with triplet chemotherapy plus bevacizumab responded to treatment versus 24% of subjects treated less intensively (p = 0.02 by Fisher’s exact test). In 31 KRAS G12V evaluable patients, response rate (18 PR, 58%) was significantly higher than BRAF-mutant (p = 0.04). Overall survival was significantly longer in KRAS G12V as compared to BRAF-mutant patients (33 versus 16 months; HR = 2.47, 95% CI 1.27-4.60; p = 0.007).

Conclusions. In metastatic CRC, BRAF mutations are associated with chemoresistance and appear to exert a stronger negative prognostic effect than KRAS G12V mutation.

Background. Understanding the risk factors of colorectal cancer (CRC) is crucial to develop effective strategies for its prevention. Type 2 diabetes mellitus (DM) is associated with an increased risk of CRC and epidemiological studies identified a correlation between these diseases.

Aim. To evaluate prevalence of CRC in a cohort of caucasian patients with type 2 DM and the association with other variables known to be related with increased CRC.

Methods. We retrospectively evaluated 741 type 2 DM patients followed between 2000 and 2008 for CRC incidence. Patients were stratified based on gender, age, body mass index (BMI), alcohol and FANS assumption, family history for cancer, blood glycated hemoglobin, hypertension, hypertriglyceridemia, age at diabetes onset and disease duration, treatment with insulin, metformin, sulphonylureas, gliindes or other hypoglycemics.

Results. In our cohort mean age was 67±9.6 years (48.6% women) and mean BMI 29.9±5.4. Hypertension was present in 81.2% of patients and hypertriglyceridemia in 40.8%. Mean age at DM onset was 51.2±11.1 years, median duration of disease was 168 months (range 12-768) and mean blood glycated hemoglobin level was 7.6±1.4%. Patients were treated with insulin in 310 cases (41.8%), metformin in 485 (65.5%), sulphonylureas in 68 (9.2%), gliindes in 263 (35.5%) while 115 received other drugs. At a median follow-up of 132.5 months (range 33.3-175.7) 56 cases of cancer (prevalence 7.56%) occurred; among these 14 were CRC (prevalence 1.88%). Median duration of DM to CRC diagnosis was 156 months (range 1-768). At the univariate analysis older age (p = 0.001), and diabetes duration (p = 0.001) were related to higher risk of cancer, while metformin seemed to be protective (p = 0.058). In CRC patients, older age (p = 0.001) and diabetes duration (p = 0.001) were related to higher CRC risk, such as sulphonylureas therapy (p = 0.01).

Conclusions. CRC prevalence in our cohort of type 2 DM patients was higher compared to that from AIRTUM for southern Italy in 2006 (0.3%). Furthermore we hypothesize that sulphonylureas may play a role in CRC carcinogenesis altering the physiological insulin secretion.

B32 MANAGEMENT OF PATIENTS WITH COLORECTAL LIVER METASTASES: RESULTS OF BOLOGNA MULTIDISCIPLINARY TEAM (MDT) EXPERIENCE

Di Fabio F.1, Rojas Limpe F.L.1, Ercolani G.2, Pini S.1, Giampalma E.3, Castellucci P.2, Serra C.2, Pinna A.D.2, Goffi R.3, Martoni A.1, Pinto C.

1Medical Oncology Unit, 2Liver Surgery Unit, 3Radiology Unit, 4Nuclear Medicine Unit, 5Medicine Unit, S. Orsola-Malpighi Hospital, Bologna

Background. The main guidelines recommend sharing therapeutic strategy for patients with colorectal liver metastases among a multidisciplinary team. The aim of this study is to analyse the efficacy of multidisciplinary management of patients with colorectal liver metastases.

Methods. Since 2006 an MDT of various specialists (oncologists, radiotherapists, radiologists, nuclear physicians and hepatobiliary surgeons) from the Policlinico S. Orsola-Malpighi, Bologna, has met to discuss and plan therapy strategy for patients with hepatic metastases from colorectal cancer, as well as other types of malignancy. Data for the present analysis were extracted from a database collected prospectively.

Results. Between March 2006 and April 2012 a total of 173 patients were evaluated in 46 meetings, the median number of single case discussions was 2 (range 1-7). Primary tumours considered: 139 (80%) colon-rectum, 6 (3.5%) breast, 5 (2.9%) stomach, 4 (2.3%) hepatocarcinoma, 3 GIST (1.7%), 3 neuroendocrine tumours (1.7%), 3 (1.7%) pancreas, 3 biliary tract (1.7%), 2 endometrium (1.2%); 1 anus (0.6%), 1 oesophagus
Background. Patients older than 75 years of age are usually excluded from metastatic colorectal cancer (mCRC) studies based on a combination chemotherapy containing oxaliplatin. Our group conducted three phase II trials in elderly patients evaluating this strategy in recent years. An exploratory cohort of patients aged at least 75 years was included in this study.

Patients and methods. In all, 67 previously untreated patients were analyzed. Oxaliplatin was combined with capecitabine in two studies and with uracil-tegafur (UFT) plus leucovorin in the third study. In one of these, bevacizumab was also added to chemotherapy. The median age of treated patients was 77 years (range 75-89 years), 38 patients (57%) were men, and everyone had a good performance status (0 to 1). Patients had widespread disease, with the most frequent distant sites including liver, lung, and peritoneum.

Results. All patients were assessable for toxicity and for response to treatment. The observed overall response rate was 45% (95% CI 32.5%-57.0%), comparable to younger patients [51% (95% CI 38.8-62.6%), p = .49]. The estimated median overall survival (OS) time was 19.3 months (95% CI 13.8-24.7 months), and median progression-free survival (PFS) time was 8.7 months (95% CI 7.6-9.7 months). These results do not seem to differ from those in younger patients <75 years. The most common grade 3-4 adverse events included diarrhea, fatigue, peripheral neuropathy, and neutropenia. In any case, the toxicity was never statistically different from that in younger patients.

Conclusions. The efficacy of oxaliplatin-based treatment was maintained in patients ≥75 years. This study demonstrates that a strategy involving a multi-agent chemotherapy could perform well in this population.

B33 OXALIPLATIN-BASED CHEMOTHERAPY IN PATIENTS ≥75 YEARS OLD WITH METASTATIC COLORECTAL CANCER: AN EXPLORATORY COHORT OF THREE PHASE II STUDIES

Rosati G.¹, Cordio S.², Aprile G.³, Butera A.⁴, Avallone A.⁵, Tucci A.⁶, Novello G.⁷, Caputo G.⁸, Reggiardo G.⁹, Bordonaro R.²

¹Medical Oncology Unit, S. Carlo Hospital, Potenza; ²Medical Oncology Unit, Garibaldi Hospital, Catania; ³Department of Medical Oncology, University Hospital, Udine; ⁴Medical Oncology Unit, S. Giovanni di Dio Hospital, Agrigento; ⁵Department of Gastrointestinal Medical Oncology, National Cancer Institute, Napoli; ⁶Medical Oncology Unit, Civil Hospital, Nola; ⁷Medical Oncology Unit, Vittorio Emanuele Hospital, Catania; ⁸Medical Oncology Unit, Civil Hospital, Cataltigrone; ⁹Biostatistic Unit Medi Service, Genoa

Background. Patients older than 75 years of age are usually excluded from metastatic colorectal cancer (mCRC) studies based on a combination chemotherapy containing oxaliplatin. Our group conducted three phase II trials in elderly patients evaluating this strategy in recent years. An exploratory cohort of patients aged at least 75 years was included in this study.

Patients and methods. In all, 67 previously untreated patients were analyzed. Oxaliplatin was combined with capecitabine in two studies and with uracil-tegafur (UFT) plus leucovorin in the third study. In one of these, bevacizumab was also added to chemotherapy. The median age of treated patients was 77 years (range 75-89 years), 38 patients (57%) were men, and everyone had a good performance status (0 to 1). Patients had widespread disease, with the most frequent distant sites including liver, lung, and peritoneum.

Results. All patients were assessable for toxicity and for response to treatment. The observed overall response rate was 45% (95% CI 32.5%-57.0%), comparable to younger patients [51% (95% CI 38.8-62.6%), p = .49]. The estimated median overall survival (OS) time was 19.3 months (95% CI 13.8-24.7 months), and median progression-free survival (PFS) time was 8.7 months (95% CI 7.6-9.7 months). These results do not seem to differ from those in younger patients <75 years. The most common grade 3-4 adverse events included diarrhea, fatigue, peripheral neuropathy, and neutropenia. In any case, the toxicity was never statistically different from that in younger patients.

Conclusions. The efficacy of oxaliplatin-based treatment was maintained in patients ≥75 years. This study demonstrates that a strategy involving a multi-agent chemotherapy could perform well in this population.

B34 XELOX AND BEVACIZUMAB AS FIRST-LINE TREATMENT IN FIT ELDERLY PATIENTS OVER 70 YEARS OF AGE WITH METASTATIC COLORECTAL CANCER: THE BOXE STUDY

Ferrara D.¹, Bilancia D.¹, Avallone A.², Aprile G.³, Butera A.⁴, De Pauli F.³, Reggiardo G.⁵, Rosati G.¹

¹Medical Oncology Unit, S. Carlo Hospital, Potenza; ²Department of Gastrointestinal Medical Oncology, National Cancer Institute, Naples; ³Department of Medical Oncology, University Hospital, Udine; ⁴Medical Oncology Unit, S. Giovanni di Dio Hospital, Agrigento; ⁵Biostatistic Unit Medi Service, Genoa

Background. The addition of bevacizumab to oxaliplatin-based chemotherapy significantly improved progression-free survival (PFS) in patients with metastatic colorectal cancer (MCRC). However, clinical trials have been conducted primarily in younger patients with only a small proportion of elderly patients. Moreover, an increased risk of arterial thromboembolic events has been observed in some trials in older patients. This phase II study was designed to evaluate the efficacy and safety of XELOX (capecitabine plus oxaliplatin) plus bevacizumab in fit patients over 70 years of age with MCRC.

Methods. Treatment consisted of bevacizumab 7.5 mg/kg and oxaliplatin 130 mg/m² on day 1, plus capecitabine 1000 mg/m² twice daily on days 1-14, every 3 weeks up to a maximum of 8 cycles. Patients with a radiological response or stable disease could be maintained on bevacizumab monotherapy up to progressive disease. Patients were followed by a quality of life (QoL) assessment with EORTC-QLQ-C30 questionnaire. The primary study endpoints were safety and response rate.

Results. A total of 44 patients were recruited. In an intention-to-treat analysis, the overall response rate was 52% (95% CI 37%-68%), with 86% of patients achieving disease control. Me-
dian PFS and overall survival were 11.5 months (95% CI 10.0-12.9 months) and 19.3 months (95% CI 16.5-22.1 months), respectively. Four patients (9%) underwent liver metastasectomy with curative intent. In all, 10 patients (23%) had grade 3/4 adverse events (AEs), the most common being diarrhea (9%), neutropenia (7%), peripheral neuropathy (7%), and stomatitis (7%). This did not result in QoL impairment. No patients died because of treatment-related AEs. The low incidence of bevacizumab-associated AEs (hypertension, thromboembolic events and gastrointestinal perforation) was not consistent with that of previous reports in elderly patients.

Conclusions. XELOX plus bevacizumab is effective and has a manageable tolerability profile with QoL maintenance when administered to fit elderly patients with MCRC.

**B35 BEVACIZUMAB (B) COMBINED TO CHEMOTHERAPY FOR FIRST-LINE TREATMENT OF ELDERLY PATIENTS WITH ADVANCED COLORECTAL CANCER (CRC): RESULTS FROM A LARGE COMMUNITY-BASED ITALIAN OBSERVATIONAL STUDY**


1Azienda Ospedaliero-Universitaria, Udine; 2Azienda Universitaria Pisana, Istituto Toscano Tumori, Pisa; 3Istituto Oncologico Veneto, IRCCS, Padova; 4Ospedale S. Carlo, Potenza; 5Ospedali Riuniti, Ancona; 6Istituto Nazionale Tumori, Napoli; 7Ospedale Garibaldi, Catania; 8CRO, IRCCS, Aviano (PN); 9Ospedale S. Orsola-Malpighi, Bologna

**Background.** It is accepted that elderly patients with advanced CRC should be treated upfront with B combined to chemotherapy, although recent analyses demonstrated safety for its use. Aim of this large observational cohort study was to investigate the efficacy and safety of this strategy in the national clinical practice.

**Methods.** Two hundred and fifteen elderly patients from 9 Italian centers who received first-line B combined with chemotherapy were enrolled. Demographics and comorbidities were captured, along with efficacy and toxicity results. Pre-defined endpoints were RR, PFS, OS and safety. Survival curves were generated with Kaplan-Meier methodology.

**Results.** Median age was 72 (66-84) and 192 patients were over 69 years. PS was 0-1 in the large majority (96%). Comorbidities at study entry were noted in 153 pts (72%): cardiovascular (including hypertension) in 107 (49%), diabetes 32 (15%), respiratory 15 (7%), endocrine 10 (5%), neurological 10 (5%), renal 7 (3%), and other diseases 51 (24%). Comprehensive geriatric evaluation with ADL, IADL and CIRS scores was available for only 64 pts (29%) reporting median values of 6, 8 and 20 respectively. Overall, 66 patients were completely fit, while 149 had at least one comorbidity. Bevacizumab was prescribed combined to 5-FU alone (i.v. or oral) in 27 patients (12.6%), oxaliplatin-based doublet in 75 (35.2%) or irinotecan-based combination in 111 (52.1%). Eighty-one pts had chemotherapy dose reduction, and 23 interrupted B before progression. Disease control was achieved in 86%, median PFS was 8.8 months, and median OS was 18.9 months. After response or disease stabilization, 76 pts (35%) were maintained on B alone or B plus 5-FU. Main toxicities were neutropenia (44%), anemia (37.5%), diarrhea (40.8%), mucositis (25.8%) and hand-foot syndrome (14.1%). Sensorial neurotoxicity was frequent among pts receiving oxaliplatin. Specific B-induced toxicities were induced or worsened hypertension in 48 pts (22.5%), proteinuria in 24 (11%), and venous or arterial thromboembolism in 16 (7.5%). No differences in bone marrow toxicity were noted among fit versus vulnerable patients. Systemic and gastrointestinal toxicities were also similar, except for mucositis (p = 0.003). Specific antiangiogenic side-effects were slightly more frequent among those with comorbidities, with a higher rate of hypertension (p = 0.045) and proteinuria (p = 0.005), but no venous or arterial thromboembolic events.

**Conclusions.** To treat elderly CRC pts with B and chemotherapy is safe and major efficacy endpoints did not differ from expected, even if elderly patients with comorbidities may suffer higher rate/grade of specific toxicities. Geriatric evaluation is underused in the common practice and better tools are required to select elderly to be treated with antiangiogenics.

**B36 RANDOMIZED, DOUBLE-BLINDDED, MULTICENTER, PHASE III STUDY OF FOLFOX4 PLUS PREGABALIN OR FOLFOX4 PLUS PLACEBO FOR PATIENTS WITH EARLY STAGE COLORECTAL CANCER: AN INTERIM ANALYSIS**

De Tursi M., Carella C., Adamo P.F., Garufi C., Tortora G., Ficorella C., Iacobelli S. on behalf of CINBO (Consorzio Interuniversitario Nazionale per la Bio-Oncologia)

**Background.** Peripheral neuropathy is the main oxaliplatin dose-limiting toxicity in colorectal cancer treatment. To date, no treatment has proven to be effective in prevention of this toxicity. Aim of our study was to evaluate efficacy and safety profile of pregabalin (Lyrica®) given postoperatively along with chemotherapy in patients with stage II or III colorectal cancer. The present interim analysis assessed feasibility, compliance and complications of the combined treatment.

**Methods.** From January 2007 to December 2009, a total of 122 pts over a planned sample size of 240 patients were randomly allocated to receive postoperatively FOLFOX4 every 2 weeks for 24 weeks. Pregabalin started at the dose of 75 mg PO bid for 2 weeks and, if well tolerated, dose was escalated up 150 mg until the end of treatment. The primary endpoint was incidence of moderate to severe neuropathy (>G2) assessed according the NCI-CTC criteria.

**Results.** Demographic data were similar between groups and there were few protocol violations (5-6 per cent). There was a trend toward lower incidence of neuropathy (>G2) in one of the two groups (28% vs 42%, p = 0.07). There were no significant differences in grade 3-4 chemotherapy induced hematologic toxicity between groups (12% vs 14%; p = 0.26). The most common non-hematologic toxicities were somnolence (10%), dry mouth (9%) and constipation (5%).

**Conclusions.** Treatment compliance was acceptable and toxicity expected. No reason for early stop of the study was recognized.

**B37 NOTCH AND DLL4 EXPRESSION IN BEVACIZUMAB-TREATED COLON CANCER PATIENTS**
Background. In order to investigate mechanisms of resistance to angiogenesis inhibitors, we correlated Delta-like 4 ligand (DLL4) and Notch expression with response and survival in a series of bevacizumab treated colon cancer patients. DLL4-mediated Notch signalling has recently emerged as an attractive target for angiogenesis-based cancer therapies, given that DLL4 is an important component of Notch-mediated stem cell self-renewal and vascular development. DLL4-induced Notch signalling mediates tumour-resistance to anti-VEGF therapy by inducing the formation of large vessels and activating multiple pathways in tumours.

Methods. Notch and DLL4 expression was evaluated by immunohistochemistry (IHC) on 49 primary colon cancer patients enrolled within randomized clinical trials assessing first-line bevacizumab plus chemotherapy.

Results. Notch positivity was localized to the cytoplasm of malignant epithelial cells. In all, 7 out of 46 (15%) evaluable primary tumours had a high Notch expression. Response rate was available in 44 cases (6 cases with high and 38 with negative Notch expression). Four of the 6 cases (67%) with high Notch expression had progressive disease compared with 2/38 (5%) Notch negative cases (p = 0.001). Median progression-free survival (PFS) was 2.4 months for patients with high Notch expression compared with 10.0 months for Notch negative cases. Membranous and/or cytoplasmic DLL4 immunoreactivity of tumour vessels was observed in 14/31 (45%) evaluable colon cancers. DLL4 expression was observed in 3/4 cases who had PD. Patients with negative DLL4 expression showed a median PFS of 10.97 months compared with 8.97 months for patients with DLL4 expression.

Conclusions. Clinical trials investigating the therapeutic efficacy of bevacizumab in colon cancer did not explore the impact of DLL4-Notch pathway on response and clinical outcome. Notwithstanding the limited power of the present analysis, these data seem to suggest that high Notch and DLL4 expression might be involved in tumour resistance to bevacizumab. Updated results on a wider cohort of patients will be presented at the meeting.

**B38 HYPERMETHYLATION OF THE KEAPI GENES ASSOCIATED WITH DISEASE PROGRESSION IN METASTATIC COLORECTAL PATIENTS TREATED WITH CHEMOTHERAPY**

Parrella P.1, Maiello E.2, Barbano R.1, Latiano T.P.2, Pasculli B.1, Muscarella L.A.1, la Torre A.1, Fazio V.M.1

1Laboratory of Oncology, 2Department of Oncology, 3Breast Unit, “IRCCS Casa Sollievo della Sofferenza”, San Giovanni Rotondo, FG

**Background.** Aberrant methylation of the KEAPI (Kelch-like ECH-associated protein 1) gene promoter is emerging as a main mechanism of dysregulation of the Nrf2 (nuclear factor-erythroid 2-related factor 2) which plays a pivotal role in the cellular response to oxidative stress. Under basal conditions, Nrf2 is retained in the cytoplasm by the binding with Keap1 and it is maintained at a reduced level by the Keap1-dependent ubiquitination and proteasomal degradation systems. Reduced Keap1 expression by promoter aberrant methylation allows Nrf2 to translocate in the nucleus and to activate the detoxification pathway leading ultimately to drug resistance.

**Materials and methods.** We determined KEAPI promoter methylation status in 50 metastatic colorectal cancer (CRC) and 9 normal colonic mucosa samples by using quantitative methylation specific PCR in real time (QMSP). The median age of the patients cohort was 65 (IQR 57-74) years. At diagnosis 12 patients were staged Duke D and 38 were staged as Duke C. As first-line treatment the FOLFOX or FOLFIRI therapeutic schemes were used.

**Results.** Methylation was detected in 20 out of 50 CRC (40%) and methylation levels were significantly higher in tumour samples (median 0.65, IQR 0.8-0.28) as compared with normal colonic mucosa (median 0, IQR 0-0.08) (p = 0.03). Tumours from patients who experienced disease progression had significantly higher methylation levels (median 0.53; IQR 0-7.61) as compared with patients showing partial response (median 0, IQR 0-2.21) or disease stability (median 0, IQR 0-0) (p = 0.03 Kruskall Wallis Test).

**Conclusions.** Our results suggest that Keap1 aberrant methylation is a frequent event in colorectal cancer and is associated with response to chemotherapeutic treatments. We are currently confirming this association on an extended cohort of 130 metastatic colorectal cancer patients.

**B39 COLON CANCER STEM CELL GENETIC PROFILE AS PREDICTOR OF RELAPSE IN RESECTED PATIENTS**

Giampieri R.1, Scartozzi M.1, Lorettelli C.1, Piva F.2, Mandolesi A.3, Del Prete M.1, Bittoni A.1, Maccaroni E.4, Faloppi L.2, Bianconi M.5, Bearzi I.3, Casinu S.1

1Clinica di Oncologia, AO Ospedali Riuniti, Università Politecnica delle Marche, Ancona; 2Dipartimento di Odontostomatologia e Scienze Cliniche, Università Politecnica delle Marche, Ancona; 3Anatomia Patologica, AO Ospedali Riuniti, Università Politecnica delle Marche, Ancona; 4Scuola di Specializzazione in Oncologia, Università Politecnica delle Marche, Ancona

Adjuvant therapy for resected colorectal cancer is usually proposed to patients with high relapse risk. Indeed, even if stage of the disease is the most important factor influencing this choice, it is also suspected that tumour biology could play a major role in increasing the risk. We tested a panel of genetic markers of stemness in resected Dukes stage B and C colorectal cancer and their impact on prognosis.

We performed k-means unsupervised clustering (K = 2) using the mRNA expression data of 66 genes. The algorithm divided the patients into two groups and most of the patients clustered in a manner consistent with relapse-free survival, defined as the time between primary surgery and first radiological sign of metastatic involvement or patients death, whichever came first.

A total of 62 patients were analysed and respectively 12 and 50 patients were allocated in group A and B, regardless of stage.
Thirty-six (58%) patients relapsed during the follow-up period (range 1.63-86.5 months). A significantly different median relapse-free survival was observed between the 2 groups (22.18 vs 42.85 months, p = 0.0296). Interestingly enough, even if group A had a worse outcome in terms of risk of relapse, a higher percentage of stage B patients could be found in this group (83%) when compared with the group B (52%). Among all genes tested, those with the higher “weight” in determining allocation into one of the two groups were CD44, ALCAM, DTX2, HSPA9, CCNA2, PDX1, MYST1, COL1A1 and ABCG2.

This analysis supports the idea that, other than stage, biological variables, such as expression levels of colon cancer stem cell genes, may be relevant in determining an increased risk of relapse in resected colorectal cancer patients.

B40 THE INCIDENCE OF VENOUS THROMBOEMBOLISM (VTE) IN METASTATIC COLORECTAL CANCER (mCRC) PATIENTS


SC Oncologia, AOU Maggiore della Carità, Novara

Background. VTE, that is deep vein thrombosis or pulmonary embolism, is a frequent complication in cancer patients and affects morbidity and mortality. We evaluated the prevalence of VTE in patients with histologically confirmed diagnosis of mCRC related to potential risk factors and overall survival (OS).

Materials and methods. We performed a retrospective analysis of 221 mCRC patients receiving chemotherapy with or without monoclonal antibodies, according to guidelines. We evaluated the incidence of VTE in relation to: gender, age, tumour grade, concomitant antiplatelet therapy and/or anticoagulation, concomitant treatment with bevacizumab or capicitabine, history of thromboembolic disease, chronic venous disease, cardiovascular disease, traumatic disease, use of erythropoiesis stimulating agents (ESAs), presence of central venous catheter (CVC), concomitant radiotherapy (RT) on primary tumour or metastatic sites.

Results. 33/221 patients (14.93%) experienced a VTE event. Of these, 12/33 (36.3%) received bevacizumab and 19/33 (57.5%) capicitabine. 11/33 (33%) had a history of chronic venous disease, 28/33 (84.8%) had a CVC, 3/33 (9%) were treated with ESAs, 12/33 (36.3%) had cardiovascular disease, 7/33 (21.2%) had experienced VTE prior to cancer diagnosis, 11/33 (33%) received RT, 1/33 (3%) developed VTE after trauma. Two of the risk factors analyzed were statistically significant for the occurrence of VTE: chronic venous disease and history of thromboembolic disease. The use of bevacizumab or capicitabine did not increase the incidence of VTE (p = 0.464). The median OS was 34.48 months, in VTE subgroup was 29.46 months, without significant difference between the two groups (p = 0.49). In the VTE subgroup, no difference was found in survival between patients undergoing treatment with or without bevacizumab (p = 0.95).

Conclusions. According to our analysis, mCRC patients with a history of thromboembolic disease or chronic venous disease have a higher risk of developing VTE during therapies. These patients may benefit from prophylactic therapy with low-molecular-weight heparin to prevent the VTE onset. These data need to be validated by larger studies.

B41 GENERATION OF TUMOUR-SPECIFIC CYTOTOXIC T-LYMPHOCYTES SUITABLE FOR ADOPTIVE IMMUNOTHERAPY FROM PERIPHERAL BLOOD OF ADVANCED COLORECTAL CANCER PATIENTS

Carluccio S., Delbuè S., Ferrante P., Bregni M.

University of Milan; Ettore Sansavini Health Science Foundation, Lugo; Azienda Ospedaliera Ospedale di Circolo, Busto Arsizio

Introduction. Adoptive cell transfer (ACT) immunotherapy is based on the selection of tumour-reactive lymphocytes from tumour-infiltrating lymphocytes, their ex-vivo activation and numerical expansion, and reinfusion to the autologous tumour-bearing patient after a lymphoablative chemotherapy. Promising results have been achieved in metastatic melanoma (Dudley et al., 2005) and other solid tumours as nasopharyngeal carcinoma and soft-tissue sarcoma (Comoli et al., 2005). In an effort to adapt the feasibility of this strategy to other solid tumours, namely advanced colorectal cancer, we aimed to obtain large numbers of autologous anti-tumour-specific cytotoxic T lymphocytes (CTL) generated by stimulation of patients peripheral blood mononuclear cells with dendritic cells pulsed with apoptotic tumour cells.

Materials and methods. Forty-nine patients affected by colorectal carcinoma were enrolled in the study. Tumour biopsies were obtained at surgery, together with 100 mL of heparinized peripheral blood upon written informed consent. Tumours were dissociated to a single-cell suspension and cultured in CellGro medium (CellGenics) supplemented with 20% FBS, in order to obtain tumour cell line for every patient. Dendritic cells (DCs) were generated from previously separated PBMCs, using a positive selection of CD14+ cells, cultured in presence of IL-4 and rhGM-CSF. Anti-tumour CTLs were elicited using DCs as antigen-presenting cells, autologous apoptotic tumour cells as source of antigens, and CD8+ -enriched effectors, with weekly stimulation. To evaluate the cytotoxic activity of CTLs, IFN-gamma secretion was assessed by ELISPOT.

Results. Tumour cell lines and dendritic cells were successfully obtained from 12 out of 49 patients. To date ELISPOT was performed for two patients: strong IFN-gamma secretion was detected at the third, fourth and fifth stimulation for one patient, and weakly at the third stimulation for the other patient.

Conclusions. Our preliminary data show that generation of tumour-specific cytotoxic T lymphocytes suitable for ACT immunotherapy is feasible from peripheral blood in patients with colorectal cancer.

Sponsored by Umberto Veronesi Foundation.

B42 CHEMOKINE RECEPTOR CXCR4: WHAT IS ITS ROLE IN GASTROINTESTINAL CANCER?

Lombardi L.1, Tavano F.2, Piepoli A.2, Di Maggio G.1, Latiano T.P.1, Nanni L.1, Andriuli A.2, Di Sebastian P3, Maiello E.1

1Department of Oncology, 2Department and Laboratory of Gastroenterology, 3Surgical Unit, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo (FG)
**Introduction.** Multiple metastases are the predominant cause of colorectal cancer (CC) and pancreatic cancer (PC) related mortality. Chemokines receptors have been implicated in cancer metastatic process by directing the migration of tumour cells to sites of metastases. However, their clinical relevance in gastrointestinal cancer has not been defined. The aim of our study was to evaluate the possible role of CXCR4 as prognostic factor in CC and PC.

**Materials and methods.** Quantitative determination of CXCR4 in serum samples collected before and after surgery from 36 CC and 23 PC patients with adjuvant (Ad) or metastatic (Meta) disease (19 Ad- and 17 Meta-CC; 15Ad-PC and 8 Meta-PC) and from 31 healthy controls (HC) enrolled as controls group was performed by means of ELISA. Relative expression levels of CXCR4 in matched-pairs of tumour and adjacent normal tissue samples, collected from the same 36 CC and 15 Ad-PC patients, were determined by means of qRT-PCR using the Quantifast SYBR Green PCR kit.

**Results.** Compared to HC, preoperative CXCR4 serum levels were increased in both CC and PC patients. Postoperative serum levels were higher than those observed preoperatively, in 42% and 47% of patients with Ad- and Meta-CC, respectively. Conversely, in 53% and 50% of patients with Ad- and Meta-PC, CXCR4 serum levels decreased after surgical resection. Furthermore, higher levels of CXCR4 were associated with advanced stages in PC with lymph nodes insolvent. In addition, CXCR4 was over-expressed in tumour compared to normal tissue in 42% and 41% of patients with Ad- and Meta-CC, and in 73% of patients with Ad-PC. In relation to clinical phenotype, all these patients had stage T3N1 disease in both diseases.

**Conclusions.** Our data showed that CXCR4 levels may be associated with tumour stage and disease progression in CC and PC patients. Further studies with larger samples size might confirm the role for CXCR4 as prognostic factor and/or marker of patients response to therapy.

---

**B44 AN EXPLORATORY ANALYSIS OF AMPK AND ACC ACTIVATION IN COLORECTAL PRIMARY TUMOURS AND THEIR CORRESPONDING METASTASES**

Griggiuolo G.1, Zulato E.2, Digrasla L.3, Mescoli C.4, Bergamo F.1, Esposito G.2, Nardin M.3, Mioranza E.1, Zago G.1, Lonardi S.2, Indraccolo S.2, Rugge M.3, Zagonel V.2

1U.O. Oncologia 1, Istituto Oncologico Veneto, IRCSS, Padova; 2Sezione di Oncologia e Immunologia, Università degli studi di Padova, Padova; 3Radiodiagnostica Oncologica, Istituto Oncologico Veneto, IRCCS, Padova; 4Istituto di Anatomia Patologica, Università degli Studi di Padova, Padova

**Background.** AMPK is a well known oncosuppressor, with prognostic significance in many neoplasms; it acts as a central metabolic sensor, activated in energy-stress conditions. ACC is a central enzyme in cell metabolism activated through phosphorylation by AMPK. In pre-clinical models AMPK activation level correlates with necrotic response when tumours are treated with bevacizumab. Our goal was: 1) to evaluate the concordance of these markers’ activation in primary tumours and corresponding metastases, 2) to investigate their correlation with clinical data, in particular radiological response to FOLFIRI. Results. This retrospective study analyzed histological pretreatment material from 32 patients with mCRC treated with FOLFIRI-bevacizumab to evaluate AMPK and ACC activation in primary CRC and its metastases using immunohistochemistry. The intensity was scored from 0 (negative) to 3 (intense), and then dichotomized in low (0-1) and high (2-3) activation categories. pAMPK and pACC intensity scores in primary tumours and metastases were compared using Spearman’s correlation test. Radiological response has been going to be evaluated using both RECIST and morphologic criteria (Chun Criteria) (not available at time of writing).

**Results.** pAMPK was defined high in 20 (63%) primary and in 21 (66%) of the corresponding metastases while pACC in 23 (72%) primary tumours and 19 (59%) metastases. As attended from biological knowledge, AMPK and ACC activation correlat-
showed that chemotherapy impacts significantly on the risk of unplanned presentation within 15 days (OR 3.8, 95% CI 1.4-10.2) and 21 days (OR 3.8, 95% CI 1.4-10.2) since last treatment. Risk of presentation was not affected by receiving chemotherapy within 7 days (OR 0.8, 95% CI 0.4-1.5). Trend of risk is depicted in the figure below.

Conclusions. Advanced CRC outpatients exposed to systemic chemotherapy often reported symptoms or toxicities, that clustered in the 2nd and 3rd week after treatment and caused unplanned presentations. Also, some delay between the onset of symptoms and the unplanned presentation may be hypothesized. To early recognize and effectively treat cancer symptoms or treatment-related toxicities may be cost- and time-saving, improving the management of outpatients unplanned presentations.

B45 ASSOCIATION BETWEEN CHEMOTHERAPY AND RISK OF UNPLANNED PRESENTATION IN COLORECTAL CANCER (CRC) PATIENTS. A CASE-CROSSOVER STUDY


Department of Medical Oncology, University Hospital of Udine

Background and aim. Management of unexpected events is part of the strategy of cancer patients care. Cancer outpatients frequently have unplanned presentations particularly within the first few weeks after receiving chemotherapy. This study sought to identify an association of exposure to chemotherapy with risk of unplanned presentation in a population of CRC pts.

Methods. Retrospective data were collected for CRC outpatients who presented to our acute oncology clinic between October 1, 2006 and September 30, 2009. Demographic, clinical and treatment information was collected, including: reason for presentation, treatment setting, ECOG PS, comorbidities, chemotherapy regimen and cycles received. A case-crossover design was applied to assess the relationship between transient exposures to a trigger event (chemotherapy) and the onset of an acute outcome (unplanned presentation).

Results. During the study period, 229 CRC pts made 469 unplanned visits. Most of pts (median age 70 yrs) had PS 0-1 and advanced stage. 52% of pts reported at least 3 symptoms at the time of unplanned presentation. Pain, fatigue and anorexia were reported frequently. 72% of unplanned presentations occurred within 30 days since last chemotherapy. The case-crossover study showed that chemotherapy impacts significantly on the risk of unplanned presentation within 15 days (OR 3.8, 95% CI 1.4-10.2) and 21 days (OR 3.8, 95% CI 1.4-10.2) since last treatment. Risk of presentation was not affected by receiving chemotherapy within 7 days (OR 0.8, 95% CI 0.4-1.5). Trend of risk is depicted in the figure below.

Conclusions. Advanced CRC outpatients exposed to systemic chemotherapy often reported symptoms or toxicities, that clustered in the 2nd and 3rd week after treatment and caused unplanned presentations. Also, some delay between the onset of symptoms and the unplanned presentation may be hypothesized. To early recognize and effectively treat cancer symptoms or treatment-related toxicities may be cost- and time-saving, improving the management of outpatients unplanned presentations.

B46 IRINOTECAN PLUS CAPECITABINE (XELIRI) AS SECOND-LINE CHEMOTHERAPY IN ELDERLY PATIENTS WITH K-RAS MUTATED METASTATIC COLORECTAL CANCER: RESULTS OF A MONOCENTRIC PHASE II STUDY

Rozzi A.1, Corona M.1, Nardoni C.1, Falbo P.T.1, Ziparo V.2, Mercantini P.2, Lanzetta G.1

1 Clinical Oncology Unit, Istituto Neurotraumatologico Italiano (I.N.I.), Grottaferrata (Rome); 2 Surgical and Medical Department of the Clinical Sciences, Biomedical Technologies and Translational Medicine, Sant’Andrea Hospital, Faculty of Medicine and Psychology, University of Rome “La Sapienza”

Background. Elderly pts are generally underrepresented in clinical trials. Few data exist about the role of second-line chemotherapy in older pts with K-RAS mutated metastatic colorectal cancer (MCRC). In this study we evaluated safety and efficacy of irinotecan plus capecitabine as second-line chemotherapy in elderly pts (>70 yrs) with MCRC.

Patients and methods. From November 2008 to September 2011 we consecutively recruited twenty-one elderly patients with K-RAS mutated pretreated MCRC. Mean characteristics of pts were as follows: M:F = 13:8, median age 74 yrs (range 72-81), median ECOG PS 1 (range 0-1), median number of metastatic sites 2 (range 1-4). In metastatic setting, as first-line treatment, fifteen pts (71%) received FOLFOX4 plus bevacizumab regimen while four pts (29%) progressed after FOLFOX4 only. Capecitabine 2000 mg/m2/day dd.1 → 14 q21d plus irinotecan 250 mg/m2 q21d were administered until appearance of unacceptable toxicity or progressive disease.

Results. To date, all pts are evaluable for efficacy and toxicity. No CRs were observed. Five pts (24%) had PR, six pts (29%) showed SD with a disease control rate (DCR) of 53%. Ten pts (47%) experienced progressive disease. Median progression-free survival (mPFS) was 4.2 months (range 2.4-7.6 months) with a median overall survival (mOS) of 9.1 months (range 4.1-12.6 months).

Toxicity was substantially acceptable. No G4 haematological toxicities were observed: five pts (24%) developed G3 neutropenia, four pts (19%) had G3 anemia. Among non-haematological toxicities, grade 3 diarrhoea, stomatitis and asthenia were reported in two (9%), three (14%) and five pts (24%), respectively.

Four pts (19%) developed G3 hand/foot syndrome. No treatment-related deaths were registered.

Conclusions. In spite of the small number of pts enrolled, capecitabine plus irinotecan, administered as second-line treat-
ment, demonstrated an interesting activity with an acceptable profile of toxicity in elderly pts with K-RAS mutated MCRC. This regimen could represent an interesting therapeutic option in this setting.

B47 TIME TO SKIN TOXICITY IS RELATED TO RESPONSE RATE IN PATIENTS WITH COLORECTAL CANCER TREATED WITH CETUXIMAB: A RETROSPECTIVE ANALYSIS


Dipartimento di Scienze Radiologiche, Oncologiche e Anatomopatologiche, Day Hospital Oncologico, Sapienza Università di Roma

Background. Cetuximab is a monoclonal antibody against EGFR that induces primarily skin toxicity. Skin toxicity has been related to progression-free survival in pts treated with cetuximab. This retrospective analysis aims to evaluate the correlation between time to onset of skin toxicity and the best response rate.

Methods. All patients treated with cetuximab from January 2007 to May 2012 were included in final analysis. Data about general patients characteristics and history of disease were collected. All patients had CT scan at baseline and every two-three months after the beginning of therapy. Response rate (RR) was evaluated according to RECIST criteria (v 1.1) and it was related to the time to skin toxicity (TTST: from the start of therapy to the diagnosis of any grade of skin toxicity). The relationship between RR and TTST was evaluated with one-sided Spearman test.

Results. Forty-nine pts were included in final analysis: 60% were male, the median age was 63 yrs (range 33-81). All patients were K-Ras wild type, 90% of patients received cetuximab as second or third-line of therapy. RR was: partial response in 34.6%, stable disease in 22.4% and progression of disease in 42.8% of patients.

94% of pts experienced skin toxicity: grade 1-2 in 87% and grade 3-4 in 13% of cases respectively. Median TTST was 14 days (95% CI 12.5-15.5). A negative relationship was found between TTST and RR (r = -0.247; p = 0.049). Different thresholds of TTST were tested to assess difference in RR (7, 14, 21 and 28 days), but not significant differences were found.

Conclusions. Most of patients develop skin toxicity during treatment with cetuximab. Even if the predictive role of skin toxicity is well known, in our population we report that as the earlier is the toxicity the greater is the response. This data should be confirmed with further trials to detect the specific time of skin toxicity onset predictive of the best response rate.

B48 CHEMOTHERAPY (CT) DISCONTINUATION IN PATIENTS WITH STAGE II-III COLON CANCER RECEIVING ADJUVANT FOLFOX4 REGIMEN. A MONOINSTITUTIONAL ANALYSIS

Chilelli M.G., Moscetti L., Signorelli C., Fab bri M.A., Padalino D., Nelli F., Primi F., D’Auria G., Ruggeri E.M.

Medical Oncology, Ospedale Belcolle, Viterbo

Background. Oxalplatin-based chemotherapy represents the standard adjuvant chemotherapy regimen for primary colon cancer Dukes stage C, however acute and long-term toxicity is not negligible.

Methods. We have retrospectively analysed the clinical data of 84 pts affected with resected colon cancer treated with adju vant FOLFOX-4 regimen from July 2004 to November 2011, to assess the side effects and the causes of discontinuation of adju vant CT.

Results. The main pts characteristics were: M/F 50/34 pts (59.5% 40.5%); median age 63.5 yrs (range 36-78 years); Dukes C2 49 pts, Dukes C3 19 pts, Dukes C1 2 pts, Dukes B2-3 14 pts. The total number of CT courses administered/planned were 942/1008 (93.4%), median number of cycles administered was 12 (range 3-12). Sixty patients have completed the treatment (71.4%) and 24 pts (28.6%) did not. The main reason for discontinuation was CT toxicity and treatment-related complication in 15 pts (62.5%): persistent grade (G) 2 peripheral neuropathy 6 pts, neutropenia 5 pts (1 G3 and 4 persistent G2), jugular thrombosis CVC related 2 pts, hypokaliemia G3, neutropenia G2, thrombocytopenia G1 pt, G4 allergic reaction to oxaliplatin 1 patient. Nine pts (37.5%) interrupted treatment because of refusal or decreased compliance. The CT dose has been reduced in 36 pts (42.8%) because of toxicity. The most frequent causes for reduction were: neutropenia 12 pts, diarrhea 11 pts, peripheral neuropathy 7 pts, thrombocytopenia 5 pts. Other toxicities for reduction were: nausea and vomiting 1 patient. Overall, the G3-4 toxicities occurred in 28/84 patients (33.3%). There was no treatment related death.

Conclusions. Our retrospective analysis confirms that the FOLFOX-4 regimen used in the adjuvant setting is safe and mostly well tolerated. The sample will be enlarged to perform a subset analysis for age and to evaluate the persistence of long term toxicity.

B49 ERC1, BAX AND TP53 FOR PROGNOSTIC ASSESSMENT IN ADVANCED COLORECTAL CANCER (CRC) PATIENTS RANDOMIZED TO FIRST-LINE UFT/LEUCOVORIN (LV) PLUS IRINOTECAN (TEGAFOX) VERSUS UFT/LV PLUS OXALIPLATIN (TEGAFOX)

Biondani P.1, Pietrantonio F.1, Perrone F.2, Milione M.2, de Braud F.1, Bertarelli G.3, Mariani L.3, Melotti F.2, Pelosi G.2, Cortinovis D.4, Scuro M.2, Tessari A.1, Di Bartolomeo M.1

1Medical Oncology Unit 1, 2Pathology Unit, 3Medical Statistics and Biometry Unit, Fondazione IRCCS, Istituto Nazionale dei Tumori, Milan; 4Medical Oncology Unit, AO San Gerardo, Monza

Background. In current, the choice of first-line chemotherapy in advanced CRC is not based on predictive biomarkers. In particular, apoptosis-related biomarkers may be related to chemosensitivity and Bax-negative CRC may display higher responses to irinotecan (Fallik et al., Cancer Res, 2003). Selected biomarkers including ERCC1, Bax and TP53 were assessed within a multicenter, phase II, randomized trial of TEGAFIRI vs TEGAFOX (Bajetta et al., Br J Cancer, 2007).

Methods. Tissue blocks were available for a subset of 49 pts enrolled from August 2002 to October 2004 at the coordinator center “Istituto Nazionale dei Tumori” of Milan. ERC1, Bax
and TP53 expression were assessed by immunohistochemistry, with dicotomic discrimination. Association with RECIST response by logistic univariate regression and corrected Chi square test; progression-free (PFS) and overall survival (OS) curves were plotted by the Kaplan-Meier method and compared by log-rank test. Correlation with PFS and OS by univariate and multivariate Cox’s proportional hazard model.

**Results.** Overall, response rate was 20/49 (41%), with 4 complete and 16 partial responses. Responses were significantly lower in Bax-positive as compared to Bax-negative [Odds Ratio (OR) = 0.26; p = 0.03 by logistic regression]; 25% (6/24) vs 56% (14/25) (p = 0.05 by Chi square). No significant difference in terms of outcome in TEGAFOX-treated pts; in TEGAFIRI subgroup, Bax-positive pts still displayed lower response rate versus Bax-negative (OR = 0.11; p = 0.03 by logistic regression): 18% (2/11) vs 67% (8/12) (p = 0.05 by Chi square). ERCC1 and TP53 failed to show correlation with response. In the overall population and both treatment subgroups, no significant differences were observed in terms of PFS and OS according to selected biomarkers. Outstanding data on TP53 gene sequencing by mean of polymerase chain reaction will be presented at the meeting.

**Conclusions.** Bax-negative CRC patients had significantly higher chance to respond to doublet UFT-based chemotherapy, in particular when irinotecan-based. Although Bax expression is associated with drug-induced apoptosis, a low protein level may identify a specific CRC phenotype with higher likelihood of response to irinotecan.

B50 PREOPERATIVE 5-FLUOROURACIL-OXALIPLATIN CHEMOTHERAPY AND RADIOTHERAPY IN LOCALLY ADVANCED RECTAL CANCER: LONG-TERM RESULTS OF A PHASE II TRIAL


°Medical Oncology Unit, ‡Radiotherapy Unit, †Surgical Clinic and Therapy Department, ¥Surgical Science Department, Pathology Department, Parma University Hospital; °Medical Oncology and Hematology Unit, Piacenza Hospital; †Clinical Oncology, Ancona University Hospital; *Oncology Unit, Bolognini-Seriate Hospital, Bergamo

**Purpose.** To evaluate activity, safety and long-term survival of preoperative 5-fluorouracil-oxaliplatin based chemotherapy and radiotherapy in locally advanced rectal cancer.

**Patients and methods.** We evaluated sixty-six patients with resectable, locally advanced (T3-4 and/or nodal involvement) adenocarcinoma of the rectum, treated with preoperative concomitant chemotherapy (oxaliplatin 60 mg/m² weekly and 5-fluorouracil 200 mg/m²d infused continuously for five days, over a period of five weeks) and radiotherapy (45 Gy in 25 fractions of 180 Gy, five days per week). Pathological complete response was the primary endpoint; safety, long-term survival and time to relapse were secondary endpoints.

**Results.** Fifty-five patients (83%) completed all five weeks of chemotherapy while only one patient did not receive the full planned dose of radiotherapy. Toxicity was moderate: no grade 4 adverse events were observed; grade 1-2 diarrhea was the most common adverse event (30%), that reached grade 3 in 3% of cases. Sixty-four patients were radically operated and sphincters preservation was possible in 82% of cases. The rate of pathological complete response was 16.5%; further 46.5% of patients experienced a partial disease response and 35.5% had stable disease. 5-fluorouracil-based adjuvant treatment was performed in 75% of cases; of these, 43% received FOLFOX regimen. At a median follow-up of 73.5 months, 23 patients (34.8%) had relapsed: two patients (3%) had a local recurrence; nineteen patients (28.8%) had distant metastases and two patients (3%) had both local and distant recurrences. After 5 years follow-up, 62% of patients did not show any recurrence disease and 70% was alive. Only for descriptive purposes we analyzed time to relapse and overall survival according to pathologic complete response: concerning time to relapse, the two groups (ypCR vs other responses) were statistically different (p = 0.047). No significant differences were found in terms of overall survival.

**Conclusions.** Preoperative chemoradiotherapy with 5-fluorouracil and oxaliplatin results effective, feasible and well tolerated, with positive results in terms of survival and local control of disease.

B51 PATTERN OF ADVERSE HISTOPATHOLOGICAL FEATURES AND RELATION WITH TUMOUR BUDDING IN STAGE II COLORECTAL CANCER: A MONO-INSTITUTIONAL STUDY


Colorectal Cancer Unit, Oncologia Medica 1, AOU San Giovanni Battista, Torino

**Introduction.** After surgical excision of stage II colorectal cancer it is fundamental to identify those patients with the highest risk of disease recurrence. A careful analysis of histopathological report can help in this operation. High histological grade (HG), lymphovascular invasion (LVI), (PI), pT4 and less than 12 lymph nodes sampled have been recognized as adverse prognostic factors from several guidelines1-3. The role of tumoral budding (TB) and the association of TB with other histopathological adverse features are not so clear; however an association of TB with LVI, lymph node involvement and survival has been documented in retrospective series4-6.

**Methods.** We reviewed the case histories of 95 consecutive patients with colorectal stage II cancer, referred to our division from 2008 to 2010. The pattern of the main histopathological adverse features (TB, LVI, PI, HG, pT4 and number of sampled nodes) in recurring patients has been analyzed.

**Results.** At a median follow-up of 2.8 years, 11 patients experienced recurrent disease: 9 had resected colon cancer and 2 resected rectal cancer; mean age at diagnosis was 77 years. Three patients occurred after adjuvant treatment. All patients had G2 histological grading. The other histopathological characteristics of recurrent patients are listed in the Table below.

<table>
<thead>
<tr>
<th>Recurrent patients</th>
<th>LVI +/PI+</th>
<th>LVI-/PI+</th>
<th>LVI+/PI-</th>
<th>LVI-/PI-</th>
</tr>
</thead>
<tbody>
<tr>
<td>High grade TB</td>
<td>1</td>
<td>0</td>
<td>4 (2*, 1+ , 10)</td>
<td>0</td>
</tr>
<tr>
<td>Low grade TB</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0 (4*)</td>
</tr>
<tr>
<td>Undetermined TB</td>
<td>(4*)</td>
<td>2 (1*)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

TB: tumoral budding; LVI: lymphovascular invasion; PI: perineural invasion; +: pT4; @ <12 sampled nodes; * patients that received adjuvant treatment.
Conclusions. The most frequent pattern seen in recurring stage II patients at our institution was pT3,G2, high grade TB/LVI+/PI-. Further studies are needed to better define the relative role of histopathological prognostic features.

References


B52 CHEMOTHERAPY FOR PATIENTS AGED 80 YEARS AND MORE: OUR EXPERIENCE

Leo S.1, Accettura C.2, Giampaglia M.1, Licchetta A.1, Misciagna G.2, Guerra V.2, Saracino V.1, Gambino A.1, Lupo L.3, Petrucciuti L.1, Lorusso V.1

1U.O. Oncologia Medica, “Vito Fazzi” Hospital, Lecce; 2U.O. Epidemiologia e Statistica, IRCCS Castellana Grotte (Ba)

Background. Elderly patients ≥80 years with advanced cancer must be allowed to balance the potential risks and benefits of treatment when deciding whether or not to have chemotherapy. A geriatric assessment in oncology practice could improve the cancer care management of elderly patients. Age is not a discriminating factor when treatment options are being considered but little is known about safety and outcomes among oncological patients aged 80 years and older who received anti-cancer treatment.

Methods. We conducted a retrospective review of patients ≥80 years old who received anti-cancer treatment in our center of Geriatric Oncology between September 2011 and 30 April 2012. All patients underwent screening for comprehensive geriatric assessment including: ADL, IADL, BMI, MMSE, and Charlson Comorbidity Index.

Results. Twenty-seven patients (median age 80.3, range 80-91) were identified. Colon-rectal cancer was the most frequent malignancy (13 pts), followed by lung (4), gynecological (4), pancreatic (2), prostatic (2), renal (1) and head and neck (1). The most common chemotherapeutic regimens were capecitabine (11 pts) followed by carboplatin (4), gemcitabine (3), docetaxel (2) and vinorelbine (2). In total, 4 pts were treated with doublet chemotherapy regimens and the “target therapy” was in 5 pts (ce-tuximab in 2, panitumumab in 2 and sunitinib in 1). The dose adjustment or dose reduction due to toxicity was not observed. The median progression-free survival was 10 months (range 2-144) and the median overall survival was 12 months (range 3-216). Nineteen patients, treated with chemotherapy, had a relapse of disease. Disease-free survival time was directly associated (Cox proportional hazard model) with performance status and being fit and inversely with body mass index, no relationship was found with Charlson comorbidity index; furthermore, the previous associations were not statistically significant (p >0.05).

Conclusions. Chemotherapy was well tolerated. Our data confirm that management of elderly patients suffering from cancer must take into account the global status of the patients, including medical, psychocognitive and social dimensions.

B53 LIVER MALIGNANCY: OUR EXPERIENCE

Jirillo A.2, Trojniak M.P.1, Imbevaro S.2, Rescigno P.2, Palozzo A.C.3

1Oncology Pharmacy Department, 2Evaluation and Introduction of New Drugs in Cancer Therapy Unit, Istituto Oncologico Veneto IRCCS, Padova

Background. Cetuximab is a potent inhibitor of epidermal

Conclusions. Using this software we provide accurate quantitative assessment of the response to bevacizumab based chemotherapy in liver mCRC showing a good correlation between imaging and laboratory values.

B54 EFFECTIVENESS OF CETUXIMAB IN REAL LIFE PRACTICE

Jirillo A.2, Trojniak M.P.1, Imbevaro S.2, Rescigno P.2, Palozzo A.C.3

1Oncology Pharmacy Department, 2Evaluation and Introduction of New Drugs in Cancer Therapy Unit, Istituto Oncologico Veneto IRCCS, Padova

Background. Cetuximab is a potent inhibitor of epidermal
growth factor receptor EGFR and its efficacy has been demonstrated for the treatment of metastatic colorectal cancer in large randomized trials.

Methods. A prospective observational study was run, using institutional data collected through web-based National Oncology registry, from July 2006 to March 2012 as part of the mandatory surveillance program. The registry allows prospective investigations and is a valuable data source for effectiveness evaluations. The patients affected by metastatic colorectal cancer with EGFR expression were treated with cetuximab in combination with irinotecan based on standard schedule until disease progression.

Results. In overall study population (91 patients, M55/F36), the median time to progression (TTP) and overall survival (OS) were 3.0 months CI 95% 2.4, 4.1 and 6.2 months CI 95% 4.3, 9.5, respectively. Twelve patients achieved partial response and 35 patients achieved stable disease, making the disease control rate 51.6%. Grade 1-2 rash and diarrhea were the most frequent adverse events.

The COX regression model in subgroup analysis showed significantly improved survival outcomes, in terms of TTP and OS, for patients with cetuximab in first/second-line therapy compared to third/fourth ones. Furthermore, a subgroup on sequential previous combination treatment of irinotecan followed by oxaliplatin has significantly prolonged TTP 3.5 months and OS 8.6 months compared to a subgroup on first oxaliplatin and second irinotecan with OS 6.4 months and TTP 2.7 months. Significantly improved response was reported for patients with drug related adverse events.

Conclusions. This post-marketing evaluation has revealed significantly better survival for first/second-line chemotherapy and for irinotecan followed by oxaliplatin based treatment schedule. In overall the effectiveness was inferior to the outcomes reported in the approval RCTs. The post-marketing studies in real life practice are needed in order to verify both effectiveness and safety in general population, testing for external validity of the randomized trials.

B55 SYSTEMATIC ANALYSIS OF HUMAN ONGENIC VIRUSES IN COLON CANCER

Fiorina L.1, Ricotti M.1, Vanoli A.1, Luinetti O.3, Paolucci S.2, Brugnatelli S.1, Pauli M.3, Pedrazzoli P.1, Baldanti F.2, Perfetti V.1

1 Dipartimento Onco-Ematologico, Sezione di Oncologia, 2 Dipartimento di Medicina Diagnostica e dei Servizi, Sezione di Virologia Molecolare, 3 Dipartimento di Medicina Molecolare, Sezione di Anatomia Patologica, Università di Pavia, IRCCS, Policlinico “San Matteo”, Pavia

Background. Tumour suppressor genes, DNA repair genes, and proto-oncogenes are involved in colon carcinogenesis. Because of its location, natural exposure to carcinogenic environmental factors may also play a role, and in this view, several studies investigated the presence of various viral DNA in primary tumour samples. However, results were conflicting and no association is widely accepted.

Methods. We undertook a systematic PCR-based DNA analysis of human viruses possibly involved in colon cancer, including polyoma virus (JCV, BKV and the recently identified Merkel cell polyoma virus, MCPyV), HPV, HTLV, HHV-8 and EBV. Archival primary tumour samples from 44 consecutive patients (stages B1: 7/44, 16%; B2: 15/44, 34%; C1: 2/44, 5%; C2: 15/44, 34%; D: 5/44, 11%; G2: 32/44, 73%; G3: 12/44, 27%) were evaluated. Quality of extracted DNA samples was verified by means of amplification of the housekeeping gene beta-2-microglobulin (DNA amplicons >10^3 copies). Positive controls included viral infected human samples from various pathologies and plasmid DNA.

Results. No evidence of DNA fragments from JCV (using primers covering different areas of large T-antigen), HPV, HTLV and HHV-8 (0/44, 0%) was detected, whereas 23/44 (52%) tumours were positive for EBV DNA.

Conclusions. Our data argue against a role for human polyoma, as well as for other major oncogenic viruses (HPV, HTLV and HHV-8) in colon cancer. On the other hand, a high frequency of EBV-DNA sequences was reported in colon carcinoma (52%). This observation focuses attention on EBV and deserves future investigations on its role in the pathogenic process.

B56 PRIMARY RESISTANCE TO FIRST-LINE BEVACIZUMAB IN METASTATIC COLORECTAL CANCER: IMPLICATIONS ON PROGNOSIS

Maccaroni E.1, ScartoZZi M.2, Giampieri R.2, Del Prete M.1, Bittoni A.2, Faloppi L.1, Bianconi M.1, Cavalcini S.2

1 Scuola di Specializzazione in Oncologia, Università Politecnica delle Marche, Ancona; 2 Clinica di Oncologia, AO Ospedali Riuniti, Università Politecnica delle Marche, Ancona

A role of bevacizumab after first-line failure is currently in study. We focused our analysis on patients who progressed directly under first-line bevacizumab and assessed if lack of effect could be managed with second-line chemotherapy.

We conducted a retrospective analysis on metastatic colorectal cancer patients treated in the 2008-2011 period with first-line bevacizumab. Stratification criteria were sex, age, performance status, metastatic sites, metachronous vs synchronous metastases, chemotherapy backbone, RAS status.

Chest-abdomen CT scan was performed every 3 months. Response was scored according to RECIST criteria.

Progression-free survival for patients who achieved a partial response, a stable disease or progression were respectively 10.6 vs 8.5 vs 3.0 months (p <0.0001).

146 patients were eligible for analysis. Sixty (41%) partial responses, 54 (37%) stable disease and 32 (22%) progressions were seen. Median overall survival was 18.5 months and median progression-free survival was 8.2 months.

No significant differences were seen in regards to stratification criteria for different response groups.

Progression-free survival for patients who achieved a partial response, a stable disease or progression were respectively 21.3 vs 19.7 vs 9.1 months (p <0.0001).

All 32 patients who directly progressed under bevacizumab based-treatment received a second-line chemotherapy regimen and in 16 (50%) it was anti-EGFR based (either cetuximab or panitumumab). The remaining 16 patients received standard chemotherapy. Only a trend towards better overall survival for anti-EGFR based regimens (10 vs 7.78 months, p = 0.26) was seen.

In our analysis a dismal survival of 9.1 months was seen for patients who directly progress under first-line bevacizumab, regardless of the treatment received in second-line. It is thus sug-
gusted that, even if overall survival is the primary endpoint of therapy, disease control rate should also be considered, because failure of first-line treatment may jeopardize global outcome.

**B57 ROLE OF RADIOFREQUENCY ABLATION OF LIVER METASTASES IN MULTIDISCIPLINARY TREATMENT OF METASTATIC COLON RECTAL CANCER: A RETROSPECTIVE ANALYSIS**


*Sezione Oncologia, °U.O. Radiologia, ^U.O. Chirurgia Generale, Ospedale di Pistoia; †U.O. Oncologia, Ospedale di Pescia

**Background.** Liver is the more important site of metastatic disease in colon rectal cancer (CRC). In the last years new important local approaches are available and multitreatment protocol is evermore recommended for management of liver metastases (LM).

**Aim.** This is a retrospective analysis that reports the feasibility and activity of local radiofrequency ablation (RFA) in multitreatment protocol of management of LM from CRC.

**Materials and methods.** From January 2010 to March 2012, 26 patients, 10 male, 16 female with a total of 50 LM were treated with RFA: 30 LM with US-guided percutaneous RFA and 20 LM with US-intraoperative RFA. Fourteen pts were receiving also chemotherapy. Median number of treated LM for RFA-session was 2 (range 1-6).

Median age of pts was 68 years (range 56-82). Median interval between diagnosis of CRC and hepatic progressive disease was 9 months (range 0-63); median interval between hepatic progressive disease and RFA was 7 months (range 0-37).

**Results.** Twenty of 26 pts have 6-month follow-up. The 1-month follow-up demonstrated total necrosis (referred as absence of contrast enhancement in CT scan) in 39 LM (78%) and partial necrosis (referred as residual contrast enhancement in CT scan) in 11 LM (22%). Six LM with partial necrosis were retreated with RFA. The 6-month follow-up showed new LM in 4 pts, extrahepatic disease in 1 patient and both in 4 pts. No major complications occurred. Three pts had fever after RFA, 8 pts had mild abdominal pain recovered in 24 hours, 3 pts had perihepatic effusion recovered in 24-48 hours. One patient had pneumothorax recovered without chest-drain.

Conclusions. Our study showed that RFA was a feasible and active local procedure for the treatment of LM from CRC. This approach may play an important role in the multidisciplinary management of this disease. Further studies are necessary to define patient setting, RFA timing and best combination with systemic therapies.

**Background.** FOLFIRI is a standard chemotherapy regimen both in first and second-line colorectal cancer treatment. Bevacizumab demonstrated to improve results when added to chemotherapy in first- and second-line. Data for combination with irinotecan based chemotherapy in first-line are available in randomized and not randomized trials. There are only few data supporting FOLFIRI plus bevacizumab as second-line chemotherapy although bevacizumab combined with infusional 5-FU/LV plus oxaliplatin (FOLFOX) in the second-line setting has demonstrated a survival benefit.

**Methods.** We collected data from 14 consecutive patients treated with oxaliplatin-based chemotherapy without any biological agent who received second-line chemotherapy with FOLFIRI + bevacizumab. Five patients progressed during adjuvant FOLFIRI, 8 patients were pre-treated with FOLFOX and 1 patient with FOLFOXIRI. Median age was 64 years (range 42-75). Median PS was 0 (range 0-2). Male/female distribution was 11/3, and primary colon/rectum was 11/3. Eight patients were K-RAS WT and 6 K-RAS mutate. Median cycles were 12 (range 3-37). After 12 cycles stop and go strategy (2 months off, 2 months on) was used both for chemotherapy and for bevacizumab.

**Results.** No CR was seen, 8 patients achieved a PR (57.1%) and the disease control rate (DCR) was 78%. The median PFS was 10 months (range 7.31+), OS was 13.5 months (4.41+). Six patients were still alive without progression. Response for K-RAS status was 3 PR and 3 SD in K-RAS mut and 5 PR and 3 PD in K-RAS WT.

Toxicity was manageable with no grade 3/4 neutropenia and diarrhea. The bevacizumab-related adverse events were grade 2 hypertension in one patient, proteinuria grade 1-2 in four patients. One patient experienced anterior optic nerve ischemia and one ischemic ictus cerebri with complete recovery after bevacizumab discontinuation.

Conclusions. The FOLFIRI plus bevacizumab regimen is an active, well tolerated second-line chemotherapy treatment for patients with metastatic colorectal cancer. The high DCR and PFS showed in this report seem to justify more extensive trials.

**B59 PREDICTIVE ROLE OF NEUTROPHILS COUNT IN COLORECTAL CANCER CHEMO-IMMUNOTHERAPY**

Botta C.1, Ciliberto D.1, Rotundo M.S.1, Staropoli N.1, Caraglia M.2, Tassone P.1, Tagliaterra P.1, Correale P.3

1Medical Oncology Unit, Campus “Salvatore Venuta”, Magna Gracia University and Tommaso Campanella Cancer Center, Catanzaro; 2Department of Biochemistry and Biophysics, Second University of Naples, Napoli; 3Medical Oncology Unit, Oncology Department, Siena University Hospital

**Background.** Chemo-immunotherapy demonstrated activity in cancer patients. However, a survival benefit is achieved by a small (about 20%) subgroup of patients only, regardless of the malignancy. We conducted a phase 3 trial (GOLFIG-2) comparing GOLFIF (gemcitabine + FOLFOX + GM-CSF + IL-2) chemo-immunotherapy with FOLFIRI alone in patients with metastatic colorectal cancer (mCRC). In this trial, GOLFIF regimen showed a significant advantage in terms of progression-free survival (PFS) with about 20% of patients still not progressed after a median follow-up of 48 months. We carried out an exploratory retrospective analysis in the aim to identify variables predictive of long-term survival.
Patients and methods. Different clinic and laboratory baseline characteristics from 93 patients enrolled in the GOLFIG-2 trial have been evaluated. Categorical variables were generated from continuous and median values were used as cut-off. Kaplan-Meier descriptive statistics were used for survival while log-rank test and Cox’s regression model were used for correlative analysis.

Results. No significant differences were observed in the two treatment arms between patients characteristics at baseline. Neutrophil cells count <4500 at baseline was predictive of better PFS only in the GOLFIG group (HR = 0.47; p = 0.03). Median PFS in the group of patients with lower neutrophils count was 12.16 months compared with 7.67 months in the group with a higher neutrophils count. Similar results were obtained in overall survival (HR = 0.35; p = 0.004). No significant correlations were seen between others variables and survival.

Conclusions. GOLFIG regimen seems to provide the major benefit in patients with a low neutrophils count at baseline. Prospective confirmatory studies are needed in this setting.

B60 Fournier Gangrene and Bevacizumab

Fattoruso S.I.S.1, Pacetti U.1, Evangelista S.1, Di Grazia C.2, Corelli S.2, Stagnitti F.2, Cardillo F.1

1 U.O.S.D. of Oncology, “A. Fiorini” Hospital, Terracina (LT), AUSL of Latina; 2 U.O.C. of General Surgery, “La Sapienza”, University of Rome (Polo Pontino)

Background. Fournier’s gangrene is a severe form of necrotizing fascitis that affects the external male genitalia. It can be a complication of uncontrolled diabetes in elderly or immunosuppressed people and may be associated with Streptococcus pyogenes, causing tissue necrosis and it may extend to the penis and the abdominal wall leading to patient death.

It represents a surgical emergency and is treated successfully with hyperbaric therapy. The mortality rate remains high at 40%, and can reach 78% in case of septic state.

Case report. This is a case report of a male of 70 years, PS 0, without comorbidities, submitted, on 04.07.2010, to a segmental transverse colon resection for adenocarcinoma of the large intestine, G3, ulcerated with 10/11 metastatic lymph nodes, free margins (pT4 pN2b stage III C, EGFR +, K-ras mutated in codons 12 and 13).

A CT scan performed on 23.08.10 showed multiple hepatic lesions.

On 12 september 2010 he started a treatment according to the scheme FOLFIRI + avastin (5 mg/kg) with partial response of liver disease after 6 cycles of treatment.

During the 7th cycle, in the absence of predisposing factors, appeared a sharp and progressive pain in the perineum.

On clinical examination we noticed a blue-violet-erythematous lesion (Figure 1) that over 24 hours extended to the scrotum with onset of fever and cold sweat.

The patient was hospitalized for emergency surgery where intravenous antibiotic therapy was instituted and it was carried out a surgical toilette in more stages (Figure 2).

Histological examination of skin excised, cited: widespread necrosis of the skin and subcutaneous soft tissues in agreement with the clinical diagnosis of Fournier’s gangrene.

The local hyperbaric therapy was performed. After 20 days of hospitalization and continuous hyperbaric therapy he had almost complete resolution of the ulceration. (Figure 3).

After 1 month the patient resumed chemotherapy without anti-VEGF agent.

Conclusions. This is the second case described in the literature of Fournier’s gangrene in a patient with colon cancer treated with bevacizumab.
The tyrosine kinase TrkA (tropomyosin related kinase A) is the receptor for nerve growth factor (NGF) that plays an important role in the development and maturation of central and peripheral nervous system. The physiological expression of TrkA is typically restricted to subsets of neuronal crest-derived cells, and it is not generally expressed in normal tissues.

TrkA was originally isolated from a human colon carcinoma as a transforming oncogene generated by a somatic rearrangement that fused the non-muscle tropomyosin gene (TPM3) to the kinase domain of TrkA. After this original report, no other cases of TPM3-TrkA rearrangements in colon have been described in literature, although ~5-12% of papillary thyroid carcinomas (PTC) harbour chromosomal rearrangements involving the kinase domain of TrkA fused with activating sequences from different genes (TPM3, TPR, TFG).

Interestingly, we recently found that the colon carcinoma cell line KM12 is exquisitely hypersensitive to TrkA inhibitors, and demonstrated that this is due to the presence in this cell line of a TPM3-TrkA rearrangement, resulting in the expression of constitutively activated TrkA kinase (Ardini et al., EJC, S8: 39-40, 2010).

These observations open up the possibility that TrkA gene rearrangements may be a low frequency recurring genetic aberration in colon carcinomas, and that tumours bearing such mutations would potentially be sensitive to TrkA inhibitors. We describe the development of different methodological approaches to detect TrkA expression in a large series of retrospective clinical samples, with the objective of confirming the existence and determining the frequency of this rearrangement in colorectal cancer.

Background. Preoperative radiotherapy (RT) combined with capecitabine is often the treatment of choice in patients with locally advanced rectal cancer (LARC). We would assess the safety and efficacy of a metronomic schedule of capecitabine combined with preoperative radiotherapy.

Materials and methods. From January 2009 to January 2012, 22 patients (19 males and 3 females with a median age of 71 years, range 44-82) with locally advanced rectal cancer (LARC) (cT4N2 22.7%, cT4N0 9.1%, cT3N2 22.7%, cT3N1 18.2%, cT3N0 22.7% and cT3Nx 4.6%) were enrolled. In all patients histology was adenocarcinoma. Only 11 patients (50.0%) had a PS 0 whereas 10 (45.5%) had PS 1 and 1 patient (4.5%) PS 2. One group (16 patients) received pelvic RT (45 Gy, 5 days/week, for 5 weeks) and another group (6 patients) received pelvic RT plus boost on rectum (45 Gy + boost 5.4 Gy, 5 days/week, for 5 weeks). All patients received preoperative chemotherapy with metronomic capecitabine 1500 mg/die, in a single dose within half an hour lunch, for 5 weeks for all the course of radiotherapy. Fourteen patients underwent surgery in 6-8 weeks after completion of the chemoradiotherapy, four patients after 8 weeks, two patients did not undergo surgery (too early) and two patients were lost to follow-up.

Results. At the time of analysis 18 patients were evaluable for response. Downstaging was ypT4N1 5.60%, ypT3N2 11.1%, ypT3N1 5.60%, ypT3N0 33.3%, ypT2N1 5.60% and ypT2N0 38.8%. Only 8 patients achieved a downstaging below 0-1 cm whereas 10 patients between 2-3 cm. Grade 1 of WHO haematological toxicities (leucopenia) occurred in 1 patient (4.5%) and grade 1 of not-neutropenic fever occurred in 1 patient (4.5%). We also observed grade 3-4 of WHO gastrointestinal toxicities (diarrhea) only in 1 patient (4.5%) whereas grade 1-2 occurred in 7 patients (31.8%). Grade 2 of lack of appetite and asthenia occurred in 3 patients (13.6%). Overall, we did not observe any hand-foot syndrome, nausea and vomiting.

Conclusions. Our data show that a schedule of metronomic capecitabine combined with preoperative radiotherapy may be beneficial in terms of downstaging of disease and tolerability in patients with locally advanced rectal cancer (LARC).
Session C * Supportive and palliative care

C1* APREPITANT IS ACTIVE IN THE MANAGEMENT OF BIOLOGICAL THERAPIES RELATED SEVERE PRURITUS: A PHASE II STUDY

Santini D.1, Guida F.M.1, Schiavon G.2, Venditti O.1, Frezza A.M.1, Imperatori M.1, Spoto C.1, Berti P.1, Vincenzi B.1, Tonini G.1

1Università Campus Bio-Medico, Roma; 2Department of Medical Oncology, Erasmus University Medical Center, Daniel den Hoed Cancer Center, Rotterdam, Netherlands

Introduction. Itch is a common dermatologic side effect of anti-epidermal growth factor receptor antibodies and tyrosine kinase inhibitors and may have a dramatic impact on patients quality of life. Aprepitant, a neurokinin-receptor inhibitor, showed efficacy in treating refractory pruritus. We designed a pilot single center phase II study evaluating the effects of aprepitant in managing biological therapy-induced pruritus.

Methods. Forty-five cancer patients treated with biological therapies were enrolled and divided in: 1) patients affected by itch refractory to standard treatment (“refractory group”) and 2) patients who did not receive any treatment for pruritus (“naïve group”). The intensity of itch was evaluated with Visual Analogue Scale (VAS) score. All included patients had severe pruritus (VAS score ≥7). In the refractory group aprepitant (125 mg on day 1; 80 mg on day 3 and on day 5) was administered after at least 1 week of standard systemic treatment (steroid and/or antihistaminics). In the naïve-group aprepitant was administered, with the same schedule, after first severe pruritus onset.

Results. Forty-five (25 males and 20 females) patients were enrolled, 24 in the refractory group and 21 in the naïve-group. The median age was 64 years. Among the enrolled patients, 38% (N = 17) were affected by lung cancer, 44% (N = 20) by colorectal cancer, and 18% (N = 8) by other tumours. Severe itching occurred in 16 patients treated with erlotinib, 23 with cetuximab, 1 with lapatinib, 3 with sunitinib, 1 with imatinib and 1 with gefitinib. The median decrease in pruritus intensity at 1 week after aprepitant introduction was 93% (p < 0.0001) in the refractory group and 100% (p < 0.0001) in the naïve-group. Aprepitant was active in the majority of patients regardless of the type of biological therapy. Only 6 patients developed pruritus recurrence, with a median interval of 7 weeks from first aprepitant administration. No toxic effects potentially aprepitant-related were registered.

Conclusions. This single center phase II study showed a new therapeutic activity of aprepitant in treating biological therapy-induced pruritus, both after standard antipruritic medications failure and as a first-line therapy.

C2* NUTRITIONAL FLOW-CHART IN CANDIDATE CANCER PATIENTS TO HOME ARTIFICIAL NUTRITION ASSISTED BY ANT FOUNDATION

Ruggeri E., Agostini F., Giannantonio M., Fettucciari L., Pannuti R., Pannuti F.

ANT Italy Foundation, Bologna

Introduction. Malnutrition correlates with quality of life and survival in cancer patients. Cachexia induced by cancer has a multifactorial origin and it causes death in 20% of patients. Home artificial nutrition (HAN) can prevent death from cachexia.

Aim. To evaluate the efficacy of a nutritional flow-chart in order to identify cancer patient candidates to HAN and to prevent death from cachexia.

Materials and methods. Nutritional risk was evaluated for all patients at ANT home care using the malnutrition screening tool (MST) modified. If the patient was marnourished or at risk of malnutrition, the life expectancy was assessed using the palliative prognostic score (PPS). When the prognosis was ≥6 weeks, nutritional counseling was sought. ANT nutritionist assessed nutritional status analyzing anthropometric, biochemical and immunological parameters, and decided specific nutritional therapy based on the pathogenesis: HAN started when malnutrition was due to cancer organic complications (dysphagia, occlusion) or performed therapy (chemo/radiotherapy, surgery); drug therapy (medroxyprogesterone acetate, megestrol acetate or corticosteroid) was used when the cause was anorexia or hypermetabolism. If drug therapy was unsuccessful, HAN was set.

Results. From July 1990 to January 2012, ANT Foundation assisted 28,413 patients at home in Bologna and its province. HAN had been submitted to 587 patients (2.1%), 352 M, 235 F (age 65.3 ± 12.8 yrs). Enteral nutrition was performed in 280/587 (47.7%), the indications were: 11 anorexia, 186 dysphagia, 83 gastrointestinal obstruction; parenteral nutrition in 307/587 (52.3%), the indications were: 6 anorexia, 29 dysphagia, 272 gastrointestinal obstruction. Survival was ≥6 weeks in 462/587 patients (79%).

Conclusions. The use of a nutritional flow-chart allows to select patients candidates for HAN, and to avoid death from cachexia in 79% of cases. The low incidence of HAN over all patients assisted by ANT (2.1%) proves the efficacy of the decision-making protocol in order to prevent an excessive and indiscriminate use of nutritional therapy in patients with advanced cancer.

C3* POOLED EFFICACY ANALYSIS EXAMINING DIFFERENT PALONOSETRON-BASED REGIMENS FOR PREVENTION OF DELAYED NAUSEA IN WOMEN UNDERGOING HIGHLY EMETOGENIC CHEMOTHERAPY (HEC)

Celio L.1, Longo F.2, Brugnatelli S.3, Mansueto G.4, de Braud F.1, Lapadula V.2, Agustoni F.1, Duca M.1, Aapro M.S.5
Background. Chemotherapy-induced nausea occurs more frequently than vomiting, and women are particularly prone to experiencing delayed nausea (DN) instead of delayed vomiting. In this post-hoc analysis, we attempted to address two questions: 1) Does palonosetron plus single-dose dexamethasone result in suboptimal control of DN when compared to the same regimen with additional dexamethasone? 2) Is the combination of palonosetron, dexamethasone, and aprepitant a more effective coverage against DN?

Methods. The analysis was based upon outcomes in 510 chemo-naive women (median age 52 years; PS ECOG 0 94%; metastatic disease 4%) with solid tumours (99% breast cancer) enrolled in two phase III and two phase II trials of HEC [100% anthracycline and cyclophosphamide (AC)-based chemotherapy]. Patients received the following regimens: 1) palonosetron 0.25 mg plus dexamethasone 8 mg IV before chemotherapy (1-day regimen, N = 241); 2) the same regimen followed by dexamethasone 8 mg orally on days 2 and 3 (3-day regimen, N = 209); or palonosetron plus dexamethasone plus aprepitant 125 mg on day 1 followed by aprepitant 80 mg and dexamethasone 4 mg orally on days 2 and 3 (triple regimen, N = 60). The pre-specified primary endpoint was the proportion of patients with no DN (days 2-5 after chemotherapy initiation). The two primary comparisons were 3-day vs 1-day regimen, and triple vs 3-day regimen.

Results. The 3-day to 1-day regimen comparison was not statistically significant (DN, 46.4% vs 44.4%, odds ratio [OR] = 1.08, 95% CI 0.75-1.57; p = 0.704). The triple to 3-day regimen comparison was significant (73.3% vs 46.4%, OR = 3.17, 95% CI 1.68-5.98; p = 0.0002).

Conclusions. The present findings suggest that palonosetron plus 1-day or 3-day dexamethasone yield similar prevention of DN. The addition of aprepitant improves markedly the control of DN. Further studies in larger populations are warranted to clarify the weight of these preliminary results.

C5* PSYCHOLOGICAL DISTRESS AND SOCIAL NEEDS OF CANCER PATIENTS IN A LARGE COLLABORATIVE, HOSPITAL-BASED, QUALITY IMPROVEMENT STUDY AIMED AT THE INTEGRATION OF PSYCHOSOCIAL CARE INTO ROUTINE CANCER CARE (HUCARE PROJECT)

Saleri J.,1 Ardizzone B.2 Bani M.3, Brocchi B.4 Gelfi S.5 Marconi M.5, Pagani G.7, Piloni S.8, Previtali G.9 Sabatti E.10, Solari F.11 Sono C.12, Tagliabue L.3, Tagliani M.13 Verga P.14, Wuhrer C.15, Tomirotti M.16, Lazzarelli S.1, Colombi C.1, Gerevini F.1, Diodati F.17, Finerti S.17, Caminati C.17, Passalacqua R.1

1Istituti Ospitalieri Cremona; 2Azienda Ospedaliera Rho; 3Azienda Ospedaliera San Gerardo Monza; 4Azienda Ospedaliera Busto Arsizio; 5Ospedali Riuniti Bergamo; 6Ospedale Sar蒙no; 7Radiotherapy, Azienda Ospedaliera San Gerardo Monza; 8Ospedale di Crema; 9Ospedale “Pseni Fenaroli”, Alzano Lombardo; 10Ospedale di Manerbio; 11Azienda Ospedaliera Casalpusterlengo, Lodoi; 12Ospedale di Gorgonzola; 13Ospedale Civile Brescia; 14Ospedale Sant’Anna Como; 15Ospedale Montichiari; 16Fondazione IRCCS, Ospedale Policlinico Mangiagalli, Milano; 17University Hospital Parma

Background. The literature reports that up to 30% of Italian cancer patients have anxiety disorders and/or depression (Passalacqua R et al., JCO 2009). HUCARE project (HUMANization of cancer CARE) started on December 2008, with the aim to assess the feasibility and effectiveness of online practice of EBM interventions that have demonstrated to improve pts psychosocial conditions. One of the main interventions of the HUCARE project was to screen all new pts for psychological distress and social needs. Here we present the results in terms of psychological status and social needs in pts followed according to the HUCARE project.

Methods. From 1st January 2011 to 31st December 2011, all consecutive new cancer patients who came to the 18 participating centers were included. The patients were screened for psychological distress and social needs. The psychological distress was measured by the Hospital Anxiety and Depression Scale (HADS) and the Social Needs was measured by the Scored Caregiver Distress Inventory (SCID). The analyses were performed using SAS software.
centers for chemotherapy were screened for distress and social needs using two validated questionnaires: Psychological Distress Inventory (PDI) (Morasso et al., 1996) (cut off point ≥35) and the Needs Evaluation Questionnaire (NEQ) (Tamburini, 2000). The questionnaires were distributed and collected by a referring nurse.

**Results.** 1,400 consecutive pts in 18 oncology units were screened, 761 female (54%). Median age was 64 years (30-83). The average PDI score was 27 (SD 5.4). 227/1400 pts (16%) had a score ≥35 (average test score 41, SD 5.5). Patients with a score ≥35 were referred to psychologist for a more thorough examination and support. The Table reports the frequency of NEQ questionnaire for the more frequent items.

<table>
<thead>
<tr>
<th>Item number</th>
<th>Item</th>
<th>Yes N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>More information about my diagnosis</td>
<td>418/1395 (30%)</td>
</tr>
<tr>
<td>2</td>
<td>More information about my future conditions</td>
<td>653/1399 (47%)</td>
</tr>
<tr>
<td>3</td>
<td>More information about the exams</td>
<td>420/1398 (30%)</td>
</tr>
<tr>
<td>4</td>
<td>More explanations on treatments</td>
<td>403/1398 (29%)</td>
</tr>
<tr>
<td>8</td>
<td>Better dialogue with clinicians</td>
<td>307/1398 (22%)</td>
</tr>
<tr>
<td>14</td>
<td>More reassured by the clinicians</td>
<td>86/1397 (20%)</td>
</tr>
<tr>
<td>12</td>
<td>More attention from nurses</td>
<td>98/139 (76%)</td>
</tr>
</tbody>
</table>

**Conclusions.** The percentage of patients with a PDI score ≥35 is lower than expected according to the value reported by literature. Similarly the needs expressed by patients are lower than expected. This could indicate that the path implemented according to the HUCARE project reduces distress and patients social needs.

HUCARE was supported by Italian Ministry of Health Lombardia Region.

C6 RESULTS OF A PHASE I STUDY OF SHORT COURSE ACCELERATED RADIATION THERAPY (SHARON) FOR COMPLICATE BONE METASTASES

Scapati A.M., Caravatta L., Macchia G., Deodato F., Massaccesi M., Valentini V., Cellini N., Morganti A.G.

**Background.** Approximately the 20-25% of patients with neoplastic disease develops bone metastases that disrupt bone homeostasis with, as a result, a loss of bone integrity on which bisphosphonates play a key role.

**Materials and methods.** The study prospectively evaluated the levels of RANK, RANKL and OPG VEGF and NTX in the peripheral blood of 49 patients with advanced breast, prostate and lung cancer receiving the standard zoledronic acid (ZA) schedule. Patients were monitored for about 12 months. The primary aim was to evaluate the predictive role of response to ZA of circulating markers compared to the objective response.

**Results.** RANKL median, at 12 months, decreased of 22% compared to baseline and OPG, instead, increased of about 96%, with a decreased in RANKL/OPG ratio of 56%. The serum NTX median levels at 4 and at 8 months were 35% and 39% compared to baseline (p <0.001). Evaluating the predictive role of response to ZA, we calculated ROC curves and the most accurate results were observed for RANKL, with an AUC of 0.74 (95% CI 0.54-0.93). Furthermore, considering as a cut-off a variation of markers of at least 25%, the positive predictive value (PPV) for RANKL was 88.4%, and those of other innovative markers ranged between 78-81%. PPV for CEA and CA15-3 was 85.6% and 61.1%, respectively.

**Conclusions.** The greater decrease of RANKL/OPG was observed after 12 infusions of ZA. The study showed that RANKL can have a role in the prediction of objective response to ZA.
C8 SURVIVAL PREDICTION OF TERMINALLY ILL CANCER PATIENTS BY CLINICAL AND LABORATORY PARAMETERS


°Medical Oncology Unit, *Department of Clinical Sciences, Parma University Hospital, Parma

Background. Although accurate prediction of survival is essential for palliative care management, no simple clinical/laboratory prediction tool has been established. Aim of this retrospective study was to assess the role of clinical and laboratory predictive factors of survival in a population of terminally ill cancer patients.

Patients and methods. The study cohort comprised 169 advanced cancer patients, no longer suitable for anticancer therapy, transferred between January 2004 and December 2010 from the Medical Oncology Unit to the palliative Care Unit of the University Hospital of Parma. Six clinical/laboratory parameters assessed on admission at palliative care ward were evaluated. They included: Braden score (BS) for decubitus risk, anorexia-cachexia syndrome (ACS), pseudocholinesterase (p-CHE), lactate dehydrogenase (LDH), haemoglobin (Hb), white blood cells count (WBC).

Results. Patients median age was 68 years (range 34-90). Primary tumours were: gastrointestinal (26%), lung (21%), breast (15%), genito-urinary M (10%) genito-urinary F (9%), head and neck (8%), others (11%). All the patients had previously been treated with more than one chemotherapy line for metastatic disease. Overall median survival (MS) was 24 days (range 1-62). Two factors were found to be indicator of a worse survival by univariate analysis: ACS (p = 0.013) and p-CHE (≤4.300 U/L vs normal, p = 0.001). Cox regression analysis revealed that only p-CHE (altered vs normal: HR = 1.68, 95% CI 1.22-2.31) was an independent predictor of survival. Median survival of pts with normal p-CHE was 1.05 vs 0.59 months in pts with reduced p-CHE levels.

Conclusions. A single, simply assessable laboratory parameter like p-CHE may be used to accurately predict survival in terminally ill cancer patients. This prognostic indicator may be useful in day-by-day therapeutic decision-making process of palliative care and medical oncology specialists.

C9 HOW INTEGRATE CANCER TREATMENTS AND PALLIATIVE CARE IN THE TRAJECTORY OF CANCER PATIENTS. A SURVEY ON MODELS OF INTEGRATION IN ITALIAN ESMO DESIGNATED CANCER CENTERS


Background. The early integration of palliative care (PC) is effective but the current state of the art in Italian Cancer Centers is unknown.

Aims. To determine the models of integration of PC in Italian Cancer Centers “ESMO Designated Centers of Integrated Oncology and Palliative Care” (ESMO-DCs).

Methods. A questionnaire has been sent by e-mail to the executives of the Italian ESMO-DCs.

Results. Twenty questionnaires were sent with a response rate of 100%. The geographical distribution of ESMO-DCs is unbalanced: 12 (60%) in the Northern, 6 (30%) in the Central, 2 (10%) in the Islands and none in the Southern Italy. ESMO-DCs organization is oriented to PC integration through an oncologist PC-oriented in 18 (90%); guidelines (LG) of symptomatic treatment in 18 (90%); PC beds in 14 (70%) and PC offices in 14 (70%). ESMO-DCs showed a good integration with home care (HC): in 9 (45%) HC is managed by palliative care physicians (PCPs); in 6 (30%) by general practitioners (GPs); in 3 (15%) by oncologists and in 2 (10%) by PCPs with GPs. When HC is not directly managed by oncologists, ESMO-DCs achieve the integration through home visits in 6/17 (35%), meetings and/or GL sharing with PCPs and GPs in 11/17 (65%) and 6/17 (35%), respectively. ESMO-DCs showed a good integration with hospices (Hs): in 14 (79%) Hs are managed by PCPs; in 2 (11%) by PCPs with GPs, in 1 (5%) by GPs and in 1 (5%) by oncologists. When Hs are not directly managed by oncologists the ESMO-DCs achieve the integration through hospice visits in 7/17 (41%), meetings and/or GL sharing with PCPs and GPs in 11/17 (65%) and 7/17 (41%), respectively. The integration model of reference for most ESMO-DCs is integrated care model (see Bruera E., JCO 2010).

Conclusions. ESMO-DCs are not representative of Italian situation and lack in the South of Italy. The integrated care model of ESMO-DCs is simultaneous care-oriented but its achievement is different by Center. The “ESMO-DCs” experience is challenging for Oncology Units to improve early integration of PC, continuity of care and quality of assistance of cancer patients.

C10 CURCUMA LONGA EXTRACT IS EFFECTIVE IN IMPROVING INFLAMMATORY STATUS AND REDOX BALANCE IN PATIENTS WITH CANCER RELATED CACHEXIA AND OXIDATIVE STRESS

Panzone F., Mameddu C., Cau M.C., Antoni G., Leo F., Macciò A., Mantovani G., Serpe R.

°Department of Medical Oncology, University of Cagliari; °Nutri search srl, Parco Scientifico e Tecnologico della Sardegna, Pula, Cagliari

Background. Curcumin (diferuloylmethane) is the biologically active compound of Turmeric (Curcuma Longa) and has long been used in traditional Asian medicine to treat diseases ranging from heartburn to arthritis: it is thought to have antioxidant and antiinflammatory properties.

Aim. To assess the antioxidant and antiinflammatory properties of a curcumin extract in advanced cachectic cancer patients.

Methods. From September 2011 to March 2012, 15 cachectic patients (M 7/F 8; age range 55-85 yrs) with cancer at different sites were enrolled, all stage IV. Twenty-one age/sex matched healthy controls were studied. All enrolled patients had inflammation and oxidative stress (high blood levels of proinflammatory cytokine interleukin-6 (IL-6), high levels of blood C-reactive protein (CRP), high levels of ROS, low levels of blood antioxid-
C11 EVALUATION OF RISK FACTORS FOR CHEMOTHERAPY-ASSOCIATED THROMBOSIS IN OUTPATIENT SETTING: A SINGLE CENTER STUDY

Torchio M., Cavalli C., Franceschetti B., Zanirato S., Olgiati A., Danova M.
Medicina Interna e Oncologia Medica, Ospedale Civile di Vigevano, A.O. di Pavia

Background. Venous thromboembolism (VTE) is a negative predictor of survival in cancer patients. A number of clinical risk factors for cancer-associated VTE have been identified and a score model (Khorana), for prediction of risk of VTE in cancer outpatients, has been developed. We applied this scoring system in consecutive pts to evaluate the distribution of risk factors for VTE.

Patients and methods. We prospectively tested the Khorana’s score in adult pts, followed at our outpatient department from August 2011 to April 2012 with advanced cancers (breast, NSCLC, colorectal, pancreatic/gastric, urogenital, LNH, HD and MM), receiving a first or second-line of chemotherapy (CT). We then stratified our pts into low, intermediate and high risk group for VTE, and we performed a sub-analysis for both cancer type and anticancer agents utilized.

Results. We analyzed 86 pts, 45F /41M; median age 62.3, range 35-83 yrs; 18 breast, 10 NSCLC, 20 colorectal, 9 pancreatic/gastric, 18 urogenital, 10 among LNH, HD and MM. Thirty pts received 5-FU-containing regimens, 15 cisplatin, 19 oxaliplatin, 28 gemcitabine, 5 vinca alkaloids, 13 biologic agents. Thirty-one pts had a Khorana’s score = 0 (low risk, 36%), 25 pts = 1 and 21 pts = 2 (intermediate risk, 53.4%), 5 pts = 3, 3 pts = 4 and 1 pt = 5 (high risk, 10.4%). No patient with breast, colorectal and NSCL cancer had a score >2; high risk was found only among hematological, urogenital and pancreatic/gastric pts and treated with one of the CT agents with higher impact on VTE.

Conclusions. Current international guidelines don’t recommend routine prophylaxis in outpatients with advanced cancer undergoing CT but suggest to carefully consider those with high risk of VTE. In our series of pts, this population was around 10%. The quantification of VTE risk, especially in view of the recently suggested identification of new independent factors, is mandatory for the correct implementation of guidelines on the prophylactic approach.
Italy is the European tail-end when it comes to analgesic narcotic drugs consumption for severe and middle pain. In order to spur the use of these drugs, along with various initiatives addressed to sanitary operators, in June 2009 Italian Ministry of Health introduced a law to simplify their prescription (especially non-injective opioid drugs).

This remarkable study, following an international excursion and observation of last years' Italian trend detecting a good tendency – still very far from European standards –, is intended to monitor drug prescriptions on Italy’s whole territory and particularly on Friuli Venezia Giulia (Northern Italy), Abruzzo (Central Italy) and Calabria (Southern Italy) territories, using articulate data of the first six months of the year 2010 and comparing them with those of the first six months of the year 2011.

We particularly monitored, for each territory, the following parameters: cost, units, unitary costs, Daily Definite Doses (DDD) for each therapeutic class, active principle and administration way.

The most used drugs in Italy resulted to be codein + paracetamol association and tramadol, both for low-medium pain (over 70% of prescriptions).

The research underscores a national trend of growing consumption of these narcotic oral drugs, comparing first semester of 2010 with first semester of 2011. In this period the increase is 496,469 units (+8.29%).

There has been a cost increase of 9,772,201 euro (+17.2%), while the DDD increased of 1,37 (+8.44%).

Further accounts and articulate data for each Region will be available on the extended version of the work.

C14 CHOLINESTERASE AS A PROGNOSTIC INDEX IN CANCER PALLIATIVE CARE PATIENTS

Tempera S1,2, Mazzoli M.1, Stumbo L.1, Gori B.1, Donini L.M.2

1Residential and home care for palliative care, “Merry House” Aclia (Rm); 2Experimental Medicine Department, Medical Pathology, Food Science and Endocrinology Section, “Sapienza” University of Rome

Introduction. Cholinesterase (PCHE) is considered a prognostic index validated in geriatric patients. There is no scientific evidence about the terminally ill cancer patients.

Aims. To verify the correlation between values of cholinesterase and prognosis in palliative care oncological patients.

Methods. We conducted an observational study that included 40 patients, 17 males and 23 females, mean age 69.2 ± 13 (37-87) with solid tumours of different type treated in a setting of palliative care. Metastatic disease was diagnosed in 70.8% of patients. In these patients, we measured the values of cholinesterase and its correlation with PAP score, already validated prognostic index, ESAS score and survival to three weeks.

Results. We observed an average value of cholinesterase of 4669 ± 2413 IU/mL (182-10,361), less than the threshold in 45% of cases. Patients with high PAP score presented a low value of PCHE (r = 0.75, p = 0.000), showing a significant correlation for all items, with higher values for the items anorexia (r = 0.71, p <0.001), Karnofsky Index (r = 0.63, p <0.001) and clinical prediction of survival (r = 0.68, p <0.001). We found also a correlation between values of PCHE and ESAS, both in the total score (r = 0.76, p <0.000) and the single items. After three weeks, 11 patients, whose average PCHE values were below standard, died; 29 patients showed average PCHE values within the normal range (3030 ± 1568 vs 5291 ± 2404, p = 0.05).

Conclusions. In our sample the PCHE proved to be a good prognostic index. Further studies on samples of many more patients will be required to include PCHE in the already validated scales for the assessment of prognosis in palliative cancer patients.

C15 EFFICACY AND SAFETY OF A TWO-DRUG COMBINATION REGIMEN FOR CANCER-RELATED CACHEXIA IN THE CLINICAL PRACTICE

Madeddu C., Dessi M., Panzone F., Serpe R., Antoni G., Mantovani G.

Department of Medical Oncology, University of Cagliari, Cagliari

Background and aims. To test the safety and efficacy of a two-drug combination (including nutraceuticals, i.e. antioxidants) with carnitine + celecoxib for the treatment of cancer-related anorexia/cachexia syndrome (CACS) in the clinical practice. Primary endpoints: safety, increase of lean body mass (LBM) and improvement of quality of life. Secondary endpoints: increment of physical performance (tested by grip strength and 6-min walk test, 6MWT) and decrease of inflammation (assessed by serum levels of IL-6 and Glasgow prognostic score, GPS).

Patients and methods. Outpatients with advanced cancer at different sites with CACS (i.e. loss of body weight >5% of the pre-illness or ideal weight in the last 3 months) were eligible to receive: L-carnitine 4 g/day + celecoxib 300 mg/day. All patients received as basic treatment polyphenols 300 mg/day, lipico acid 300 mg/day, carbocysteine 2.7 g/day, vitamins E, A, C, all orally. Treatment duration was 4 months.

Results. From June 2011 to April 2012, 50 patients with advanced cancer (all stage IV) at different sites were enrolled: 40 completed the treatment and were evaluable (mean age 63.8 ± 9.6, range 32-81 years). Results showed a significant increase of LBM (by dual-energy X-ray absorptiometry and by L3 computed tomography) from baseline as well as physical performance assessed by 6MWT. Quality of life (assessed by EORTC-QLQ-C30 and EQ-5D) also improved significantly. ECOG PS and GPS decreased significantly. The treatment was safe, no grade 3-4 toxicities occurred and no patient had to discontinue the treatment due to severe adverse events.

Conclusions. The results of the present study confirm the efficacy and safety of the two-drug combination regimen previously shown in a randomized clinical trial (Madeddu et al., Clinical Nutrition, 31: 176-182, 2012). Therefore, this simple, feasible, effective, safe, with favorable cost-benefit profile, two-drug approach could be suggested in the clinical practice as a treatment for CACS.

C16 RETROSPECTIVE ANALYSIS OF PAIN MANAGEMENT IN ITALIAN ONCOLOGICAL CARE CENTERS
Mammucari M.1, Borgonovo K.2, Di Costanzo F.3, Cognetti F.4, Bernardi G.5, Boni C.6, Agostara B.7, Pronzato P.8, Colucci G.9, Barni S.2

1Medico di Assistenza Primaria, Roma; Medical Oncology 2Treviglio (BG); 3Firenze, 4Roma; 5Pavia; 6Reggio Emilia, 7Palermo, 8Genova, 9Bari

Introduction. The management of painful oncologic patients is different between treating centers, depending on human resources and hospital organization. We decided to perform a retrospective study to explore different approaches to oncological painful patients in different Italian Cancer Units.

Materials and methods. We evaluate in 8 Italian cancer hospitals all consecutive pts during 5 days in order to investigate level of pain in the previous 7 days and in the following two weeks from basal visit. Patients and oncologists filled up a questionnaire (type of pain, intensity, site of pain, and analgesic therapy).

Results. 265 pts were enrolled. Median VAS (visual analogic scale) pain at baseline was 2.9 measured by oncologist. The pts described somatic pain in 32.4%, visceral pain in 12.5%, neuropathic pain in 13.9% and mixed pain in 41.2%. The current analgesic therapy at baseline had been prescribed by oncologist in only 38.2%. The basal analgesic treatment was confirmed in 57.3%, adjusted in 34%, and changed in 8.6%. At baseline we detected NSAID’s in 69.4% of pts, weak opioids in 34% of pts, strong opioids in 38.9% and 27.7% of pts also had adjuvants (24.5% pregabalin, 57.1% steroids, 18.4% other drugs).

At first weekly follow-up (216 pts) the analgesic therapy was confirmed in 72.2% and adjusted in 27.8%. New drugs prescribed at first follow-up were NSAID’s in 43.3%, weak opioids in 21.7%, strong opioids in 86.7%, adjuvants in 55%

At second weekly follow-up (131 pts): 80.9% of therapies were confirmed and 19.1% adjusted.

90.3% therapies of 72 pts coming to third follow-up were confirmed. In 85.7% of the adjusted therapies an adjuvant was prescribed.

Conclusions. Our data suggest a poor utilization of adjuvants by physicians in oncologic patients, especially when therapies are not prescribed by oncologists. Furthermore, our data confirmed the need of a close follow-up to improve analgesic therapy as demonstrated by the more reduced number of therapy adjusted at subsequent follow-up.

C18 CONJUGATED LINOLEIC ACID (CLA) IS EFFECTIVE IN INDUCING LYMPHOMONOCYTES PROGRESSION THROUGH THE CELL CYCLE IN CANCER PATIENTS WITH CACHEXIA

Serpe R.1,2, Madeddu C.2, Banni S.1, Mulas F.2, Macciò A.2, Mantovani G.2

1Nutrisearch srl, Pula, Cagliari; 2Department of Medical Oncology, University of Cagliari, Cagliari

Background. Cancer patients with cachexia often have immunological disorders such as chronic activation of the innate response with production of inflammatory cytokines, especially IL-2, IL-6 and TNF-alpha, depression of the specific immune response and decrease of the elastic and proliferative T and B lymphocyte capacity and hyper production of reactive oxygen species (ROS). The term conjugated linoleic acid (CLA) refers to a group of geometric and positional isomers of linoleic acid with conjugated double bonds. Among the possible isomers, there is growing interest for cis-9, trans-11 (c-9, t-11) and trans-10, cis-12 (t-10, c-12) for their peculiar properties in modulating metabolic processes and immune function by affecting eicosanoid biosynthesis and induction of PPARs.

Methods. From January to March 2012, 30 stage IV cachectic patients (M/F 18/12; age range 55-85 yrs) with cancer at different sites were enrolled. Twenty-one healthy subjects were studied as controls. CRP, IL-6 and TNF-alpha levels as well as the oxidoreductive balance of all enrolled patients were found higher compared to control. Peripheral blood lymphomonocytes (PBMCs) from patients were incubated for 72h with or without 30 microM or 60 microM of a 50:50 “c-9, t-11” and “t-10, c-12” CLA mix-
ture in the free form, to assess the extent of cell cycle proliferation towards the S phase by cytofluorometry.

**Results.** A significant increase of the proliferative response was observed with PHA plus CLA 30 microM (18%) and 60 microM (23%) compared to PHA alone. Interestingly, the proliferative response of PBMCs to CLA 30 microM alone has shown a significant activating capacity, increasing the progression to S phase (5.35 ± 2.87% vs 1.89 ± 1.01% at baseline, p <0.05).

**Conclusions.** In keeping with the known immunomodulatory properties of CLA, our *ex vivo* study showed a marked activity of CLA in the progression into cell cycle of PBMCs from cancer patients. Additional phase III clinical studies are warranted in order to evaluate whether CLA administration may be beneficial to improve immune response of cancer patients with cachexia.

*Dr. Roberto Serpe was supported by grant CRP1_296 from the Regione Autonoma della Sardegna by PO Sardegna FSE 2007-2013 (L.R.7/2007) titled “Promotion of scientific and technological research in Sardinia”.

---

**C19 THE CONTRIBUTION OF MEDICAL ONCOLOGY UNIT TO ENSURE THE CONTINUITY OF CARE FOR ADVANCED CANCER PATIENTS OUTSIDE THE HOSPITAL. A PROJECT FROM S. ORSOLA-MALPIGHI HOSPITAL IN BOLOGNA**


*Medical Oncology Unit, ESMO Designated Center of Integrated Oncology and Palliative care 2011-2013, S. Orsola-Malpighi Hospital Bologna; †Fondazione ANT Bologna

**Introduction.** The clinical course and care of patients with advanced cancer, and hence no longer likely to benefit from cancer treatment, requires close integration between the hospital, usually represented by the departments of oncology, haematology and radiation, and the professional and social facilities committed to assist these patients in the surrounding territory.

**Methods.** The project moves from merely “bureaucratic” integration to setting up a “real” palliative care network. This means in practice one weekly outpatient or day hospital session in which patients participate directly or through direct contact (phone, e-mail, etc.) with the hospital oncologist, nurse, hospital and home care psychologist, general practitioner (GP) and the hospital and home-care palliative doctor or outpatient specialist in the case of a voluntary organisation or hospice. The case is collectively discussed by the professionals before the patient arrives.

**Results.** From March 2011 to March 2012, 64 patients, all with advanced cancer, took part in the project, 26 (40%) women and 34 (57%) men, median age 70 years. In 11 cases no anti-cancer treatment was carried out, 28 patients underwent at least one line of chemotherapy, 14 two lines and 12 more than three lines of chemotherapy. Of the 64 patients, 52 were being looked after by the customer services home care foundation of ANT, 10 by their GPs, while hospice admission was proposed in the case of seven (10%) patients, in 15% we made more than one visit. The degree of patient and family satisfaction was very high.

**Conclusions.** It is possible to achieve integration between the hospital and its surrounding area, as part of the palliative care network, with a multi-professional team creating a personalized treatment plan. The primary objective of the project is to improve “coverage” by the entire care network and reduce recourse to emergency admission.

---

**C20 PREVALENCE OF PAIN IN CANCER PATIENTS AGED 70 YEARS OR MORE: A PROSPECTIVE OBSERVATIONAL STUDY**

Zafferri V.1, Brunello A.1, Lonardi S.1, Basso U.1, Bergamo F.1, Fiduccia P.1, Corrias M.2, Capovilla E.2, Zaganel V.1

1Medical Oncology Unit 1, 2Psycho-Oncology Service, Istituto Oncologico Veneto, IRCCS, Padova

**Background.** Information among prevalence of pain in elderly cancer patients (ECP) is limited.

**Aim.** To evaluate, in ECP, prevalence of pain, intensity, relationship to cancer or concomitant diseases, functional interference, gender differences, correlation between pain and stage of cancer, correspondence between patients self-reported pain and oncologist assessment.

**Patients and methods.** ECP referred to our Oncology Unit from 01-2011 to 04-2012 were enrolled. Pain was assessed through a semi-structured interview, a short form of the McGill pain questionnaire (SF-MPQ) and the brief pain inventory (BPI); pain was also assessed through the numerical rating scale (NRS) by the physician.

**Results.** Enrolled ECP are 287, median age 77 years (range 70-92); 44.3% males. Main tumour types are: gastrointestinal (39.2%), breast (30.8%), urological (14.3%), other sites (15.7%). ECP reporting pain in the last week (median NRS 3.0, range 1-8) are 43.9%, and in 46.7% this is related to cancer. No differences in pain scores are observed between women and men. ECP with early disease experience lower intensity of pain (median NRS 2.5, range 1-7), compared to those with advanced cancer (median NRS 3.0, range 1-8, p = 0.039).

A significant difference is present between sensory and affective features of pain (p = 0.004) measured through SF-MPQ, while intensity and interference levels are not relevant (<5 points of BPI).

Self-reported pain is stated by 126 ECP, whereas oncologists reporting of pain is present for 75 ECP (59.5%). For patients who have both evaluations (N = 61) a significant difference in NRS intensity is observed between ECP self-reported pain (median 5, range 0-9) and oncologists assessment (median 3, range 1-8, p = 0.003).

**Conclusions.** Pain was reported by 43.9% of ECP, and in almost half this was cancer-related. Pain was of low-intermediate intensity. Our data show that there is under-estimation of prevalence and intensity of pain by physicians, who report pain in clinical charts in less than two thirds of patients. A greater attention to pain assessment is necessary among oncologists.

Supported by Regione Veneto (Ricerca Finalizzata 2010) and Ministero della Salute (Ricerca Finalizzata Giovani Ricercatori 2009; GR-2009-1606663).

---

**C21 EARLY PALLIATIVE HOME CARE: THE THIRD SECTOR’S ROLE BETWEEN INTEGRATION AND SUSTAINABILITY**

---
Varani S., Samolsky-Dekel A.R., Pannuti R., Pannuti F.

Fondazione ANT Italia Onlus, Bologna

Clinicians agree upon the benefits derived from early activation of palliative care for oncological patients. Yet, palliative care still begins in a very advanced phase of disease (Bruera E et al., J Clin Oncol, 2010).

The Eubiosia Project is a national program of free oncological home care, effectively integrated with the territorial network through an early beginning of assistance for both patient and family.

The average length of ANT assistance, for 9297 patients cured at home throughout 2011, is equal to 127 days. Among 1382 patients assisted in 2011 in the ODO ANT in Bologna, only 20% was in charge for less than 30 days, the 41% from 1 to six months, and the 39% for more than six months. The 67% of the sample didn’t undergo any public hospitalization in the last 100 days of life and the 12% was hospitalized for less than 7 days. In the last 30 days, the percentage of patients who didn’t undergo any hospitalization increases to 74%, whereas the 12% was hospitalized for less than 7 days. The 80% of patients assisted in 2011 deceased at home; this percentage varies from 91.7% (in the South of Italy) to 57% (in Bologna). The average of medical accesses in the last 30 days of assistance is about one every 2.6 days, while nursing accesses are one every 4 days; the total amount of the accesses is one every 1.6 days.

The early activation of palliative care can improve the quality of life of patients, by favouring the treatment of the symptoms and by affecting positively the management of the end of life. In early phase, the team of palliative care can perform a supportive role by cooperating actively with the medical oncology; afterwards, palliative care team can take in charge the whole care of the patient in the end of life, in order to simplify treatment and reduce health care costs.

C22 SKELETAL-RELATED EVENTS IN BONE METASTATIC PATIENTS TREATED WITH BISPHOSPHONATES AT MEDICAL ONCOLOGY, UNIVERSITY OF L’AQUILA


Medical Oncology, “S. Salvatore” Hospital, University of L’Aquila

Since 1995, 329 bone metastatic patients (BMP) were followed at Medical Oncology Division, San Salvatore Hospital, L’Aquila. Treatment with bisphosphonates was administered in 204 patients (62%). Overall skeletal-related events (SREs) during follow-up were 140 (69%). SREs before onset of treatment with bisphosphonates were 99 (71%) (group 1), after treatment were 87 (88%) vs 35 (85%); ibandronate 9 (9%) vs 2 (5%); and ibandronate followed by intravenous bisphosphonate 3 (3%) vs 4 (10%). Median duration of treatment was 20 months (range 1-43 months) vs 15 months (range 1-29 months), 11 months (range 1-49 months) vs 40 months (range 2-57 months) and 19 months (range 15-23 months) vs 30 months (range 9-44 months), respectively. SREs in 2 groups were: pathologic fracture, 3 (3%) vs 0; bone radiotherapy, 73 (74%) vs 35 (85%); bone surgery, 1 (1%) vs 0. The first occurring SRE in 2 groups was: pathologic fracture in 22 patients (22%) vs 6 (15%); spinal cord compression, 3 (3%) vs 0; bone radiotherapy, 73 (74%) vs 35 (85%); bone surgery, 1 (1%) vs 0. Time to first SRE was 0 and 2.5 months, respectively. Median time to skeletal metastases was 36 months vs 51. Median survival after first SRE was 18 months vs 20. Median survival after bone diagnosis was 32 months vs 31. Zoledronic acid and/or intravenous pamidronate were used in

C23 DOES BRAIN IRRADIATION INCREASE RISK OF INTRACRANIAL BLEEDING IN PATIENTS SUFFERING FROM BRAIN METASTASES AND TREATED WITH LOW MOLECULAR WEIGHT HEPARIN (LMWH)? A SINGLE INSTITUTION EXPERIENCE


Medical Oncology Department, San Vincenzo Hospital, Taormina; *Centro Neurolesi, IRCCS Bonino Pulejo, Messina

Background. Hypercoagulability-related thrombosis and metastatic dissemination to the brain both commonly develop among cancer patients. Most pts carrying brain metastases undergo brain irradiation. Stereotactic or gamma knife based irradiation seem to make brain metastases more prone to bleed over whole brain treatment. Furthermore, anticoagulative treatments might increase the risk of bleeding when used to treat thromboembolic events.

Aim and methods. To report single-institutional clinical outcomes of pts suffering from irradiated brain metastases and treated with LMWH as to occurrence of cerebral hemorrhage. To this end, the charts of all cancer pts harboring brain metastases and treated with LMWH between October 2000 and February 2011 were retrospectively reviewed.

Results. A total of 26 pts harboring irradiated brain metastases were administered LMWHs: calcium nadroparin (19 pts); enoxaparin (4 pts); reviparina (2 pts); parnaparin (1 pt). Site of primary tumour: lung (17), breast (7), colon (1) and pancreas (1). Reason for anticoagulative treatment: deep vein thrombosis and/or pulmonary embolism (9 pts); superficial thrombophlebitis (12 pts); mild disseminated intravascular coagulation (4 pts); Raynaud phenomenon (1 pt). Only one patient underwent non-fatal brain hemorrhage during enoxaparin treatment. This patient had been previously treated with stereotactic radiotherapy.

Conclusions. Our study seems to confirm that a higher risk of intracranial bleeding correlates with concomitant use of LMWH and stereotactic based brain radiotherapy. On the contrary, LMWH administration seems to be safer in pts treated with whole brain irradiation.

C24 PRELIMINARY RESULTS OF A SURVEY ON THE USE OF COMPLEMENTARY AND ALTERNATIVE MEDICINE (CAM) AMONG TUSCANY’S CANCER PATIENTS

*Medical Oncology Unit, Azienda Ospedaliero-Universitaria Careggi, Firenze; **Oncologic Department, Azienda Sanitaria, Firenze; "Carrara City Hospital, Massa-Carrara

Background. The purpose of this study was to investigate how many pts had integrated conventional treatments and which complementary and alternative medicine (CAM) they used in the Tuscan area. In a previous study we had already evaluated this setting four years ago; (Joahennesen et al., Tumori, 94: 406-410, 2008).

Methods. Between March and May 2012 a survey was carried out on pts followed in three different institutions: one university and two community hospitals used a modified version of questionnaires by Molassiotis et al. (Ann Oncol, 16: 655-663, 2005).

Results. 411 pts were screened; 280 (68.1%) of them had accepted to participate in this survey. Incidence of CAM use was of 30% (17% in previous study). The characteristics of responders were: 54.6% women, 41.1% aged between 51 and 65 years, the most represented level of education was diploma (35.6%). Characteristics of pts receiving CAM were: 55% women, 35% aged between 51 and 65 years; the level of education was: 8.4% primary school, 19.3% secondary, 43.4% diploma and 27.7% university degree (1% missing data). The type of CAM used was 19% homeopathy, 36% herbal medicine, 13% traditional medicine (agopuncture, ayurveda etc.), 32% others (vitamins and minerals, spiritual groups, relaxation techniques etc.). Only 42 pts (50.6%) reported to have discussed CAM therapy with their oncologist.

Conclusions. This study has shown an increase in CAM therapy (30% vs 17%) in comparison to four years ago in pts that had received conventional oncological treatment. The knowledge of this phenomenon by medical oncologists is an essential point for evaluating the philosophy of the pts, the outcome of CAM and to prevent any adverse interactions with conventional treatments.

C25 CULTURAL DIFFERENCES IN DELIVERING END OF LIFE CARE: A RETROSPECTIVE STUDY IN ITALY


*Giorgio Prodi Center for Cancer Research, University of Bologna Alma Mater Studiorum and Academy of Sciences of Palliative Medicine, Bologna; **NY University; ***Giorgio Prodi Center for Cancer Research, University of Bologna Alma Mater Studiorum; ****PhD students on Medical Oncology Curriculum in Palliative Care, University of Bologna

The provision of palliative care is becoming worldwide extremely connected to social changes and needs. The different characteristics that influenced palliative care delivery in each country need to be understood in consideration of the increasing immigration trends from countries in which cultural and religious aspects intensely influence end of life (EOL) choices. The research project proposed aims at showing various aspects that can intervene in delivering palliative care in hospices and palliative care organizations to patients with different cultural background. The project reckons that cultural, religious, social, and political differences at the end of life could significantly influence patients decision on the preferred place to die, and palliative care professionals need to be properly trained in order to understand patients necessities. Cultural differences have a long history in Italy in which, historically, the North and the South developed different patterns accordingly to the cultural conception of their inhabitants.

The historical configurations and the recent massive immigration from North Africa, Asia, and Eastern Europe forced Italian public health structures and palliative care organizations to become more focused on cultural issues, in terms of education programs and care provision. Accordingly, Italy represents a suitable arena for developing tailored tools in delivering palliative care, allowing multicultural attention. The aim is to present at AIOM national congress the results of two simultaneous studies.

The survey is about advanced cancer foreign patients assisted in Oncological Unit at Sant’Orsola Bologna Hospital and about their care process after being dismissed.

The retrospective analysis in collaboration with several Italian hospices is based on the knowledge of the main issues that can be generated in taking care of patients with different backgrounds. It will be presented also the Italian immigrations recent trends as a necessary framework of the whole research project.

The research has been partially sustained by the Italian Ministry of University and Research MIUR in the framework of the PRIN program.

C26 NUTRITIONAL AND PHARMACOLOGICAL SUPPORT IN ADVANCED CANCER PATIENTS WITH MALNUTRITION


*Medical Oncology Unit, ‡Palliative Care Unit, ‡Oncology Department, Santa Maria Annunziata Hospital, Azienda Sanitaria Firenze

Introduction. Malnutrition is often associated with adverse outcomes in cancer patients. Weight loss in oncology concerns muscle and fat loss and is the expression of a catabolic metabolism induced by an abnormal host response to tumour presence. cachexia is the final cause of death in more than 20% of cancer patients.

Purpose. To determine whether a nutritional and pharmacological support could improve advanced cancer patients body weight.

Patients and methods. From June 2011 till January 2012 we conducted a pivotal experience in our institution. We prospectively enrolled 20 advanced cancer patients with a weight loss equal to or exceeding 5% of the initial body weight, previous to cancer diagnosis and during the last 6 months. Patients characteristics are summarized in Table 1.

Table 1 - Patients characteristics

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Patients (N = 20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, N (%)</td>
<td>14 (70%)</td>
</tr>
<tr>
<td>Age, yrs, median (range, yrs)</td>
<td>66 (28-82)</td>
</tr>
<tr>
<td>Solid malignancy, N (%)</td>
<td>100%</td>
</tr>
<tr>
<td>• colon cancer, N (%)</td>
<td>9 (45%)</td>
</tr>
<tr>
<td>• gastric cancer, N (%)</td>
<td>4 (20%)</td>
</tr>
<tr>
<td>• pancreatic cancer, N (%)</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>• ovarian cancer, N (%)</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>• breast cancer, N (%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Weight loss isolated, N (%)</td>
<td>12 (60%)</td>
</tr>
<tr>
<td>Weight loss associated to serum proteins reduction, N (%)</td>
<td>8 (40%)</td>
</tr>
<tr>
<td>Weight loss degree versus initial body weight</td>
<td></td>
</tr>
<tr>
<td>• 5%, N (%)</td>
<td>4 (20%)</td>
</tr>
<tr>
<td>• 8%, N (%)</td>
<td>6 (30%)</td>
</tr>
<tr>
<td>• 10% N (%)</td>
<td>10 (50%)</td>
</tr>
</tbody>
</table>
We provided to all patients daily oral administration of ascorbic acid (1 g), eicosapentaenoic acid and docosahexaenoic acid association (3 g), methylprednisolone (16 mg) and nutritional support (1 pudding with 200 kcal and 12.5 g of proteins). In addition, patients with low serum albumin, prealbumin and total proteins levels received, every day, whey proteins (20 g) or branched aminoacids supplements (20 g).

**Results.** Patients with a 5% of weight loss regained the initial weight in 60 days; the 6 patients with 8% of weight loss recovered the original body weight in 90 days. The remaining cohort of patients is still regaining the original weight and, at present, has already recovered the 60% of the whole weight loss. Furthermore in those patients receiving whey proteins or aminoacids supplements we obtained the normalization of reduced serum parameters.

**Conclusions.** The described supportive therapy is simple, easy to administer, not expensive and associated to a good compliance. The results we obtained are the expected results, in fact early nutrition supplementation contrasted weight loss and allowed a good weight recovery with normalization of blood nutritional parameters and improvement in patients quality of life.

**C27 HIGH OPIOID DOSAGE RAPID DETOXIFICATION MODEL IN PALLIATIVE CARE**


*Pain Therapy and Palliative Care Unit, Hospice, Infermi Hospital, Rimini; **Department of Radiotherapy Barbieri-Mazzarotto, Sant’Orsola-Malpighi Hospital, Bologna; **Pain Therapy Center of Sol et Salus, Torrepedrera, Rimini

**Background.** Major opioids are used for the treatment of cancer pain, in accordance with the World Health Organization (WHO) recommendations. Chronic opioid administration, however, can induce toxicity, tolerance and/or hyperalgesia. Opioid rotation is the treatment option in this case, however, due to the inaccuracy of available equianalgesic tables, it can expose patients to long periods of ineffectiveness and/or development of withdrawal syndrome, overdose or toxicity. In order to overcome this issue, we developed a method of rapid detoxification from opioids.

**Aims.** To assess feasibility and efficacy of our opioid detoxification protocol in patients affected from chronic cancer pain.

**Settings/patients.** We studied 15 patients, with chronic cancer pain, who were in therapy with high doses of opioids (≥100 mg of morphine sulfate dose equivalent) and needed opioid rotation or therapeutic variation because of opioid toxicity, inefficacy, tolerance or hyperalgesia. Each patient received a fixed dose of envenous morphine and clonidine plus oral ketoprofen or ibuprofen, and oral lorazepam, if required, for at least three days, suspending the previous opioid therapy. We monitored withdrawal symptoms, pain intensity, type and intensity of adverse events.

**Results.** The characteristics of the sample were the following: 12 (80%) males, and 3 (20%) females, mean age 67.6 years, detoxification reasons: two (13.3%) hyperalgesia, 9 (60%) tolerance and 4 (26.7%) inefficacy. All patients completed the rapid detoxification treatment.

Average duration of the detoxification protocol was 6.86 ± 6.4 days (range 3-22). Withdrawal symptoms were experienced by 4 (26.6%) patients, however they were of mild-moderate intensity, and did not result in protocol interruption. The average NRS for pain decreased significantly (p <0.05) from 8.3 ± 1.57 to 3.6 ± 1.4 at the end of the detoxification; and to 2.4 ± 1 at the end of the rotation or therapeutic adjustment.

**Conclusions.** Our detoxification protocol was effective in preventing any relevant withdrawal signs in patients needing a therapeutic change because of opioid-induced tolerance, hyperalgesia or toxicity.

**C28 CHEMOTHERAPY IN ONCOLOGICAL PATIENTS NEAR THE END OF LIFE: A RETROSPECTIVE SINGLE CENTER ANALYSIS**

Borghi E., Basiella L., Martinelli B., Pinotti G.

Medical Oncology, Ospedale di Circolo-Fondazione Macchi, Varese

**Background.** Prescription of palliative chemotherapy (PCT) represents a delicate equilibrium between toxicity and potential clinical benefit. Since PCT has been increasingly used in patients with a short life expectancy during the last decade, both evaluation of patients’ prognosis and recognition of the importance of high-quality end-of-life care play a key role.

**Patients and methods.** We retrospectively evaluated the use of PCT near the end of life (last month and last two weeks) in patients who died of advanced solid cancers in our institution in 2010 and the correlation between PCT, causes and place of death.

**Results.** 143 patients were included in this analysis, Median age: 67 years. M/F: 70/73. Most common cancer origin: breast (20.3%), lung (17.5%), stomach (10.5%) and colon-rectum (9.1%).

In the last month of life, 21% of patients received PCT. Median age: 65 years. Age <50 years: 13.3%. Male: 56.7%. Most common cancer origin: breast (16.7%), lung (16.7%), stomach (13.3%). Median chemotherapy lines received: 2. PCT: monocytchemotherapy in 76.7%.

In the last 2 weeks of life, 11.9% of patients received PCT. Median age: 68 years. Age <50 years: 17.6%. Male: 41.2%. Most common cancer origin: colon-rectum (17.6%), breast (11.8%), lung (11.8%), stomach (11.8%). Median chemotherapy lines received: 2. PCT: monochemotherapy in 62.5%.

We observed that 60% and 64.7% of patients treated respectively in the last month and two weeks of life had at least one hospital admission in the last three months of life versus 54.1% of patients who didn’t receive PCT in the last weeks of life. Hospitalizations were mainly due to advanced cancer symptoms. Table below shows place of patients’ death.

<table>
<thead>
<tr>
<th>No PCT in last weeks of life</th>
<th>PCT in the last month of life</th>
<th>PCT in the last two weeks of life</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hospital</strong></td>
<td>41%</td>
<td>43.3%</td>
</tr>
<tr>
<td><strong>Hospice</strong></td>
<td>21.3%</td>
<td>13.3%</td>
</tr>
<tr>
<td><strong>Home palliative care</strong></td>
<td>6.6%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>31.1%</td>
<td>43.4%</td>
</tr>
</tbody>
</table>

**Conclusions.** A sizeable proportion of patients with a short life expectancy receive PCT. The awareness to ensure the patient not only the best therapies but also the best quality of life helps
the physician to define advanced cancer patient’s therapeutic program. Physician-patient relationship plays a key role in this decisional process.

C29 TRANSPERSONAL THERAPY COMBINED WITH BEST SUPPORTIVE CARE IN HOSPICE IMPROVES PATIENT’S QUALITY OF LIFE AND QUALITY OF DEATH

Aragona M., Samiani R.A., Picone G.S., Lupo G., Scorza N., Grasso C., Schepisi G., Altavilla G.

Human Pathology Department, Medical Oncology and Hospice Unit, University of Messina

Introduction. The experience of dying is extremely difficult both for patients and families. The time at the end of life is different for each person. Transpersonal medicine is particular useful in this context because of the possibilities to overcome the boundaries from the perception of personality and identity towards the perception of unity: this is a modified state of consciousness, peak experience, very useful to guide subjects in the uncertainty of death and dying.

Methods. Transpersonal psychotherapeutic model applied in our Oncological Hospice is originated by J. Grossman’s work with main-body-spiritual approach, bioenergetics, breathing, deep meditation in modified state of consciousness and peak experiences induction.

Twenty-six terminal ill patients with their caregivers were studied in hospice and 50% of them received a transpersonal treatment of preparation to death and 50% constituted a control group.

Patients quality of life (QoL) and quality of death (QoD) were evaluated by visual analogical scales according to Curtis-Smith criteria, modified, and administered to health care staff. Pain, pharmacological sedation and state of consciousness before the end of life were also evaluated.

Results. Twenty-six patients, that received best supportive care, were divided in a study transpersonal group (13 patients) and a control group (13 patients).

QoL improved in transpersonal patients group (5.39 ± 0.87) with respect to controls (4.5 ± 1.13) with significative difference (p = 0.035)

QoD improved in transpersonal patients group (5.95 ± 0.94) compared to controls (5.09 ± 1.11) with significative difference (p = 0.045).

No significative differences were observed for the other parameters.

Conclusions. Verbal interventions are frequently inapplicable in dying patients. Other methods, like transpersonal, that use modified state of consciousness, are necessary.

Our data show that receiving specific transpersonal intervention allows patients to approach death with better QoL and to live quietly the experience of dying (improvement of QoD score), compared to patients in the control group. All patients received the best supportive care.

This research is in progress, but suggests the usefulness of this method in this extremely difficult clinical context.

C30 PALLIATIVE SEDATION/TERMINAL SEDATION (PS/TS): OUR EXPERIENCE IN SERVICE PALLIATIVE CARE CANCER HOME CARE


U.O. Aziendale Oncologia Medica-ODO, Olbia; *Psychologist Association P. Secchi Onlus

Terminal/Palliative Sedation (TS/PS) is a drug induced reduction of vigilance, till lose the consciousness, in order to reduce or abolish the perception of intolerable and uncontrollable symptoms. In our Oncological Palliative Home Care Service, we evaluated the feasibility of the TS/PS at home in patients with refractory symptoms. We also assessed the impact of palliative sedation on the patient’s family. From January 2011 to April 2012, 214 terminal cancer patients were assisted at home. Seventy-one patients showed refractory symptoms in their last life-time (69.5% respiratory distress, 23% delirium, 7% occlusive syndrome, 0.5% bleeding). In 52 patients was performed planned TS/PS, whereas in 19 patients out of 71 emergency palliative sedation was performed. In the 27% of circumstances the decision was shared with the patient and in 73% with family members.

The most frequent tumors were lung and breast cancer, sarcomas and glial cell tumors. Midazolam is the drug we used in 95% of cases, intravenous continuous infusion with an elastomeric pump associated with other drugs useful for the control of symptoms (morphine, haloperidol, butyl-scopolamine). The induction dose of midazolam was between 10 and 45 mg and the maintenance one between 80 and 1200 mg/day (the highest doses were necessary in young patients treated with high doses of morphine). Grade 3-6 sedation (Ramsay scale) was obtained in 95% of patients within 6 hours; the monitoring of life parameters was performed every 4-6 hours till reach the desired level of sedation and the average duration of sedation was 1.8 days. During the period of the TS/PS was administered NaCl 500 cc/24 hours.

Conclusions. In this small study we would show that the TS/PS can be performed at home and that we can get a good control of the emotional stress (both in the relatives and in the medical staff) which inevitably appears when the patient has a high degree of pain.

<table>
<thead>
<tr>
<th>Ramsay scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Anxious and agitated patient</td>
</tr>
<tr>
<td>2 Partner, oriented, quiet patient</td>
</tr>
<tr>
<td>3 Responds only to controls</td>
</tr>
<tr>
<td>4 Responds to strongly stimulation</td>
</tr>
<tr>
<td>5 Responds to slightly stimulation</td>
</tr>
<tr>
<td>6 No response to stimulation</td>
</tr>
</tbody>
</table>

C31 ZOLEDRONIC ACID VERSUS DENOSUMAB IN METASTATIC BONE DISEASE: SYSTEMATIC REVIEW OF THE LITERATURE

Garigliano D., Rossi M., Ciliberto D., Tagliaferri P., Tassone P.

1Medical Oncology Unit, University of Magna Gracia and Tommaso Campanella Cancer Center, Catanzaro

Background. The efficacy of zoledronic acid (ZA), about incidence of skeletal related events (SREs), in patients with cancer bone disease was showed in many studies, while recent findings highlight its role as antineoplastic agent. Denosumab (Den), a monoclonal antibody directed towards RANKL, has shown a clinical impact on patients with cancer bone disease.
**Objective.** To perform a systematic review and a meta-analysis of studies that compare ZA and Den, with principal endpoints: SRE incidence, toxicity and clinical outcomes.

**Methods.** Data were retrieved from full papers and abstracts from medical databases (Pubmed, Cancerlit, Embase, Medscape and Cochrane) and selected meeting abstracts (ASCO, ESMO). Hazard ratios (HRs) of SREs, overall survival (OS) and progression disease (PD) and risk ratios (RRs) of adverse events were performed by the fixed-effects model and random-effect model respectively. The consistency of the results was evaluated by performing the test of heterogeneity (I² Statistic ([Q-df]/Q×100)).

**Results.** Three randomized trials were selected. Metastatic bone disease including multiple myeloma, breast cancer and prostate cancer were evaluated each independently in 1 study. Primary endpoints were: first SRE, OS, PD. 5729 patients were randomized to receive monthly ZA (4 mg i.v.) versus monthly Den (120 mg sc). Overall, SRE rates were lower in presence of Den than with ZA. HR of SREs demonstrates an advantage for treatment with Den (p = 0.001; HR = 0.828; 95% CI 0.76-0.90). Adverse event rates were not different between ZA and Den, except for hypocalcemia, which is more frequent with Den (RR = 0.52; 95% CI 0.284-0.944; p = 0.032). Clinical outcomes were evaluated and no statistical difference was found for OS (HR = 0.98; 95% CI 0.91-1.06; p = 0.626) and PD (HR = 1.02; 95% CI 0.96-1.09; p = 0.533).

**Conclusions.** Denosumab is more efficacious in reducing the occurrence of SREs, although no difference on the clinical outcome was observed.

C32 MAJOR ISSUE IN CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY (CIPN): LACK OF STANDARDIZED MEASUREMENT SCALES. CI-PERINOMS STUDY: VALIDITY AND RELIABILITY IN CIPN ASSESSMENT

Cortinovis D.1 , Cazzaniga M.E.1 , Cavaletti G.2, Giuntini N.1, Canova S.1 , Alberti P .2, Bidoli P .1 on behalf of the CI-Perinoms Study Group

1SC Oncologia Medica, 2SC Neurologia, H. S. Gerardo, Monza

**Background.** Chemotherapy-induced peripheral neuropathy (CIPN) is a dose-limiting adverse event of anticancer drugs. A simple and valid method to assess CIPN has not yet been individuated so far; lack of a gold standard measure is still an unmet clinical and scientific need, in particular mandatory to design consistent neuroprotective trials. This study was performed to select a valid and reproducible outcome measure among existing scales.

**Patients and methods.** These scales were selected to be tested, after a revision of literature and an expert consensus meeting: National Cancer Institute Common-Toxicity-Criteria (NCI-CTC), Total Neuropathy Score (TNSc), modified INCAT sensory sumscore (mISS), European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 and CIPN20 quality of life measures. Two hundred and eighty-one cancer patients, with a proven stable cancer and multiple myeloma were enrolled. Inter-/intra-rater agreement was calculated through K-Cohen coefficients and 95% confidence intervals. Validity tests were performed, through Kruskal-Wallis equality-of-populations rank test, relating mISS and TNSc to NCI-CTC grades.

**Results.** From September 2008 to December 2010, 281 patients affected by colorectal, breast, ovarian, non-small cell lung cancer and multiple myeloma were enrolled. Inter-/intra-rater observer scores (i.e. r >0.7) were obtained for TNSc, mISS, and NCI-CTC sensory/motor subscales. Test-retest values were high also for EORTC QLQ-C30 and for the CIPN20. Acceptable validity scores were obtained through for mISS and TNSc compared to NCI-CTC (p values 0.04 to <0.001).

**Conclusions.** Proper validity and reliability scores were demonstrated for selected scales. This does not imply that they are equally reliable in CIPN assessment, since responsiveness issues have not yet been fully investigated. However presented results will help to answer this need, allowing further studies aimed to elect the gold standard measure among those instruments. Subsequently it will be possible to design neuroprotective trials on a solid methodological background.

C33 CASE-CONTROL PHASE II CLINICAL TRIAL TO ASSESS EFFICACY AND SAFETY OF THE SAME ANTINEOPLASTIC TREATMENT IN ELDERLY “FIT” COMPARED TO ADULT PATIENTS WITH CANCER AT DIFFERENT SITES

Mantovani G., Massa E., Dessi A., Dessi M., Orgiano L., Tanca F.

Department of Medical Oncology, University of Cagliari

**Background.** We designed a case-control phase II open, prospective non-randomized trial in elderly “fit” (~65 yrs) cancer patients compared to well-matched adult (45-65 yrs) cancer pts to assess whether the same standard antineoplastic treatment could achieve comparable results as for efficacy and safety. Planned sample size:125 pts per arm. Endpoints: safety, QoL, PFS, ORR, dose intensity.

**Patients and methods.** Only elderly “fit” pts at MGA were included. Inclusion criteria for elderly: histological diagnosis of cancer with either advanced disease with measurable lesions or radically resected (adjuvant setting); life expectancy >3 months; adequate baseline functional parameters; written informed consent. Inclusion criteria for adults: the same as for elderly plus ECOG-PS 0-1.

**Results.** At September 2011, 254 pts were enrolled, 127 elderly and 127 adults, all evaluable for toxicity. Elderly pts clinical characteristics: M/F ratio 69/58; mean age 70.8 ± 4.5 years. Adult pts: M/F ratio, 58/69; mean age 53 ± 5.4 years. Tumour sites: colorectal (23.5%), head and neck (16.4%), breast (14.1%), lung (11.7%), ovarian (9.3%); prostate (6.2%), NHL (4.7%), gastric (4.7%), liver (4.7%), uterus (3.9%), pancreas (0.8%); 92.1% of pts were stage IV, 5.9% stage III and 2.0% stage II. In the elderly no grade 4 toxicity was observed, hematological and non-hematological grade 3 toxicities were observed in 12.21% and 13.8% of pts, respectively. In the adults, grade 4 hematological and non-hematological toxicity were observed in 3.8% and 1.9% of pts, respectively; grade 3 hematological toxicity in 23.2% and non-hematological toxicities in 21.3% of patients. The difference was statistically significant (p = 0.042) in favour of the elderly. In September 2011, 234 pts were assessable for response: the ORR was 50.7% for elderly and 51.1% for adults. No differences were observed for quality of life and dose intensity between the two groups. PFS was 10.6 mos (3-12+ mos) for elderly and 9.05 mos (3-12+) for adults.
Conclusions. The promising results of this single Institution study warrant to be confirmed by a larger clinical trial.

C34 PSYCHOLOGICAL FUNCTIONING OF ELDERLY LONG-TERM CANCER SURVIVORS: AN ITALIAN DESCRIPTIVE STUDY

Annunziata M.A.1, Muzzatti B.1, Giovannini L.1, Flaiban C.1, Mattioli V.2, Tirelli U.3

1SOSD di Psicologia Oncologica, IRCCS Centro di Riferimento Oncologico di Aviano, Aviano (PN); 2UO di Anestesia e Rianimazione, IRCCS “Giovanni Paolo II”, Bari; 3SOC di Oncologia Medica A, IRCCS Centro di Riferimento Oncologico di Aviano, Aviano (PN)

Background. Ageing itself modifies people quality of life and functioning. Cancer may deteriorate this natural process by adding further physical and/or psychological symptoms that often persist for long time after treatment completion. In this study the psychological functioning of 65+ years old Italian long-term cancer survivors (i.e. persons free from cancer and its treatments for at least 5 years) has been assessed by describing depressive and anxious states, health status and post-traumatic growth and by associating them with several socio-demographic and clinical variables.

Methods. Ninety elderly (age range 65-80 years; Mdn = 70) long-term cancer survivors (survival length range 5-31 years; Mdn = 10) compiled the State-Trait Anxiety Inventory, the Zung Self-rating Depression Scale, the Short Form 12 Health Survey Questionnaire, and the Post-traumatic Growth Inventory.

Results. 10.3% and 15.4% of the sample were, respectively, possible and probable cases for the state anxiety whereas 13.5%, 15.7% and 6.7% displayed, respectively, mild, moderate and severe depression. Both state anxiety and depression were associated with gender (p = 0.010; p = 0.048), but not with education, marital status, cancer type, survival length, other health problems, physical health status was associated with marital status (p = 0.013) and other health problems (p = 0.006), but not with gender, education, cancer type, survival length whereas mental health status was associated only with other health problems (p = 0.018). Finally, post-traumatic growth was associated with cancer type (p = 0.023) and other health problems (p = 0.013), but not with gender, education, marital status, survival length.

C35 THE IMPORTANCE OF NEGATIVE PREDICTIVE VALUE FOR THE ACCURACY OF VULNERABLE ELDERLY SURVEY AS A PRESCREENING TEST


*Oncology Department, San Giacomo Hospital, Novi Ligure; Epidemiology Department SSEPI ASL AL;Geriatric Department ASL AL

Introduction. The importance of prognostic value of the Comprehensive Geriatric Assessment (CGA) is well known in geriatric oncology. Although this tool of assessment is considered too time consuming, there is no consensus on the use of alternative abbreviated screening methods for the evaluation of older patient disabilities.

Aim. To evaluate if Vulnerable Elderly Survey 13 (VES 13), according to the negative predictive value (NPV), could be an useful tool in order to identify those vulnerable patients able to avoid the more elaborate CGA procedure.

Materials and methods. The participants in this study underwent VES 13 administered at first entry in Oncology department and were later assessed by a geriatrician of the National Health System using CGA. A score of ≥3 for VES 13 identified individuals as vulnerable. As for CGA we defined an index of disability a score of ≥5 for CIRS, ≥7 for ADL or IADL and ≥5 for SPMSQ. Finally, the specificity, sensibility, positive predictive value (PPV), and negative predictive value (NPV) of VES 13 vs CIRS, ADL, IADL and SPMSQ were estimated.

Results. 117 patients (70 males and 47 females) entered the study. The median age was 78.8 years. The most important re-

<table>
<thead>
<tr>
<th>Table C35 - Comparison between VES 13 and CGA tools</th>
</tr>
</thead>
<tbody>
<tr>
<td>VES13</td>
</tr>
<tr>
<td>&lt;3</td>
</tr>
<tr>
<td>CIRS</td>
</tr>
<tr>
<td>Disability</td>
</tr>
<tr>
<td>Tot</td>
</tr>
<tr>
<td>IADL</td>
</tr>
<tr>
<td>Dependence</td>
</tr>
<tr>
<td>Tot</td>
</tr>
<tr>
<td>ADL</td>
</tr>
<tr>
<td>Dependence</td>
</tr>
<tr>
<td>Tot</td>
</tr>
<tr>
<td>SPMSQ</td>
</tr>
<tr>
<td>Moderate/severe impairment</td>
</tr>
<tr>
<td>Tot</td>
</tr>
</tbody>
</table>

LL = Lower Limit 95% CI; UL = Upper Limit 95% CI; Sens = Sensibility; Spec = Specificity; PPV = Positive Predictive Value; NPV = Negative Predictive Value; LR+ = Likelihood Ratio positive; LR- = Likelihood Ratio negative.

References. None.

Conclusions. Although present data show elderly psychological functioning being quite similar to psychological functioning of cancer survivors of other age groups, a substantial minority report anxiety and/or depressive levels that ask for clinical attention. Further research should extend the study of other relevant psychological dimensions (e.g. cognitive functioning, fear of relapse) to elderly long-term cancer survivors too.
mark of this study is the high correlation between VES 13 and the CGA tools in terms of NPV. In fact, the NPV of VES was 74.6% for CIRS, 90.1% for IADL, 93.0% for ADL and 100% for SPMSQ. As for PPV, on the contrary, the VES 13 showed no accuracy. The PPV for CIRS was 39.13%, for IADL 63.04%, for ADL 23.91% and for SPMSQ 15.22%.

Conclusions. We can conclude that, taking into consideration its high NPV, VES 13 demonstrated sufficient accuracy in identifying elderly vulnerable patients with cancer, so that it could be useful as a prescreening test in order to spare the more time consuming CGA for this set of individuals.

C36 COGNITIVE IMPAIRMENT AND ORAL CHEMOTHERAPY IN ELDERLY CANCER PATIENTS

Locatelli C., Spazzafulmo L., Leo S.*, Invitto S.*, Bovino C.*, Ciccarese G.*, Cicchiera M.

UOC Oncologia, INRCA-IRCCS, Roma; °UO Oncologia Vito Fazzi, Lecce; *Università del Salento, Lecce

Epidemiological and economic considerations will result in an increasing level of de-hospitalization in the future planning and organization of health services in oncology.

In this scenery, oral chemotherapy has been assuming a more important role.

To many patients, swallowing a pill is less unpleasant than repeated drug infusions and more convenient, requiring fewer office visits.

A central issue encountered by clinicians in the introduction of oral therapy is the potential non-adherence to treatment by patients, in terms of wrong dosage (under/over dosing) and/or delayed recognition of toxicity.

Consequently, for a good management of treatment it is essential that patients are cognitively appropriate to be instructed on the proper way of taking the therapy.

We performed a larger study, “Psych-Onc: Psychiatric and Oncological patients. Epidemiology of psychiatric disorders in adult oncological patients”. In this paper we reported only the results from the neuropsychological battery, sensitive to the effect of cognitive impairment.

The neuropsychological battery includes: MMSE; Rey-Osterrieth Complex Figure (ROCF); Rey Auditory Verbal Learning Test (immediate and delayed recall); Progressive Raven’s Matrices and phonemic verbal fluency test.

Results. 250 patients were recruited in 4 Centers. 168 (67.2%) are <65 yrs = Young Group (YG) and 82 (32.8%) are >65yrs = Older Group (OG). Median age is 57.6 yrs. The YG consisted of more female 81% versus 40.2%.

There is no significant difference between age and stage of disease, measure of intelligence and language competence. Significant differences between age and cognitive abilities, memory (short and long term) and executive abilities were found with a worse performance by OG (Table 1).

We think that for a conscientious management of oral therapy at home, physicians should test every time the elderly patient’s ability to understand information about the proper use of each medication (dosage, timing) and the recognition of adverse drug reactions.

Physicians need a quick tool to verify every time the patient’s ability to manage in autonomy and safety the oral therapy.

C37 FEBRILE NEUTROPENIA IN CANCER PATIENTS MANAGED AT A SINGLE INSTITUTION: A RETROSPECTIVE ANALYSIS OF RISK FACTORS

Pella N.1, Giangreco M.2, Foltran L.1, Ermacora P.1, Rihawi K.1, Mazzer M.1, Menotti P.1, Bin A.1, Pisa F.2, Fasola G.1

1Dipartimento di Oncologia, 2Istituto di Igiene ed Epidemiologia Clinica, Azienda Ospedaliero-Universitaria “S. Maria della Misericordia”, Udine

Background. Febrile neutropenia (FN) is one of the most frightening complications of chemotherapy (CT) in cancer patients in terms of morbidity, mortality and healthcare costs. Clinical and management behaviours were retrospectively investigated as potential risk factors.

Methods. Medical records of 105 consecutive pts admitted for FN to our Department between 2006 and 2011 were reviewed. Risk assessment was calculated by the validated Multinational Association for Supportive Care (MASCC) scoring index1 to distinguish between high-risk cases scoring <21 and low-risk cases >21 points. Other clinical parameters were analyzed: age, ECOG performance status (PS), primary tumour site, type and setting of CT, presence of indwelling i.v. catheter. The adherence to most compelling statements of ESMO guidelines2 was analyzed as well. The distribution of these variables was compared through Chi-square or Fisher test (significance level set at p = 0.05). Odds ratios (OR) (95% CI) were calculated through unconditional logistic regression to estimate the relative risk.

Results. MASCC high-risk (OR = 6.75, CI = 1.05-43.39), age >70 years (OR = 8.40, CI = 1.29-54.59) and presence of indwelling i.v. catheter (OR = 7.24, CI = 1.12-46.66) significantly correlated with mortality; ECOG PS, type and setting of CT didn’t. Receiving palliative CT (OR = 2.37, CI = 1.02-5.51) and presence of indwelling i.v. catheter (OR = 4.30, CI = 1.12-16.69) significantly correlated with length of hospitalization. We couldn’t find any correlation between GCSFs prophylaxis or type of antibiotic used and principal outcomes measured in our population.

Table C36

<table>
<thead>
<tr>
<th>Test</th>
<th>Cognitive function</th>
<th>YG scores under cut-off</th>
<th>OG scores under cut-off</th>
<th>Pearson Chi-squared</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mini Mental State Examination</td>
<td>Cognitive abilities</td>
<td>0.6%</td>
<td>8.5%</td>
<td>11.143 p &lt;0.001</td>
</tr>
<tr>
<td>Rey auditory verbal learning immediate</td>
<td></td>
<td>1.0%</td>
<td>30%</td>
<td>15.175 p &lt;0.001</td>
</tr>
<tr>
<td>Rey auditory verbal learning delayed recall</td>
<td></td>
<td>6%</td>
<td>15%</td>
<td>5.341 p &lt;0.021</td>
</tr>
<tr>
<td>Rey-Osterrieth Complex Figure Delayed recall</td>
<td></td>
<td>20.04%</td>
<td>39.02%</td>
<td>9.154 p = 0.002</td>
</tr>
<tr>
<td>Progressive Raven’s Matrices</td>
<td>Measure of intelligence</td>
<td>7.2%</td>
<td>6.3%</td>
<td>0.080 p = 0.777</td>
</tr>
<tr>
<td>Phonemic verbal fluency</td>
<td>Language competence</td>
<td>11.1%</td>
<td>13.9%</td>
<td>0.397 p = 0.529</td>
</tr>
<tr>
<td>Copy Rey-Osterrieth Complex Figure</td>
<td>Executive abilities</td>
<td>22.9%</td>
<td>47.3%</td>
<td>14.028 p &lt;0.001</td>
</tr>
</tbody>
</table>
Conclusions. In our retrospective analysis MASCC scoring index correlated with mortality only. Other clinical parameters like age >70 years, presence of indwelling i.v. catheter and palliative setting of CT were detected as potential risk factors for death or length of hospitalization.

References

C38 HEALTH RESOURCE UTILIZATION (HRU) ASSOCIATED WITH SKELETAL-RELATED EVENTS (SRES) IN PATIENTS WITH BONE METASTASES (BM) IN ITALY: A PERSPECTIVE OF THE REGIONAL HEALTH AUTHORITIES (RHAS)

Cavallo M.C.1, Gerzeli S.2, Tarricone R.1, Rognoni C.3, Cortinovis D.4, Cheli A.5, Gozzo M.6
1Centre for Research on Health and Social Care Management (CERGAS), Bocconi University, Milan; 2Department of Political and Social Sciences, 3Laboratory for Biomedical Informatics, Department of Industrial and Information Engineering, University of Pavia, Pavia; 4SC Oncologia Medica, Ospedale S. Gerardo, Monza; 5Amgen Dompè Italy

Background. Bone metastases/lesions are commonly associated with skeletal-related events (SREs) and are likely to result in increased patient morbidity. A more comprehensive understanding of the economic burden of SREs is needed to assess future resource requirements and evaluation of new treatments that prevent or delay these events.

Objectives. To estimate the cost of SREs in patients with bone metastases secondary to solid tumours (i.e. breast, prostate and lung) from the perspective of a third-party payer.

Methods. In a previously reported prospective multinational observational study (Hechmati et al., ISPOR US, 2011), HRU associated with SREs (spinal cord compression [SCC], surgery to bone [SB], pathologic fracture [PF] or radiation to bone [RB]) was collected. This analysis uses data for patients with bone metastases secondary to breast, prostate or lung cancer, with a life expectancy >6 months, ECOG ≤2, and who were enrolled in centers in Italy after experiencing a SRE. Physician-attributed HRU data were collected retrospectively for the 90 days prior to enrolment and prospectively for up to 18-21 months across 95 European sites for 631 eligible patients. A previous cost-conversion analysis (Hechmati et al., ISPOR EU, 2011) estimated costs by SRE type using the Italian national reimbursed fees. Our analysis estimated the economic burden due to each HRU category by SRE type in the 21 RHAs, using the 2012 reimbursed RHA fee for each of the following categories, i.e. inpatient stays, day care, outpatient visits, emergency-room visits, home healthcare, nursing home, long term care facility stays and diagnostic procedures.

Results. Median cost per SCC management across RHAs was 3814.91 € (SD 972); median cost per SB management was 2116.06 € (SD 316) and median cost per RB management was 2398.33 € (SD 707). The highest costs due to SREs management for SCC, SB, PF and RB were registered in the regions of Umbria, Bolzano, Umbria and Piedmont respectively.

Conclusions. Costs per SRE event varied depending on the type of HRU and local tariffs, however all SREs examined in this analysis were associated with substantial costs to the regional payer. Preventing SREs can reduce a regions financial burden associated with management of patients with bone metastases secondary to solid tumours.

C38BIS NURSING INTERVENTION IN EMPOWERMENT AND MONITORING OF PATIENTS TAKING ORAL CHEMOTHERAPY: EVALUATION OF TOXICITY, IMPROPER ACCESSES TO HOSPITAL AND RISK OF INCORRECT DOSING

Lunardi G., Ciccarelli L., Alestra S., Orlando B., Terzi A., Zivelonghi S., Coati F., Nicodemo M., Cirillo M.
Oncologia Medica, Ospedale Sacro Cuore Don Calabria - Negar (VR)

Background. There is an increasingly frequent use of oral chemotherapy medications. Since March 2011, we organized a nursing intervention for patient empowerment and phone-based surveillance of patients taking oral chemotherapy.

Patients, who had to assume oral drugs, after the briefing with the physician, received by nurses all necessary information about treatment and the associated risks. With drug delivery, patients received a diary (detailed for each treatment) reporting all instructions given from nurses. Nurses contacted patients by phone during the first two cycles of chemotherapy to assess patient adherence to treatment and their side effects.

We evaluated whether such nursing intervention may influence: toxicity, improper accesses to hospital and risk of incorrect dosing.

Methods. Data regarding toxicity (namely grade ≥2 according to CTCAE), improper accesses to hospital and risk of incorrect dosing, were collected from patients who received nursing intervention. We compared these data with matched retrospective ones obtained from consecutive patients who received oral chemotherapy before March 2011.

Results. Eighty-one patients received nursing intervention (group A), while comparable retrospective data were obtained from 88 patients (group B).

Toxicity of grade 3 was recorded in 6% of group A and in 13% of group B patients. Improper accesses to hospital were 6% in group A and 11% in group B. No incorrect dosing was recorded in group A, while 3 patients (3%) in group B made mistake in drug dosing (two wrong dose and one duration of chemotherapy).

Conclusions. Nursing intervention based on patient empowerment, on a diary and a phone-based surveillance may be useful to prevent the occurrence of severe toxicities, to decrease improper accesses to hospital and to minimize the risk of incorrect drug dosing.

C39 THE TREATMENT OF BREAKTHROUGH CANCER PAIN (BTCP) AND THE CORRELATION WITH ANXIETY AND DEPRESSION IN LUNG CANCER PATIENTS

...
Fulvi A.1, De Santis S.1, Ricciardi S.1, Gori B.1, Del Signore E.1, Ciurturii P.2, D’Antonio C.1, de Marinis F.1

11st Oncological Pulmonary Unit, 2Clinical Psychology Service, San Camillo High Specialization Hospital, Rome

Introduction. Cancer patients who experienced symptoms such as pain, enjoying an advantage in Quality of Life (QoL) with treatment and it implies considerable psychological burden. Breakthrough pain describes reports of pain that ‘breaks through’ around the clock analgesia.

Methods. It was conducted one observational study on cancer patients in advanced stage, with chronic pain base controlled by at least 3 days with oxycodone and naloxone. All subjects have compiled the Hospital Anxiety and Depression Scale (HADS). BTcP and chronic pain are evaluated with NRS (numerical rating scale). The effectiveness of rescue medication is evaluated as the difference of the intensity of pain from the baseline, at 10 minutes after taking the medication (pain intensity difference PID) and the subjective evaluation of efficacy expressed by the patient with 5 points scale to GI (General Impression).

Results. From April 2011 to October 2011 were observed 35 patients with a-NSCLC which showed moderate-intensity pain severe in 80% of cases (28 patients) and 17 patients (60%) with BTcP. The origin of the BTcP was related to the neoplasm and metastases (75%); in 10% of cases was attributable to radiotherapy and chemotherapy. The daily average of the episodes was 2 per day. About BTcP therapy, all patients were treated with oral transmucosal fentanyl citrate. Fentanyl is effective in producing results in significant differences in intensity of pain, such as a reduction of at least 2 points on the GI scale, and a significant pain relief with the average two PID. Clinically levels of anxiety (HADS anxiety ≥11) were found in 22% and 63% respectively, while depressive symptoms (HADS depression ≥11) were found in 18% and 76% respectively.

Conclusions. This study confirms the high prevalence of anxiety and depression in patients that experienced BTcP and chronic pain and that the application of the guidelines on cancer pain and recommendations on BTcP allow an effective control of cancer pain in most patients.

C40 “OSPEDALIZZAZIONE DOMICILIARE ONCOLOGICA”: THE TRADITIONAL MODEL OF CARE ALTERNATIVE TO HOSPITALIZATION IN THE TERMINAL CANCER PATIENT


UO Aziendale Oncologia Medica e ODO, *Area Programazione Controllo Committenza, ASL 2, Olbia

Each year about 250,000 people in Italy that should be followed with 160,000 well-palliative approach are ill with cancer. In Europe palliative care (PC) is a growing care sector due to increasing prevalence of chronic diseases characterized by a high final phase of suffering and the growing interest in developing interventions aimed at improving the quality of human life particularly in its final stages. ASL 2 of Olbia is on an organizational model called ODO-care (home hospitalization cancer), centered on activation network CP. Center has doctors and nurses experienced in assessing and treating pain. Team is formed by oncologists and nurses of OUC oncologia Medica ASL 2 Olbia; the GP is part of the team. Three doctors and 3 nurses are on duty on weekdays in the service of CP. The nights and holidays are covered on call for urgent action, a mobile unit. From July 2006 to December 2011, were cared 645 patients for a total of 27,412 days, the visits were: 10,298 cancer doctors, 11,597 nurses, 1,997 GPs, 527 psychologists; access at home were 16,690 with average IA of 0.61. In 2011, 160 patients were followed up terminals with a mean age of 68.8 years, with different neoplasias. Patients were assisted in 20 municipalities in the district of Olbia, for a total of 4887 days, with an average stay of 30.5 days and an average cost of 3000 euros. The clinical visits were: 2357 medical oncologists, 2453 nurses, 618 GPs, 42 psychologists, the number of accesses 3135 with an IA 0.64. Only 7% of patients died in hospital. Fundamental task of ODO was to strengthen the protection of unfit patients. Service has offered the patient a timely continuity of care reducing anxiety for patients and families. Ensuring continuity of care improves the quality of life of patients by increasing its level of safety. The costs, mainly due to human resources, are limited when compared to the intensity of care delivered.

C41 EFFICACY AND TOLERABILITY OF ZOLEDRONIC ACID IN METASTATIC BONE DISEASE: SYSTEMATIC REVIEW OF THE LITERATURE

Garigliano D.1, Rossi M.1, Ciliberto D.1, Tagliaferri P.1, Tassone P.1

1Medical Oncology Unit, University of Magna Grecia and Tommaso Campanella Cancer Center, Catanzaro

Background. Several studies have demonstrated the efficacy of zoledronic acid (ZA) on incidence of skeletal related events (SREs) in patients with cancer bone disease.

Objective. The aim of this systematic review and meta-analysis is to compare the efficacy of ZA and other bisphosphonates (BPs) and to evaluate the rates of SREs and the toxicity profiles.

Methods. Data were obtained by selecting 7 studies from the common medical databases (Pubmed, Cancerlit, Embase, Medscape and Cochrane) and selected meeting abstracts (ASCO, ESMO and AIOM). Hazard ratio (HR) of SREs and risk ratio (RR) of adverse events were performed by the fixed-effects model and random effect model. The consistency of the results was evaluated by performing the test of heterogeneity (I² Statistic ([Q-df]/Qx100)). Data analysis was performed by STATA™ SM v.12.0.

Results. Breast cancer and multiple myeloma were evaluated in 4 and 2 out of 7 studies, respectively. NSCLC and metastatic bone disease were considered each independently in 1 out of 7 studies. ZA was compared with pamidronate (4 out of 7), ibandronate (2 out of 7), clodronate (1 out of 7). HR demonstrates an advantage for ZA treatment with reduction of the SREs (HR = 0.81; 95% CI 0.73-0.89; p = 0.001). Adverse event rates were not

<table>
<thead>
<tr>
<th>Year</th>
<th>N. patients</th>
<th>Day of hospitalisation</th>
<th>Medical visits</th>
<th>Nursing visits</th>
<th>GP visits</th>
<th>Psychologist visits</th>
<th>IA</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006/2011</td>
<td>645</td>
<td>27412</td>
<td>10298</td>
<td>11597</td>
<td>1997</td>
<td>527</td>
<td>0.61</td>
</tr>
<tr>
<td>2011</td>
<td>160</td>
<td>4887</td>
<td>2357</td>
<td>2453</td>
<td>618</td>
<td>42</td>
<td>0.64</td>
</tr>
</tbody>
</table>

 IA: Increase in the quality of life; HR: Hazard Ratio; SRE: skeletal related events; BTcP: breakthrough pain; NRS: numerical rating scale; GI: Global Impression; BPs: bisphosphonates; ZA: zoledronic acid; ESMO: European Society for Medical Oncology; AIOM: Italian Society of Medical Oncology; ASCO: American Society for Clinical Oncology; GI: Numerical Rating Scale; HADS: Hospital Anxiety and Depression Scale; BTcP: breakthrough pain; GPs: General Practitioners; GPs: General Practitioners; HR: Hazard Ratio; SREs: Skeletal Related Events; I²: Heterogeneity; CI: Confidence Interval; 95% CI: 95% Confidence Interval; P: p-value; P: p-value; P: p-value.
different among BPs, except for fever which was more frequent with ZA (RR = 0.64; 95% CI 0.42-0.97; p = 0.033). Occurrence of osteonecrosis of the jaw (ONJ) was evaluated on retrospective and prospective studies. There was an increased incidence in MM and prostate cancer patients. A trend for ONJ occurrence was observed in the presence of ZA treatment.

**Conclusions.** Our meta-analysis confirms that ZA is the golden standard for prevention of SREs in cancer bone disease. The impact of ZA on ONJ and renal failure as compared to other bisphosphonates needs additional investigation.

### C42 SIMULTANEOUS CARE: TRANSLATING THEORY INTO PRACTICE FROM AN ORGANIZATIONAL POINT OF VIEW

Varese P.¹,², Comeri L.², Bellingeri P.², Musso M.³, Volgarino N.⁴, Traverso E.¹, Danielli A.¹, Silvera E.², Barisone A.², Moscatiello P.¹, Panthakhe L.¹, Porrotto S.⁵

¹Medicina a indirizzo oncologico, Presidio Ovada, ASL AL Piemonte; ²UOCP, ³Psiconcologia, ⁴SITRO, ASL AL; ⁵Direzione Sanitaria Presidio Ovada

**Introduction.** Simultaneous care is considered the most effective method for taking care of an oncologic patient. In most countries, the in-patient and the out-patient receive different treatment options and palliative care units very often are rigidly separated from oncologic services.

**Methods.** In order to increase home care for oncological patients in any stage of disease and not only at the end of life we have defined a common action protocol between hospital and health district. The protocol implies: once a week the visit of a nurse of the home care staff to in-patients likely to need home care at the discharge and weekly meetings between the home care staff and the DH and the hospital ward team.

In 2012 we developed a form to improve communication between hospital and health district. The form reports: diagnosis, treatment, nursing, support needs, social needs, life expectancy. The visit of the home care nurse and the home care physician makes easier the home care plan and assures the in-patient and his family about the continuity of care.

For the patients in chemotherapy the protocol is very useful to plan supportive care at home and makes easier to admit patients in palliative care.

**Results.** We have compared the first four months of 2011 and 2012 in order to verify the influence of the better communication between hospital and health district.

<table>
<thead>
<tr>
<th>Period</th>
<th>Number of patients entered into palliative care</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1.2011-30.4.2011</td>
<td>9</td>
</tr>
<tr>
<td>1.1.2012-30.4.2012</td>
<td>22</td>
</tr>
</tbody>
</table>

As in the same period we had no modifications of the total numbers of patients admitted in hospital the increase is undoubtedly related to the protocol in use.

**Conclusions.** The protocol (communication form and visit) is now common practice in our center.

It avoids urgencies and decreases conflicts with relatives.

The apparent waste of time is greatly repaid by the better plan of activities both of the health district and the hospital.

### C43 EFFECTIVENESS AND TOXICITY OF ZOLEDRONIC ACID (ZA) IN PATIENTS SUFFERING FROM BONE METASTASES OF SOLID TUMOURS


Department of Medico-Surgical Sciences and Biotechnologies, Oncology Unit, S.M. Goretti Hospital, “Sapienza” University of Rome, Polo Pontino

**Background.** In patients with bone metastases the occurrence of skeletal related events (SRE) is reduced by use of ZA. Major toxicities are renal safety, electrolyte abnormalities and osteonecrosis of jaws (ONJ); we analyzed incidence of these and the improvement of bone pain obtained in these patients.

**Methods.** Forty-two patients (average age 66 years) were treated by ZA 4 mg every 4 weeks. Serum creatinine and calcium levels analysis (SCL; SCa²⁺L) and oral examination were performed before and during administration of ZA. Bone pain was evaluated by Numerical Rate Scale (NRS).

**Results.** Patients received median 7 doses of ZA. Regarding SCL, we found a median baseline value of 0.99 mg/dL and a median final value of 1.2 mg/dL. Median highest SCL value during ZA therapy was 1.25 mg/dL and in 7 patients (16.6%) an increase of SCL ≥0.5 mg/dL occurred. Regarding SCa²⁺L, we found a median baseline value of 8.9 mg/dL and a median final value of 8.7 mg/dL. During treatment median lower SCa²⁺L was 8.4 mg/dL. Hypocalcemia (median SCa²⁺L 7.9 mg/dL) occurred in 19 patients (45%), inducing to stop the treatment; these patients were treated with a daily supplementation of 880 UI cholecalciferol plus 1000 mg calcium carbonate and they restarted when SCa²⁺L was ≥8.4 mg/dL without interruptions. A depletion of cortical bone of jaw was reported in 5 patients, who received 1 year of ZA; ONJ did not hit any patient. Regarding pain evaluation, 25 patients at beginning of therapy complained bone pain (NRS 1-3 = 8%; NRS 4-7 = 40%; NRS 8-10 = 52%); among these, only 4 patients continued to complain bone pain (NRS 8-10) during ZA.

**Conclusions.** ZA has been demonstrated to be safe with a low rate of renal toxicity, electrolyte abnormalities and absence of ONJ, even if some features, such as few number doses and careful selection of patients, should be considered; besides, it also has been shown to improve bone pain in almost all of patients.

### C44 OXYCODONE + NALOXONE (ON) VERSUS OXYCODONE (O) IN PATIENTS WITH CHRONIC CANCER PAIN. ANALGESIC EFFICACY AND BOWEL CONSTIPATION EVALUATION: OUR EXPERIENCE


U.O.C. Oncologia Medica, A.O. Bolognini, Seriate (BG)

**Background.** Oxycodeone is a systemic pure agonist opioid of μ and k receptors in brain, spinal cord and peripheral organs. Constipation is one of the most frequent side effects for which no tolerance is established. Naloxone is an antagonist of all types of opioid receptors: his task is to counteract the constipation by blocking the action at the level of opioid receptors in GI tract. Our
study evaluated the analgesic efficacy of ON combination versus O in opioid-naïve patients with moderate to severe chronic cancer pain, constipation as side effect and impact on quality of life.

Methods. From September 2011 to April 2012, 24 patients were enrolled (14 females/F, 10 males/M), mean age 68 ± 8 years, with metastatic tumours (F: 6 breast, 3 lung, 2 colorectal, 2 ovary, 1 uterus; M: 4 prostate, 3 colorectal, 3 lung). Most common sites of metastases were: bone (13), liver (9), lung (5). All patients had persistent pain within 24 hours of intensity equal to greater than 6 NRS scale with a mean of 7.6 and presence of at least 2 episodes/day BTcP.

Twelve patients received oxycodone (O) and 12 patients received combination oxycodone/naloxone (ON). Maximum dosage used was 80 mg/day of oxycodone and 40 mg/day of naloxone. Duration of observation was 8 weeks.

Results. In both groups was achieved a significant and comparable reduction of pain with decreased NRS average from 7.6 to 3.5 in group O and from 7.6 to 3.7 in group ON. At randomization bowel function index (BFI) was comparable between 2 groups: BFI has improved significantly in group ON since second week and in all subsequent evaluations (35 ±12 vs 70 ±15) with a percentage of laxatives use reduced to 34% in group ON when only 1 patient dropped out for diarrhea. QoL was better in ON group.

Conclusions. ON combination ensures effective and equivalent analgesia compared to O improving bowel function and QoL.

C45 NUTRITIONAL AND PHYSICAL ACTIVITY INTERVENTION IN EARLY STAGE BREAST AND COLORECTAL CANCER PATIENTS

Pegoraro M.C.1, Forni C.1, Schiavo G.2, Martelletto L.2, Ceschin G.2, Marchi S.2, Fracca I.3, Giabardo C.1, Padovani M.1, Binato S.1, Magazù M.1, Barana D.1, Oliani C.1

1UOC Oncologia, 2Servizio Dietetica e Nutrizione Clinica, 3Servizio Igiene e Sanità Pubblica, ULSS Ovest Vicentino

Body mass index (BMI) seems to correlate to clinical outcome in early stage breast and colorectal cancer patients. Overweight and obese breast cancer women or pts that put on weight during adjuvant treatment have an increased risk of treatment complications, disease recurrence and a more elevated global mortality than normal weight women. Epidemiological studies have shown that overweight and obesity are correlated with a higher risk of developing colorectal cancer. Since March 2012 a dietetics and physical activity program is run at the Oncology Unit in collaboration with the Nutritional Service in ULSS Ovest Vicentino. The attendance to this project is offered to early stage, BMI >25 kg/m² colorectal and breast cancer pts and breast cancer pts who have put on a 5% weight during the adjuvant chemotherapy and or hormone therapy and willing to undertake a dietetic treatment.

The first nutritional evaluation comprises all the clinical anamnestic data, the medical examination, the body composition measurement through bioelectric impedance analysis (BIA), the measure of resting energy expenditure using indirect calorimetry, the measure of energy expenditure through arm-band, and biochemistry tests. The first evaluation includes a dietary 24 hours recall to investigate the dietary habits and intakes. The EORTC QLQ-C30 quality of life questionnaire and psychological interview are also carried out. A personalized nutritional intervention and regular leisure-time exercises or walking groups are therefore established. Patients are successively followed monthly by a dietician and the psychologist in order to verify compliance, strengthen motivation and monitor the weight trend. After six months of treatment all the parameters and measurements at the start of treatment are reassessed in order to evaluate the efficacy of the intervention. The aim of the project is to avoid further weight gain and to prove the feasibility of lifestyle modification in everyday oncology practice in order to improve quality of life and possibly prognosis in early stage colon and breast cancer patients.

Supported by Regione Veneto.

C46 PAIN-FREE HOSPITAL PROJECT (OSD) AT SANT’ORSOLA-MALPIGHI HOSPITAL IN BOLOGNA: HOW TO EXTEND THE APPLICATION OF LAW 38 TO THE DAY HOSPITAL


Department of Hematology-Oncology-Radiotherapy, S. Orsola-Malpighi Hospital, Bologna

Since 2002, as part of the OSD of S. Orsola-Malpighi Hospital, Bologna has been on the Committee for Hospitals Without Pain (OSD), and as of 2003/2004 systematic measurement of pain has been introduced in the Onco-Hematology Department. In May 2009, the OSD program was accredited by the service. Since May 2011 we had extended the monitoring of cancer pain to the Day Hospital of Oncology, Radiotherapy and Hematology.

We conducted an observational study of 75 patients attending our day hospital during the last week of April 2012. Median age was 64 years (range 37-82), median KPS 80% (range 60-100), male/female 45/30. Sixteen patients presented with lung cancer, 22 urogenital, 22 gastrointestinal; there were 8 breast and ovary cancer cases, and 7 other cancer patients. 52% of patients had multiple metastatic sites and 16% bone; the majority of patients were on ongoing treatment with chemotherapy (60/75, 80%), 12% were on targeted therapy and 12/75 (16%) radiotherapy. Of the 75 patients interviewed, 37% had pain (28 pts), average NRS 6 (range 2-10), 40% (30/75) of patients had pain relief sets (2 pts being treated NRS 0). Nine patients received oxycodone, 6 fentanyl trans-dermal, 6 codeine/paracetamol, 9 other drugs, and the other 60% had a prescription for analgesic therapy required.

We identified indicators to monitor the process: 1) number of patients with pain/number of patients who were making their first visit to DH; 2) number of diary delivered to patients/number of patients discharged from the DH supplied with analgesics; 3) evaluation of direct prescription of analgesics. Data from the Department (still preliminary). Indicator No. 1 = 12%, No. 2 = 63%, data not yet available for the last indicator.

Conclusions. The preliminary results indicate that in a day hospital setting it is possible to detect and monitor pain and prescribe analgesics appropriately.

C47 THE EVALUATION FORM FOR PAIN CONTROL AND “GIORNATA DEL SOLLIEVO”: A MONOCENTRIC EXPERIENCE OF A “ONE DAY PREVALENCE MODEL” INVESTIGATION
Background. Pain management is one of the most important aspects of care for hospitalized patients. Assessment systems include subjective (self-report) and objective (physiological and behavioral) parameters. In our Institute the pain-free hospital Committee (COSd) works to improve strategies for pain control. Since 2002 the “pain evaluation form” has been endorsed by our Institution and every two years the Giornata del sollievo takes place in our hospital.

Methods. Using a “one day prevalence model” investigation, voluntary patients respond to a series of questions about pain intensity, features and its impact on quality of life in order to obtain evaluation items on perceived pain. Surveys are divided by 3 disciplines including surgical, medical and oncological areas. Pain is evaluated by Numeric Rating Scale (NRS). We analysed data from oncological area detected in 2009 and 2011.

Results. The 2011 “Giornata del Sollievo” involved 644 voluntary patients: 167, 422 and 55 patients from surgical, medical and oncological areas respectively. From oncological area 35 women and 20 men took part in the survey: 27.3% didn’t report any pain (NRS 0), 32.7% experienced mild pain (NRS 1-3), 31% told about moderate pain (NRS 4-7). 9% had an intense pain (NRS 8-10). In 2009 only 40 oncological patients participated in the survey. Furthermore we observed that 47% and 17% of them reported moderate and intense pain respectively.

Conclusions. The increased attention for oncological pain and the use of a pain evaluation form may have led to greater pain control improving quality of life and outcome in cancer patients respectively. It should increasingly become an important feature in management of oncological patients.

C49 PHASE II CLINICAL TRIAL USING AMINOTROFIC® IN THE PREVENTION OF ANOREXIA AND CACHEXIA IN CANCER PATIENTS RECEIVING CHEMOTHERAPY: EVALUATION OF THE EFFICACY AND SAFETY

Capparella V., Pace R., Rauco A.M., Lugini A.
Hospital “San Camillo de Lellis”, Medical Oncology Unit, Rieti

Introduction. Food shortage in cancer patients is associated with a poor prognosis. Treatments and disease have a major impact on nutritional status. An improvement of the nutritional status of patients with cancer can change the prognosis, quality of life and functional status, facilitating improved tolerance to treatment. Aminotrofic® is a supplement of amino acids with vitamins B6 and B1, shown to provide useful nutrients for muscle trophism.

Methods. From November 2011 to April 2012, 30 cancer patients received Aminotrofic® at a dose of 2 sachet/day. All patients included in the study performed chemotherapy: 70% of the patients performed a treatment for metastatic disease. The treatment duration was at least 4 months. The following variables were evaluated: 1) nutritional status; 2) clinical status; 3) quality of life; 4) adherence to the chemotherapy.

Results. Of 30 patients, 28 completed the treatment and were assessable. All evaluable patients did not show a significant reduction in body weight, appetite and quality of life. The 28 evaluable patients also completed the chemotherapy program.
**Conclusions.** Aminotrof® found to be safe and effective in this setting of the study. The relevant data is represented by adherence of patients to chemotherapy treatment in relation to the maintenance of an adequate performance status. A randomized phase III study is warranted.

**C50 “IL FILO DI ARIANNA”: A BOND BETWEEN ONCOLOGICAL DAY HOSPITAL, PALLIATIVE CARE UNIT HOSPITAL AND HOME. A SINGLE CENTER EXPERIENCE**


*Medical Oncology Unit, Palliative Care Unit, Ospedale Civile di Guastalla, AUSL Reggio Emilia*

**Background.** The time to discontinuation of active cancer treatment and the beginning of palliative care is one of the most critical steps for patients and their families.

**Patients and methods.** This project aimed to create a multidisciplinary team to facilitate the convergence of the teamwork for terminal patient with the best use of specific powers. We evaluate the effectiveness of this multidisciplinary approach (oncology nurse coordinator, medical oncology, primary care physician, home and hospice care nurse coordinator, palliative specialist, psychology). This multidisciplinary approach between hospital, hospice and home is based on the needs expressed by patients and their families and the observation of perceived satisfaction. The meetings were held at the discharge from active treatment and at changes of decision-making. It was also created a single board detection of pain.

**Results.** From January 2010 to January 2011 were evaluated 40 patients with metastatic disease and out of chemotherapy treatment. Six patients have been entrusted to residential care. All the patients have taken advantage from early activation of multidisciplinary team with an improvement of quality of life and in mood. We obtained also an improvement of the management of side effects and pain.

**Conclusions.** This experience is showing that the construction and the validation of a comprehensive clinical care pathway, with early activation of a multidisciplinary team, allows a greater listening to the needs expressed by the patient, a greater adherence to palliative therapy, a cost reduction for the most life-saving therapies and adequacy of guidelines management with European standards (suspension within 3 months from the supposed date of death).

**C51 EFFICACY OF ORAL PROLONGED RELEASE OF OXYCODONE/NALOXONE COMBINATION ON PAIN AND OPIOID INDUCED CONSTIPATION IN PERSISTENT CANCER PAIN PATIENTS IN A DAY HOSPITAL SETTING AT HUMANITAS CENTRO CATANESI ONCOLOGIA**


*Department of Medical Oncology, Humanitas Centro Catanese di Oncologia, Catania*

**Introduction.** Opioids are the first choice drugs in persistent cancer pain. They can induce a bowel dysfunction due to activation of opioid receptors in the submucosal and myenteric plexuses. Bowel opioid receptors blockade obtained by simultaneous oral administration of naloxone and oxycodone restores normal bowel function counteracting opioid-induced constipation (OIC) without reduction in analgesia.

**Aim.** Aim of the study was to analyze efficacy on persistent cancer pain and OIC of prolonged release of oxycodone/naloxone (PR-OX/PR-NAL).

**Methods.** We admitted thirty-six cancer patients aged ≥18 years, 16 M, 20 F (M/F ratio 0.8) with persistent cancer pain treated by WHO 2^nd^ step opioids with poor results. They received round-the-clock 3^rd^ step opioid therapy (20 mg bid PR-OX/PR-NAL). The mean age was 60 years (range 31-78), median ECOG PS = 2. Were excluded patients with symptomatic brain metastases, history of drug addiction, alcohol abuse and pregnant women. During the last 7 days prior to each visit were evaluated pain (twice-daily using the 0-11 NRS VAS) and bowel function as BFI. Laxatives were lactulose or senna, hyperosmotic saline cathartics such as magnesium sulphate or sodium phosphate were not used. The observation period was 28 days.

**Results.** At the first visit, the worst pain 24 hours prior to the visit was 6.8±1.3 points and 3.14±1.6 at the 28^th^ day. The average daily pain intensity was 3.8 (range 0-9.1). The mean BFI was 38.2±30.9 at the start and 26.7±23.98 in the last 7 days of the study.

**Conclusions.** The analgesic efficacy is documented by the value of worst and average pain at the baseline and at the 28^th^ day. The mean BFI value can be explained by a valid counteracting action of PR-OX/PR-NAL on OIC but also by the fact that this study also included patients without bowel dysfunction at the first visit (50% of the patients had no constipation) and by a mild prophylactic use of non saline laxatives. PR-OX/PR-NAL achieved good pain control and reduced OIC.

**C52 OPIOIDS THERAPY IN ADVANCED CANCER PATIENTS IN MEDICAL ONCOLOGY UNIT (MOU)**

Ferrari V., Noventa S., Consoli F., Ferrari L., Valcamonico F., Grisanti S., Amoroso V., Nonnis D., Marpicati P., Arcangeli G., Simoncini E.

*U.O. Oncologia Medica A, Spedali Civili, Brescia*

**Aims.** We analyzed the use of opioid drugs in advanced cancer patients in MOU. Cancer pts experience a lot of symptoms and pain is one of the most common and feared.

**Methods.** From 15^th^ July to 15^th^ August we have planned an observational study on prevalence and intensity of pain at the beginning, during and at the end of hospitalization, drugs and way of administration used in comparison with a similar 2004 study. We observed 75 pts (45 m/30 f) median age 56 yrs, PS ECOG was 0-1 in 64 pts, PS 2 in 4 pts, PS 3 in 2 pts and PS 4 in 5 pts. Three pts were receiving adjuvant chemotherapy (CT), 7 pts neoadjuvant CT, 51 pts were in palliative CT and 13 pts in supportive care. Sixty-one pts had a life expectancy greater than 90 days and 14 less than 90 days. Pain was assessed at the admission, and at least once a day during hospitalization with NRS-11 and every pain with NRS ≥4 was considered uncontrolled. At the admission 11% of pts experienced NRS 4-6, 4% NRS ≥7; prevalence of pain was 44%. 56% of pts with NRS 0-3 and 1% of pts
Conclusions. Comparing the data of patients treated for pain in 2004 and 2012, the prevalence of uncontrolled pain at admission and at discharge is comparable. In 2012 we prefer the new formulations and oral administration, we observed a correlation between pain management, prognosis and length of stay.

### Table 1 - Pain treatment at admission and discharge

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Admission (%)</th>
<th>Discharge (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxycodone + paracetamol</td>
<td>45</td>
<td>34</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>14</td>
<td>16</td>
</tr>
<tr>
<td>Morphine</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>Fentanyl TD</td>
<td>14</td>
<td>13</td>
</tr>
<tr>
<td>Fentanyl TD + morphine</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Tramadol + paracetamol</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Codeine + paracetamol</td>
<td>7</td>
<td>6</td>
</tr>
</tbody>
</table>

C53 FENTANYL BUCCAL TABLET VERSUS SULFATE MORPHINE IN BREAKTHROUGH CANCER PAIN

Barzelloni M.L., Mogavero A., De Filippo M., De Luca P., Citera M., Carnicelli P.


Introduction. The concept of breakthrough cancer pain (BtCP) was introduced in the literature by Portenoy and Hagen in 1990 and is defined as a transient exacerbation of pain, moderate to high intensity, which occurs spontaneously or in response to a precipitating factor in patients with analgesic therapy at doses and fixed schedules, adequate control of chronic pain.

Methods. In the observational study 20 patients with metastatic cancer, treated with fentanyl buccal tablet for BtCP starting from an initial dose of 400 micrograms were enrolled in a period of 12 months. In the control arm, which used morphine sulfate 10 mg every 8 hours in combination with chronic therapy, 20 more patients with metastatic disease were enrolled. Pain assessment was calculated with the scale Numerical Rating Scale (NRS) before and after each episode of pain to assess response to treatment.

Results. Patients receiving fentanyl buccal tablets have achieved a better control of BtCP episodes than patients treated with fixed doses of sulfate morphine. The scores of the NRS for the first group of patients showed high scores of 10 and minimum of 7 during the stages of pain episodes that have regressed to values of 0-2 in 7-10 minutes after administration of fentanyl. In the second group the highest and lowest scores of the NRS were the same as the first group, but the resolution of pain symptoms did not occur as quickly, because patients had to meet the schedule of administration of sulfate morphine.

Conclusions. The use of a drug for the BtCP is useful and essential for improving the quality of life of patients in advanced stages of disease, phase in which preserving the quality is the main objective. Fentanyl buccal tablet has proven to be a quick and effective drug in controlling pain and improving the quality of life of patients.

C54 COMMUNICATION WITH CANCER PATIENTS ABOUT PALLIATIVE AND END-OF-LIFE CARE

Biasco G.1,2, Moroni M.1,2, De Panfilis L.1

1Academy of the Sciences of Palliative Medicine, 2“Giorgio Prodi” Center for Cancer Research, University Alma Mater Studiorum, Bentivoglio-Bologna

Communication with a cancer patient and his family goes on a dynamic way. Steps of communication concern: the seriousness of illness and the chances of cure, the ineffectiveness of the treatment, the opportunity to start a palliative care programme, the end-of-life decisions.

The moment when palliative care should be offered depends on the attitude of the team that has in charge the patient. In general palliative care is offered when cancer-directed therapy is no more effective. Nevertheless there is an increasing trend to suggest delivering palliative care earlier, at cancer diagnosis and not at the end of the cure, thus encouraging a synergy between palliative care providers and oncologists. This attitude would both increase the quality of life of the patient and limit risks of a discontinuity of clinical management.

Decision about the delivery of palliative care should be based on a candid communication between physicians and patients, so as to allow the latter to make grounded decisions concerning treatment and the time necessary for each possible intervention to be carried out. Physicians should know the case history and the possibilities offered by palliative care as well as have a cross-cultural competence to understand and speak in relation to the culture, expectations and real needs of the patient and his family at each stage of illness.

C55 MOVEMENT DISORDERS IN CLINICAL ONCOLOGY PRACTICE

Passarin M.G.1, Zaninelli M.2, Pedersini R.3, Sava T.4, Bomprezzi C.1, Faedi M.3, Franceschi T.2

1U.O.C. di Neurologia, Ospedale Bufalini, AUSL Cesena, FC; 2U.O.C. di Oncologia, Ospedale Orlandi, ULSS 22, Bussolengo, VR; 3U.O.C. di Oncologia, Spedali Riuniti, Brescia; 4U.O.C. di Oncologia, Azienda Ospedaliera Universitaria Integrata, Verona; 5DH Oncoematologia, Ospedale Bufalini, Cesena IRST, FC

Chorea and other movement disorders are mainly described in paraneoplastic syndromes. Movement disorders due to metastases or chemotherapy are considered rare events and therefore described in the literature mainly as case reports. There is increasing evidence of a correlation between cancer and neurodegenerative disorders, in particular melanoma and Parkinson’s disease (PD). The aim of the present study was to evaluate the prevalence of movement disorders due to either primitive tumour, metastases, chemotherapy, or concomitant neurological diseases in patients with cancer. In the period from January to December 2010 we analyzed 550 cancer pts followed at the Oncology Unit of ULSS 22 (Regione Veneto). Among these, we identified 115 pts who had neurological disease either already present before cancer diagnosis or due to metastases, acute and chronic toxicity, radiotherapy sequelae. Thirty-two (5.8% of total pts seen) showed movement disorders: 1 pt had Parkinson’s disease already present before cancer diagnosis (3.1%), 20 had pos-
C56 COPING WITH CANCER: ASSOCIATION BETWEEN COPING STRATEGIES AND ANTHROPOLOGICAL PROFILE


*U.O. di Psico-oncologia, 2U.O. di Oncologia, P.O. Paola, 3U.O. di Oncologia, P.O. di Castrovillari, 4Dipartimento Salute Mentale, ASP Cosenza

Background. Cancer patients cope with their illness in a variety of ways, the prevalent coping method in individual patient being affected by medical, social, psychological and spiritual factors. Some studies suggested that religious involvement and spirituality could be associated with coping skills, better recovery from illness, less anxiety and depression. We used an anthropological perspective to analyse relationships between anthropological profile and coping strategies in cancer patients belonging to different settings (Castrovillari Arbëreshë community and Paola community). Little is known about coping strategies in ethnic minorities such as Arbëreshë community, an ethnic minority group particularly represented in some areas of the province of Cosenza (such as the area of Castrovillari). In Arbëreshë community people have been able to preserve their language, values and traditions mainly by maintaining the Greek-Bizantine rite, which represents the backbone of their cultural identity.

Methods. 100 outpatient cancer patients from two Oncologic Centers (50 from Paola Medical Oncology- group C- and 50 from Castrovillari Medical Oncology - group P) entered the study from March 2010 to October 2010. All participants completed the COPE TEST. In group P age range was 41-70 years, 65% was female, 80% was married (15% unmarried, 5% widow/widower). In group C age range was 39-73 years, 62% was female, 65% was married (26% unmarried, 4% widow/widower), 26% belonged to Arbëreshë community.

Results. In group P, 60% reported a “cognitive restructuring and acceptance” coping while remaining 40% reported an “emotional and instrumental support” coping. In group C, 70% of patients reported an “addressing operatively the disease” coping, while remaining 30% had an “acceptance” coping.

Conclusions. These results suggest that anthropological profile affects coping mechanism in geographical areas in which Arbëreshë community is present. Arbëreshë culture particularly influences anthropological profile especially through determinism and awareness of distressing situations in which psychological and psychosocial resources are activated. We are going to warrant future research in order to test this hypothesis.

C57 ABOUT DISCREPANCIES IN PAIN VISUAL ANALOGIC SCALE (VAS) COLLECTION IN DAY HOSPITAL (DH) ONCOLOGICAL PATIENTS


1Medical Oncology Treviglio-Caravaggio (BG); 2Medico di Assistenza Primaria, Roma; Medical Oncology Firenze3, Roma4, Pavia5, Reggio Emilia6, Palermo7, Genova8, Bari9

Introduction. In our daily working, we have observed some discrepancies between what patients refer to the oncologist and what they refer to nurse about pain, and chemotherapy toxicities. Large data about a monoinstitutional observational study confirm the reluctance of patients to reveal their pain, especially to the oncologist. Now we want to study discrepancies about pain relevance in different Italian Cancer Units.

Materials and methods. We evaluate in 8 Italian cancer hospitals all consecutive pts during 5 days in order to investigate level of pain in the previous 7 days and in the following two weeks from basal visit. Oncologists and nurses filled up a questionnaire about intensity of pain measured with VAS at basal and follow-up visit; the patients reported also VAS of the day before visit.

Results. 265 pts were enrolled, 59% female and 41% male; median age 61.5. In 88% ECOG PS was 0-1; 72.8% of pts reported metastatic disease and 86.4% were under chemotherapy. 80.8% of patients had a caregiver, wich was in 90.2% consort or children. At baseline visit median intensity of pain measured with VAS was 2.9 collected by oncologist, 3.4 collected by nurse, and 3.5 reported by patient for the previous day.

After therapy adjustment, the patients came in follow-up after two weeks and median intensity of pain was: 2.6 collected by oncologist, 3.5 collected by nurse, and 2.9 reported by patient for the previous day.

Conclusions. Our data seems to confirm, as observed in previous monoinstitutional experience, the trend of oncological patients to undervalue the intensity of pain when they talk with the oncologist, may be because they don’t want divert their attention from cancer care or because they think that this can be associated to worsening of disease. This data seems to show also that when the patient comes to oncological center feels better with a lower intensity of pain in ratio of global trailblazer that Cancer Units reserves to oncological patients.

C58 DEVELOPMENT OF A GUIDANCE FOR INCLUDING PATIENT-RECORDING OUTCOME IN CLINICAL RECORD: PRELIMINARY DATA

Lattuada S., Cecutti M., Posca T., Manachino D., Torazzo R., De Marino E.

Medical Oncology Division, “S. Andrea” Hospital, ASL VC, Vercelli

Background. New biologic and cytotoxic therapies have successfully improved survival and are thrown quickly on the market, but some related effects are unknown and about half of drugs given with long term conditions are not taken as prescribed. Empowerment of patient is crucial to assure compliance and assess lifestyle, quality, satisfaction and toxicity at home. Aim of this study is promoting empowering by new tools and programs.
Methods. Based on clinical practice and scientific review we developed a simple home notebook (HNB) for patients recording more relevant chemotherapy related symptoms at home and elaborated a semi-structured questionnaire in order to validate its use in clinical practice investigating patient opinion. From January to December 2011 we enrolled 160 patients with new diagnosed and metastatic cancer. Twelve start up in-depth interview and educational meetings were conducted to assess knowledge about cancer and to explain aim of the trial, drugs toxicity and how to use notebook as clinical record at home. One month later patients were recalled and were requested to fill up our questionnaire.

Results. One hundred and sixty-three HNB were delivered to 78 males (M) and 85 females (F), median age 67 years, range 42-84 years, 60 patients (37%) attended meetings requiring nearly one hour, 31 M and 29 F. Ninety-one (56%) questionnaires were filled up. Only 2 patients gave back HNB because considered themselves unable to draw, 89 did not meet difficulties in writing up, and appreciated HNB, finding it useful. They referred HNB to consulting physician to write notes in clinical record.

Conclusions. Our educational program and HNB seem to be effective models to improve empowerment and compliance of patients. They are easy to employ and useful for home care also for elderly patients. We want to extend trial and confirm our preliminary results, because we think that we can contribute to continuity of care integrating HNB in clinical record.

C59 STRENGTH AND SMILE TO FIGHT AGAINST CANCER: A SINGLE CENTER EXPERIENCE

Borasio G.2, Lattuada S.1, Posca T.1, Torazzo R.1, Sartori S.2, De Marino E.1

1S.C. Oncologia, 2Servizio di Psicologia, Ospedale “S. Andrea”, ASL VC, Vercelli

Background. Cancer strikes patients both mind and body, decreasing self esteem, own identity and part, outward appearance and social relation. In this context improving quality of life and humanized cares is crucial. Women suffering from tumour need tests and medical examinations. Aim of this study is to help patients to recover womanly beauty lost.

Methods. In November 2010, in Vercelli “Strength and Smile Association” (SSA) was founded as Italian partner joined in international project “Look Good…Feel Better”, founded in USA in 1989. It carries on an intensive activity in 25 States all over the World. SSA started in Italy in 2006 under UNIPOL (Italian Cosmetic Factories Association) shield and works at present in 31 Organizations. SSA opened a beauty center in Medical Oncology Division of “S. Andrea Hospital” in Vercelli and organized meetings offering free admittance to cancer outpatients. A psychologist promoted information, communication, relationship collaborating with beauty consultants and volunteers. During a session of make up every patient received a beauty case containing cosmetics as a present and was invited to fill up an anonymous evaluation questionnaire at the end.

Results. Since November 2010 to December 2011 fifty female outpatients attended 16 meetings which were organized monthly. Median age was 55 years, range 23-73 years. Fifty (100%) questionnaires were filled up. Thirty (30%) patients felt “better”; 26 (54%) were “satisfied”; 12 (24%) felt “fine”; no one said to look as well as before and every one was grateful.

Conclusions. We considered our program entirely successful and we think that it is an effective model to improve compliance and quality of life for patients suffering for cancer. The program is useful and applies also to elderly patients. We want to extend trial recruiting inpatients and confirm our preliminary results, because we think that we can contribute to ameliorate care integrating our psychological support into medical treatments.

C60 FREQUENCY AND SEVERITY OF IMMEDIATE ADVERSE EFFECTS OF IODINATED CONTRAST IN CANCER PATIENTS

Farolfi A.1, Della Luna C.2, Casadei C.3, Minguzzi M.2, Nanni O.4, Amadori D.1, Gavelli G.5

1Dipartimento di Oncologia, 2Farmacia Oncologica, 3Servizio di Anestesia e Rianimazione, 4Unità di Biostatistica e Sperimentazioni Cliniche, 5Dipartimento di Radiologia, Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRCCS IRST), Meldola (FC)

Introduction. Acute allergic-like reactions are a well-known, albeit rare (0.3-0.7%), complication of intravenous iodinated contrast media (ICM) injections. Cancer patients undergo routine CT scans and, thus, ICM administration, to assess the extent of disease (staging) and response to treatment. Our retrospective study aimed to assess the frequency and severity of ICM acute reactions in a cancer population.

Methods. Patients were selected from a medical records database; all had undergone at least one CT scan at IRST between 1st January 2010 and 31st December 2011. All immediate adverse events were reported to the pharmacist in charge of drug vigilance. The following information was retrieved from the medical records: demographic characteristics, type of cancer, previous number of contrast-enhanced CT scans, ICM premedication, chemotherapy regimen and severity of the reaction.

Results. Of the 7866 CT scans performed with ICM, 77 immediate adverse events were recorded (31 males and 46 females). Median age was 62.9 years (range 29-83 years). The reactions were considered severe in 9 (11.2%, 2 males and 7 females) patients and clinical patterns were as follows: shock in 5 (6.5%) patients, angioedema in 3 (3.9%) patients and death in one (1.3%) patient. Twenty-seven (35.1%) patients were undergoing chemotherapy at the time of the adverse event; 6 (22.2%) with a platinum-based regimen, 6 (22.2%) with 5-FU-based therapy, 5 (18.6%) with a taxane-containing schedule, 2 (7.4%) with platinum-taxane chemotherapy and 8 (29.6%) with various other schemes.

C61 ONCOLOGIST’S MONITORING IN A COMPLEMENTARY ALTERNATIVE MEDICINE SURGERY


*Department Oncology, °Complementary Alternative Medicine (CAM), Campo di Marte Hospital, Lucca

Background. Chemotherapy may induce dysgeusia resulting in weight loss while hormonal therapy for hormone-responsive tumours can cause weight gain, urinary retention and hot flashes.
In order to tackle side effects of anticancer treatment many patients turn to CAM (phytotherapy, homeopathy) although some of them might interfere with pharmacokinetics and pharmacodynamics of antineoplastics by increasing toxicity or, sometimes, reducing effectiveness. On this basis we started a surgery where an expert in complementary medicine and a medical oncologist provide qualified information and evidence-based indications about CAM and their potential interactions with anticancer drugs.

Methods. Patients access to the surgery by appointment. They come from Tuscany and other Italian regions. Near all patients are referred by their medical oncologists. Baseline history and physical examination were performed and biochemistry required: all concomitant medications were registered and potential interactions among them were analyzed. In all patients were calculated BMI. Follow-up visits were organized on a monthly basis depending on the main problem.

Results. Between October 2010 and April 2012, 89 patients were registered: 12 males and 77 females. Median age 56 years (range 32-88); 61 patients had breast cancers, 6 gynecologic, 8 gastrointestinal, 2 head and neck, 3 prostate, 1 brain, 4 lung and 4 hematologic malignancies. 23/89 patients had metastatic disease. 40% of patients asked for information about CAM and their “role” in reducing anticancer therapy side-effects. 10% of patients were using CAM for other purposes before cancer diagnosis and they needed to continue during anticancer treatments: most are women with high level of education. 17% of patients were using “heretic therapy” in particular 3 patients were taking skorpion venom together with hormonal treatment.

Conclusions. This surgery allows us: to reduce the probability of anticancer treatment discontinuations in favour of drugs of unproven efficacy; to investigate interactions between CAM and antiblastics and to advise patients about the potential harmful effect of “heretic therapy”.

C62 SURVEY OF PSYCHOLOGICAL AND INFORMATION NEEDS IN ONCOLOGY PATIENTS

Martellucci I.1, Petrosino R.2, Paganini G.1, Migali C.1, Francini E.1, Berardinelli N.2, Reda M.A.2, Francini G.1

1Medical Oncology Unit, Oncology Department, 2Clinical Psychology, Mental Health Department, Siena University Hospital

Introduction. The management of patients with cancer should be based on a multidisciplinary approach and global care from the first meeting with oncologist. The aim of our research is to evaluate psychological and support needs of patients and the importance of care environment in an oncology setting.

Materials and methods. Fifty oncology patients (28 men and 22 women) under chemotherapy referred to the Day Hospital, with different type of cancer, were evaluated. Patients were asked to complete a questionnaire. Qualitative data were assessed as frequency, Fisher’s exact test and Spearman’s correlation were used to evaluate the association between answers and relationship among socio-demographic data.

Results. Perception of patient about the diagnosis understanding and the psychological support of health professional staff decreases with increasing patient’s education degrees (p = 0.044) and decreasing age (p = 0.014); there is a strong correlation between places and time dedicated to communication and understanding of the words of oncologist (p = 0.0005, rho 0.5) and between appropriate places of care and time dedicated to communication (p <0.001, rho 0.48); the need of a psychologist decreases with the increased perception of property of communication places (p = 0.02); consultation with psychologist is more useful for patients saying they have a “perfect” understanding of their disease (p = 0.014) thinking that the psychologist should be enclosed in the hospital staff (p = 0.026).

Conclusions. Our study suggests the importance of places suitable for communication between doctors and patients in the Oncology Unit for improving the management of cancer patients. The psychologist should be enclosed in the oncologic health staff.
Session D • Thoracic and lung cancers, head and neck tumours

D1* ADHERENCE TO 2009 AIOM LUNG CANCER GUIDELINES: THE RESEARCH FOR THE IDENTIFICATION OF THE MOST EFFECTIVE AND HIGHLY ACCEPTED CLINICAL GUIDELINES FOR THE CANCER TREATMENT (RIGHT3) PROJECT

Barni S.1, Maiello E.2, Ardizzoni A.3, Cappuzzo F.4, Maranzano E.5, Novello S.6, Bennati C.7, Crinò L.2

1Azienda Ospedaliera di Treviglio-Caravaggio, Treviglio, Bergamo; 2IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, Foggia; 3Azienda Ospedaliero-Universitaria di Parma, Parma; 4Ospedale di Livorno, Livorno; 5Azienda Ospedaliera Santa Maria di Terni, Terni; 6AOU San Luigi, Università di Torino, Torino; 7Azienda Ospedaliera di Perugia, Perugia

Clinical oncology societies develop and regularly update evidence-based guidelines in order to improve the quality of care of patients with cancer and reduce variability in cancer care.

In 2004 AIOM created the RIGHT (Research for the identification of the most effective and highly accepted clinical guidelines for cancer treatment) program, successfully applied to colorectal and breast cancer guidelines (Barni S et al., Tumori, 97: 559-563, 2011). The third part of the program, called RIGHT3, aims to evaluate the concordance between AIOM lung cancer guidelines and clinical practice in Italy.

RIGHT3 is a retrospective observational study conducted in a sample of 53 Italian centers for lung cancer care representative of 230 AIOM centers. Indicators were evaluated to verify the concordance between 2009 AIOM lung cancer guidelines and clinical practice about staging and treatment (surgery, chemotherapy and radiotherapy) of I-II-IIIA, IIIB and IV stages patients. Patients with NSCLC diagnosis who had their first visit at the oncology center during 2010 and followed-up for at least 6 months were included.

Among the 708 enrolled, 228 I-II-IIIA stage, 158 IIIB stage and 300 IV stage patients were eligible for analyses.

Preliminary results showed that 95% of I-II-IIIA stage patients received a cyto-histological diagnosis and <65% underwent PET. 88% of I-II stage patients underwent lobectomy and more than 30% of II-III stage patients undergoing complete surgery were treated with adjuvant chemotherapy.

30% of IIIB stage patients received concomitant and 70% sequential chemo-radiotherapy respectively.

As regards stage IV patients, more than 30% of them had a molecular analysis; platinum-based first-line treatment was prescribed sequentially chemo-radiotherapy respectively.

Such results highlight the need to continue improving the standards of lung cancer care and to correctly evaluate adherence to guidelines, in order to successfully update AIOM guidelines as well as to better plan health care interventions.

D2* EPIDERMAL GROWTH FACTOR RECEPTOR MUTATIONS IN ITALIAN NON-SMALL CELL LUNG CANCER PATIENTS: RESULTS FROM THE EGFR FASTNET PROGRAM

Normanno N.1, Pinto C.2, Taddei G.L.3, Troncone G.4, Graziano P5, De Maglio G.6, Mottolese M.7, Ludovini V.8, Zupo S.9, Larocca L.M.10, Roz E.11, Russo A.12, Palmieri G.13, Perrone G.14, Boldorini R.L.15, Di Maio M.1, Ardizzoni A.16, Crinò L.17, Perrone F.1, Clemente C.18, Marchetti A.19

1Istituto Nazionale Tumori, Fondazione G. Pascale, Napoli; 2Policlinico S. Orsola Malpighi, Bologna; 3Università degli Studi di Firenze; 4Università Federico II, Napoli; 5Azienda Ospedaliera S. Camillo Forlanini, Roma; 6Azienda Ospedaliera Universitaria, Udine; 7Istituto Nazionale Tumori Regina Elena, Roma; 8Ospedale S. Maria della Misericordia, Perugia; 9Istituto Nazionale per la Ricerca sul Cancro, Genova; 10Policlinico A. Gemelli, Roma; 11Casa di Cura La Maddalena, Palermo; 12Policlinico Universitario P. Giaccone, Palermo; 13Istituto di Chimica Biomolecolare, CNR, Sassari; 14Policlinico Universitario Campus Biomedico, Roma; 15Azienda Ospedaliera “Maggiore della Carità”, Novara; 16Azienda Ospedaliera, Parma; 17Azienda Ospedaliera Silvestrini, Perugia; 18Casa di Cura S. Pio X, Milano; 19Università G. d’Annunzio, Chieti

Background. Epidermal growth factor receptor (EGFR) mutation testing is mandatory for appropriate selection of treatment for patients with advanced non-small cell lung cancer (NSCLC).

Methods. The EGFR FASTnet program was designed to facilitate the exchange of biological material, clinico-pathological data and reports between medical oncologists, pathologists and referral laboratories. EGFR mutational analysis was carried by Sanger sequencing, Real-Time (RT)-PCR, Pyrosequencing, and other techniques. The Italian Association of Medical Oncology (AIOM) and the Italian Society of Pathology and Cytopathology (SIAPeC) have full access to the anonymous EGFR FASTnet database.

Results. As of December 31, 2011, 503 oncologists, 135 pathologists and 38 referral laboratories joined the EGFR FASTnet program. The enrolled cohort of 3819 pts with advanced NSCLC was significantly enriched for adenocarcinoma histology (3172 [83%]), female sex (1361 [36%]) and smoking history (never smoker 911 [24%], former smoker >15 yrs 880 [23%], light smoker 194 [5%]). EGFR mutations were found in 520 cases (14.6%): 334 in exon 19 (9.4%), 163 in exon 21 (5%), RT-PCR in 174 (5%), Pyrosequencing in 636 (18%) and other techniques in 736 (21%). EGFR mutational testing was performed in 520 cases (14.6%): 334 in exon 19 (9.4%), 163 in exon 21 (4.6%), 7 in exon 18 (0.2%) and 16 in exon 20 (0.4%). Proportion of mutated cases was slightly higher with RT-PCR (p = 0.049). A higher mutation rate was found in never smokers (32%), light smokers (18.7%) and former smokers >15 yrs (12.4%), as well as in adenocarcinoma (15.7%) and females (25.2%). EGFR mutations were also reported in 17/227 (7.5%) squamous carcinomas. However, 16/17 EGFR mutation positive patients with squamous carcinoma were never- or former-smokers.

Conclusions. The patients for EGFR mutational screening are spontaneously selected by medical oncologists according to known predictive factors. The results of the mutational analysis from clinical practice in Italy are consistent with data from literature. Never- and former-smoker NSCLC pts with squamous carcinoma should be tested for EGFR mutations.

D3* SKIN RASH AND OUTCOME IN NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS TREATED WITH ANTI-EGFR TYROSINE KINASE INHIBITORS (TKIS)
Borgonovo K., Petrelli F., Cabiddu M., Ghilardi M., Cremonesi M., Maspero F., Barni S.

Medical Oncology Division, A.O. Treviglio-Caravaggio, Treviglio

Introduction. Cutaneous toxicity has been observed with all agents that target epidermal growth factor receptor (EGFR), and is therefore considered a class effect. Dermatological toxicity in the form of acneiform rash is a common event in NSCLC patients treated with anti-EGFR TKIs. One of the more interesting and useful clinical observations is the association of clinical benefit with development of this form of skin toxicity. We have performed a systematic review to evaluate the predictive value of skin rash in terms of response and survival in patients with NSCLC treated with erlotinib (E) or gefitinib (G), in prospective clinical trials or in retrospective case series.

Materials and methods. We searched PubMed (until January 2012) for articles reporting the correlation of skin rash with survival, progression and response rate. Hazard ratios with 95% confidence intervals (HRs) for progression (PFS/TTP) and survival, progression and response rate. Hazard ratios with 95% confidence intervals (HRs) for progression (PFS/TTP) and survival. We have performed a systematic review to evaluate the predictive value of skin rash in term of response and survival in patients with NSCLC treated with erlotinib (E) or gefitinib (G), in prospective clinical trials or in retrospective case series.

Results. Twenty-four publications were included in this meta-analysis (17 prospective trials and 7 retrospective case series) for a total of 3032 patients. The occurrence of skin rash represents an independent predictive factor for OS (HR = 0.30; p <0.00001) (Table 1) and progression (HR = 0.50; p <0.00001) (Table 2). In addition, patients who developed grade 2-4 rash were more likely to respond to treatment compared to patients with no rash (42% vs 7%). The result for survival meta-analysis appears similar for G and E.

Conclusions. The occurrence of skin rash during treatment with anti-EGFR TKIs for NSCLC represents a significant predictor of efficacy of these drugs, and could be useful in patients with unknown EGFR mutation status.

D4# PROGNOSTIC RELEVANCE OF FIBROBLAST GROWTH FACTOR RECEPTOR 1 (FGFR1) GENE COPY NUMBER IN PURE LUNG SQUAMOUS-CELL CARCINOMA

De Maio L.1, Andreozzi M.2, Rossi E.1, Landi L.1, Salvini J.1, Lani E.1, D’Incecco A.1, D’Arcangelo M.1, Minuti G.1, Incarbone M.3, Terracciano L.2, Cappuzzo F.1

1Istituto Toscano Tumori, Oncologia Medica, Ospedale Civile, Livorno; 2Pathology Department, Basel University, Basel, Switzerland; 3Thoracic Surgery, Ospedale S. Giuseppe-Multimedica, Milan

Table 1 D3 - Forrest plot for meta-analysis of skin rash occurrence and OS

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perez-soler 2004</td>
<td>-2.996</td>
<td>0.468</td>
<td>9.2%</td>
<td>0.05 [0.02, 0.13] 2004</td>
<td>0.51 [0.41, 0.63] 2004</td>
</tr>
<tr>
<td>Veronese 2005</td>
<td>-1.204</td>
<td>0.207</td>
<td>17.0%</td>
<td>0.30 [0.20, 0.45] 2005</td>
<td>0.50 [0.41, 0.60] 2005</td>
</tr>
<tr>
<td>Wacker 2007</td>
<td>-1.338</td>
<td>0.141</td>
<td>19.1%</td>
<td>0.29 [0.22, 0.38] 2007</td>
<td>0.50 [0.41, 0.60] 2007</td>
</tr>
<tr>
<td>Uhlm 2009</td>
<td>-1.02</td>
<td>0.286</td>
<td>14.3%</td>
<td>0.36 [0.21, 0.63] 2009</td>
<td>0.50 [0.41, 0.60] 2009</td>
</tr>
<tr>
<td>Cadranel 2009</td>
<td>-1.204</td>
<td>0.295</td>
<td>14.0%</td>
<td>0.30 [0.17, 0.53] 2009</td>
<td>0.50 [0.41, 0.60] 2009</td>
</tr>
<tr>
<td>Faehling 2010</td>
<td>-0.616</td>
<td>0.251</td>
<td>15.5%</td>
<td>0.54 [0.33, 0.88] 2010</td>
<td>0.50 [0.41, 0.60] 2010</td>
</tr>
<tr>
<td>Mazzoni 2011</td>
<td>-0.799</td>
<td>0.39</td>
<td>11.1%</td>
<td>0.45 [0.21, 0.97] 2011</td>
<td>0.50 [0.41, 0.60] 2011</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>100.0%</td>
<td>0.30 [0.21, 0.43] 2011</td>
<td>0.50 [0.41, 0.60] 2011</td>
</tr>
<tr>
<td>Heterogeneity: Tau = 0.16; Chi² = 21.55, df = 6 (P = 0.001); I² = 72%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 6.47 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2 D3 - Forrest plot for meta-analysis of skin rash occurrence and PFS/TTP

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio</th>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dudek 2006</td>
<td>-0.669</td>
<td>0.321</td>
<td>8.2%</td>
<td>0.51 [0.27, 0.96] 2006</td>
<td>0.50 [0.41, 0.60] 2006</td>
</tr>
<tr>
<td>Wacker 2007</td>
<td>-1.05</td>
<td>0.152</td>
<td>17.9%</td>
<td>0.35 [0.26, 0.47] 2007</td>
<td>0.50 [0.41, 0.60] 2007</td>
</tr>
<tr>
<td>Perng 2008</td>
<td>-0.562</td>
<td>0.129</td>
<td>19.7%</td>
<td>0.57 [0.44, 0.73] 2008</td>
<td>0.50 [0.41, 0.60] 2008</td>
</tr>
<tr>
<td>Lilienbaum 2008</td>
<td>-0.799</td>
<td>0.3</td>
<td>9.0%</td>
<td>0.45 [0.25, 0.81] 2008</td>
<td>0.50 [0.41, 0.60] 2008</td>
</tr>
<tr>
<td>Tiseo 2009</td>
<td>-0.386</td>
<td>0.097</td>
<td>22.4%</td>
<td>0.68 [0.56, 0.82] 2009</td>
<td>0.50 [0.41, 0.60] 2009</td>
</tr>
<tr>
<td>Uhlm 2009</td>
<td>-0.616</td>
<td>0.264</td>
<td>10.6%</td>
<td>0.54 [0.32, 0.91] 2009</td>
<td>0.50 [0.41, 0.60] 2009</td>
</tr>
<tr>
<td>Cadranel 2009</td>
<td>-0.868</td>
<td>0.287</td>
<td>0.0%</td>
<td>0.42 [0.24, 0.74] 2009</td>
<td>0.50 [0.41, 0.60] 2009</td>
</tr>
<tr>
<td>Faehling 2010</td>
<td>-0.777</td>
<td>0.232</td>
<td>12.3%</td>
<td>0.46 [0.29, 0.72] 2010</td>
<td>0.50 [0.41, 0.60] 2010</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td>100.0%</td>
<td>0.51 [0.41, 0.63] 2010</td>
<td>0.50 [0.41, 0.60] 2010</td>
</tr>
<tr>
<td>Heterogeneity: Tau = 0.04; Chi² = 14.79, df = 6 (P = 0.02); I² = 59%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 6.11 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
tion. Although FGFR1 gene amplification has been reported in up to 20% of lung cancer patients with squamous-cell carcinoma (SCC), prognostic effect is unknown. Aim of the present study was to assess the prognostic role of FGFR1 gene copy number (GCN) in pure lung SCC.

Methods. A total of 378 patients were included in the present study. Pure SCC was defined as a tumour positive for P40 and negative for TTF1 using immunohistochemistry. FGFR1 was evaluated by fluorescence in situ hybridization (FISH) in tissue microarray sections from primary lung tumours. All cases with an FGFR1/centromere ratio ≥2 were considered as amplified (FGFR1 FISH+).

Results. Among patients included in the study, FGFR1 FISH analysis was successfully performed in 304 and 32 (10.5%) were FGFR1 FISH+. FGFR1 amplification was significantly associated with P40 positive status (p = 0.002) and with lack of TTF1 expression (p = 0.005). In the whole population, no difference in disease-free survival (DFS) and overall survival (OS) was detected between FGFR1 FISH positive and negative patients (DFS: 17.2 versus 17.0 months, p = 0.98; OS not reached in both groups, p = 0.2). In the group of patients p40+/TTF1 negative (N = 66), 14 (21.2%) displayed FGFR1 gene amplification. No difference in survival was detected between FGFR1 FISH+ and negative patients in p40+ versus p40 negative (OS not reached versus 46.2 months, p = 0.41 in FGFR1 FISH+/p40+ versus any negative), nor in TTF1 negative versus TTF1+ (OS not reached versus 41.8 months in FGFR1 FISH+/TTF1 negative versus other subgroups) nor in FGFR FISH+/p40+/TTF1 negative versus FGFR negative/p40+/TTF1 negative (37.3 months versus not reached, p = 0.77).

Conclusions. FGFR1 is amplified in 21% of pure lung SCC with no prognostic effect. The high percentage of gene amplification detected further support anti-FGFR1 strategies in individuals with pure SCC.

D5* CO-MORBIDITY IS A SIGNIFICANT PROGNOSTIC FACTOR IN ELDERLY PATIENTS WITH MALIGNANT PLEURAL MESOTHELIOMA (MPM): RESULTS OF A MULTICENTER SURVEY

Ceresoli G.L.1, Grossi F.2, Pasello G.3, Zucali P.A.4, Degiovanni D.5, Stinco S.1, Lorenzi E.4, Polo V.3, Ripa C.1, Dipietrantonj C.2, Giordano L.4, Favaretto A.G.3, Santoro A.4, Bott M.5

1Oncology, Cliniche Humanitas Gavazzeni, Bergamo; 2Oncology SS Antonio e Biagio General Hospital, Alessandria; 3Department of Oncology, Humanitas Cancer Center, Rozzano; 4Istituto Oncologico Veneto, Padova; 5Oncology ASL21, Casale Monferrato

Background. The incidence of malignant pleural mesothelioma (MPM) in elderly patients is increasing in Western Countries. Elderly pts with MPM are under-represented in clinical trials, and there are no specific guidelines for their management. The aim of this study was to perform a retrospective survey on this patient population in four Oncology Departments with high MPM accrual and expertise.

Methods. The clinical records of elderly pts (≥70 years old) with MPM referred from January 2005 to November 2011 to the participating centers were reviewed. For each patient, age and gender, histology, Eastern Cooperative Oncology Group Performance Status (ECOG-PS), Charlson comorbidity index (CCI) and treatment modalities were collected. The study endpoint was overall survival (OS).

Results. Out of a total of 610 cases, 210 elderly pts were identified (34% of the whole MPM population observed in the study period). Patients characteristics were: median age 75 yrs (range 70-92), M/F 132/78, epithelial/non-epithelial histology 140/70, ECOG-PS 0/1/2/unknown 130/67/9/4, CCI was 0 in 128 pts (61%), ≥4 in 59 pts (28%). Treatment was multimodality therapy including surgery in 16, chemotherapy in 153 (75%) and best supportive care only in 41 pts (19%). Chemotherapy was mainly pemetrexed-based. Median OS was 11.0 months. In a multivariate model, non-epithelial histology, age ≥75 yrs and the presence of co-morbidities according to CCI (HR 1.15; 95% CI 1.07-1.23, p <0.001) were all significantly correlated to a shorter OS. In the same model, treatment with pemetrexed was associated with improved OS. Age and co-morbidity were not significantly correlated.

Conclusions. Pemetrexed-based chemotherapy is feasible in selected elderly pts with MPM. Comorbidity is a significant prognostic factor, and should be carefully considered in patients selection. Prospective dedicated trials in elderly pts with MPM selected according to comorbidity scales are warranted.

D6* PROGNOSTIC CORRELATION OF NUTRITIONAL FACTORS AND C-REACTIVE PROTEIN (CRP) IN LOCALLY ADVANCED HEAD AND NECK CARCINOMA (LAHNC) TREATED WITH DEFINITIVE OR POSTOPERATIVE CHEMORADIATION (CRT)

Bergamini C.1, Bossi P.1, Locati L.1, Granata R.1, Resteghini C.1, Imbimbo M.1, Fallai C.2, Orlandi E.2, Tana S.2, Ferraro L.3, Licitra L.1

1Head and Neck Medical Oncology, 2Radiotherapy, 3Otorinolaryngology Surgery, Fondazione IRCCS, Istituto Nazionale dei Tumori, Milano

Background. Head and neck cancer patients experience nutrition problems due to the disease itself and/or to the effects of CRT and surgery. Malnutrition can impact on clinical outcome and reduce treatment efficacy. We reviewed the prognostic role of clinical and laboratory nutritional factors and CRP in LAHNC pts treated with definitive or postoperative CRT.

Patients and methods. From 2004 to 2010, 305 pts with LAHNC were treated with definitive CRT (82%) or surgery plus postoperative CRT (18%). Baseline and 3 months after therapy values of body mass index (BMI), haemoglobin (Hb) and lymphocytes (Ly) were collected; CRP was considered only at baseline. Weight loss, the highest CRP and the lowest Hb level reached during CRT were reviewed. In case of severe dysphagia during CRT, the feeding tube was placed. All parameters were analysed as prognostic factors for mortality by means of a Cox multivariable analysis.

Results. Median age was 56 years, M/F ratio 231/74 (76%/24%), median ECOG 0. Site of primary cancer was: oropharynx (33%), nasopharynx (27%), larynx-hypopharynx (14%), oral cavity (12%), and other sites (14%); stage IV was most represented (79%). Median follow-up time was 28 months (range 1-138). Low BMI (<18.5), Hb (<12 g/dL), Ly (<900/mmc) were detected respectively in 5%, 18% and 14% of the pts at baseline and in 10%, 43% and 58% three months after therapy. CRP >5 mg/dL was identified in 27% of the pts at baseline. According to CTCAE v3.0, G3 dysphagia was observed in
40.3% of pts; among these, 83% pts were supported by nasogastric tube and 4% pts by gastrostomy. Thirty-seven percent experienced >10% weight loss during CRT. High levels of baseline CRP (p = 0.0114) and low Ly (p = 0.0026) 3 months after CRT were identified as prognostic factors for mortality.

Conclusions. Pretreatment and posttreatment nutritional factors have an impact on LAHNC pts prognosis. Whether their early hypercorrection could translate in better pts outcome is worth studying.

D7 CISPLATIN + VINORELBINE (DDP + VNB) IN RECURRENT/METASTATIC SALIVARY GLAND MALIGNANCIES (RMSGM): A FINAL REPORT OF 60 CASES

Airoldi M.1, Garzaro M.2, Pedani F.1, Raimondo L.2, Carnio S.1, Riva G.2, Salonia L.2, Pecorari G.2, Fora G.1, Giordano C.2

12nd Medical Oncology Division, Medical Oncology Department, San Giovanni Battista Hospital, Turin; 21st ENT Division, Physics Pathology Department, University of Turin, Turin

Background. RMSGM are not amenable to the usual treatment with surgery and postoperative radiotherapy. The role of chemotherapy (CT) for RMSGM is palliative only. VNB showed moderate activity in our experience (Bull Cancer, 85: 892, 1998) and in a randomized phase II trial we had demonstrated that the DDP + VNB combination had a better outcome than VNB alone (Cancer, 91: 541, 2001). In this abstract we report the final results of this combination in 60 cases.

Methods. From April 2001 to February 2009, 60 cases with RMSGM were enrolled. All patients received the following regimen: DDP 80 mg/m² d 1 + VNB 25 mg/m² d 1, 8 every 3 weeks. The study foresees a maximum of 6 cycles.

Results. Patients characteristics were as follows: 35 males (58%) and 25 females (42%); median age 56 yrs (range 20-68); median ECOG PS 1 (0-2); histology: adenocarcinoma 15 (25%), adenoid cystic ca. 34 (57%), others 11 (18%); site of disease: local 30 (50%), mts ± local 30 (50%). Forty-two pts received DDP + VNB as first-line CT (70%) while 18 pts (30%) had the combination as second-line CT (30%). After a median of 5 cycles of first-line DDP + VNB responses were: 3 CR (7%), 10 PR (24%), 14 NC (33%) and 15 PD (36%). Forty-two pts received DDP + VNB as second-line CT; 4 months (1-12) for second-line CT. G3-4 toxicity: neutropenia (20%), anemia (12%), nausea/vomiting (12%), peripheral neuropathy (3%).

Conclusions. DDP + VNB is an effective first-line CT in RMSGM; second-line CT has a low palliative activity. Toxicity seems acceptable. This regimen could be suitable for an integrative treatment with new biologic target agents.

D8 ACTIVITY OF EGFR-HER2 DUAL INHIBITOR AFATINIB IN LUNG CANCER PATIENTS WITH ACQUIRED RESISTANCE TO REVERSIBLE EGFR-TKIS

Cappuzzo F.1, De Marinis F.2, Galetta D.2, Landi L.1, Bennati C.4, Ricciardi S.2, Currà M.F.4, Chiari R.4, Metro G.4, Catino A.2, D’Incecco A.1, D’Arcangelo M.1, Minuti G.1, Salvini J.1, Lani E.1, Ludovini V.4, Marchetti A.5, Crinò L.4

1Istituto Toscano Tumori, Ospedale Civile, Livorno; 2High Specialization Hospitals, Oncological Palmonary 1st Unit, San Camillo-Forlanini, Rome; 3Istituto Tumori “Giovanni Paolo II” IRCCS, Bari; 4SC di Oncologia Medica, Ospedale S. Maria della Misericordia, Perugia; 5University of Chieti, Chieti

Background. Although lung adenocarcinomas harboring activating epidermal growth factor receptor (EGFR) mutations respond dramatically to reversible EGFR tyrosine kinase inhibitors (TKI), all patients inevitably develop acquired resistance. Afatinib, an irreversible EGFR-HER2 dual inhibitor, demonstrated some activity in non-small cell lung cancer (NSCLC) pts progressing after at least 3 months of EGFR-TKI therapy.

Materials and methods. We analyzed 68 advanced lung adenocarcinoma patients resistant to EGFR-TKIs according to criteria used in the LUX-Lung 1 trial (Miller VA, Lancet Oncol, 2012) and treated with afatinib at the daily dose of 40-50 mg in three Italian centers. The drug was given as compassionate use.

Results. The study included individuals with a median age of 62.6 year. The majority was female (N = 35/51.5%), never/former smoker (N = 58/85.2%), with good PS (0-1; N = 57/83.8%) and pretreated with ≥2 therapy lines (N = 60/88%). EGFR status was assessed in 60 cases and 43 pts (63.2%) harbored a mutation in exon 18 (N = 3/7%), in exon 19 (N = 25/51.8%), in exon 20 (T790M; N = 24/7%) and in exon 21 (N = 12/27.9%). Among the 66 pts evaluable for toxicity, 39.3% had skin rash (G3 = 7.5%) and 18.1% diarrhea (G3 = 3.0%). Among the 47 pts evaluable for efficacy, response rate (RR) was 10.6%, disease control rate (RR+stable disease) was 66%, median progression-free survival and overall survival were 3.0 months and 4.2 months respectively. EGFR resulted mutated in 4 of 5 responders including 1 pt with T790M mutation. In 9 pts in which tumour biopsy was repeated before starting afatinib therapy only 2 pts had T790M mutation, with no evidence of response.

Conclusions. In “real life” experience afatinib showed encouraging activity in pretreated NSCLC with manageable toxicity profile.

D9 CUSTOMIZED FIRST-LINE CHEMOTHERAPY ACCORDING TO ERCC1 AND RRM1 SNPs IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS: A PHASE II STUDY


*SOD Oncologia Medica, AOU Careggi, Firenze; 1Centro Coordinamento Sperimentazioni Cliniche-ITT and AOU Careggi, Firenze; 2SOD Diagnostica Genetica, AOU Careggi, Firenze; 3Oncologia Medica, Versilia Hospital, Lido di Camaiore; 4Oncologia Medica, Pontedera Hospital, Pontedera; 5Oncologia Medica, Ospedale S. Maria Annunziata, Firenze

Introduction. Excision repair cross complementation group 1 (ERCC1) and ribonucleotide reductase 1 (RRM1) expression levels are predictive of chemotherapy (CT) efficacy in some malignancies. Customized CT has several advantages: patients are
more likely to be treated with agents that they will respond to, pts can be spared the toxicity of agents that they are resistant to.

Methods. We planned a phase II multicentric trial in two steps based on Simon design. Patients affected by advanced NSCLC are treated with first-line CT according to single nucleotide polymorphisms (SNPs) of ERCC1 (T118C and C8092A) and RRMI (-37C >A and -524T >C), which are supposed to be correlated with specific expression levels. CT is delivered as follows: treatment A (low ERCC1 and RRMI1) cisplatin + gemcitabine; treatment B (low ERCC1, high RRMI) cisplatin + docetaxel; treatment C (high ERCC1, low RRMI1) gemcitabine + docetaxel; treatment D (high ERCC1 and RRMI1) docetaxel + vinorelbine.

Results. We report the first step analysis for futility: 42 pts were enrolled from January 2010 to November 2011; 40 pts received at least 1 cycle of CT; median age was 66 years (range 47-72); 30 (75%) pts were males; 21 (52%) pts showed ECOGPS0, 19 (48%) PS1; 36 (90%) pts had stage IV, 4 (10%) IIIIB; 23 (58%) pts had adenocarcinoma, 14 (35%) squamous; 25 (62%) pts received treatment A, 3 (8%) treatment B, 11 (27%) treatment C, 1 (3%) treatment D. As primary endpoint we assessed the overall best response and found a 55% response rate (RR) [38.7-70.4; 95% CI] in the intention-to-treat population. Subgroups analysis showed 71.4% RR in squamous patients. As secondary endpoints we evaluated progression-free survival (PFS), overall survival (OS) and safety. The median follow-up time is 7.1 months, PFS and OS are in progress. CT was well tolerated: 17 (42%) pts showed grade 3-4 toxicity and there were no treatment related deaths.

Conclusions. We observed an increase of RR in NSCLC pts treated with CT according to ERCC1 and RRMI SNPs status, the treatment strategy used overcomes the first step of the study.

D10 SMRP AND CT AS TOOLS OF SCREENING FOR MESOTHELIOMA IN ASBESTOS EXPOSED WORKERS: A STUDY ON 1704 SUBJECTS

Mencoboni M.1, Galli R.2, Dini G.2, Bruzzone A.1, Del Corso L.1, Mortara V.3, Filiberti R.4, Caruso P.5, Marrone P.6, Spigno F.2

1Medical Oncology, Villa Scassi Hospital, ASL 3 Genovese, Genoa; 2Occupational Medicine, University of Genoa, Genoa; 3INAIL, Genoa; 4Enviromental Epidemiology, National Cancer Institute, Genoa; 5Radiology Unit, Ospedale Evangelico, Genoa; 6Laboratory Unit, National Cancer Institute, Genoa

Background. The soluble mesothelin-related peptide (SMRP) is a candidate marker in the diagnosis of pleural malignant mesothelioma, as well as a prognostic marker.

Objective. To evaluate SMRP and incidence of malignant mesothelioma in an asbestos exposed cohort.

Subjects and methods. 1704 subjects (median age 62) retired or still working in shipbuilding, iron and steel industries were enrolled in the study. A questionnaire on individual characteristics was administered by trained personnel. On the basis of this questionnaire we calculated a score of exposure. All subjects underwent clinical examination and were followed for three years, with annual clinical examination and collection of serum samples for SMRP serial measurement. All subjects with SMRP >1.5 underwent a low dose CT, as well as an equal number of controls.

Results. Median baseline SMRP was 0.45 nmol/L (range 0.1-4.45). SMRP was higher than 1.5 nmol/L (defined as cut-off) in 46 participants. Nine subjects had recognized lung cancer at the time of screening (median baseline SMRP 0.65 nmol/L, range 0.10-1.74) and 109 had recognized tumours at other sites (median 0.52 nmol/L, range 0.10-3.03). Median follow-up was 31.5 months. During follow-up, recurrent or metastatic tumours were observed in 17 out of 118 tumours (median baseline SMRP 0.75 nmol/L, range 0.18-2.41), 49 subjects developed a new tumour (median baseline SMRP 0.50 nmol/L, range 0.10-2.36). Only one pleural mesothelioma occurred, 31 months after the enrolment. SMRP was 0.17 nmol/L at baseline and 0.20 nmol/L at the second dosage, 12 months before the MPM occurrence. Twenty-five subjects without any evidence of neoplastic disease showed an increase of SMRP above the cut-off at the third sample collection.

Conclusions. We cannot confirm the predictive role of SMRP for mesothelioma because we observed only one mesothelioma. We can affirm that no subject developed mesothelioma within 12 months if SMRP were low. The low number of mesotheliomas could be due to low median age of population.

D11 THE ITALIAN EXTERNAL QUALITY ASSURANCE FOR SOMATIC EGFR MUTATION TESTING IN NON-SMALL CELL LUNG CANCER

Normanno N.1, Pinto C.2, Taddei G.L.3, Gambacorta M.4, Castiglione F.5, Clemente C.5, Marchetti A.6

1Istituto Nazionale Tumori, Fondazione G. Pascale, Napoli; 2Policlinico S. Orsola Malpighi, Bologna; 3Università degli Studi di Firenze; 4Ospedale Niguarda, Milano; 5Casa di Cura S. Pio X, Milano; 6Università G. d’Annunzio, Chieti

Background. Assessment of epidermal growth factor receptor (EGFR) mutations is mandatory to choose the most appropriate first-line treatment for non-small cell lung cancer (NSCLC) patients. The Italian Association of Medical Oncology (AIOM) and the Italian Society of Pathology and Cytology (SIAPeC) started an external quality assessment (EQA) scheme for EGFR testing in 2011.

Methods. Ten specimens (3 biopsies and 7 surgical specimens) with known EGFR mutation status were validated in 3 referral laboratories and provided to 47 laboratories participating in the EQA. Participating laboratories registered at the www.eegrquality.it website, and were requested to perform DNA extraction and analysis using their usual method and to submit their results within a 4-week timeframe. A board of experts evaluated the results according to a pre-defined scoring system that assigned 2 points to the correct genotype and 0 points to false-negative or false-positive results. The threshold to pass the EQA was set at ≥18/20 points. Centers failing to pass the I round were offered to participate to a II round.

Results. All the centers participating in the EQA submitted the results within the timeframe. DNA sequencing (79%) was the main methodology used by the participants, while few centers used Pyrosequencing (17%) or Real-Time PCR (4%). A significant number of analytical errors was observed, including both false-negative and false-positive results. Fourteen out of 47 centers (30%) did not pass the I round having reached a score ≤18 points. A difference was observed between the testing methods: 0/10 laboratories that used Pyrosequencing or Real-Time PCR failed, whereas 14/37 (38%) laboratories that employed PCR/s-
quencing made analytical errors. Eight of the 14 centers that failed in the I round, passed the II round. Overall, 41/47 (87%) of the Italian centers passed the EGFR EQA.

Conclusions. The results of the first Italian quality assessment for EGFR testing in NSCLC suggest that EGFR mutational analysis is performed with good quality in the majority of Italian centers.

D12 MULTICENTER EXPERIENCE OF RESECTED THYMIC EPITHELIAL TUMOURS (TETs): AN OBSERVATIONAL REPORT ON BEHALF OF FONICAP (FORZA OPERATIVA NAZIONALE INTERDISCIPLINARE CONTRO IL CANCRO DEL POLMONE)

Genestreti G.1, Burgio M.A.1, Ampollini L.2, Rolli L.2, Sanna S.3, Scarpi E.4, Monti M.4, Monti S.1, Giannone L.5, Santo A.6, Mezzetti M.6, Gavelli G.7, Casanova C.8, Buosi R.9, Amadori D.1

1Department of Medical Oncology, IRCCS Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST), Meldola; 2Department of Thoracic Surgery, University Hospital, Parma; 3Department of Thoracic Surgery, Murgagni-Pierantoni Hospital, Forlì; 4Unit of Biostatistics and Clinical Trials, IRCCS Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST), Meldola; 5Department of Medical Oncology, University Hospital, Verona; 6Department of Thoracic Surgery, San Carlo Clinic, Milan; 7Department of Radiology, IRCCS Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST), Meldola; 8Department of Medical Oncology, Civil Hospital, Ravenna; 9Department of Medical Oncology, Civil Hospital, Novara

Aim. TETs are rare tumours. As a result few large-scale prospective trials are lacking. This retrospective multicenter analysis assesses patient characteristics and clinical outcome after complete surgical resection and adjuvant treatments (AT).

Methods. All medical reports of TETs patients between 2000 and 2007 have been reviewed. Surgical intervention included complete removal of the thymus, mediastinal fat tissue and suspici-ous lesions. Histological classification was based on WHO criteria and the staging system proposed by Masaoka was used. Ad-juvant chemotherapy comprised anthracycline- and platinum-based regimens, while adjuvant radiotherapy was delivered to ir-radiation fields covering the primary tumour bed. Overall sur-vival (OS) was calculated from the date of diagnosis until patient death or last follow-up visit. Disease-free survival (DFS) was de-fined as the interval between surgery and first documented recur-rence. OS, DFS and 95% confidence intervals (95% CI) were es-timated by the Kaplan-Meier method.

Results. Sixty-two patients were analyzed (30 [48%] males and 32 [52%] females). Median age was 60 years (range 33-86). At the beginning of their cancer history 20 (32%) patients had myasthenia. At clinical staging 31 (50%) patients had stage I disease, 19 (30%) stage II, 5 (8%) stage III, 2 (4%) stage IVa and 5 (8%) had stage IVb. Histology was as follows: 11 (19%) A tu-mour type, 19 (30%) AB type, 7 (12%) B1 type, 11 (17%) B2 type, 11 (17%) B3 type and 5 (8%) C type. At pathological stag-ing there were 30 (48%) stage I disease, 22 (35%) stage II, 3 (6%) stage III, 2 (3%) stage IVa and 5 (8%) stage IVb. Post-surgery treatment consisted of CHT in 3 (5%) patients and RT in 16 (26%) patients. After a median follow-up of 71 months (range 1-145) DFS and OS were as follows:

<table>
<thead>
<tr>
<th>Events</th>
<th>48 months</th>
<th>60 months</th>
<th>72 months</th>
<th>48 months</th>
<th>60 months</th>
<th>72 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>% DFS (95% CI)</td>
<td>% OS (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Events</td>
<td>48 months</td>
<td>60 months</td>
<td>72 months</td>
<td>48 months</td>
<td>60 months</td>
<td>72 months</td>
</tr>
<tr>
<td>9</td>
<td>89</td>
<td>89</td>
<td>86</td>
<td>7</td>
<td>97</td>
<td>95</td>
</tr>
<tr>
<td>(80-97)</td>
<td>(80-97)</td>
<td>(76-96)</td>
<td>(92-100)</td>
<td>(88-100)</td>
<td>(85-100)</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions. TETs are rare, indolent tumours. Surgery shows good results which can be further improved by AT such as chemotherapy and/or radiotherapy.

Supported by GIPO.

D13 CYTOCHROME P450 1B1 (CYP1B1) POLYMORPHISMS ARE ASSOCIATED WITH ACTIVITY AND EFFICACY OF DOCETAXEL IN NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS

Tibaldi C.1, Vasilie E.2, D’Incecco A.1, Caponi S.2, Giovannetti E.3

1U.O. Oncologia Medica, Azienda USL 6, Livorno; 2U.O. Oncolo-gia Medica, Azienda Ospedaliero-Universitaria Pisana, Pisa; 3Di-partimento di Oncologia Medica, VUMc, Amsterdam, Paesi Bassi

Background. The CYP1B1 is a mono-oxygenase involved in the metabolism of anticancer agents in a variety of tumours. Al-though CYP1B1 does not metabolize directly docetaxel, its over-expression is associated with resistance to docetaxel, a drug commonly used for second-line treatment of NSCLC patients. Several functional single nucleotide polymorphisms (SNPs) have been associated with CYP1B1 expression and activity.

Methods. The objective of this study was to retrospectively evaluate the correlation between CYP1B1 SNPs and the outcome of chemotherapy with docetaxel in NSCLC. CYP1B1 genotyping was performed on blood samples of 56 NSCLC patients treated with docetaxel in second or further lines of treatment. Associations between CYP1B1 4326C >G (leading to the 432LeuVal transition) and 4390A >G (453AsnSer) polymorphisms with treatment response, progression-free survival (PFS) and overall survival (OS) were estimated using Pearson $\chi^2$ test, Kaplan-Meier curves and log-rank test; a multivariate analysis was performed using Cox proportional hazards modeling.

Results. A total of 56 pretreated stage IIIb-IV NSCLC were enrolled in the analysis. Median age was 66 years (range 46-80). Forty-three patients were male; only 5 were never smokers. Performance status (PS) was 0 in 18 patients, 1 in 27, and 2 in 11. Histology was adenocarcinoma in 20 patients, squamous carcino-ma in 22, other NSCLC in the remaining 14. Docetaxel was used in a three-weekly or weekly schedule; the median number of cy-cles was 3 (range 2-6). Median PFS and OS of the entire group of patients were 2.3 and 8.1 months.

At univariate analysis, stage, PS and CYP1B1-4326C >G SNP resulted associated with PFS and OS. Patients with CC, CG and GG genotype had a PFS of 3.7, 2.5 and 1.8 months and an OS of 14.3, 9.2, 3.1 months, respectively. CYP1B1-4326C >G SNP was associated also with treatment response. Multivariate analysis confirmed the prognostic/predictive role of CYP1B1-4326 SNP with both PFS (p = 0.017) and OS (p = 0.002).

Conclusions. CYP1B1-4326C >G (432LeuVal) polymor-phism emerged as possible prognostic/predictive marker of activity/efficacy of docetaxel in NSCLC patients.
**D14 RIBONUCLEOTIDE REDUCTASE SUBUNIT 2 (RRM2) PREDICTS SHORTER SURVIVAL IN RESECTED STAGE I-III NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS**

Rijavec E.¹, Dal Bello M.G.¹, Savarino G.², Sini C.¹, Barletta G.¹, Genova C.¹, Truini M.³, Pronzato P.², Merlo D.⁵, Pfeffer U.², Grossi F.¹

¹Lung Cancer Unit, ²Integrated Molecular Pathology, ³Department of Epidemiology and Biostatistics, National Institute for Cancer Research, Genoa

**Background.** Biomarkers can help in identifying patients with early-stage NSCLC with high risk of relapse and poor prognosis. The aim of this study was to investigate the relationship between the levels of expression of 7 biomarkers, various clinicopathological characteristics and their prognostic significance.

**Methods.** Tumour tissue from 82 radically resected stage I-III NSCLC pts was consecutively collected to investigate the mRNA expression and protein levels of the following biomarkers using quantitative reverse transcriptase real-time PCR (qRT-PCR) and immunohistochemistry (IHC) with a tissue microarray technique: excision repair cross-complementation group 1 (ERCC1), breast cancer 1 (BRCA1), ribonucleotide reductase subunit 1 (RRM1), RRM2, p53R2, thymidylate synthase (TS) and class III beta-tubulin (β-Tub-III).

**Results.** On an univariate analysis, p53R2 expression was significantly higher in adenocarcinoma (ADK) compared to squamous cell carcinoma (SSC) samples (p = 0.002) and in stage I compared to stage II-III (p ≤0.001). ERCC1 expression was significantly higher in females compared to males (p = 0.03), and β-Tub-III expression was significantly higher in ADK than in SSC (p = 0.03). Patients with lower RRM2 expression survived longer than pts with higher RRM2 expression (p = 0.069). The multivariate analysis confirmed RRM2 as an independent prognostic marker of shorter survival (p = 0.031). The comparison between survival curves with qRT-PCR and IHC showed similar results with a trend towards longer survival among ERCC1 negative pts, BRCA1 negative pts, p53R2 positive pts and among pts with low levels of RRM1 and RRM2, although the difference was not statistically significant with both methods. qRT-PCR and IHC have shown that β-Tub-III and TS had no significant impact on survival.

**Conclusions.** This is the first study that identifies RRM2 expression as a negative prognostic factor in resected stage I-III NSCLC. Moreover, we have demonstrated the differential expression of p53R2 and β-Tub-III in ADK compared to SSC and higher expression of p53R2 in pts with stage I compared to stage II-III NSCLC.

**D15 THE IMPACT OF INDUCTION CHEMOTHERAPY ON CISPLATIN DOSE INTENSITY DURING CHEMORADIOTherapy (CTRT) IN Oropharyngeal squamous cell cancer (OPC)**

Granata R.¹, Bossi P.¹, Orlandi E.², Locati L.¹, Bergamini C.², Resteghini C.¹, Ibba T.³, Scaramellini G.³, Fallai C.², Licitra L.¹

¹Head & Neck Cancer Medical Oncology Unit, Department of Medical Oncology, ²Department of Radiotherapy, ³Department of Otolaryngology, Fondazione IRCCS, Istituto Nazionale dei Tumori, Milan

**Background.** Induction (IC) with TPF (taxotere, cisplatin, 5-FU) has been associated with improved outcome in advanced head and neck squamous cell cancer patients. Full dose of cisplatin (300 mg/m²) during CTRT has been demonstrated to impact on patients outcome. The aim of the current study is to investigate whether the IC could impact on cisplatin dose intensity during CTRT in a homogeneous population of OPC.

**Materials and methods.** The study population consisted of 101 pts with stage III-IV OPC treated from 07/2004 to 12/2011 with IC (N = 53) plus CTRT or CTRT alone (N = 48). IC consisted of TPF, while weekly 50 mg/m² or 3-weekly 100 mg/m² cisplatin was administered concurrently with RT (planned chemotherapy dose = 300 mg/m²; planned RT dose = 66-70 Gy, 3DRT or IMRT with a conventional or accelerated fractionation). Carboplatin substituted cisplatin in case of creatinine clearance less than 60 mL/min. HPV status, concurrent cisplatin dose intensity and RT overall treatment time (OTT) were analyzed.

**Results.** Stage IV pts were 100% in the IC group and 83% in CTRT, while HPV positive OPCs were detected in 58% and 63% of the cases respectively. TPF median number of cycles was 3, with induction cisplatin median dose administered of 200 mg/m². RT median total dose administered was 70 Gy in both groups. Accelerated fractionated RT was adopted in 65% of CTRT alone group and in 21% of IC group. Two pts (1 in each group) did not complete CTRT because of cardiovascular events. Mean and median dose intensity of cisplatin concurrent to RT in the IC group was 77.7% and 75% (35%-100%) while in CTRT group was 86% and 91.7% (33%-100%), with a p value = 0.014. In 11 pts (21%) treated with IC and only in 1 pt (2%) treated with CTRT alone cisplatin was substituted with carboplatin. No different cisplatin dose intensity was identified in HPV positive versus HPV negative cases. Prolonged OTT (longer than 5 days) was observed in two patients in IC group due to sepsis and severe mucositis as well as in one patient in CTRT group due to machine failure.

**Conclusions.** Concurrent cisplatin dose intensity was significantly reduced in pts receiving IC compared to CTRT alone, irrespective of HPV status. Whether this has an impact on the results of IC followed by full dose CT/RT has to be clarified.

**D16 OUTCOME OF OROPHARYNGEAL CANCER ACCORDING TO TREATMENT IN DIFFERENT RISK-PROFILE GROUPS: ANALYSIS OF A RETROSPECTIVE SERIES OF PATIENTS TREATED IN A TERTIARY CANCER CENTER**

Bossi P.¹, Granata R.¹, Orlandi E.², Perrone F.³, Locati L.¹, Fallai C.², Ferrari L.⁴, Pilotti S.³, Scaramellini G.², Licitra L.¹

¹Medical Oncology, ²Radiotherapy, ³Molecular Pathology, ⁴Otolaryngology, Fondazione IRCCS, Istituto Nazionale dei Tumori, Milan

**Background.** Epidemiology and outcome of oropharyngeal cancer (OPC) are changing in the last decades, due to the role of HPV infection. No different treatment modality has been identified as more effective in treating OPC according to HPV or smoking status.
Materials and methods. Two series of locally advanced (stage III-IV) squamous cell OPC patients treated at our Institution were considered: 1) treated with surgery followed by radiotherapy (dose 50-66 Gy), from 1/1991 to 7/2000 (surgical series); 2) receiving concurrent chemoradiation (CTRT) (RT dose = 66-70 Gy), with/without induction docetaxel, cisplatin, 5-fluorouracil (TPF) chemotherapy (CT), from 7/2004 to 3/2011 (CTRT series).

Smoking habits and tumor p16 expression were analyzed in order to stratify each series according to Ang risk profile (low, intermediate, high risk).

Results. Globally, 171 pts were considered, 56 in surgical and 115 in CTRT series. In CTRT series, 40% of the pts received induction TPF chemotherapy; in surgical series 57% of the pts had extracapsular extension and/or microscopically involved surgical margins.

<table>
<thead>
<tr>
<th></th>
<th>Surgical series</th>
<th>CTRT series</th>
</tr>
</thead>
<tbody>
<tr>
<td>p16 expression</td>
<td>39%</td>
<td>59%</td>
</tr>
<tr>
<td>Stage III</td>
<td>13%</td>
<td>7%</td>
</tr>
<tr>
<td>Stage IV</td>
<td>87%</td>
<td>93%</td>
</tr>
<tr>
<td>Low risk</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>Intermediate risk</td>
<td>23%</td>
<td>41%</td>
</tr>
<tr>
<td>High risk</td>
<td>57%</td>
<td>39%</td>
</tr>
</tbody>
</table>

Five-year OS for p16 positive pts was 50% in surgical and 88% in CTRT series, while for p16 negative was 38% and 49% respectively (p <0.0001).

When stratifying for risk profile, 5-yr OS of low risk CTRT pts was 100% vs 54% of surgical pts (p = 0.0042) and 5-yr DFS was 93% vs 53% (p = 0.0079); 5-yr OS of intermediate risk CTRT pts was 76% vs 46% of surgical pts (p = 0.0141) and 5-yr DFS was 79% vs 38% (p = 0.0359). High risk CTRT pts had a 5-yr OS of 51% vs 36% of surgical pts (p = 0.1902) and a 5-yr DFS of 24% vs 36% (p = 0.6411).

Conclusions. In this retrospective analysis, low and intermediate risk OPC pts had a greater survival benefit when treated with CTRT compared with surgery followed by RT. Although with the limits of different RT techniques and lack of CT in adjunct to postoperative RT, these data should be considered as hypothesis generating for new trials design.

D17 A STATIC DIAGNOSTIC BIOPSY IN PATIENTS WITH MUTATED EGFR LUNG ADENOCARCINOMA MAY BE INSUFFICIENT TO GUIDE THERAPEUTIC DECISIONS

Pitini V., Santarpia M., Arrigo C., Tomasello C., Benechci S., Picone A., Monaco F., Altavilla G.

Medical Oncology, Thoracic Surgery Unit, University of Messina, Messina

Background. Approximately 70% of the patients whose lung cancers harbor EGFR mutations acquire drug resistance after a response to EGFR tyrosine kinase inhibitors (TKIs) treatment; this acquired resistance is mainly due to a secondary mutation in EGFR (T790 M) in about 50% of patients, amplification of MET in 15%, PIK3CA mutations in 5%, an unknown mechanism in almost 30%, and SCLC transformation in some patients. Furthermore, clinical experience revealed that cancers with acquired resistance can respond again to TKIs, after a drug-free interval. To aid in identification and treatment of these patients we examined a cohort of patients whose cancers were assessed with tumour biopsies at multiple times before and after their treatment with TKIs.

Methods. Twenty-one lung adenocarcinomas pts (10 male, 11 female, median age 53 years) with EGFR mutations at 19 or 21 exons received TKIs, as first-line treatment. All showed a clinical response and all relapsed (mTTP 10 months). At the time of relapse a new biopsy was performed, histologic samples were reviewed to re-confirm the diagnosis, EGFR and MET amplification were identified by FISH, while EGFR mutations have been tested by DNA sequencing.

Results. At the time that drug resistance was acquired all pts retained their original activating EGFR mutations, 9 pts developed EGFR T790M resistance mutation with pronounced EGFR amplification in 3, 2 developed MET amplification, 8 biopsies did not reveal any new mutations, two pts were found to have a diagnosis of small cell lung cancer in their drug resistant tumour biopsies and responded well to conventional chemotherapy regimen. Fifteen of 19 confirmed lung adenocarcinoma patients underwent a cisplatin-pemetrexed chemotherapy regimen and at the time of progression 10 of them accepted to undergo a new biopsy. Three pts (after 4, 5 and 6 months break from treatment with TKIs) lost T790M mutation and their disease responded to a second-line course of erlotinib.

Conclusions. In our cohort of pts with acquired EGFR resistance some patients lost acquired T790M mutation and became sensitive to EGFR inhibitor, in addition, two pts underwent the histologic transformation from NSCLC to SCLC at the time of TKI resistance.

D18 ERLOTINIB ROLE IN PRETREATED EGFR WILDTYPE CAUCASIAN PATIENTS: A RETROSPECTIVE OBSERVATIONAL STUDY

Gori B., Del Signore E., Fulvi A., Ricciardi S., Migliorino M.R., Belli R., Condò S., De Santis S., Colacchi A.M., de Marinis F.

1st Oncological Pulmonary Unit, San Camillo High Specialization Hospital, Rome

Introduction. Erlotinib in UE was approved in unselected A-NSCLC patients (second/third-line and switch maintenance) and in EGFR mutated patients.

Methods. We conducted a retrospective mono-institutional observational study (Jan 2007- May 2012) of 191 Caucasian pts with A-NSCLC, EGFR wild-type (WT), who received erlotinib in 2nd, 3rd, 4th, 5th line of therapy. All pts were considered for survival, analyzing clinical characteristics for pts in second-line.

Results. In 108 pts (57%) who received erlotinib in second-line, median PFS was 8.4 weeks (wks) with an overall survival (OS) of 16.8 wks: 59 pts (55%) with ECOG PS 1 had mPFS 12.6 wks and mOS 21 wks, compared with 49 pts (45%) with PS 2-3 who had 4.2 wks and 8.4 wks respectively. We defined different groups: 19 pts (32%) female, adenocarcinoma, PS1, never/former smokers had as mPFS 25.2 wks and mOS 37.8 wks against 7 pts (12%) male, squamous, current smokers with mPFS of 8.4 wks and mOS of 16.8 wks. In subsequent lines where 83 pts (43%) had mPFS and mOS of 8.4 wks and 21.0 wks, the PS is decisive: PS 1 63 pts (76%) showed 12.6 wks and 25.2 wks of mPFS and
mOS compared to 4.2 wks and 8.4 wks of 20 pts (24%) with PS 2-3.

Conclusions. 90% of the Caucasian patients do not express the EGFR mutation. Erlotinib is a standard treatment in second/third-line, without adequate studies comparing with chemotherapy in wild-type population. This retrospective analysis, original for the assessment of EGFR mutational status, confirms the predictive/prognostic role of the PS 1 for the WT EGFR pts treated with erlotinib across all the lines (p = 0.001). Moreover, the results of the second-line shows that it is possible to identify a group of WT pts with positive predictive characteristics (PS 1, ADC, never/former smokers, female) to receive a greater benefit in survival (p = .03) with the use of erlotinib.

D19 PHARMACOGENETIC STUDY OF PATIENTS WITH ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) TREATED WITH SECOND-LINE PEMETREXED OR PEMETREXED-CARBOPLATIN

Tiseo M.1, Giovannetti E.2, Tibaldi C.3, Camerini A.4, Di Costanzo F.5, Barbieri F.6, Burgers J.A.7, Vincent A.7, Peters G.J.3, Smit E.F.8, Ardizzoni A.1

1Division of Oncology, University Hospital of Parma; 2Department of Medical Oncology, VU University Medical Center, Amsterdam, The Netherlands; 3Division of Oncology, Azienda USL-6 of Livorno; 4Division of Oncology, Hospital, Lido di Camaiore; 5Division of Oncology, University Hospital Careggi, Firenze; 6Division of Oncology, Azienda Policlinico di Modena; 7Netherlands Cancer Institute, Amsterdam, The Netherlands; 8Division of Pulmonary Medicine, VU University Medical Center, Amsterdam, The Netherlands

Purpose. To correlate candidate polymorphisms affecting pemetrexed and carboplatin activity with clinical outcome of patients with advanced non-small cell lung cancer (NSCLC) treated in second-line with pemetrexed or pemetrexed plus carboplatin.

Methods. Functional polymorphisms in thymidylate synthase (TS), reduced folate carrier (RFC), gamma-glutamyl hydrolase (GGH), methylenetetrahydrofolate reductase (MTHFR) and xeroderma pigmentosum group D (XPD) genes were evaluated in 208 patients enrolled in the randomized phase II trials NVALT-7 and GOIRC-02.2006, comparing second-line pemetrexed with pemetrexed plus carboplatin, as well as patients treated with the same regimens outside of these trials. Univariate and multivariate analyses correlated genotyping data with response, clinical benefit, toxicity, progression-free survival (PFS) and overall survival (OS) using Pearson’s test, log-rank test and Cox proportional hazards model.

Results. Patients harbouring the MTHFR-T667T variant had significantly longer PFS (5.4 versus 3.4 months; p = 0.012) and OS (16.4 versus 8.5 months; p = 0.026) than patients with CC-CCT genotypes. No correlations were observed for other polymorphisms, except for XPD-Gln751Gln, which was associated with shorter PFS (p = 0.021) and OS (p = 0.044) in the subgroup of patients treated with pemetrexed plus carboplatin. Multivariate analysis confirmed the prognostic significance of MTHFR-C677T both in risk of disease progression (CC-CCT genotypes hazard ratio [HR] 1.94, 95% CI 1.15-3.28; p = 0.012) and of death (HR 2.00, 95% CI 1.12-3.54; p = 0.018).

Conclusions. MTHFR-C677T polymorphisms appear to predict survival differences in pemetrexed-treated NSCLC. These results should be validated in larger and adequately designed prospective studies using pemetrexed.

D20 PROGNOSTIC VALUE OF ERBB FAMILY RECEPTORS, MYC AND MITOGEN-ACTIVATED PROTEIN KINASE (MAPK) IN PATIENTS WITH EARLY-STAGE NON-SMALL-CELL LUNG CANCER

Ludovini V.1, Bellezza G.2, Bianconi F.3, Chiari R.1, Bennati C.1, Metro G.1, Ragusa M.4, Vannucci J.4, Pistola L.1, Fiacco A.1, Tofanetti F.R.1, Siggillino A.1, Puma F.4, Sidoni A.2, Crinò L.1

1Medical Oncology Division, S. Maria della Misericordia Hospital, Perugia; 2Institute of Pathological Anatomy and Histology, 3Department of Surgical and Medical specialties & Public Health, 4Department of Thoracic Surgery, University of Perugia, Perugia

Background. EGFR deregulation has been extensively studied in non-small-cell lung cancer (NSCLC), but less is known about the expression and role of other ErbB receptors and their downstream signal transductions. MYC and MAPK are key downstream components of the EGFR pathway and have significant roles in cell survival, proliferation, and growth. This study evaluates the prognostic role of EGFR, ErbB2, ErbB3, ErbB4, MYC and MAPK by immunohistochemistry (IHC) in early stage NSCLC.

Methods. 109 NSCLC were evaluated: median age was 67 years (range 40-84); Male/Female: 93/16; squamous (SCC)/adenocarcinoma (ADC)/BAC/other: 52/36/3/18; smoker/never smoker: 100/9, and stage I/II/III: 67/17/25. The tumours with ≥10% positive cells were classified positive, further confirmed by Receiver Operating Characteristic (ROC) analysis.

Results. EGFR was expressed in 55.9%, ErbB2 in 24.7%, ErbB3 in 33.9%, ErbB4 in 27.5%, Myc in 23.8% and MAPK in 27.5% of patients, respectively. EGFR and ErbB3 were associated with SCC (p <0.0001 and p = 0.004, respectively) whereas ErbB2 and MYC with ADC (p = 0.004 and p <0.001, respectively). EGFR and ErbB3 were significantly associated (p = 0.003), as well as MAPK and ErbB4 (p = 0.02). At a median follow-up of 75 months the contemporary over-expression of EGFR, ErbB2 and MAPK was associated with shorter disease-free survival (DFS) (p = 0.002) and overall survival (OS) (p <0.0001). At multivariate analysis adjusting for stage, the co-expression of EGFR, ErbB2 and MAPK was an independent predictor for worse DFS and OS (p = 0.004 and p <0.001, respectively).

Conclusions. Our results suggest that in early stage NSCLC the co-expression of EGFR, ErbB2 and MAPK predicted a worse prognosis. Such features may have important implications for future targeted therapies.

We thank AIRC for supporting the study.

D21 MANAGEMENT OF METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS PROGRESSING AFTER FIRST-LINE TREATMENT: PRELIMINARY RESULTS FROM THE “LIFE” ITALIAN OBSERVATIONAL STUDY
DE MARINIS F.1, ARDIZZONI A.2, NOVELLO S.3, CAPPUZZO F.4, FONTANINI G.5, GROSSI F.6, SANTO A.7, CORTINOVIS D.8, Favaretto A.9, LORUSSO V.10, GALETTA D.11, MAIOLANI M.12, GRIDELLI C.13 on behalf of LIFE study team

1Azienda Ospedaliera San Camillo Forlanini, Roma; 2Azienda Ospedaliera Universitaria di Parma, Parma; 3A.O.U. San Luigi Gonzaga, Orbassano; 4Istituto Toscano Tumori, Ospedale Civile, Livorno; 5Azienda Ospedaliero-Universitaria Pisana, Pisa; 6Istituto Nazionale per la Ricerca sul Cancro, Genova; 7GIVOP, AOUI, Verona; 8Ospedale San Gerardo, Monza; 9Istituto Oncologico Veneto, IRCCS, Padova; 10Ospedale V. Fazzi, Lecco; 11Ospedale Oncologico Bari, Bari; 12Ospedale Niguarda Ca’ Granda, Milano; 13A.O.R.N. San Giuseppe Moscati, Avellino

An important proportion of advanced NSCLC patients experience disease progression after first-line treatment (AFLT). The primary endpoint of “LIFE” study is to evaluate the clinical approach in metastatic NSCLC alive patients progressing AFLT according to clinical practice; secondly to describe patient management based on molecular analyses.

This observational, multicenter study including a cross-sectional and a 6-month longitudinal phase, started on July 2011 and involved 60 pneumology and oncology sites. Eligible patients were aged ≥18 years, with a stage IIIB-IV NSCLC and experienced disease progression AFLT within 6 months before the enrolment. All patients are alive at inclusion and spontaneously refer to the oncologist.

Here we report the preliminary results on 532 eligible patients in the cross-sectional phase, ended on January 2012. Clinical features are the following: 70% of the patients were male, median age was 65 years (min 28, max 84), 78% were stage IV, 72% were adenocarcinoma, 31% were current and 42% were former smokers.

Among patients alive AFLT, 2% received best supportive care, 12% were treated in second-line clinical trials and 86% received second-line treatment according to clinical practice. Among the latter, 64% received chemotherapy (80% single agent) and 36% were treated with tyrosine-kinase inhibitors, mostly erlotinib (94%). Palliative radiotherapy, as a second-line treatment, was administered to 10% of patients according to clinical practice.

At enrolment, 58% of patients were evaluated for EGFR, KRAS (14%) and ALK (14%) mutations. Concerning EGFR mutations, 86% of the tissue samples were histological while 14% were cytological. Median time from request to result was 12 days.

The preliminary results of “LIFE” study show that in advanced NSCLC alive patients who experienced disease progression AFLT, molecular analyses were evaluated mainly on histological specimens and 28% of the second-line treatment were erlotinib. The longitudinal phase will allow us to describe further lines in the real life setting.

This study is supported by Boehringer Ingelheim Italia S.p.A.

D22 CLINICAL IMPACT OF KRAS MUTATION STATUS IN EGFR WILD TYPE (WT) ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS TREATED WITH PLATINUM-BASED CHEMOTHERAPY: A RETROSPECTIVE ANALYSIS

Metro G.1, DURANTI S.1, DE ANGELIS V.1, CHIARI R.1, BENNATI C.1, CURRA M.F.1, GIANNARELLI D.2, LUDOVINI V.1, MINOTTI V.1, CRINO L.1

1Santa Maria della Misericordia Hospital, Azienda Ospedaliera di Perugia; 2Regina Elena Cancer Institute, Roma

Background. In this retrospective analysis we assessed whether KRAS mutation would affect the clinical outcome of EGFR WT advanced NSCLC pts treated with a first-line platinum-based chemotherapy.

Methods. One hundred and ninety-five EGFR WT, advanced NSCLC pts were included in the analysis. Study pts were treated at the Medical Oncology of the Perugia Hospital from Jan 2005 to March 2012. EGFR (exons 18 to 21) and KRAS (codons 12, 13 and 61) genes were amplified by nested PCR and sequenced in both sense and antisense directions.

Results. Median age was 60 years (29-81); 181 pts (92.8%) were PS 0 or 1 and 155 pts (79.4%) belonged to the non-squamous subtype. Platinum + a third generation agent and platinum + pemetrexed were the most commonly administered regimens (94.4% of the total). Seventy-five pts (38.4%) were KRAS mutations (MUTs), of which 60 patients at codon 12 (COD 12 MUT), 12 patients at codon 13 (COD 13 MUT) and 3 patients at codon 61 (COD 61 MUT). The most common amino acid changes found were: Gly12Cys (29 pts), Gly12Val (11 pts) and Gly13Cys (10 pts). Disease control rate (PR + SD) was significantly lower in KRAS MUTs (54.7% vs 75%, respectively, p = 0.005). A significantly shorter PFS was noted for the KRAS MUT subgroup compared with the KRAS WT population [5.1 vs 6.6 months, respectively, p = 0.02; HR = 1.43 (95% CI 1.05 to 1.95)]. Similarly, a significant difference was observed between the two groups in terms of OS [13.7 vs 26.1 months, respectively, p = 0.02; HR = 1.56 (95% CI 1.06 to 2.30)]. In the KRAS MUT subgroup, OS for COD 12 MUT, COD 13 MUT and COD 61 MUT was 17.2, 10.2 and 8.0 months, respectively, p = 0.17. Multivariate analysis for PFS and OS confirmed that KRAS mutation was an independent predictor of poorer outcome.

Conclusions. EGFR WT/KRAS MUT platinum-treated advanced NSCLC patients appear to experience a less favorable outcome compared with the EGFR WT/KRAS WT genotype.

D23 NEW BIOMARKERS TO PREDICT RESPONSE TO PEMETREXED-BASED CHEMOTHERAPY IN NON-SMALL CELL LUNG CANCER: FROM 5,10-METHYLENETETRAHYDROFOLATE REDUCTASE PROMISES TO miRNAs REVOLUTION

Tindara F.1, Bronte G.2, Savio G.3, Ferraro G.1, Proto C.1, Berenato R.1, Noto L.1, Chiofalo G.1, Russo A.2, Adamo V.1

1U.O.C. Terapie Integrate in Oncologia, Dipartimento di Patologia Umana, Università di Messina; 2Sezione di Oncologia Medica, Dipartimento di Scienze Chirurgiche e Oncologiche, Università di Palermo; 3Divisone di Oncologia Medica, Dipartimento di Oncologia, ARNAS Civico, Palermo

Background. There is still a lack of clinical biomarkers for predicting the therapeutic response to pemetrexed in patients with advanced non-small cell lung cancer (NSCLC). 5,10-methylenetetrahydrofolate reductase (MTHFR) gene is a key enzyme for intracellular folate homeostasis and metabolism. The gene’s 3′-UTR has solid predictions for extremely conserved miRNA binding sites, some of which were identified as being altered in cancer cells. The aim of the study was to evaluate the involvement of circulating miR-22, miR-24 and miR-34a in the response to pemetrexed and investigate the correlations with MTHFR gene expression profile.

Methods. A total of 22 consecutive patients affected by ad-
D24 FIRST-LINE CISPLATIN-FRACTIONATED DOUBLET FOR UNFIT PATIENTS WITH ADVANCED/METASTATIC NON-SMALL CELL LUNG CANCER

Mansueto G.1, Narducci F.2, Quadrini S.2, Evangelista M.L.2, Sperduti I.3, Gamucci T.1

1Medical Oncology Unit, Fabrizio Spaziani Hospital, Frosinone; 2Medical Oncology Unit, SS Trinità Hospital, Sora; 3Biostatistics Unit, Regina Elena Cancer Institute, Rome

Background. Standard treatment for unfit patients with advanced or metastatic (stage IIIb-IV) non-small cell lung cancer (NSCLC) is single-agent chemotherapy. Such patients are usually not suitable for cisplatin-based chemotherapy due to poor performance status (PS) and/or significant comorbidity that could enhance toxicity of high-dose cisplatin. They also are not able to tolerate hydric load that is recommended for cisplatin at higher doses. We aimed to investigate a schedule of fractionated cisplatin as first-line treatment in unfit pts with stage IIIb/IV NSCLC.

Methods. Forty-two consecutive unfit patients with advanced/metastatic NSCLC were treated. They all had poor PS (ECOG 2) and/or significant comorbidity and were not eligible for a standard cisplatin-based chemotherapy doublet. Median age was 65.6 years (range 46–77), stage IIIb/IV = 15/27 pts. Histology was as follows: squamous cell 62.4%, adenocarcinoma 37.5%, other/NOS 0.1%. All pts received CDDP 35 mg/m² d 1-8 and/or cisplatin (500 mg/m² d 1) according to histology, for a maximum of 6 cycles. Maintenance therapy with pemetrexed was allowed in patients with non-squamous histology in response or stable disease after cisplatin. Progression-free survival (PFS) and clinical benefit rate (CBR) were evaluated as efficacy endpoints. Response rate was made according to RECIST criteria. Toxicity profile was also measured. Haematopoietic growth factors support was based on current guidelines.

Results. Thirty-three patients are currently evaluable for efficacy and 35 for toxicity. Mean number of cycles administered per patient was 5.03 (211 cycles in total). Maintenance treatment with q3w pemetrexed was performed in 10 patients (23.8%) (mean 4.3 cycles per patient). Five patients in response after cisplatin received thoracic radiotherapy. A partial response (PR) was observed in 42.5% of pts and a stable disease (SD) in 35.4% of pts, for an overall clinical benefit rate (CBR) of 77.9%. Survival evaluation showed a median progression-free survival (PFS) of 10.1 months (Kaplan-Meier), with 31.9% of patients progression-free at 1 year. The log-rank test was used to assess differences between subgroups. Patients with adenocarcinoma had significantly better PFS than those with squamous histology (11 vs 8 months, p = 0.03). Hematological G3-G4 toxicity was reported as follows: neutropenia 48.4% (3% febrile), thrombocytopenia 27.2% and anaemia 9.0%. A one-level (25%) dose reduction was required in 39.3% of patients. One patient died for cardiac failure during treatment.

Conclusions. Fractionated CDDP seems to be effective in our patients population with advanced or metastatic NSCLC. Adequate supportive care measures help to manage severe toxicity, that was mainly haematological.

D25 WHOLE-BODY DIFFUSION MRI AND SKELETAL LESIONS IN THYROID CANCER: DIAGNOSTIC AND THERAPEUTIC IMPLICATIONS

Locati L., Granata R., Potepan P., Aliberti G., Civelli E., Bossi P., Montin E., Liclira L.

Fondazione IRCCS, Istituto Tumori, Milan

Background. Bone metastases affect at least 40-50% of patients with metastatic thyroid cancer. 99mTc scintigraphy is commonly employed to assess bone lesions, although it lacks of accuracy. 18F-FDG PET/CT bone scintigraphy is not suitable for assessing lytic lesions that usually characterize differentiated thyroid cancer (DTC). We compared the accuracy of 18F-FDG-PET/CT and whole-body diffusion imaging (WB-DWI) for detection and therapy monitoring of bone metastases. We investigated the role of WB-DWI in thyroid cancer, in particular a) sensitivity and specificity in the assessment of bone metastases compared to other imaging techniques; b) evaluation of response of bone lesions during TKIs.

Materials and methods. We reviewed the baseline staging radiologic records of the patients with known metastatic disease submitted to WB-DWI at the baseline staging. For our first purpose, we have included only patients with at least one another bone radiological imaging. We considered as false-positive a positive bone imaging not confirmed by histopathology or/and another imaging technique or by two imaging exams. A false-negative was a negative finding on bone imaging and a positive one on another imaging method but histopathology or by two imaging methods. For each imaging modality, sensitivity, specificity and accuracy were calculated. For the secondary aim, we considered only patients scanned by WB-DWI at baseline and during TKI treatment.
Results. Since 2010, nine MTC (5M/4F) and five DTC (3M/2F) patients were considered. Results are listed in the Table.

<table>
<thead>
<tr>
<th></th>
<th>WB-DWI</th>
<th>Bone scan</th>
<th>Bone CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of exams</td>
<td>14</td>
<td>12*</td>
<td>12*</td>
</tr>
<tr>
<td>True-positive</td>
<td>10</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>True-negative</td>
<td>4</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>False-positive</td>
<td>0</td>
<td>1 (MTC)</td>
<td>0</td>
</tr>
<tr>
<td>False-negative</td>
<td>0</td>
<td>1 (DTC)</td>
<td>1 (MTC)</td>
</tr>
<tr>
<td>Sensitivity%</td>
<td>100</td>
<td>88</td>
<td>88</td>
</tr>
<tr>
<td>Specificity%</td>
<td>100</td>
<td>80</td>
<td>100</td>
</tr>
<tr>
<td>Accuracy%</td>
<td>100</td>
<td>86</td>
<td>92</td>
</tr>
</tbody>
</table>

*Other than WB-DWI, one DTC patient and one MTC patient were staged by 18F-FDG-PET/CT and by Gallium-68 PET/CT, respectively.

In five (4 MTC/1 DTC) out of eight (62%) true-positive bone scans, WB-DWI was able to show a higher number of metastatic lesions. Bone CT did not identify all lesions; it was useful mainly to quantify the risk of fracture in lytic lesions.

WB-DWI was employed in three patients (2 MTC/1 DTC) to assess the bone response during TKI, demonstrating a cystic evolution in the responding lesions (apart from the histotype).

Conclusions. In our hands WB-DWI is the best imaging method to identify bone lesions from thyroid cancer. It could potentially address unmet clinical and therapeutic needs for a reliable measure of bone lesion response in these rare tumours.

D26 METRONOMIC ORAL VINORELBINE AS FIRST-LINE TREATMENT IN ELDERLY PATIENTS WITH ADVANCED NON-SMALL-CELL LUNG CANCER: FIRST-STEP RESULTS OF A PHASE II TRIAL (MOVE TRIAL)

Camerini A., Donati S., Valsuani C., Puccetti C., Tartarelli G., Petrella M.C., Puccinelli P., Amoroso D.

Oncologia Medica, Ospedale Versilia e Istituto Toscano Tumori, AUSL 12 di Viareggio

Background. Metronomic administration of cytotoxic drugs could interfere with angiogenesis process without worsening safety profile. Single agent metronomic oral vinorelbine could be an option for elderly patient with advanced non-small cell lung cancer (NSCLC).

Patients and methods. Eighteen chemotherapy naïve elderly (≥70 yrs) patients with stage IIIB-IV NSCLC were prospectively recruited. Median age was 80.5 yrs, M/F 15/3, prevalently squamous histology with a significant portion of PS 2 (9/18) and a median number of serious co-morbid illnesses of 3. Study treatment consisted of oral vinorelbine 50 mg three times weekly (Monday-Wednesday-Friday). Primary endpoints were overall response rate (ORR), clinical benefit (CB) and safety. According to the protocol we present first-step results.

Results. Patients received a median of 7 (range 3-20) cycles. ORR was 16% with 2 partial and 1 complete responses; 10/18 experienced stable disease lasting more than 12 weeks leading to an overall CB of 72.2%. Median time to progression was 6.5 (range 3-15) and median overall survival 9 (range 4-20) months. Treatment was well tolerated. On a total of 133 cycles we did not observe any G3/4 toxicity with the exception of a G3 diarrhoea and a G3 fatigue episode. Regardless of severity main toxicities observed were fatigue in 40%, anemia in 35.5%, diarrhoea in 16%, nausea in 12% and vomiting in 10% of patients.

Conclusions. Metronomic oral vinorelbine is safe in elderly patients with advanced NSCLC with interesting activity. First-step results met the protocol-defined significance level of clinical activity. Study accrual will continue to a total of 43 pts.

D27 LUNG CANCER (LC) RISKS IN WOMEN WITH PREVIOUS BREAST CANCER (BC): ANALYSIS OF CLINICOPATHOLOGICAL CHARACTERISTICS AND BIOMARKER EXPRESSION

Sini C., Barletta G., Genova C., Rijavec E., Dal Bello M.G., Diaz Gaitan N., Donato C., Pronzato P., Grossi F.

Lung Cancer Unit, National Cancer Institute for Cancer Research, Genoa

Background. Several studies in BC patients suggest that radiotherapy techniques and smoking are associated with an increased risk of developing LC in the ipsilateral lung. The aim of this study is to evaluate whether there are clinicopathological characteristics and biomarker profiles based on BC and LC tissues in pts with previous BC and whether these can be used to predict an increased risk of developing a subsequent LC. The BC and LC biomarkers profile will be compared with the biomarker profile in pts with only BC or only LC.

Methods. From 2006 to 2011, thirty-five pts with previous BC underwent LC resections. BC and LC tissues are used to evaluate estrogen receptors (ER), progesterone receptor (PgR), aromatase, human epidermal growth factor receptor 2 (HER 2), ki-67, breast cancer 1 (BRCA1), breast cancer 2 (BRCA2), p53, epithelial growth factor receptor (EGFR), Kirsten rat sarcoma viral oncogene (KRAS) mutations, excision repair cross-complementing 1 (ERCC1), ribonucleotide reductase (RRM1), thymidylate synthase (TS) and class III β-tubulin (β-tub-III). Immunohistochemistry, real-time PCR and gene sequencing for EGFR and KRAS mutations were used.

Results. The median age at BC diagnosis was 59.9 years. The mean time between BC and LC diagnosis was 6.1 years. Seventeen pts (48.6%) were never smokers, 6 pts (17.1%) were former smokers and 13 pts (37.3%) were smokers at the time of BC diagnosis. Twenty-four patients (69%) received adjuvant radiotherapy after BC resection, and 14 of these pts (58%) had ipsilateral LC. Adenocarcinoma was the most common LC (28 pts, 80%) followed by squamous cell carcinoma (5 pts, 14%) and SCLC (2 pts, 6%). Biomarker studies are ongoing, and the final results will be presented at the conference.

Conclusions. In this study, adjuvant breast radiotherapy and smoking do not seem to be strictly associated with the development of LC in pts with previous BC. Biomarker studies could increase our knowledge about the relationship between etiological factors, individual susceptibility and gene-environment in developing subsequent LC.

D28 ELECTRONIC DATABASE ANALYSIS OF CLINICAL OUTCOME: FIRST-LINE CHEMOTHERAPY IN ADVANCED NON-SMALL CELL LUNG CANCER ELDERLY OR PS 2 PATIENTS
Background. In Italy, EGFR mutation is not a prerequisite to prescribe erlotinib in patients with advanced NSCLC previously treated with chemotherapy. Its efficacy is supposed to be comparable to that of second-line chemotherapy, however, some concerns have been raised on its activity in pts with poor PS, squamous histology and EGFR wild-type status.

Methods. We reviewed medical records of pts treated with erlotinib in the last 5 years in our center, in which EGFR mutation was not determined. Response was evaluated by CT scan every two months.

Results. Since January 2006 we treated with erlotinib 200 pts with advanced NSCLC as 2nd/3rd/4th line of therapy. Median age was 67 (range 23-90), 74% males and 26% women. Histology was ADK in 55%, SQM in 33.5%, BAL in 3.5% and other in 8%. Stage IIIb/IV was 18.5%/81.5%. PS was 0/1/2/3 in 20.5%/62%/13.5%/4%. Never/ex/current smokers were 13.5%/73%/13.5%, while 66.5%/29.5%/4% of pts were treated as 2nd/3rd/4th line therapy. According to RECIST criteria, 15 (7.5%) pts achieved PR, 83 (41.5%) SD and 102 (51%) progressed. The characteristics of responding pts were as follows: 11/4 women/men; 6/8 never/ex/current smokers; 6/7/20 with PS 0/1/2; line of therapy 2nd/3rd/4th in 12/3/0 pts. PR was 6.8% in ADK, 14.2% in BAL, 3.1% in SQM, 6.3% in others, while CBR was 66.4% in ADK, 57.1% in BAL, 20.9% in SQM, 43.8% in others. The median duration of response was 11 months (range 3-30). Median duration of SD was 9.5 months (range 2-27). Responding pts had a median survival of 27 months (range 3-103).

Conclusions. Erlotinib was more effective in ADK than in SQM pts; women were more likely to respond, and response rate was observed in 2nd/3rd line and in pts with PS ≤2. However, the scant number of responding patients suggests that EGFR mutation status should be performed prior to erlotinib prescription, in order to select pts more likely to respond and achieve more efficient cost/benefit ratio.

D30 PROSPECTIVE CORRELATIVE STUDY OF FDG-PET SUV AND PROTEOMIC PROFILE (VERISTRAT) OF NON-SMALL CELL LUNG CANCER PATIENTS TREATED WITH ERLOTINIB

Bulotta A.1, Tiseo M.2, Gregoor V.1, Lattieri F.3, Ippolito M.4, Baldari S.4, Cosentino S.4, Scarlatteli M.4, Rodier H.6, Bordonaro R.3, Ardizzoni A.2, Gianni L.1, Soto Parra H.J.7

1Department of Oncology, Istituto Scientifico San Raffaele, Milan; 2Unità di Oncologia Medica, Azienda Ospedaliero-Universitaria, Parma; 3Medical Oncology, Garibaldi Hospital, Catania; 4Nuclear Medicine, Cannizzaro Hospital, Catania; 5Nuclear Medicine, University Hospital of Parma, Parma; 6Biodexis Inc., Broomfield, CO; 7University Hospital Policlinico Vittorio Emanuele, Catania

Background. Matrix Assisted Laser Desorption Ionization Time of Flight Mass Spectrometry was used to create and validate a plasma proteomic algorithm VeriStrat (VS), based on 8 m/z peaks, and able to select advanced NSCLC pts who may benefit from EGFR TKIs. The algorithm was associated with PFS and OS of patients treated with EGFR TKIs and not with chemotherapy. Standardized uptake value (SUV) is of prognostic value for survival in NSCLC. Aim of the current study was to analyze the OS and TTP in advanced NSCLC pts treated with erlotinib (E) according to baseline VS classification and baseline SUVs of FDG-PET.

Methods. Plasma samples were collected before the beginning of E. Acquired spectra were classified according to the VS algorithm. The FDG-PET was performed the day before the beginning of E.

Results. Thirty-eight NSCLC pts on E therapy were analyzed: median age 62 years, 63% were males, 53% had adenocarcinoma histology, response rate was 26%, median OS 10 mos, TTP 3.4 mos. Twenty-six (68%) were classified as VS good, 12 (32%) as poor. TTP and OS for VS good and poor were 4.1 vs 2.1 mos (HR = 0.86, log-rank p = 0.6) and 11.1 vs 4.1 mos (HR = 0.45,
log-rank p = 0.02), respectively. Baseline SUV levels were associated with TTP (Wilcoxon test p = 0.001) but not with OS. All poor classified pts had SUV ≥7 and had the worst TTP and OS; VS good classified patients had worse TTP and OS if their baseline SUV level was >7 than those who were VS good and had SUV <7 (see Table).

Conclusions. We confirmed that pts with VS poor classification have significantly shorter OS than those classified as VS good. Patients with VS good profile and with low baseline SUV levels may benefit more from EGFR TKI than VS good pts with high SUV.

<table>
<thead>
<tr>
<th>SUV</th>
<th>Median TTP (mos)</th>
<th>Median OS (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7</td>
<td>VS good 13.8</td>
<td>VS poor 16</td>
</tr>
<tr>
<td>≥7</td>
<td>VS good 2.1</td>
<td>VS poor 10.5</td>
</tr>
<tr>
<td>p value</td>
<td>0.02</td>
<td>0.05</td>
</tr>
</tbody>
</table>

D31 VENOUS THROMBOEMBOLISM IN LUNG CANCER: RETROSPECTIVE ANALYSIS OF DATA IN OUTPATIENTS TREATED AT ONCOLOGY DEPARTMENT OF NOVARA

Borra G., Buosi R., Galetto A., Alabiso O.

Amedeo Avogadro, Western Piedmont University, Maggiore della Carità Hospital, Novara

Background. Venous thromboembolism (VTE) is the leading cause of mortality and morbidity in patients with cancer. The estimated risk of VTE in cancer patients is 0.5%/year and 0.04%/month. In small cell (SCLC) and non-small cell lung cancer (NSCLC) the cumulative incidence is 3%/year. We performed a retrospective analysis of all NSCLC treated at our Oncology to assess the incidence of VTE in patients undergoing systemic treatments.

Methods. All outpatients with NSCLC treated from January 2008 to May 2011 have been enrolled.

We analyzed as VTE risk factors: age, sex, histological type, ECOG, BMI (body mass index), stage, chemotherapy regimen, CVC (central venous catheter) presence, use of erythropoietin, baseline LMWH (low molecular weight heparin) and ASA (acetylsalicylic acid).

All outpatients (symptomatic or not) were evaluated for VTE events with venous ecocolordoppler for TVP and with angioTC for pulmonary thromboembolism.

Results. 355 patients were evaluated, 307 eligible for analysis. Median age was 68 years. The histological types were: 7% NAS, 60% adenocarcinoma, 31% squamous-cell carcinoma and 2% large-cell carcinoma. Thirty-six DVT (deep vein thrombosis) cases (12%) have been reported; 21 in patients undergoing chemotherapy: 14 during and 7 at the end of treatment. The incidence was significantly higher for patients treated with cisplatin. It has been documented a correlation with stage disease: 26.5% of total VTE occurred in locally advanced and metastatic stages (IIIB/IV); 18.8% in stage IIIA. There was also a significant correlation with non-squamous histology (p = 0.015) and ECOG 0-1 (p = 0.010) but there wasn’t correlation with other risk factors.

Conclusions. According to our data we think that outpatients with advanced lung cancer should receive thromboembolic pro-

D32 FACTORS INFLUENCING THE ADOPTION OF THE PET SCAN IN THE PREOPERATIVE STAGING OF LUNG CANCER PATIENTS: A POPULATION BASED COHORT STUDY IN THE PIEDMONT AND VALLE D’AOSTA REGIONAL CANCER NETWORK

Bertetto O., Viale M., Mistrangelo M., Ceccarelli M.*, Castiglione A.*, Di Cunzo D.*, Monagheddu C.*, Ciccone G.*

Department of Oncology Network Piedmont and Valle d’Aosta; *Cancer Epidemiology, AOU San Giovanni Battista in Turin CPO Piedmont

Introduction. The execution of a positron emission tomography (PET) scan in the staging of potentially operable non-small cell lung cancer (NSCLC) patients is strongly recommended by most guidelines (including the Piedmont Regional Guideline on Lung Cancer, 2004). The increasing availability of PET centers in the Region during the last years allows us to study the adoption of this recommendation.

Objectives. To describe the time trend of the proportion of NSCLC patients receiving a preoperative PET and to identify individual and structural factors that influenced its access.

Materials and methods. Through the health regional databases (including outpatient records) we identified the cohort of all resident lung cancer cases with a surgical procedure with curative intent (N = 3033) and whether they received or not a preoperative PET, from 2004 to 2009. With a multilevel logistic regression model we analyzed several individual factors and the role of the Regional Cancer Network, through the multidisciplinary teams (GIC) and the case management services (CAS).

Results. During the study period there was a sharp increase in the use of preoperative PET (from 39% to 78%, Figure 1). The accessibility to the exam was not influenced by patient socio-demographic characteristics (age, sex, education level, marital status), while it was reduced by the distance between the patient residence and the nearest PET center. Patients managed by the Regional Cancer Network centers (CAS/GIC) showed a higher probability to undergo a PET scan than those who did not receive any CAS/GIC visits (Adj-OR = 2.67, 95% CI 1.96-3.63). In 2004-2006 there was a strong variability between regional hospitals, but this difference was markedly reduced after 2007 (Figure 2).

Figure 1 - Time trend of the proportion of surgical lung cancer patients undergoing a preoperative PET in Piedmont.
Conclusions. During the study period, we have recorded a remarkable increase of the adoption of the guideline recommendation to perform a preoperative PET scan in potentially operable lung cancer cases, with a progressive reduction of the inter-hospital variability. Patients managed by the Regional Cancer Network centers showed a higher probability to be appropriately staged with a PET.

D33 CETUXIMAB CONTAINING REGIMEN AS INDUCTION THERAPY IN HEAD AND NECK CANCER (SCCHN): OUR EXPERIENCE

Campitello M.1, Plastino F.1, Cassano A.1, Rodriguez M.G.1, Cerchiaro E.1, Dadduzio V.1, Marsico V.1, Bussu F.2, Paludetti G.2, Almadori G.2, Barone C.1

1Divisione di Oncologia Medica, 2Divisione di Otorinolaringoiatruia, Università Cattolica Del Sacro Cuore, Roma

About 60-70% of patients with SCCHN presents with locally advanced stage and surgery with or without radiotherapy represents the standard approach. The need to obtain organ preservation, to improve OS and QoL induced to develop new strategy including perioperative chemotherapy with platinum, taxane and S-FU based schedule. Few experiences evaluated cetuximab in neoadjuvant setting, although it was approved with radiation therapy for treatment of locally advanced SCCHN and in combination with platinum-based-chemotherapy for the treatment of recurrent and/or metastatic disease. We analyzed cetuximab in locally advanced SCCHN as induction therapy.

From January 2010 to September 2011 we enrolled 24 patients with locally advanced disease. 15 patients were not candidates in first instance to surgery while 9 patients were potentially resectable. We started chemotherapy with platinum (100 mg/m2, 5-FU (1000 mg/m2/die for four days) and cetuximab (400 mg/m2 loading dose, then 250 mg/m2 every week). We obtained a complete radiological response (RR) in 10 patients (41%) and a partial RR in 14 patients (58%). Twenty-one patients (87%) underwent surgery, 17 after 4 courses, 4 after 6 courses of CT; other 3 patients (12%) were not yet resectable (all these 3 patient were not initially resectable). In 17 patients (70%) the pathological examination showed a complete response, in the other 4 patients (16%) there was a partial response >80% of necrosis in tumour tissue. Common high grade toxicity (G3/G4) was stomatitis (30%), folliculitis (45%), diarrhea (5%) and neutropenia (10%).

Cetuximab could have a role not only in the metastatic or recurrent setting of patients, but also in locally advanced disease. A great number of patients (100%) showed a RR, 87% of patients were resectable after 4-6 courses of chemotherapy and 70% of these showed a complete PR. Toxicity profile was acceptable with very low rate of G3/G4 toxicities. Induction therapy could allow organ preservation strategy in patients not suitable for surgery. EGFR and HPV status may aid to define a new standard neoadjuvant treatment.

D34 A FUNCTIONAL GENETIC VARIANT IN MicroRNA-196a2 AND RISK OF CISPLATINUM TOXICITY IN NSCLC PATIENTS


*Clinical Pharmacology, *Clinical Oncology, “Luigi Sacco” University Hospital, Milan

Background. Small non-coding RNA molecules known as microRNAs (miRNAs) can function as tumour suppressors and oncogenes. Recently it was shown that a single nucleotide polymorphism (SNP) rs11614913 in the miRNA 196a2 gene (the C allelic variant), is associated with increased susceptibility of non-small cell lung cancer (NSCLC) and with longer survival in a subset of patients characterized by a low stage disease1. However, no data are available on the potential role of this polymorphism in the determination of chemotherapy-related toxicity.

Patients and methods. We analyzed 59 consecutive patients with NSCLC and treated with cisplatin-based regimens between September 2011 and May 2012. Genotypes from blood were retrospectively evaluated by pyrosequencing and real time PCR. The SNP analyzed (rs11614913) was located in pre-miR-196A2. Renal toxicity was recorded and classified according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0; 2009) for each single cycle. Statistical analysis was performed by using Fisher exact test and odds ratios (OR) with 95% confidence interval (CI) were calculated.

Results. Fifty-nine pts were enrolled (34 M±25 F), median age 66.5 years (range 51-71), ECOG 0-1. Cisplatin dose was 75 mg/m2/day 1 associated with gemcitabine in 33 pts, pemetrexed in 20 pts and docetaxel in 6 pts for 3 cycles. Renal toxicity was recorded by serum and urine analysis that showed arising of serum creatinine in 6 patients. Homozygous genotype rs11614913 (T/T) were 10.2%, heterozygous were 55.9% and wild type were 33.9%; these data are consistent with frequencies previously reported in Caucasian population. We found that 6 patients harboring the homozygosis for T allele had a significant higher risk to develop grade 2 and 3 renal toxicity during the treatment (OR 8.6, 95% CI 1.38-53.7).

Conclusions. Several studies did establish the role of miRNA SNP in objective response, survival and susceptibility to various kind of cancer. This study provides the first analysis suggesting a role of a SNP among miRNA196A2 gene as a marker of renal toxicity risk during cisplatin-based therapy. Further studies on a larger cohort of patients are needed to confirm these findings.

References
D35 SEQUENTIAL USE OF VINORELBINE (V) FOLLOWED BY GEFITINIB (G) INDUCES A SYNERGISTIC EFFECT IN NON-SMALL CELL LUNG CANCER (NSCLC) CELL LINES

Barletta G., Dal Bello M.G., Alama A., Sini C., Rijavec E., Genova C., Bruzzo C., Cavalieri Z., Grossi F.
Lung Cancer Unit, National Institute for Cancer Research, Genoa

Background. Preclinical studies with tyrosine kinase inhibitors (TKI) demonstrate that these agents enhance the antitumour activity of cytotoxic chemotherapy. The aim of this study is to identify potential additive, synergistic or antagonist effects between V and G in vitro as a rationale for further investigations in the clinical setting.

Methods. Human lung cancer cell lines with wild-type (A-549) and mutant-type EGFR genes (NCI-H1975) and a mouse lung cancer cell line (JCRB-1348) were used as in vitro models to evaluate the antitumour activity of G and V using three different schedules: G followed by V, V followed by G and the two drugs concurrently. We also evaluated the antiproliferative efficacy of repeated weekly V doses along with sequential or continuous G.

Results. Confronting different schedules on the A-549, NCI-H1975 and JCRB-1348 cell lines, we found that the V-G sequence was more potent than either the G-V sequence or the concomitant administration of the two drugs. A synergistic effect on the NCI-H1975 cells was found at the highest concentration of V with every concentration of G that was tested but only in the V followed by G sequence. A synergistic growth inhibitory effect was observed only when the A-549 and NCI-H1975 cells were exposed to V first (day 1 and day 8) and were then treated with G (from day 1 to day 8 or from day 9 to day 21) compared with V alone or G intermittent or continuous.

Conclusion. This study suggests that the schedule of V followed by G is superior to other sequences of V and G in treating NSCLC cell lines. This finding is encouraging as a proof of the possible benefit of combining an EGFR targeting compound with a cell cycle-2-specific drug and could be a rationale for a new treatment strategy in patients with advanced EGFR-mutated NSCLC. The molecular mechanisms involved in the synergism between V and G will be the object of further studies.

D36 FREE DRUGS IN LUNG CANCER TRIALS: AN ANALYSIS OF PHARMACEUTICAL COST SAVINGS

Genova C.1, Diaz Gaitan N.1, Rijavec E.1, Barletta G.1, Sini C., Dal Bello M.G.1, Donato C.1, Pronzato P2, Grossi F.1
1Lung Cancer Unit, 2Medical Oncology A, National Institute for Cancer Research, Genoa

Background. The cost of new anticancer drugs has dramatically increased in recent years. The global financial crisis forced the implementation of countermeasures to limit pharmaceutical expenses. Sponsored clinical trials that provide drugs free of charge may be an useful tool for reducing drug costs. The aim of this analysis is to evaluate the effect of clinical trials on pharmaceutical expenditure savings.

Methods. We evaluated the cost of drugs administered in clinical practice and in clinical trials (considering only the standard regimens that were also administered in clinical practice) in 2010 at the Lung Cancer Unit of the National Institute for Cancer Research in Genoa. The cost of drugs was calculated based on the price charged at our Institute in 2010. The supposed cost of experimental treatments that replace standard therapy was converted into the cost of the treatments that would have been chosen in clinical practice. The grants that cover the cost of radiological and laboratory exams and the operating costs of each study were calculated.

Results. From 1/1/10 to 12/31/10, 196 patients affected by lung cancer or pleural mesothelioma were treated; 152 patients (77.6%) were treated in clinical practice or in non-sponsored trials (18 patients in 4 trials), while 44 (22.4%) received a standard treatment in one of the sponsored clinical trials enrolling patients in 2010. The number of administered cycles was 601, of which 436 (72.5%) were administered in clinical practice or non-sponsored trials and 165 (27.5%) were administered in sponsored clinical trials. The overall cost of care (excluding supportive care and hospitalization) was 965,854.70 euro. The cost of drugs administered in clinical practice or in non-sponsored trials was 718,724.50 euro (74.4%), while the cost of drugs administered in clinical trials was 247,130.20 euro (25.6%). The grants provided by pharmaceutical companies amounted to 235,965.84 euro.

Conclusions. Participation in sponsored clinical trials in which drugs are provided free of charge offers substantial savings on drug expenditure.

D37 VINORELBINE AS SECOND-LINE CHEMOTHERAPY (SLC) IN PEMETREXED-PLATINUM PRETREATED PATIENTS WITH MALIGNANT PLEURAL MESOTHELIOMA (MPM). A SINGLE INSTITUTION EXPERIENCE

Bertolo E., Biaggi G., Gattoni E., Giaretto L., Muzio A., Oletti M.V., Botta M.
SOC Oncologia, Santo Spirito Hospital, Casale Monferrato (AL)

Background. MPM is a rapidly progressive tumour with a poor prognosis. The benefit of first-line standard pemetrexed-platinum compounds chemotherapy (FLC) in MPM has been established. Currently, SLC is increasingly used, because many patients are not fit at the progression of the disease, but there is not a standard regimen and clinical benefit is uncertain. Vinorelbine has shown activity in first-line setting; we want to evaluate the efficacy and safety of this drug in pemetrexed-pretreated patients with MPM at the time of the progression of the disease.

Patients and methods. From January 2009, 26 patients in relapsed disease after FLC (6 female and 20 male), received SLC. The median age was 63 years (range 42-81). All patients had performance status ECOG less than or equal to 1 (100%). A certain asbestos exposure was observed in 22 patients. Histology was epithelial in 21, mixed in 4 and sarcomatoid in 1. All patients were pretreated with pemetrexed: 1 in monochemotherapy, 21 in combination with carboplatin, 3 with carboplatin and bevacizumab and 1 with cisplatin.

Results. The median time to progression (TTP) after FLC was 8 months (range 1-43). Five patients (19%) had TTP >12 months and were retreated with pemetrexed regimen: median TTP was 11 months (range 10-31). The others 21 patients had a short TTP.
median 5 months (range 1-11): they were treated with vinorelbine 25 mg/m² intravenously on day 1 and 8 every 3 weeks. Median TTP was 5 months (range 2-10). Pemetrexed-regimen retreated patients at progression received vinorelbine as third-line: their median TTP was 7 months (range 4-13). In both groups hematologic toxicity was acceptable: grade 3 neutropenia in 15% of the patients. Non-hematologic toxicity was mild.

Conclusions. Patients with prolonged TTP with pemetrexed-regimen FLC can have benefits with re-challenge in SLC. Vinorelbine as SLC seems partially active in patients with short TTP after FLC but also in third-line therapy in re-challenge SLC pemetrexed regimen.

D38 PROGNOSTIC SIGNIFICANCE OF EGFR, HER-2, CEA ON CIRCULATING TUMOUR CELLS IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

Loretelli C.1, Galizia E.2, Scartozzi M.1, Giampieri R.1, Gagliardini D.1, Brugiat C.1, Cascini S.1, Cellerino R.1

1Clinica di Oncologia Medica, Ospedali Riuniti, Ancona; 2Oncologia Medica, Ospedale “E. Profili”, Fabriano

Purpose. Non-small cell lung cancer (NSCLC) lacks validated biomarkers to predict clinical outcome in patients receiving chemotherapy. The aim of this study was to assess the role of circulating tumour cells (CTCs) in providing prognostic information of metastatic NSCLC patients receiving chemotherapy.

Patients and methods. In this single-center prospective study, blood samples for CTCs analysis were obtained from patients with previously untreated metastatic NSCLC, before starting standard chemotherapy.

CTCs were measured using an epithelial cell adhesion molecule-based immunomagnetic technique. Immunomagnetic bead enrichment for cells expressing epithelial cell adhesion molecule (EpCAM) was performed, followed by multi-marker quantitative real-time PCR of a panel of marker genes: EGFR, HER-2, CEA.

Results. We analysed 45 patients with metastatic NSCLC: 24 adenocarcinoma, 8 squamous cell carcinoma and 13 poorly differentiated.

EGFR, HER-2 and CEA expression were found in CTCs of respectively 12, 5 and 11 patients.

Globally, 31 patients (68.9%) progressed during treatment, whereas disease control (i.e. patients with partial/complete response or stable disease) was achieved in 14 patients (31.1%).

EGFR expression was detected in 11/31 patients with disease progression (35.5%) and in only 1 out of 14 patients with disease controlled (7.1%) (p = 0.07). HER-2 expression was detected in 3/31 patients with disease progression (9.7%) and in 2/14 patients with disease controlled (14.3%) (p = 0.64). CEA expression was detected in 10/31 patients with disease progression (32.3%) and in 1/14 patients with disease controlled (7.1%) (p = 0.13).

Only EGFR expression in CTCs showed a correlation with clinical outcome, expressed by progression-free survival (PFS). Patients with and without EGFR expression in CTCs were homogeneous for clinical characteristics (age, sex, histologic tumour type).

PFS was 2.8 versus 2.3 months (p = 0.03) respectively for patients without and with EGFR expression.

Conclusions. CTCs are detectable in patients with metastatic NSCLC and could show novel prognostic factor for this disease.

Further validation is warranted before routine clinical application.

D39 THE ROLE OF CHEMOTHERAPY AFTER ERLOTINIB TREATMENT IN PATIENTS WITH ADVANCED NSCLC: POST-PROGRESSION SURVIVAL ANALYSIS

Trojiani M.P.1, Palazzo A.C.1, Mazurek M.2, Jirillo A.2

1Oncology Pharmacy Department, 2Evaluation and Introduction of New Drugs in Cancer Therapy Unit, Istituto Oncologico Veneto IRCCS, Padua

Erlotinib is a potent inhibitor of EGFR tyrosin-kinase activity and its efficacy has been demonstrated for the treatment of advanced non-small cell lung cancer (NSCLC) in large randomized trials.

A prospective observational study was run, using institutional data collected through web-based Oncology registry, from December 2006 to May 2011. The patients with NSCLC after at least one line chemotherapy, were treated with erlotinib (150 mg/day orally) until disease progression. Every patient was checked prospectively for toxicity, clinical outcomes, previous line treatments, length of treatment and for treatments following erlotinib using hospital databases.

In overall study population (130 patients), the median time to progression (TTP) and overall survival (OS) were 2.4 and 4.4 months, respectively and 1-year survival rate was 25%. Four patients achieved partial response and 23 patients achieved stable disease, making disease control rate 21%. Grade 1-2 rash and diarrhoea were the most frequent adverse events.

The subgroups analysis showed significantly improved OS for patients with chemotherapy post-erlotinib (pemetrexed, docetaxel) compared to those with no chemotherapy post-erlotinib, 12.7 months and 3.0 months (p <0.0001), respectively. The main prognostic factors, such as age, sex, histology, ECOG performance status, smoking status, treatment line and the median time to relapse of previous line treatments were equally distributed between these two subgroups. The data of EGFR mutation and EGFR FISH positive status were available for 21% of the patients, however we did not find a significant association between EGFR expression and treatment response in both groups.

This evaluation has revealed significantly improved survival with chemotherapy post-erlotinib regardless of the EGFR expression, giving evidence of other existing mechanisms.

The post-marketing studies in real life practice are needed in order to verify both effectiveness and safety in general population, testing for external validity of the randomized trials. Moreover, the post-progression survival assessment may be crucial to determine real clinical impact of investigational drug in combination with other treatments as it usually lacks in the approval RCTs.

D40 PREVALENCE OF EGFR, KRAS, AND BRAF MUTATIONS AMONG PATIENTS WITH NON-SMALL CELL LUNG CANCER FROM SARDINIA

Colombino M.1, Palomba G.1, Defraia E.2, Porcu G.3, Pazzola A.4, Cordero L.5, Fadda G.M.6, Ortu S.7, Mura S.8, Baldini P.1, Murgia R.9, Carta A.7, Sotgiu M.I.2, Guerzoni D.2, Saba E.M.2, Scotto T.9, Contu A.4, Tanda F.9, Palmieri G.1, Cossu A.9 on behalf of the Sardinian Translational Oncology Group (STOG)
BACKGROUND. Somatic activating mutations of the epidermal growth factor receptor (EGFR) gene have been associated with dramatic tumour responses and favorable clinical outcomes using EGFR tyrosine kinase inhibitors (EGFR TKIs) in patients with non-small cell lung cancer (NSCLC).

Methods. From July 2010, a total of 341 tumour tissues from patients with NSCLC and ascertained Sardinian origin were enrolled, of whom 20 were excluded from the series because of tissue DNA degradation. Genomic DNA was isolated and screened for mutations in EGFR and KRAS genes by automated DNA sequencing.

Results. Overall, 32 (10%) out of 321 analyzed patients carried an EGFR mutation. Somatic mutations in EGFR gene were quite equally distributed between exon 19 (N = 17; 53%) and exon 21 (N = 15; 47%). No mutation was found in exon 18 of EGFR among the first 270 enrolled patients; thereafter, mutation analysis was focused on EGFR exons 19 and 21 only. No significant difference in distribution of EGFR mutations according to the age at diagnosis was observed [EGFR mutated: median age, 61.5 (range 37-80); EGFR wild-type: median age, 66 (range 31-85)]. Females presented a significantly higher frequency of EGFR mutations in comparison to males [23/105 (21.9%) vs 9/216 (4.2%)], respectively (p = 0.023). According to the smoking history (when available on clinical records), a significant preponderance of EGFR mutations were observed in never smokers (25/63; 39.7%) as compared to former smokers (4/78; 5.1%) and smokers (3/61; 4.9%) (p <0.01). Among patients whose somatic DNA was available for further analyses, we detected 42/251 cases (16.7%) with KRAS mutations in never smokers [32/166 (19.3%) vs 10/85 (11.8%), respectively]. According to the smoking history, a significant difference was observed (p = 0.0346).

Conclusions. EGFR and KRAS mutations are mutually exclusive. KRAS mutations were slightly more prevalent in males than females [32/166 (19.3%) vs 10/85 (11.8%), respectively]. According to the smoking history, a significant difference was observed (p = 0.0346).

D41 ERYTHROCYTE MEAN CORPUSCULAR VOLUME CHANGE DURING PEMETREXED CHEMOTHERAPY IN ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS

Bordi P., Buti S., Tiseo M., Panni S., Novello S., Bria E., Rapetti S., Pilotto S., Camisa R., Ardizzoni A.

1 Oncology Unit, University-Hospital of Parma, Parma; 2 Oncology Unit, Hospital of Cremona, Cremona; 3 Thoracic Oncology Unit, University Hospital of Orbassano, Torino; 4 Medical Oncology, University Hospital of Verona, Verona

Introduction. Pemetrexed (Pem) has been approved for the treatment of advanced non-small cell lung cancer (NSCLC) nonsquamous histology, both as first and second-line therapy with or without platinum compounds, respectively. Pem is an antimetabolite drug, that inhibits enzymes involved in nucleotides bio-synthesis arresting cancer cells cycle. Literature data show the effect of antimetabolities on increment of erythrocyte mean corpuscular volume (MCV) in cancer patients treated with capcitabine and, recently, a positive correlation between increased MCV and response to capcitabine-based therapy has emerged (Arslan, Tumori, 2011; Dellapasqua, Breast, 2012). The study aim was the evaluation of Pem impact on MCV change and its possible correlation with disease control rate (overall response + stable disease rate) (DCR), progression-free survival (PFS) and overall survival (OS) in NSCLC patients.

Methods. A retrospective collection of clinical and laboratory data (including basal MCV and maximum MCV occurred during Pem therapy) in 165 advanced NSCLC pts treated with Pem from 4 Italian centers was performed.

Results. Patients characteristics: 59% men, median age 64 years (range 36-83), 58% ECOG PS 0, 90% stage IV, 87% adenocarcinoma histotype, 74% current or ex-smokers, 59% as first-line, 41% as second-line, 68% in combination with a platinum compound, median cycle 4 (range 1-29). All pts received vitamin B12 and folic acid supplementation.

Mean MCV significantly increased from basal (89.6 fl) to “during treatment” (94.8 fl), with mean ΔMCV = 5.2 fl (t test for paired data, p <0.0001). The median time from therapy start to maximum MCV was 2.3 months. Results are summarized in Table 1.

Conclusions. Pem induces significant increase of erythrocyte MCV. ΔMCV >5 fl on Pem therapy appears to be correlated with better DCR, PFS and OS. These data should be related to a decreased metabolism of Pem and subsequent increased drug exposure in pts who develop higher ΔMCV during treatment. A larger prospective evaluation could better clarify these findings.

Table 1 - Results

<table>
<thead>
<tr>
<th>DCR</th>
<th>PFS (months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ΔMCV &gt;5 fl (68 pts)</td>
<td>84%</td>
<td>6.9</td>
</tr>
<tr>
<td>ΔMCV ≤5 fl (97 pts)</td>
<td>62%</td>
<td>3.6</td>
</tr>
<tr>
<td>p</td>
<td>0.002</td>
<td>0.0019</td>
</tr>
</tbody>
</table>

D42 HEDGEHOG (HH) SIGNALING IS A PREDICTOR OF CLINICAL OUTCOME FOR ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)


1 Clinica di Oncologia Medica, 2 Anatomia Patologica, Università Politecnica delle Marche, AOU Ospedali Riuniti di Ancona; 3 Chirurgia Toracica, AOU Ospedali Riuniti di Ancona

Background. Lung cancer still remains the leading cause of cancer deaths in the world and it lacks validated biomarkers to predict clinical outcome. The Hh pathway is critical for cell growth and differentiation. The aim of our study is to evaluate
the role of the Hh signaling in the prediction of clinical outcome for advanced NSCLC.

Methods. In this single-center prospective study, we determined the expression of Hh-related molecules including Ptc1 and Gli1 (nuclear and cytoplasmic) by immunohistochemistry in histologic samples (biopsies and surgical specimens) of advanced NSCLC patients. All the neoplastic area included in the slides was considered and both cytoplasmic and nuclear stainings were evaluated, according to the positive neoplastic cells. The intensity of the staining was evaluated and scored as follows: 0 (absent), 1+ (low), 2+ (medium) and 3+ (high).

Results. We analyzed 25 lung cancer histological samples, 18 adenocarcinomas and 17 squamous cell carcinomas. Positivity of Gli1-cytoplasmic and Gli1-nuclear expression was expressed in adenocarcinoma at a significantly higher level and more frequently than compared to squamous cell carcinoma (p <0.05), while Ptc1 did not differ significantly in the two histotypes. Overall survival was longer in Gli1 and Ptc1 negative tumour samples compared to the positive group (p = 0.02). The 18 patients with adenocarcinoma received erlotinib as second-line therapy and those presenting a lower Gli1 and Ptc1 expression experienced a significant increase in progression-free survival.

Conclusions. At our best knowledge this represents the first study investigating the role of Hh in NSCLC patients. Our results suggest that the Hh pathway might play a major prognostic role in NSCLC with significant differences between the histotype. Furthermore it might predict the efficacy of erlotinib as second-line treatment in patients with advanced lung adenocarcinoma.

D43 THYMIC MALIGNANCIES IN THE CLINICAL PRACTICE


Department of Medical Oncology, Division of General Thoracic Surgery, Polytechnic of Marche, Ancona

Introduction. Thymomas are uncommon tumours of thymic epithelial cells. Thymic tumours are classified into types: A, AB, B1, B2, B3 and C (thymic carcinomas) according to the World Health Organization (WHO) criteria based on morphology of epithelial cells with increasing atypia from type A to thymic carcinoma.

Thymomas display significant heterogeneity from morphologic point of view, clinical behaviour, expression of immunohistochemical markers and molecular profiling.

Patients and methods. A cohort of 55 consecutive patients undergoing radical surgery at our Institution between 2002 and 2010 were eligible for our analysis.

Results. Male/female ratio was 25/30; patients median age was 57 years (range 27-84). Patients with an autoimmune syndrome as initial presentation were 22 (40%), of whom presented miasthenya gravis. According to the WHO classification system, 5/55 (9%) were type A, 30.9% (17) were type AB, 9% (5) were type B1, 20% (11) were type B2, 10.9% (6) were type B3 and 20% (11) were thymic carcinomas. According to the Masaoka staging system, 11 out of the 55 patients (20%) presented in stage I thymoma, while 52.7% (29) had stage II (17 patients stage IIA, 12 stage II B), 7.2% (4) presented in stage III and 20% (11) had stage IV. Fifty patients underwent median sternotomy with complete thymectomy (R0 = 92%). Eleven patients with locally advanced disease received induction chemotherapy, 1 received adjuvant chemotherapy and 3 palliative chemotherapy. We used cisplatin-based protocols consisting of doxorubicin, cyclophosphamide, cisplatin, vincristine. Twenty-one patients underwent radiotherapy: 17 after an incompletely resected (R1) or invasive thymomas (stage II, III and IVA) and 4 for palliative purposes. The median OS was 73.05 months.

Conclusions. Thymomas and thymic carcinoma represent a heterogeneous disease with different clinical behavior. In our large monocentric series, the choice of our therapeutic strategy was based mainly on Masaoka stage. Surgery remains the baseline attempt in thymoma therapy and, whenever possible, completeness of resection has to be aimed for because its an important prognostic factor for local control and survival. Multimodality treatment is an approach to manage primarily unresectable tumours as frequently seen in Masaoka III, IVA and IVB thymomas.
However, there are indications suggesting that EGFR-mutant lung cancer maintains partial sensitivity to TKIs after development of resistance and tumours can still be sensitive to EGFR-TKIs treatment beyond progression or re-treatment at further progression.

Given this background, we investigated the effects of continuation or removal of gefitinib in the HCC827GR5 NSCLC cell line (kindly provided by Dr. P. Janne Dana-Farber Cancer Institute Boston MA) carrying EGFR activating mutation but with acquired resistance to gefitinib (MET amplification).

Gefitinib withdrawal did not modify IC50 values regarding inhibition of cell proliferation and didn’t affect doubling time. On the contrary, in the absence of gefitinib, resistant cells showed more migrating and invasion capability, mainly related to the activation of Src pathway. In addition after 20 days of gefitinib removing, cells underwent epithelial-mesenchymal transition (EMT). Prolonged treatment with gefitinib, instead, reduced cell migration, cell invasion and EMT acquisition.

These results indicate that cells which have become resistant to gefitinib can proliferate and survive in the presence of the drug; however the maintenance of gefitinib might be important to control other malignant phenotypes of tumour cells such as loss of epithelial features and the acquisition of invasiveness.

**D45 ERLOTINIB IN METASTATIC NON-SMALL CELL LUNG CANCER (NSCLC) PATIENTS UNSELECTED FOR EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) MUTATIONS: A RETROSPECTIVE ANALYSIS OF ELDERLY PATIENTS**


Department of Radiology, Oncology and Human Pathalogy, Policlinico Umberto I, University Sapienza, Rome.

**Background.** Median age at diagnosis of NSCLC is 70 years (yrs). Erlotinib demonstrated survival advantage and good safety profile in pts with advanced NSCLC, unselected for EGFR mutations, after first or second-line treatment failure. This makes erlotinib more suitable than chemotherapy for elderly but they are generally excluded from clinical trials. We analyzed survival outcome of young and elderly and identified clinical predictive factors of response to erlotinib for elderly.

**Methods.** From January 2007 to August 2011, 170 pts with advanced NSCLC received erlotinib in second or third-line setting. We collected baseline clinical characteristics (sex, smoking habits, performance status (PS), histology) and stratified pts in two groups according to age: 74 were less than 65 yrs (young) and 96 were older (elderly). We analyzed overall survival (OS) and progression-free survival (PFS) with Kaplan-Meier method and compared the two groups with log-rank test. Then we correlated data about skin toxicity with survival outcome.

**Results.** Two groups were homogeneous for clinical characteristics (p >0.05). No differences between young and elderly were detected in terms of PFS (2.9 vs 2.9 months, p = 0.455) and OS (12.7 vs 11.2 months respectively, p = 0.672). Good PS (PS = 0) and female sex were independent predictive factors of better PFS for elderly (p = 0.005 and 0.007 respectively), while PS = 0 was associated with longer OS (p = 0.0013). Skin rash of any grade occurred in 52.1% of elderly and in 61.1% of young, without differences between the two groups (p = 0.29). Elderly who experienced skin toxicity had better PFS and longer OS than those with skin rash: 5.8 vs 2.1 months (p = 0.003) and 17.6 vs 8.5 months (p = 0.002) respectively.

**Conclusions.** Elderly benefits from erlotinib as much as young pts in terms of both OS and PFS. Among elderly good PS and female sex are positive predictive factors. Patients older than 65 yrs don’t experience greater skin toxicity than young and skin rash positive predictive role is confirmed for elderly too.

**D46 THE ROLE OF FAMILY CAREGIVER IN THE HEAD AND NECK CANCER**

Garzaro M.1, Airoldi M.2, Raimondo L.1, Riva G.1, Bartoli C.1, Carnio S.2, Fora G.2, Giordano C.1, Pecorari G.1

11th ENT Division, Clinical Physiopathology Department, University of Turin; 2nd Medical Oncology Division, San Giovanni Battista Hospital, Turin.

**Background.** The figure of family caregiver (FCG) is still largely un-investigated among head and neck cancer patients. Aim of our study was to describe in a detailed way the role of FCG, to evaluate quality of life (QoL) and psychological distress of FCGs and patients, and to investigate relationships between FCG’s wellbeing and patient’s QoL and emotional pattern.

**Methods.** Sixty couples of patients and their caregivers were enrolled in this observational cross-sectional study between 2007 and 2011 at 1st ENT Division, 2nd Medical Oncology Division and 2nd Radiotherapy Division of San Giovanni Battista Hospital of Turin. Inclusion criteria were: histological diagnosis of SCC, advanced stage (III-IV), completion of curative treatment and no evidence of disease at the enrolment.

Psychoncological assessment was performed using Distress Thermometer (DT), Stay-Trait Anxiety Inventory Manual in y1 and y2 form (STAI Y1-Y2), Beck Depression Inventory (BDI), Montgomery-Asberg Depression Rating Scale (MDRS), EORTC-QLQ-C30 and Head and Neck-35 module and Caregiver Quality of Life Index-Cancer (CQOLC).

**Results.** Patients: state and trait anxiety are 46.7% (STAI Y1 mean value 40.2 ± 10.2; cut-off 40) and 36.7% (STAI Y2 mean value 36.7 ± 8.2; cut-off 40) respectively; self reported and clinician rated depression are 31.6% (BDI mean value 8.2 ± 5.3; cut-off 9) and 48.3% (MDRS mean value 7.9 ± 5.9; cut-off 6) respectively.

FCGs: state and trait anxiety are 50% (STAI Y1 mean value 42.5 ± 9.9; cut-off 40) and 41.7% (STAI Y2 mean value 39.1±8.7; cut-off 40) respectively; self reported and clinician rated depression are 28.3% (BDI mean value 7.3 ± 4.7; cut-off 9) and 41.7% (MDRS mean value 7.6 ± 5.8; cut-off 6) respectively.

Data analysis underlined a positive association among emotional scales of patients and caregivers. Patients psychological aspects are negatively associated with caregivers QoL and vice versa.

**Conclusions.** Anxiety and depression are often present in FCGs and cured HNC patients. Long term patients QoL is the result of a frail balance between FCG and patient emotional and psychological distress. A psychological support for FCG could improve patient wellbeing.

**D47 MOLECULAR FOLLOW-UP OF AN ITALIAN COHORT OF EGFR MUTATED PATIENTS PROGRESSING AFTER TREATMENT WITH ORAL TYROSINE KINASE INHIBITORS**
Introduction. Tyrosine kinase inhibitors (TKIs) are valuable treatment options for A-NSCLC EGFR mutated patients. Since acquired resistance occurs at disease progression (PD), efforts have led to discover resistance mutations in exon 20 of EGFR gene and amplifications of C-MET. We evaluated this incidence in an Italian cohort of EGFR mutated NSCLC pts who had a PD after an oral TKI treatment.

Patients and methods. We evaluated 12 pts, 9 women and 3 men, all adenocarcinomas. Ten pts had an EGFR exon 19 deletion and 2 patients a L858R mutation in exon 21. At first PD after a TKI therapy, after previous written informed consent, a second biopsy on the PD site was performed to reassess the EGFR mutational status and c-MET amplification. EGFR mutation analysis was performed on 11 pre-treatment and all post-treatment specimens by direct sequencing while c-MET was studied by FISH on 9 cases. Seven pts received oral TKIs as first-line treatment, while other 5 pts as a second-line treatment.

Results. On the second biotic specimen T790M mutation was detected in 7 of 12 pts (58%), while a c-MET specific amplification was identified in 3 of 9 evaluated pts (33%). In one patient, T790M mutation and c-MET amplification were present concomitantly, while 2 pts exhibited a c-MET amplification without any T790M alteration. Clinical resistance was explained in the present cohort by novel EGFR T790M and/or c-MET molecular alterations in 8 of 12 assessed patients (67%). In 2 cases original EGFR TKI-sensitive mutation of the first diagnostic specimen was not detected on the site of PD. No pre-treatment EGFR T790M mutations were observed by direct sequencing.

Conclusions. EGFR T790M mutations and c-MET amplifications are common in Italian patients treated with oral TKIs that eventually develop drug resistance. Since new generation drugs are currently being developed against EGFR (irreversible TKIs) or c-MET, a "molecular follow-up" will allow to identify pts eligible for future treatment options.

D49 MULTIDISCIPLINARY TEAM (MDT) FOR THE FIRST VISIT OF HEAD AND NECK CANCER (HNC) OUTPATIENTS: ISTITUTO NAZIONALE DEI TUMORI EXPERIENCE

Locati L.1, Bergamini C.1, Ibba T.3, Fallai C.2, Orlandi E.2, Licitra L.1

1Head and Neck Medical Oncology, 2Radiotherapy, 3Otorhinolaryngology Surgery, Fondazione IRCCS, Istituto Nazionale Tumori, Milan

Background. A MDT is essential in the management of malignant tumours in cancer centers, as to the Organisation of European cancer Institutes standard requirements. Commonly, MDT meetings are regularly scheduled, they typically involve different cancer specialists who discuss often only selected clinical cases, then reporting the final therapeutic decision to the patient. We believe that HNC patients require a non-selected primary multidisciplinary approach, being a rare, complex and heterogeneous group of malignancies for whom different curative treatment options are often available for the same patient. In this context since May 2007 a MDT first visit outpatient clinic has been implemented. Aim of this work is to report about the observed patients epidemiology. We retrospectively reviewed all the records performed until February 2012. Patients demographics, cancer site, staging, treatments (received or proposed), purpose of the visit,
were evaluated. Treatment indications were formulated according to the Rete Oncologica Lombarda (ROL) guidelines that were approved after a multidisciplinary discussion among the HNC specialists (medical oncologists, radiation oncologists and HN surgeons) at the regional level.

Results. Seven hundred and eighty-two HNC outpatients have been evaluated, 71% with a new diagnosis and 25% affected by recurrent disease, including 12% with distant metastases. The main purpose of the visit was a second opinion in 76% of the cases. Primary site was 21% oropharynx, 20% oral cavity, 18% larynx-hypopharynx, 10% nasopharynx, 8% paranasal sinuses, 6% salivary glands, 6% skin cancer, 4% thyroid. Squamous cell histotype in 65% of the tumours. At the time of the MDT visit, surgery was suggested in 224 cases and chemo-radiotherapy in 192 cases. In 10% of pts the original treatment plan was modified by our MDT visit.

Conclusions. Oropharynx was the most frequent site of disease, according to the recent epidemiological data trend. Second opinion was the main purpose of the requested first visit in line with the scope of a MDT outpatient clinic.

Conclusions. No advantage for CET/RT over CT/RT were observed regarding G3-4 in-field toxicities and feasibility. Patients are still being followed-up to assess OS.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>CT/RT</th>
<th>CET/RT</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N 215</td>
<td>N 133</td>
<td></td>
</tr>
<tr>
<td>In-field mucositis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>37%</td>
<td>35%</td>
<td>0.79</td>
</tr>
<tr>
<td>Grade 4</td>
<td>4%</td>
<td>2%</td>
<td>0.45</td>
</tr>
<tr>
<td>In-field skin reaction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>13%</td>
<td>20%</td>
<td>0.07</td>
</tr>
<tr>
<td>Grade 4</td>
<td>1%</td>
<td>1%</td>
<td>0.58</td>
</tr>
<tr>
<td>RT median dose, Gy (range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm B1:</td>
<td>70 (8-70)</td>
<td>70 (35-70)</td>
<td>0.32</td>
</tr>
<tr>
<td>Arm B2:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT median duration, weeks (range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm B1:</td>
<td>7 (1-13.3)</td>
<td>8 (5-14)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Arm B2:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pts with RT interruption ≥3days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm B1:</td>
<td>32%</td>
<td>38%</td>
<td>0.22</td>
</tr>
<tr>
<td>Arm B2:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RT modification due to acute toxicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arm B1:</td>
<td>37%</td>
<td>40%</td>
<td>0.58</td>
</tr>
</tbody>
</table>

D51 QOL AND ADHERENCE TO I.V. OR ORAL CHEMOTHERAPY TREATMENT IN ELDERLY PATIENTS WITH ADVANCED NSCLC

Bordonaro S.1, Butera A.2, Spinato F.3, Antonelli G.4, Gabbia V.5, Caruso M.5, Sciaccia D.5, Tralongo P.5

1Medical Oncology, RAO, ASP 8 Siracusa; 2Medical Oncology, “S. Giovanni di Dio” Hospital, Agrigento; 3Medical Oncology, “Giovanni Paolo II” Hospital, Sciacca, (AG); 4Medical Oncology “S. Vincenzo” Hospital, Taormina (ME); 5Medical Oncology “La Maddalena”, Palermo; 6Medical Oncology “Humanitas” CCO, Catania; 7Medical Oncology, IOM, Via Gregorio (CT)

Background. In elderly patients with advanced stage NSCLC the identification of the best treatment-related quality of life becomes the main discriminating endpoint.

Patients and methods. In this multicenter study, 71 elderly (≥70 yrs) patients with advanced (IIIB-IV) NSCLC were randomly allocated to receive as first-line treatment either gemcitabine intravenously (1000 mg/m2) or oral vinorelbine (60 mg/m2) both on days 1 and 8, every 21 days. The primary objective was the evaluation of the QoL, while the secondary one was the assessment of treatment adherence. The EORTC QLQ-C30 v 2.0 and QLQ-LC13 questionnaires have been used to evaluate the quality of life and an “ad hoc” questionnaire to estimate the adherence/compliance to treatment in patients receiving oral vinorelbine. The questionnaires were filled at baseline and every 3 cycles.

Results. Fifty patients (44 males), median age 76.2 years, were evaluated. All patients filled in the QoL questionnaires at baseline, 23 of them after three cycles of treatment. Differences of mean score values of items recorded at each assessment were calculated. Referring to QLQ-C30, there was a gain of 11.4 points as regards physical function and 23.3 points for emotional function in the vinorelbine arm compared to a loss of 8.5 and 1.6 points in the gemcitabine arm. A higher improvement of the symptoms nausea and vomiting and sleep disturbance in the vinorelbine arm in comparison with gemcitabine (-8.1 vs +1.6 points and -36.3 vs +15 points, respectively) was also observed. Patients treated with oral vinorelbine showed improvements of the majority of QLQ-LC13 scores and completed a higher number of cycles as compared to gemcitabine. Most patients (93.5%) responded positively to the satisfaction questionnaire of oral vinorelbine.
Conclusions. Oral vinorelbine may provide an advantage in terms of patient preference since, without reducing the effectiveness, is able to maintain an acceptable toxicity profile which results in a gain of the level of quality of life.

D52 THE PREDICTIVE VALUE OF CLINICAL VARIABLES IN PATIENTS AFFECTED WITH NON- SMALL CELL LUNG CANCER (NSCLC) TREATED WITH PEMETREXED (PEM) PLUS PLATINUM-BASED REGIMEN: A RETROSPECTIVE ANALYSIS

Fabbrini M.A.1, Mosceti L.1, Nelli F.1, Gamucci T.3, Mansueti G.3, Narducci F.3, Quadrini S.3, Sperduti I.4, Passaro A.2, Campenni G.2, Cortesi E.2, Martelli O.5, Bianchetti S.6, Angelini F.6, Pellegrino A.7, Pavese I.7, Chilelli M.1, Ruggeri E.M.1

1U.O. Oncologia Medica, AUSL Viterbo; 2Oncologia Medica B, Policlinico Umberto I, Roma; 3Oncologia Medica, Ospedale SS Trinità, Sora (Fr); 4Unità di Biostatistica, Istituto Regina Elena, Roma; 5Oncologia, Ospedale S. Giovanni, Roma; 6Oncologia, Ospedale Regina Apostolorum, Albano; 7Oncologia, Ospedale Fatebenefratelli S. Pietro, Roma

Background. PEM plus platinum-based regimen is a standard of care in chemonaïve advanced non-squamous NSCLC patients. This retrospective multicenter analysis was performed to evaluate the predictive value of clinical variables for PFS in an unselected population.

Methods. Data were obtained by reviewing the clinical data of pts affected with advanced NSCLC treated from 2009 to 2011. 193 pts were retrieved. Main characteristics were: median age 63 years (range 33-79); male/female (M/F): 67%/33%; ECOG PS 0-1, 97%; weight loss >5%, 34%; current smoker 31%. Stage IV disease 81%; ≥1 site of metastases 79%. Brain metastases 28% of pts at diagnosis.

Results. All 193 pts are evaluable for analysis. 158 pts (82%) received the cisplatin- and 35 pts (18%) the carboplatin-based regimen. Most pts received at least 2 cycles of therapy and 21% received PEM maintenance treatment. The overall disease control rate observed was 69% (CR+PR = 44%, SD 25%). At a median follow-up of 6.7 months (range 1-22), the median PFS was 6 months (95% CI 5-7) with a 1-year PFS rate of 16.8%. In the dian follow-up of 6.7 months (range 1-22), the median PFS was 6

Pistillucci G.1, Sciaccia V.1, Ciorra A.1, Cironio C.1, Di Palma T.1, Calabretta F.1, Lugini A.2, Rossi R.1, Veltri E.1

1U.O. Oncologia Medica, Ospedale Santa Maria Goretti, Latina; 2U.O. Oncologia Medica, Ospedale San Casino de Lellis, Rieti

Background. Maintenance chemotherapy with pemetrexed is not the standard treatment of choice in patients with locally advanced or metastatic epitheliomorphc malignant pleural mesothelioma (EMPM). We would assess the safety and efficacy of a treatment with pemetrexed until progression disease after 4 or 6 cycles of induction therapy with or without platin.

Materials and methods. From July 2008 to September 2011, 11 patients (9 males and 2 females with a median age of 67 years, range 58-77) with locally advanced or metastatic epitheliomorphc malignant pleural mesothelioma (EMPM) were enrolled. In all patients history was epitheliomorphic malignant mesothelioma. Only 8 patients (72.7%) had a PS 0 whereas 3 (27.3%) had a PS 1. All patients received an induction therapy with or without platin. Each patient received an average of 6.1 cycles of induction chemotherapy. Then all patients received a maintenance chemotherapy with pemetrexed 500 mg/m2 intavenously over 10 minutes every 3 weeks. Each patient received an average of 6.5 cycles of maintenance chemotherapy. All patients received folic acid and vitamin B12 supplementation to improve safety.

Results. At the time of analysis all patients were evaluable for response. Nine patients (81.8%) had a partial response and two of these underwent surgery and obtained a complete response. Two patients (18.2%) had a stable disease. The median overall survival was 14.7 months, while median progression-free survival was 12 months. Grade 2-3 of WHO haematological toxicities (anemia) occurred in 3 patients (27.3%). We also observed grade 2-3 of WHO gastrointestinal toxicities (diarrhea, nausea and vomiting) in 2 patients (18.2%). Grade 2 of lack of appetite and asthenia occurred in 3 patients (27.3%).

Conclusions. Our data show that a maintenance chemotherapy with pemetrexed in EMPM resulted in a moderate overall survival (14.7 months). These results indicate that patients with EMPM could benefit from a maintenance treatment with pemetrexed.

D54 PEMETREXED PLUS CISPLATIN OR CARBOPLATIN AS FIRST-LINE TREATMENT FOR ADVANCED NON-SQUAMOUS NON-SMALL CELL LUNG CANCER

Pistillucci G.1, Sciaccia V.1, Ciorra A.1, Cironio C.1, Di Palma T.1, Calabretta F.1, Lugini A.2, Rossi R.1, Veltri E.1

1U.O. Oncologia Medica, Ospedale Santa Maria Goretti, Latina; 2U.O. Oncologia Medica, Ospedale San Casino de Lellis, Rieti

Background. On the basis of recent data from several phase III trials, pemetrexed plus cisplatin regimen was approved in the initial treatment of advanced stage non-squamous non-small cell
lung cancer (NSCLC). Some studies reported comparable efficacy of the combination pemetrexed plus carboplatin.

Patients and methods. From July 2009 to February 2012 we treated 46 chemonaïve patients with stage IIIB or IV non-squamous NSCLC with pemetrexed 500 mg/m² combined with cisplatin 75 mg/m² (29 pts) or carboplatin AUC 5 (17 pts) for six cycles repeated every 21 days; pts could receive additional cycles of pemetrexed at the discretion of the physician. Median age was 62 years (range 39-75), 28 patients were males and 18 females; all patients had ECOG PS 0-2. We analysed the following endpoints: progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR) and toxicity profile. We also conducted an additional analysis comparing data of efficacy for cisplatin and carboplatin subgroups.

Results. All the patients were evaluable. The efficacy for all pts was: ORR 41% (18 partial responses, one complete response), stable disease (SD) 22% (10 pts), progression disease (PD) 37% (17 pts); the DCR achieved was 63%. Efficacy for 29 pts treated with cisplatin compared to 17 pts with carboplatin was respectively: ORR 44%, SD 24%, PD 32% versus ORR 36%, SD 18%, PD 46%. Median progression-free survival (PFS) for all pts was 6 months (range 2-32) with no difference for pts treated with cisplatin or carboplatin. Both combinations were well tolerated and the main side effects were grade 3 neutropenia in 2 pts, thrombocytopenia in 3 pts and anemia in 3 pts; grade 3 stomatitis/oesophagitis was seen in one patient and two pts, treated with cisplatin, showed severe dehydration that resulted in hospitalization for both. Only four pts needed to reduce the doses of chemotherapy for grade 3 toxicity.

Conclusions. Our retrospective study in unselected patients showed that pemetrexed plus platinum-based regimens as first-line treatment are active in treating advanced non-squamous lung carcinoma and have acceptable toxicity profile. The favourable toxicity profile of pemetrexed/carboplatin suggests that this regimen is an appropriate first-line treatment option also for chemonaïve patients.

D55 IMPACT OF SPECIFIC MUTANT KRAS ON CLINICAL OUTCOME OF EGFR-TKI-TREATED ADVANCED NON-SMALL CELL LUNG CANCER PATIENTS WITH AN EGFR WILD TYPE GENOTYPE

Duranti S.1, Bennati C.1, Ludovini V.1, Metro G.1, Giannarelli D.2, Molica C.1, Siggillino A.1, Marcomigni L.1, Currà M.F.1, Scatati C.1, Pagliaungo L.1, Chiari R.1, Minotti V.1, Crinò L.1

1Santa Maria della Misericordia Hospital, Azienda Ospedaliera di Perugia; 2Regina Elena Cancer Institute, Roma

Introduction. This retrospective study was undertaken to investigate the impact of specific mutant KRAS on clinical outcome to either gefitinib or erlotinib (EGFR tyrosine kinase inhibitor, EGFR-TKI) in patients with EGFR wild type (WT) advanced non-small cell lung cancer (NSCLC).

Methods. Patients with an EGFR WT genotype who were treated with an EGFR-TKI for advanced disease at our Institution were identified. Simultaneous availability of KRAS mutation status was required for study inclusion.

Results. Sixty-seven patients were eligible. Median age was 60 years (39-84), and 10 patients (14.9%) had received an EGFR-TKI as upfront therapy. Overall, the median progression-free survival (PFS) and overall survival (OS) were 2.9 months and 18.0 months, respectively. KRAS mutant patients (N = 18) experienced a significantly shorter PFS compared with those carrying a KRAS WT genotype (N = 49) (1.6 months versus 3.0 months, respectively, p = 0.04; HR = 1.92). However, within the KRAS mutant group a great variability in terms of sensitivity to treatment was noted (PFS ranging from 0.7 months to 38.7 months). KRAS codon 13 mutant patients (N = 4) experienced the worse outcome when compared with KRAS codon 12 mutants (N = 14) and KRAS WT patients (p <0.0001 and p = 0.01 for PFS and OS, respectively).

Conclusions. Though we found that EGFR WT/KRAS mutant advanced NSCLC patients are associated with an increased resistance to treatment, specific mutant KRAS may account for differential sensitivity to an EGFR-TKI. KRAS codon 13 mutants are those who seem to experience the worse clinical outcome.

D56 TYROSIN KINASE INHIBITORS (TKI'S) IN ADVANCED THYROID CANCER: A SINGLE INSTITUTION REPORT


Department of Oncology, Hematology and Respiratory Diseases, University Hospital, Modena

Background. In advanced thyroid cancer (ATC) after the failure of first-line treatment (radiometabolic or medical) no standard therapy is defined. In literature several phase II studies with TKI’s (sorafenib, sunitinib, vandetanib) demonstrated an acceptable efficacy and toxicity profile in ATC.

Methods. From November 2007 to April 2012 at Oncology Department, Modena University Hospital, 9 patients with ATC underwent systemic therapy with TKI’s. The aim of the analysis is the evaluation of efficacy and safety of TKI’s in this setting.

Results. In 9 pts, 8 female and 1 male, median age at diagnosis 51 years (yrs), range 29-77, histologic diagnosis was as follows: 6 follicular carcinoma (67%) and 3 medullary carcinoma (33%). Stage at diagnosis was: 1 pt stage I (11%), 1 pt stage II (11%), 3 pts stage III (33%) and 4 pts stage IV (45%). At the beginning of systemic therapy, metastatic sites were bone (33%), liver (33%), lung (44%), nodes (33%). After thyroidectomy, 6 pts with follicular carcinoma underwent radiodine therapy: at progression 2 pts (22%) performed chemotherapy with doxorubicin-CDDP/CBDCA; the others, just after, underwent therapy with TKI’s. Three patients with medullary carcinoma underwent chemotherapy with 5-FU-dacarbazine (2 pts, 66%) or gemcitabine-vinorelbine (1 pt, 33%). After standard treatment, pts were treated with TKI’s: 7 with sunitinib and 2 with sorafenib. Up to April 2012, radiographic response outcomes are available on 8 pts: 1 PR (12%), 6 SD (75%) and 1 early PD (12.5%). Median PFS was 6 months for pts with follicular carcinoma, range 2-9 and 8 months for medullary carcinoma, range 7-31.

Common adverse events (any grade) were: haematological toxicity (11%), gastro-intestinal toxicity (11%), skin rash (11%), asthenia (33%), hypertension (33%).

After a median follow-up of 22 months, 8 pts (88%) are alive, while 1 died of PD (12%). Median overall survival is 5.8 yrs (range 3.5-11.4 yrs).

Conclusions. As already shown in literature, our retrospective analysis confirmed the efficacy (in terms of disease control) and acceptable safety profile of TKI’s in ATC. Confirmatory phase III studies are expected.
D57 QUALITY INDICATORS AND NON-SMALL CELL LUNG CANCER INTEGRATED CARE PATHWAY: A SINGLE CENTER EXPERIENCE

Menis J.1, Follador A.1, Valent F.2, Merlo V.1, Sibau A.1, Gaiardo M.1, Macerelli M.1, De Carlo E.1, Ceschia T.1, Parisi G.1, Giacomuzzi F.1, Tozzi V.2, Pacileo G.3, Fasola G.1

1University Hospital of Udine; 2Regione Friuli Venezia Giulia; 3Bocconi University, Milan

Background. Integrated care pathways (ICP) might be a good strategy to overview and improve the non-small cell lung cancer (NSCLC) patients management; the health care performance can be presented through properly selected/key quality of care indicators. The aim of our study was to review the quality of the health care delivered to NSCLC patients to provide evidence of clinical or organizational inappropriateness.

Methods. We retrospectively reviewed the electronic medical records of 169 NSCLC patients who had had a first access at the Oncology Department of the University Hospital Santa Maria della Misericordia (Udine) during 2010. The ICP mapping and few quality indicators had already been settled by a previous study on the 2008 population and were integrated with new up-to-date indicators. Fifteen indicators were selected on the basis of their availability, reproducibility, significance and measurability and were tested on the study population.

Results. 146 patients were considered eligible; median age was 67 years. Patients were mainly males (65%), had adenocarcinoma histology and advanced disease at the time of diagnosis (52.7%). The indicators not lined up with the benchmark were the percentage of diagnostic bronchoscopies (60.7% vs 80-85%), the number of surgical candidates who underwent mediastinoscopy for positive PET for mediastinal nodes (0 vs 100%); median time from diagnosis to surgery and to chemotherapy (58.5 vs 21 and 34 vs 21 days; p<0.0001); median time from PET to surgery (53.5 vs 14 days; p<0.0001). No extemporary cytology during bronchoscopy was performed and only 42.8% of the patients received a concomitant chemo-radiotherapy treatment for stage III disease. Few patients were enrolled in a clinical trial (2%) and 2.7% of our population received a fourth-line chemotherapy.

Stage was one of the independent variables associated with shorter time from the first chest physician examination to diagnosis (p=0.0287) and from diagnosis to the first chemotherapy administration (p<0.0001).

Conclusions. Our analysis has highlighted a good adherence to current national and international guidelines and scientific literature as far as the medical oncology treatment and the pathological diagnosis are concerned. There is still room for improvement, most of all regarding the pre-surgical procedures and timing for surgery.

D58 ROLE OF BMI IN PREDICTING THE EFFICACY OF ERLOTINIB IN NSCLC PATIENTS

Intagliata S.1, Pantano F.1, Fionniri I.1, Potestà C.1, Spoto C.1, Gamucci T.2, Narducci F.2, Mansueto G.3, Santini D.1, Tonini G.1

1Department of Medical Oncology, Campus Bio-Medico University, Roma; 2Medical Oncology Unit, Ospedale SS Trinità, Sora, ASL Frosinone; 3Medical Oncology Unit, ASL Frosinone, Frosinone

Background. Recent evidences have shown that an increase in adipose tissue leads to an elevation of the factors playing a role in the growth and survival of tumour, such as TNF-alpha, IL-6, IGF-1. In addition, a state of insulin-resistance is often associated with a body mass index (BMI) greater than 25. It is known that hyperactivation of IGF-1 pathway is associated with resistance to anti-EGFR drugs. Thus, it was suggested a mechanism of resistance to erlotinib in patients with an increase in adipose tissue. Therefore, we conducted a retrospective, multicenter study, in order to evaluate the role of BMI in predicting the efficacy of the treatment with erlotinib, in terms of progression-free survival (PFS), in patients with advanced NSCLC.

Methods. Data were collected from patients with stage IIIB-IV NSCLC with ECOG performance status between 0 and 3, treated with erlotinib. Patients received at least one prior platinum-based chemotherapy line and they were stratified in two subgroups according to BMI (≥ or <25). We use BMI’s cut-off of 25 to divide our patients in two groups based on the weight: BMI <25 normal weight, BMI ≥25 overweight. Kaplan-Meier analysis was performed to assess the BMI impact on PFS in the two BMI-stratified subgroups. The curves obtained were compared using the log-rank test.

Results. We analyzed 151 patients (101 males and 50 females) median age was 67 years. 82% of patients had taken erlotinib in second-line after platinum-based chemotherapy, while 18% in third-line. 44% of patients had a BMI over 25, while 56% lower. Our analysis showed no statistically significant correlation between patients stratified according to BMI (cut-off 25) and efficacy of erlotinib (p = 0.38). Patients with BMI <25 had a median PFS of 3.2 months, those with BMI ≥25 showed a median PFS of 3 months.

Conclusions. Based on this result we suggest that BMI, as single predictive factor, can’t be considered a predictive marker of erlotinib treatment efficacy in patients with advanced NSCLC.

D59 PROLONGED LOW-DOSES CHEMOTHERAPY IN ELDERLY PATIENTS WITH SMALL CELL LUNG CANCER: OUR EXPERIENCE

Duluc M., Iaculli A., Galdy S., Cotroneo G., Bonassi L., Nastasi G.

U.O. Oncologia Medica, A.O. Bolognini di Seriate (BG)

Purpose. To determine if prolonged low-doses chemotherapy beyond a standard number of cycles of a regimen containing platinum-doublet is preferable in elderly patients, with a good performance status and stable or responding disease.

Patients and methods. From January 2010 to January 2012 we evaluated retrospectively 15 elderly patients (median age 71, range 68-74) with histological documented SCLC stage IV, with a Karnofsky performance status of 90/80, absence of brain metastases, that received low doses of chemotherapy regimen with CBDCA (AUC 5) day 1 and etoposide 80 mg/m² day 1-3 every 4 weeks for 4 cycles. In those patients that responded to the treatment with SD or PR, maintaining a good PS, we continued chemotherapy until progression or poor PS or unacceptable toxicity. All patients at same time received the best support therapy and psychological support.

Results. Ten patients (66%) with stable disease after 4 cycles prolonged chemotherapy for 6 cycles; 4 patients (27%) with PR after 4 cycles received a total of 9 cycles, 1 patient, obtaining PR after
the first 4 cycles and SD after 8, received a total of 12 cycles (7%). The average number of cycles were 7; we saw neutropenia grade 1-2 in 26% of patients, anemia grade 2 in 53%, fatigue grade 2 in 20% and stomatitis grade 1-2 in 8 patients, no diarrhea or vomiting.

Conclusions. There are no data supporting continuation of chemotherapy after 4 cycles in SCLC; in our experience, prolonged low doses of chemotherapy in responding patients with a good PS have demonstrated an improvement in OS and quality of life with an acceptable toxicity profile.

D60 MULTIDISCIPLINARY MANAGEMENT OF MALIGNANT MESOTHELIOMA (MM) IN A HIGHLY ASBESTOS-POLLUTED DISTRICT IN THE PIEDMONT REGION


Multidisciplinary approach is the best way to define the therapeuetic strategy. Since its foundation, the Piedmont Regional Oncological Network has been promoting the activation of tumour-specific interdisciplinary care groups (ICGs) as its essential operative modality to achieve the optimal patient care, assuring the exploitation of all available regional resources. In fact, the activities of the different ICGs are coordinated and supervised at the central level. MM is a rare tumour but represents a peculiar health and social issue in the Alessandria district with the epicenter in Casale, where the incidence is almost 20 times higher than the average. To deal with this problem the MM-ICG has been constituted since 2009 by joining the expertise of specialists from Casale and Alessandria Hospitals and a dedicated biological bank (MM-BB) has been created in Alessandria. The MM-ICG is formed by all the specialists involved in MM diagnosis and treatment. A diagnostic and treatment protocol has been defined based on the available evidence and a database (DBmeso) has been created to record the patient histories linked to the regional MM registry of Piedmont. Whenever possible, tumour samples along with pleural effusion fluid, blood and serum were collected and stored in the MM-BB. Fortnightly meetings are held to discuss the most notable cases. A patient-dedicated website has been set up (www.meso.ospedale.al.it).

Almost 700 cases have been recorded in the DBmeso. The MMBB contains samples and data from more than 217 patients. Observational studies are ongoing.

The cooperation of the day-to-day practices of different specialists is mandatory in this challenging field of oncology to assure patients are treated as effectively as possible. Closer and capillary interactions with general practitioners is worth pursuing and an effort is ongoing to create a wider network with partners Universities and Research Institutes at regional, national and international level. Indeed only a close link between clinical and preclinical/translational researches can improve insights into this deadly disease and possible new treatments.

D61 LUNG LESIONS: FNAB OR CNB? COMPLICATION AND DIAGNOSTIC ACCURACY

Capalbo E., Peli M., Lovisatti M., Cosentino M., Berti E., Mariani P., Cariati M.

1School of Specialization of Diagnostic and Interventional Radiology, University of Study, Milan; 2Department of Science Diagnostic, UOC of Diagnostic and Interventional Radiology, Hospital San Carlo Borromeo, Milan

This study was performed to assess type and incidence of complications and diagnostic accuracy of fine-needle-aspiration-cytology (FNAC) and core biopsy (CNB) computed tomography (CT)-guided performed to characterize lung lesions according to variables of patient, type of lesion and technique.

In the period 2009-2011 we performed 124 lung biopsies (66 CNB and 56 FNAB) in 121 patients with a mean age of 72.4±13.8 years. Exclusion criteria were: pulmonary resection, lesions and/or pleural effusions, significant changes in blood-coagulation profile. The eventual PNX or suffusion is assessed with a TC acquisition after 5 minutes by procedure end.

Unless otherwise clinically indicated, after 4 hours of the procedure was performed a chest radiograph. The association analysis between variable considered and onset of complication is calculated with Chi-squared test.

Age is a factor influencing the complications: 31% of PNX in young and 30% of hemorrhagic suffusion in elderly, with CNB but not with FNAB. We had more complications in the right lung: 50% PNX to upper lobe with CNB and 40% suffusion to lower lobe with FNAB.

The anterior approach has more complications with CNB, while the rear with FNAB.

The CNB has more complications of FNAB both for lesions ≤3.5 cm (27% vs 18% pneumothorax), and >3.5 cm (28% vs 9% suffusion).

No significant correlation with the histologic type of lesion, with the caliber of needle and with the number of passes (probably because we used in few procedures needles with gauge different of 18 G in the CNB or 22 G in the FNAB or in which they were made more than one passage).

The diagnostic accuracy of FNAB performed with pathologist on-site who assesses adequacy of sample extemporaneously is 94.83% against 81.82% of CNB. According to dimension, diagnostic accuracy is of 95.9% for lesions between 1.8 and 3.4 cm that underwent FNB, and of 83.6% for that undergone CNB.

In lesions in which we can choose if performing CNB or FNAB under CT guidance, the last is preferable both for lower complications rate and greater diagnostic accuracy, if carried out with pathologist on-site.

D62 GEFITINIB PLUS ZOLEDRONIC ACID ROLE IN BONE METASTASES FROM EGFR MUT+VE NSCLC PATIENTS

Del Signore E., Gori B., D’Antonio C., Ricciardi S., Fulvi A., Colacchi A.M., Migliorino M.R., Belli R., De Santis S., Condo S., de Marinis F.
Introduction. 30-40% of non-small cell lung cancer (NSCLC) patients presents bone metastases (BM) at time of primary diagnosis; zoledronic acid (ZOL) represents the standard treatment to prevent skeletal related events (SREs). 10-26% of NSCLC patients are epidermal growth factor receptor (EGFR) mut+ve showing more response, progression-free survival (PFS) and quality of life (QoL) using EGFR-TKIs than standard chemotherapy. Recent studies report that TKIs (gefitinib, erlotinib) inhibit the formation of BM inducing apoptosis in EGFR+ve bone stromal cells. We presume that gefitinib plus ZOL could block the growth of NSCLC cells inside bone, delaying time of bone progression (bone PFS), time to SREs, prolonging overall survival (OS).

Methods. We evaluated 26 pts from two Institutions, EGFR mut+ve with BM from NSCLC treated with gefitinib in first or second-line plus ZOL, considering bone PFS, time to 1st and subsequent SREs and OS.

Results. Of 26 pts, 21 were treated with ZOL plus gefitinib in first-line with 6 months of bone PFS; 7 pts (33%) had bone progression, 14 (67%) had 1st SRE at BM diagnosis, 3 pts (14%) had 2nd SRE during treatment with gefitinib, 7 pts (33%) never developed SREs; OS was 9 months, with 76% survivors to 6 months and 29% to 1 year. In 5 pts treated with gefitinib in second-line bone PFS was 6 months; 4 pts (80%) had bone progression, 1 pt (20%) stability. Four pts (40%) developed 1st SRE at BM diagnosis, 1 pt (20%) had 2nd SRE during treatment. OS was 9 months with 80% survivors to 6 months and 40% to 1 year.

Conclusions. Our experience shows that pts with BM from EGFR+ve NSCLC treated with gefitinib plus ZOL in first-line receive more benefit in terms of bone PFS, time to 1st and subsequent SREs, improvement of OS and QoL referred to studies with chemotherapy plus ZOL (Hirsh V, J Thorac Oncol, 3: 228-236, 2008).

D64 EVEROLIMUS PLUS LONG-ACTING SOMATOSTATIN ANALOGS IN THYMIC EPITHELIAL MALIGNANCIES

Palmieri G.1,2, Buonerba C.1, Federico P.1, Formisano L.1, Nanni L.1, Di Lorenzo G.1,2, Marino M.3, De Placido S.1,2, Damiano V.1,2
1Dipartimento di Endocrinologia e Oncologia Clinica e Molecolare, 2CRTR-Centro Regionale Tumori Rari, Università Federico II, Napoli; 3Department of Pathology, Regina Elena National Cancer Institute, Roma

Although thymic epithelial tumours (TETs) are rare in the general population, they represent the most frequently diagnosed primary malignant tumour of the anterior mediastinum. Unlike localized disease, metastatic TETs are invariably fatal. While several chemotherapy agents have proven to be effective in TETs, somatostatin analogs are the only targeted agents with an established role in this disease. Everolimus is an mTOR inhibitor with multiple application in solid tumours, such as kidney cancer and neuroendocrine tumours. Two female patients, respectively affected by a B2 and B3 TET, were treated with everolimus (10 mg daily) at our Institution after they had received several lines of chemotherapy. They both presented a large mediastinal mass with dyspnea and pain. A clinical and radiological benefit was documented with oral everolimus in both patients, with an excellent toxicity profile (G1 diarrhea, G2 hyperglycemia, G2 fatigue). After about 18 months of treatment, both patients are still on everolimus, with no evidence of progressive disease. Given the paucity of therapeutic options for this disease and the encouraging results obtained in this report, further investigation of everolimus in TETs is warranted.

D65 TOXIC EPIDERMAL NECROLYSIS IN A LUNG CANCER PATIENT TREATED WITH GEFITINIB (IRESSA™)

Kathleen A.3,4, Tommasi M.1,2,3,4, Campari F.3,4, Dell’Oro F.3,4, Damiano V.1,2
1Oncological Pulmonary 1st Unit, San Camillo Hospital, Rome; 2Oncological Pulmonary 2nd Unit, San Camillo Hospital, Rome; 3Medical Oncology Department, University Sant Andrea Hospital, Rome; 4Department of Pathology, Regina Elena National Cancer Institute, Rome

Results. Thirty-four patients, median age 71 years (range 48-81), M/F ratio 27/7 (79.4%/20.6%). Response rate was as follows: 1 complete response (2.9%), 5 partial responses (14.7%), stable disease in 12 patients (35.3%) and progression disease in 14 cases (41.2%); 2 patients were non-evaluable (5.9%). Progression-free survival (PFS) was 5.9 months after first-line treatment. The survival analysis showed that patients with epithelial histology (N = 23, 67.6%) have a median survival of 42.8 months, whereas for those with sarcomatoid histology (N = 4, 11.8%) it was 18.7 months and 8.4 months for those with biphasic histological type (N = 4; 11.8%). The univariate analysis of clinical and pathological variables showed that sex, smoking status, and the site of the disease (right/left pleura) do not have prognostic impact. Prognosis was significantly different between responders and patients who experienced progressive disease (p <0.05). No significant differences were shown among the main histopathological factors characterizing mesothelioma (calretinin, WT-1, TTF-1 and CK 5/6), probably due to the small number of patients in the study. Median survival resulted of 18.7 months in the non-responders, while in the responders it has not yet been reached.

Conclusions. Our study confirmed that positive histology of epithelioid mesothelioma and responsiveness to first-line chemotherapy represent two major prognostic factors in mesothelioma patients.
Introduction. Platinum-based doublet chemotherapy represents the standard treatment for advanced non-small cell lung cancer (NSCLC) patients. More recently thyrosine kinase inhibitors (TKI) and a monoclonal antibody (bevacizumab) to anti-vascular endothelial-growth-factor (VEGF) have been introduced in clinical practice in selected cases. We evaluated the antitumour activity of a bio-chemotherapy treatment combining bevacizumab with metronomic chemotherapy including cisplatin and oral etoposide designated as mPEBev. Such treatment resulted very active and showed significant influence on serum VEGF and cytokine release which promote tumour growth. In the present study we have evaluated the antitumour effects of TKI inhibitor, erlotinib, started just after four mPEBev treatment cycles.

Patients and methods. Twenty-nine inoperable NSCLC patients (20 males and 9 females) with an ECOG <1, and median age of 62.9 years (range 38-84) were enrolled in this phase II trial. Twenty patients had an adenocarcinoma, 6 a squamouscellular and 3 a NAS carcinoma. All patients received erlotinib (150 mg/day) started one week after the end of chemotherapy until disease progression (PD). No anti-acid was allowed except anti-H2 antagonists. Seventeen patients showed smoking attitude and only two showed a demonstrable EGFR mutation.

Results. The treatment was well tolerated, with G3 asthenia, skin rash, conjunctivitis and diarrhoea respectively, observed in 50, 35, 17, and 15% of cases. A PD was observed in 10 patients, a SD in 10 and a PR in 9. It was also observed a median PFS of 6.2 months (ES 0.87, 95% CI 4.2-7.3) and an OS of 12.65 months (ES 1.59, 95% CI 10.83-23.46). Nineteen patients (76%) upon progression presented a good performance status and could receive a second treatment line: our statistical analysis did not identify any significant correlation with smoking status (p = 0.734), histology and response to chemotherapy.

Conclusions. Our treatment suggests that early erlotinib treatment is an active treatment for NSCLC patients undergone mPEBev bio-chemotherapy.

D67 SAFETY AND ANTITUMOUR ACTIVITY OF CARBOPLATIN (CBDCA) PLUS PEMETREXED IN PATIENTS OLDER THAN OR EQUAL TO 75 YEARS WITH ADENOCARCINOMA OF THE LUNG


*U.O. Oncologia Medica e Ematologia, A.O. G. Salvini, Rho (Milano); ° Direttore Generale A.S.L. Como

Background. As the number of elderly patients diagnosed with non-small cell lung cancer (NSCLC) increases, the number of these patients receiving chemotherapy also increases. NSCLC chemotherapy decisions in patients ≥75 years old are complex because of toxicity, comorbidity and limited data exist regarding the use of chemotherapy in these patients.

Platinum-based chemotherapy is considered a standard approach for advanced NSCLC. However, it is unclear whether elderly patients with a good performance status can tolerate platinum-doublet chemotherapy like younger patients.

The purpose of this study was to evaluate the safety and antitumour activity of carboplatin plus pemetrexed in chemo-naïve elderly pts with advanced adenocarcinoma of the lung who were ≥75 years old.

Methods. Between November 2010 and February 2012, 13 elderly pts (≥75 years) with metastatic adenocarcinoma of the lung are included in this retrospectively analysis.

Patients baseline characteristics included: 10 pts were men, median age 78 (range 75-80), 11 pts stage IV and 2 stage IIIb, 8 pts ECOG 1 and 5 ECOG 2, all patients were EGFR wt.

Regimen: carboplatin (CBDCA) AUC: 4 day 1 every 3 weeks and pemetrexed 500 mg/m2 day 1 and day 8 every 3 weeks.
and pemetrexed 500 mg/m² day 1 every 3 weeks. Therapy was continued for a maximum of six cycles in pts showing tumour re-
sponse or stable disease.

**Results.** No patient experienced G3-4 toxicities. Neutropenia G1-2 was observed in 50% of the pts, anemia G1-2 in 40% of the pts and trombocytopenia G1-2 in 10% of the patients.

Non-hematological G1-2 toxicities were: fatigue (60%), nau-
sea (15%), constipation (30%), mucositis (15%), anorexia (30%).

No serious events requiring hospitalization were reported. No
toxic related death was reported. The response was as follows:
partial response 30%, stable disease 20%. PFS 4.4 months.

**Conclusions.** Patients ≥75 years with advanced NSCLC may
obtain clinical benefit from the administration of platinum-based
doublet agent chemotherapy. Combination therapy using CBD-
CA with pemetrexed is tolerable and promising for elderly pts
with adenocarcinoma of the lung.
Session E * Breast cancers

E1* COMPARISON OF TOXICITY AFTER 2 YEARS OF ADJUVANT ANASTROZOLE (A) OR EXEMESTANE (E) OR LETROZOLE (L) OR TAMOXIFEN (T). PRELIMINARY DATA FROM THE FATA-GIM3 PHASE 3 TRIAL


Università di Napoli Federico II; Arcispedale S. Maria Nuova, Reggio Emilia; Università Federico II; Istituto Nazionale Tumori, Napoli; Università di Sassari; ASLI, Sassari; AORN Cardarelli, Napoli; Arcispedale Sant’Anna, Ferrara; IST, Genova; Istituto Regina Elena, Roma; Ospedale F. Renzetti, Lanciano; Ospedale Sacro Cuore Don Calabria, Negrar; Ospedale Unico Versilia, Lido di Camaiore; Ospedale Fatebenefratelli e Oftalmico, Milano; ASUR, Zona Territoriale 6, Fabriano; Ospedale di Busto Arsizio, Saronno; AOU, Maggiore della Carità, Novara; Università G. d’Annunzio, Chieti; Istituto di Ricerche Farmacologiche Mario Negri, Milano; Istituto Nazionale Tumori, Napoli; Seconda Università, Napoli; Istituto Nazionale Tumori, Napoli

Background. A, E, L and T have never been prospectively compared altogether for safety and efficacy. The use of upfront or early switch strategies is still matter of uncertainty. Comparing the three aromatase inhibitors (AI) and upfront vs early strategy in a single prospective trial is important for optimizing clinical practice.

Methods. We planned a phase 3 randomised trial with a 3x2 factorial design. Primary endpoint is disease-free survival. Overall, 3600 patients have been randomised to have the three upfront arms: A (1 mg/day), E (25 mg/day) and L (2.5 mg/day), all for 5 years; the three switch arms include T (20 mg/day) for 2 years followed by A, E or L (dosed as above) for 3 years.

From March 2007 to May 2012, 3560 patients have been randomised and the final sample size will be reached shortly; the present analysis of safety during the first 2 years of treatment was performed on patients entered before January 1, 2010. Adverse events are coded according to CTCAE 3.0. For this analysis, two perspectives were planned: A vs E vs L and T vs AI.

Results. 1450 patients eligible for this analysis were randomly assigned to A (N = 243), E (N = 246), L (N = 237) or T (N = 724). The table shows the adverse events (any grade) that occurred at a statistically significant different rate among the treatment arms and the relative p values.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>A (%)</th>
<th>E (%)</th>
<th>L (%)</th>
<th>T (%)</th>
<th>p value (A vs E vs L)</th>
<th>p value (T vs AI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol level</td>
<td>77</td>
<td>73</td>
<td>78</td>
<td>63</td>
<td>0.38 &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Triglycerides level</td>
<td>21</td>
<td>17</td>
<td>27</td>
<td>35</td>
<td>0.07 &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Any pain</td>
<td>13</td>
<td>43</td>
<td>40</td>
<td>21</td>
<td>0.054 &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>bone pain</td>
<td>18</td>
<td>23</td>
<td>22</td>
<td>12</td>
<td>0.39 &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>joint pain</td>
<td>21</td>
<td>31</td>
<td>24</td>
<td>10</td>
<td>0.051 &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>muscle pain</td>
<td>10</td>
<td>17</td>
<td>14</td>
<td>10</td>
<td>0.07 0.006</td>
<td></td>
</tr>
<tr>
<td>Any vaginal event</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>6</td>
<td>0.15 &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Any vascular event</td>
<td>3</td>
<td>3</td>
<td>3</td>
<td>8</td>
<td>0.82 &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>thromboembolism</td>
<td>0</td>
<td>&lt;1</td>
<td>1</td>
<td>2</td>
<td>0.61 0.0009</td>
<td></td>
</tr>
</tbody>
</table>

Conclusions. During tamoxifen cholesterol levels are lower but triglycerides are higher than with AI. Tamoxifen produces less musculoskeletal and articular pain but more vaginal and thromboembolic events. Among AI there are no relevant differences in safety profile.

 Supported by Italian Drug Agency (AIFA code: FARMSK3M3EE).

E2* SURVIVAL BENEFIT OF SURGERY OF THE PRIMARY TUMOUR IN METASTATIC BREAST CANCER: RESULTS OF A META-ANALYSIS

Petrelli F., Cabiddu M., Borgenovo K., Ghiardi M., Maspero F., Cremonesi M., Barni S.

Medical Oncology Division, A.O. Treviglio-Caravaggio, Treviglio

Introduction. The aim of surgical treatment of primary tumour in the presence of concomitant distant metastases could be to obtain control of the disease and of local symptoms. Stage IV breast cancer is treated primarily with systemic therapies. Excision of the primary breast cancer tumour in presence of synchronous distant metastases is a controversial argument, and standard recommendations are not proposed. We performed a meta-analysis with the aim of pooling the existing survival data of surgery of the breast primary tumour in stage IV disease.

Materials and methods. We searched PubMed for publications reporting data about the survival benefit of surgery of the primary tumour in female with histologically confirmed metastatic breast cancer at presentation. Hazard ratios (HRs) for survival when reported after multivariate analysis (with 95% confidence intervals) were obtained from publications and aggregated in a meta-analysis. A meta-regression weighted for extent of disease, treatment with systemic and radiotherapy and systemic therapies offered was also performed.

Results. Fifteen articles were included in this meta-analysis (all retrospective case series), for a total of 15,378 patients. The pooled HR for overall mortality was 0.69 (p <0.00001) in favor of the patients undergoing surgery (Figure). According to meta-regression, the survival benefit was independent of age, extent, site of metastatic disease and HER2 status, but was directly proportional to rate of patients exposed to systemic therapies and radiotherapy and inversely correlated to ER+ status of the population included.

Figure - Pooled analysis of hazard ratios for overall mortality for surgery versus no surgery for patients with stage IV breast cancer.
Conclusions. Our meta-analysis, despite its retrospective nature, confirms the suggestion that surgery of primary tumour in a patient with concomitant metastatic disease is beneficial in terms of survival, with a reduction in the risk of death of 30%; this result is particular significant if local surgery is offered into a multimodality therapy program.

E3* MET AND HEPATOCYTE GROWTH FACTOR (HGF) INCREASED GENE COPY NUMBERS ARE ASSOCIATED WITH TRASTUZUMAB FAILURE IN HER2-POSITIVE METASTATIC BREAST CANCER

Minuti G.1, Duchnowska R.2*, Jassem J.3#, Fabi A.4, O’Brien T.5, Mendoza A.D.5, Landi L.1, De Maio E.1, D’Arcangelo M.1, D’Incecco A.1, Slavini J.1, Larin E.1, Biennart W.3#, Rossi E.1, Varella-Garcia M.5, Cappuzzo F.1

1Department of Medical Oncology, Civil Hospital of Livorno, Istituto Toscano Tumori; 2Department of Oncology, Military Institute of Medicine, Warsaw, Poland; 3Department of Oncology and Radiotherapy, Medical University of Gdańsk, Gdańsk, Poland; 4Department of Medical Oncology, National Cancer Institute Regina Elena, Rome; 5Molecular Pathology Shared Resource, University of Colorado Cancer Center, Aurora, USA; 6for the Central and East European Oncology Group (CEEOG)

Background. The monoclonal antibody trastuzumab has remarkable efficacy in HER2-positive metastatic breast cancer (MBC), however, the response rate is limited and not all patients derive benefit from this treatment. Recently, preclinical and limited clinical data showed that aberrant MET expression in MBC is a predictor of poor prognosis and is involved in trastuzumab resistance. Aim of the present study was to investigate whether copy number gain of MET or its ligand, hepatocyte growth factor (HGF) affect trastuzumab sensitivity in HER-2 positive MBC patients.

Patients and methods. This retrospective study included 130 HER2-positive MBC treated with trastuzumab as single agent or in combination with chemotherapy. Main inclusion criteria were presence of at least one measurable lesion and availability of paraffin-embedded tumour tissue from primary cancer. MET and HGF gene copy numbers (gCN) were assessed by fluorescence in situ hybridization (FISH). Receiver operating characteristic (ROC) analysis was applied to find the best cut-off point for both MET and HGF gCN.

Results. MET FISH analysis was successfully performed in all 130 cases. ROC analysis identified a mean of 3.72 MET gCN. MET FISH positive cases (N = 36, mean ≥3.72) had a significantly higher trastuzumab failure rate (44.4% versus 16.0%; p = 0.007) and a significantly shorter time to progression (5.7 versus 9.9 months; HR 1.74; p = 0.006) than MET FISH negative cases (N = 94, mean <3.72). HGF gCN was evaluated in 84 cases (64.6%). ROC analysis identified 33 HGF FISH positive patients (mean HGF gCN ≥3.01, 39.3%). HGF FISH-positive status was significantly associated with higher risk of failure (30.3% versus 7.8%; p = 0.007) as compared with HGF FISH negative cases (N = 51, mean <3.01). MET and HGF FISH positive status was highly correlated (p <0.001) and combination of both biomarkers did not increase predictive value of either considered separately.

Conclusions. High GCNs of MET and HGF associate with an increased risk of trastuzumab failure in HER2-positive MBC. These data support further development of combining anti-HER2 and anti-MET therapy in MBC.

E4* ANALYSIS OF CORRELATION BETWEEN WEIGHT AT DIAGNOSIS, WEIGHT GAIN AFTER BREAST CANCER TREATMENT AND RECURRENCE IN WOMEN WITH EARLY STAGE BREAST CANCER (EBC)


Medical Oncology and Breast Unit, “A. Perrino” Hospital, Brindisi; Biostatistics Unit and Department of Public Health, ASL BRI, Brindisi

Background. Overweight at the time of EBC diagnosis has been linked frequently to poorer survival in most studies and some evidence suggests that women who gain weight after breast cancer diagnosis are at increased risk of cancer recurrence and death. Most previous studies on this topic have relied on retrospective chart reviews. The aim of this prospective, observational, single-center study is to determine whether weight at diagnosis and weight gain after EBC treatment are predictive of BC recurrence.

Methods. From August 1997 to March 2012, the study included a total of 520 EBC patients (stage I-IIa). We assessed weight and body mass index (BMI = kg/m2) at baseline (≤1 month after surgery) and 24 months after completion of treatment (chemotherapy ± radiotherapy). The chi square test (X2) was conducted to determine if a significant correlation exists between BC recurrence and 3 categories of BMI at diagnosis (lean weight: BMI <25; overweight: BMI 25-30; obese: BMI >25) and BC recurrence and weight changes after EBC treatment (loss of <1 kg/m2; loss of ≥1 kg/m2; gain of <2 kg/m2; gain of ≥2 kg/m2).

Results. Median age was 55 years (range 28-81); 58% of patients were postmenopausal, stage I-II in 89%; ER+/PGR+ in 69%; ER-/PGR- in 20%; HER2+ in 20%; 72% underwent conservative surgery+radiotherapy; 57% received chemotherapy (CT) and 78% received endocrine therapy alone or after CT.

Median BMI at diagnosis was 26.8, after treatment 27.7. After a median follow-up of 13 years, 194 patients recurred. Statistical analysis is reported in Table 1.

Conclusions. Our findings show that EBC patients gain weight after treatment.

<table>
<thead>
<tr>
<th>Body Mass Index at diagnosis</th>
<th>Changes after BC treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25 kg/m2</td>
<td>25-30 kg/m2</td>
</tr>
<tr>
<td>N of patients</td>
<td>179</td>
</tr>
<tr>
<td>Recurrences</td>
<td>72</td>
</tr>
<tr>
<td>p</td>
<td>0.17</td>
</tr>
</tbody>
</table>
A significant correlation was found between weight gain after EBC treatment and recurrence, suggesting that women who gain weight after breast cancer diagnosis may be at increased risk of poor outcomes.

**E6** IMPACT OF PIK3CA MUTATIONS AND P95HER2 EXPRESSION ON THE OUTCOME OF HER2-POSITIVE METASTATIC BREAST CANCER PATIENTS TREATED WITH A TRASTUZUMAB BASED THERAPY

Bona E.1,2, Fontana A.1,2, Allegreni G.3, Mazzanti C.4, Stasi I.1,2, Lucchesi S.3, Ferrarini I.1,2, Arrighi G.3, Marcucci L.3, Landucci E.1,2, Bartolini I.1,2, Laurà F.1,2, Salvadori B.1,2, Falcone A.1,2, Zavagli K.4

1UO Oncologia Medica II Universitaria; 2Polo Oncologico, Ospedale S. Chiara, OSP; Pisa e Istituto Toscana Tumori; 3UO Oncologia Medica I, Azienda USL5 di Pisa; 4Anatomia patologica Section of Molecular Pathology, Division of Surgical, Molecular, and Ultrastructural Pathology, University of Pisa and Pisa University Hospital

**Background.** Currently, no biomarkers of trastuzumab (T) clinical resistance have been validated. The aim of this pilot study was to evaluate the impact of PIK3CA mutations and p95HER2 (pHER2 truncated form) expression on the efficacy of a T-based therapy in a HER2-positive metastatic breast cancer (MBC) patients.

**Methods.** 107 HER2-positive MBC pts, treated in the last 10 years, were evaluated. Median age was 54 years (25-79); ECOG performance status was 0 in 56% of pts; all pts received several lines of treatment including T; biomarkers molecular analysis was performed in 70 tumour specimens. The IHC expression of p95HER2 was evaluated by a monoclonal antibody that specifically recognizes only the HER2 external domain; the HER2 integrity was defined by the presence of a homogeneous membrane staining (moderate or intense) in at least 30% of the cells, otherwise the HER2 was defined as p95HER2 positive. PIK3CA mutations in exons 9 and 20 were detected by automated sequencing. The molecular data were correlated to time to progression (TTP) of the first-line treatment including T and the overall survival (OS) using the Kaplan-Meier method and the log-rank test.

**Results.** Thirteen (22%) of 60 patients achieved pR; pR rates were 16% in 31 ER-positive/HER2-negative (ER+ive/HER2-ive) tumours, 29% in 14 HER2-positive tumours and 27% in 15 triple negative tumours. Sensitivity of metabolic response to identify pR was 100% in all of the three subgroups, while specificity was low, being highest in the ER+ive/HER2-ive subgroup (38%). In this subgroup the positive predictive value was 24% and the negative predictive value was 100%; this means that 18F-FDG-PET/CT was measured at baseline and after 2 cycles of PCT. SUVmax percentage changes (Δ-SUV) were compared with pR rate according to immunohistochemical BC characteristics. Metabolic response was defined as a Δ-SUV >50%.

**Conclusions.** Early metabolic non-response was always associated to pathologic non-response and poor prognosis in ER+ive/HER2-ive patients. In this subgroup 18F-FDG-PET/CT might allow to select patients who could potentially benefit from an early change of the planned therapeutic strategy.

**E7 ADDITION OF ANTHRACYCLINES (ANTHRA) TO TRASTUZUMAB (T)-BASED NEOADJUVANT CHEMOTHERAPY (CT) FOR OPERABLE/LOCALLY ADVANCED BREAST CANCER (O/LABC) PATIENTS: TREATMENT-INTERACTION ANALYSIS BALANCING PATHOLOGICAL COMPLETE RESPONSES (PCR) AND TOXICITIES

Bonomi M.1, Bria E.1, Furlanetto J.1, Pilotto S.1, Carbognin L.1, Massari F.1, Maines F.1, Melisi D.1, Giannarelli D.2, Tortora G.1

1Medical Oncology, University of Verona, Verona; 2Biostatistics, Regina Elena National Cancer Institute, Rome

**Background.** Although in the pivotal trial exploring the addition of T in neoadjuvant setting the CT backbone included Anthra, these drugs are not commonly employed in association with taxanes (Tax), because of all concerns related to the potential cardiotoxicity. With the intent to balance the advantages in combination with the drawbacks of such approach, a treatment interaction analysis of the available randomized trials was accomplished.
Methods. Randomized trials (phase II/III) including arms in which T was either combined with Tax or Anhtra-Tax, were considered. pCR (breast + axilla), breast conserving surgery (BCS), grade 3-4 neutropenia/cardiotoxicity, and febrile neutropenia (FN) events were extracted from papers/presentation and cumulated according to a random-effect model; 95% confidence intervals (CI) were derived, and interaction was determined. A sensitivity analysis according to hormonal receptors (HRs) was accomplished. Absolute differences (AD) with 95% CIs, and the number of pts needed to treat/ham (NNT/NNH) for 1 to benefit were calculated in order to derive the likelihood of being helped or harmed (LHH).

Results. Eight trials (2092 pts) with 1955 pts treated with anti-HER2 therapy (T, lapatinib and pertuzumab, alone or combined), were gathered; 824 pts undergone T plus CT. Outcome rates are shown in the Table.

<table>
<thead>
<tr>
<th>CT</th>
<th>Outcome</th>
<th>Rates (95% CI)</th>
<th>Interaction (p)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthra-TAX</td>
<td>pCR</td>
<td>42.6 (35.6, 49.8)</td>
<td>&lt;0.0001</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td>BCS</td>
<td>49.8 (31.4, 68.2)</td>
<td>0.008</td>
<td>2.0</td>
</tr>
<tr>
<td>Anthra-TAX</td>
<td>TAX</td>
<td>49.8 (31.4, 68.2)</td>
<td>0.008</td>
<td>2.0</td>
</tr>
<tr>
<td>TAX</td>
<td></td>
<td>49.8 (31.4, 68.2)</td>
<td>0.008</td>
<td>2.0</td>
</tr>
</tbody>
</table>

pCR rates were significantly higher (p = 0.02 and p = 0.009, respectively) in the HRs negative population, regardless of the CT backbone (Anhtra-Tax: HR-negative 41.6%, 95% CI 24.4, 61.0; HR-positive 33.1%, 95% CI 17.0, 54.5; Tax: HR-negative 36.6%, 95% CI 28.8, 45.2; HR-positive 21.6%, 95% CI 15.3, 29.7). No significant differences were found with the addition of Anthra to T-Tax in terms of G3-4 cardiotoxicity (1.2% vs 0.4%, p = 0.31) or FN (8.8% vs 7.5%, p = 0.67). In the Anthra-based population weighted for cardiotoxicity, LHH was 36.

Conclusions. Patients receiving T plus CT significantly benefit from the addition of Anthra to Tax CT in terms of pCR and BCS. Given the low rate of cardiotoxicity, Anthra-Tax-based CT should be still considered the reference arm for future trials.

E8 ROLE OF TEMPORARY OVARIAN SUPPRESSION OBTAINED WITH GNRH ANALOG IN REDUCING PREMATURE OVARIAN FAILURE (POF) INDUCED BY CHEMOTHERAPY IN PREMENOPAUSAL CANCER PATIENTS: A META-ANALYSIS OF RANDOMIZED STUDIES


IRCCS AOU San Martino, IST, Genova

Background. Premenopausal cancer patients treated with chemotherapy (CT) are at risk of POF. The role of GnRHa in the prevention of CT-induced POF is still controversial. We performed a pooled analysis of randomized studies that evaluated the role of GnRHa as strategy to prevent POF.

Methods. Studies were retrieved by searching the PubMed database and the proceedings of major conferences. Odds ratios (OR) and 95% CIs for CT induced POF were extracted from each trial and averaged to obtain pooled estimates using an inverse-variance model.

Results. We included in the meta-analysis 7 randomized trials involving 745 premenopausal women randomly assigned to receive chemotherapy or chemotherapy + GnRHs: five trials were carried out in breast cancer patients and two trials in patients with lymphoma. The pooled OR estimate for CT induced POF was 0.46 (95% CI 0.30-0.72).

Conclusions. Temporary ovarian suppression obtained with the use of GnRH analogues reduces the incidence of chemotherapy induced POF in premenopausal cancer patients.

E9 DIFFERENT CLINICAL BEHAVIOR AND PROGNOSIS OF DIFFERENT IMMUNOHISTOCHEMISTRY-BASED SUBTYPES OF EARLY INVASIVE BREAST CANCERS IN A MONOINSTITUTIONAL SERIES

Ferro A.1, Eccher C.2, Triolo R.1, Caldara A.1, Di Pasquale M.C.1, Moroso S.1, Russo L.1, Cuovo L.V.3, Barbareschi M.3, Galligioni E.1

1Oncologia Medica, Trento; 2Anatomia Patologica, Trento; 3Fondazione Bruno Kessler

Background. Invasive breast cancer (IBC) is a heterogeneous disease. Gene expression profiling of invasive breast cancer (IBC) has identified several biologically distinct subtypes of IBcs. As proposed by Cheang et al., immunohistochemical (IHC) markers can be used as a surrogate for the molecular classification of breast cancers. Subtypes defined by IHC panel are similar to but not fully identical to intrinsic subtypes and represent a convenient approximation.

Purpose. The aim of our study was to evaluate different clinical behavior, relationship with other clinical-pathological features and survival outcomes for patients with different subtypes of IBC as classified using four ICH markers (ER, PR, HER2 and Ki67).

Methods. We evaluated data from 3461 cases of IBC treated from 1995 to 2008 classified as: luminal A (positive ER and PR, negative HER2 and Ki67 <14%), luminal B (positive ER and/or PR, negative HER2 and Ki67 ≥14%), luminal C (positive ER and/or PR, positive HER2, any Ki67), triple negative-TN (negative ER and PR, negative HER2 and any Ki67), and HER2+ (negative ER and PR, positive HER2, any Ki67). Log-rank test and Cox regression model were performed to evaluate the impact of ICH subtypes on overall survival (OS), event-free survival (EFS) and their correlation with other known prognostic factors.

Results. We identified 909 (26.4%) luminal A, 1722 (49.9%) luminal B, 325 luminal C (9.4%), 209 (5.7%) HER2+ and 296 (8.6%) triple negative. Median age was 61 years. Luminal A was more frequently (p <0.001) associated with older age, smaller size, negative axilla involvement, low grading. There were 644 (18.6%) events (local and distant relapses, contralateral and second tumours): 100 in luminal A (11%), 334 in luminal B (19.4%), 62 in luminal C (19%), 66 in HER2+ (31%) and 84 in triple negative (28%). Different subtypes showed preferential sites of first local or distant relapses: luminal A had more frequently bone and loco-regional recurrences and less visceral relapses than other subtypes. Median disease-free interval (DFI) of 1995 to 2008 classified as: luminal A (positive ER and PR, negative HER2 and Ki67 <14%), luminal B (positive ER and/or PR, negative HER2 and Ki67 ≥14%), luminal C (positive ER and/or PR, positive HER2, any Ki67), triple negative-TN (negative ER and PR, negative HER2 and any Ki67), and HER2+ (negative ER and PR, positive HER2, any Ki67). Log-rank test and Cox regression model were performed to evaluate the impact of ICH subtypes on overall survival (OS), event-free survival (EFS) and their correlation with other known prognostic factors.

Results. We included in the meta-analysis 7 randomized trials involving 745 premenopausal women randomly assigned to receive chemotherapy or chemotherapy + GnRHs: five trials were carried out in breast cancer patients and two trials in patients with lymphoma. The pooled OR estimate for CT induced POF was 0.46 (95% CI 0.30-0.72).

Conclusions. Temporary ovarian suppression obtained with the use of GnRH analogues reduces the incidence of chemotherapy induced POF in premenopausal cancer patients.
72.7 and 72.7% in HER2+, 78.0% and 73.9% in triple negative. Luminal A presented the best prognosis among other luminal subtypes. IHC-based subtypes prognosis in terms of EFS and OS was independent of nodal status, grading, tumour size and age. Considering only luminal subtypes, luminal B and C vs luminal A IBCs were significantly associated with poor EFS in both N0 (p = 0.046) and N+ (p <0.001), in T1 (p = 0.013) and T2 (p = 0.03), in patients older than 40 years (p = 0.002).

Conclusions. In our experience IHC-based classification appeared to be a useful tool to divide IBCs in different biological entities with distinct behaviors and important implications on prognosis. Its application could help the tailoring of adjuvant therapies, to improve patients outcomes.

E10 POLYMORPHISMS INTERACTION TO PREDICT BEVACIZUMAB (BV) EFFICACY IN METASTATIC BREAST CANCER (MBC) PATIENTS: AN EXPLORATORY RETROSPECTIVE ANALYSIS

Allegrini G.1, Bacci G.2, Fontana A.3, Goletti O.11, Camerini A.4, Galligioni E.5, Ferro A.5, Giuntini N.6, Casadei V.7, Cazzaniga M.8, Fiorentini G.7, Di Lieto M.8, Marucci L.1, Pazzaglì I.1, Colletti L.1, Lucchesi S.1, Finale C.1, Bona E.9, Scalessa M.10, Orlandi P.5, Villa F.6, Morini S.9, Amoroso D.10, Artighi G.1, Filidei M.1, Di Pasquale M.2, Falcone A.3


Background. Previous retrospective studies have attempted to identify a possible role of VEGF single nucleotide polymorphisms (SNPs) to predict BV efficacy in terms of OS and PFS in MBC pts with conflicting results (Schneider 2008, Grimaldi 2011, Lambrechts 2011).

Methods. On the basis of these preliminary data, we decided to assess in a MBC population if different VEgF, VEgFR-2, IL-6, HIF-1alfa, EPAS-1 and TSP-1 genotypes could predict BV efficacy in terms of OS and PFS in MBC pts with conflicting results (Schneider 2008, grimaldi 2008). Previous retrospective studies have attempted to

Results. 102 pts have been enrolled from 8 Oncology Units. Main pts characteristics are: median age 59 years (range 32-81), ECOG-PS 0/1 in 78%/22%, hormone receptor positive 83%, previous adjuvant chemotherapy 68%, disease-free interval (DFI) <12 months 27%. After a median follow-up of 17.4 months (1.9-54.7), mPFS was 11.6 months (95% CI 10.6-12.6) and mOS was 32.4 months (95% CI 25.9-38.9). None of SNPs was individually associated with PFS. Conversely, a genetic interaction profile for PFS (http://sourceforge.net/projects/mdr/). After a median follow-up of 17.4 months (1.9-54.7), mPFS was 11.6 months (95% CI 10.6-12.6) and mOS was <12 months 27%. After a median follow-up of 17.4 months (1.9-54.7), mPFS was 11.6 months (95% CI 10.6-12.6) and mOS was 32.4 months (95% CI 25.9-38.9). None of SNPs was individually associated with PFS. Conversely, a genetic interaction profile for PFS (http://sourceforge.net/projects/mdr/).

Conclusions. Genetic interaction between VEgFR-2 rs11133360 and IL-8 rs4073 polymorphisms could predict BV response in terms of PFS. With a longer follow-up correlations with OS will be investigated. Prospective study is planned.

Study supported by the no-profit foundation FARO

E11 PHASE III TRIAL OF FIRST-LINE TREATMENT WITH GEMCITABINE PLUS DOCETAXEL VS GEMCITABINE PLUS PACLITAXEL IN WOMEN WITH METASTATIC BREAST CANCER (MBC): A COMPARISON OF DIFFERENT SCHEDULES AND TREATMENT


1Oncology, Regina Elena Institute, Rome; 2IRCCS AOU San Martino, IST, Genoa; 3Oncology, S. Maria della Misericordia Hospital, Udine; 4Clinical and Molecular Oncology, University of Naples “Federico II”, Napoli; 5AOII Regina Margherita S. Anna, Torino; 6Medical Oncology, AO SG Moscati, Avellino; 7Casa di Curia Poliamulanza, UO Medical Oncology, Brescia; 8Medical Oncology, Treviglio and Caravaggio Hospital, Treviglio (BG); 9National Institute for Cancer Research, Genoa; 10Medical Department, Eli Lilly Italy, Sesto Fiorentino (FI); 11Eli Lilly UK, Erol Wood, Surrey, UK; 12Oncology, S. Cuore-Dom Calabria Hospital, Verona

Background. Weekly (W) administration of gemcitabine + docetaxel (G+D) or gemcitabine + paclitaxel (G+P) at low doses may be associated with greater efficacy and/or lower toxicity compared to the standard 3-weekly (3W) schedule.

Methods. Patients (360) with MBC, that relapsed after one adjuvant/neoadjuvant regimen containing anthracycline (unless contraindicated) and completed for at least 12 months, were to be randomized equally to: a) D 75 mg/m² on day1 + g 1000 mg/m² on days1/8 q3W; b) P 175 mg/m² on day1 + g 1250 mg/m² on days1/8 q3W; c) D 30 mg/m² + g 800 mg/m² on days1/8/15 qW; d) P 80 mg/m² + g 800 mg/m² on days1/8/15 qW. Primary endpoint: time-to-progression (TTP). Secondary endpoints: overall survival (OS), overall response rate (ORR), overall toxicity (T).

Results. Slow accrual rate led to a futility analysis (to evaluate the chance of observing a significant result in favour of the alternative hypothesis), resulted in early study termination. 241 enrolled pts (median age 57.0 years, range 31-77) were randomized to: 3W G+D 60 (24.9%); 3W G+P 64 (26.6%); W G+D 58 (24.1%); W G+P 59 (24.5%), of which 18 (30.0%), 24 (37.5%),
E12 TRADITIONAL PROGNOSTIC FACTORS IN EARLY BREAST CANCER (EBC): DO THEY STILL HAVE A ROLE IN THE MOLECULAR ERA?

Rossi V., Sarotto I., Maggiorotto F., Tomasi Cont N., Ponzine R., Berchialla P., Aglietta M., Montemurro F.

1Division of Medical Oncology, 2Division of Surgical Pathology, 3Division of Gynecological Oncology, Institute for Cancer Research and Treatment (IRCC), Candiolo; 4Department of Public Health and Microbiology, University of Turin

Purpose. Molecular profiling identifies breast cancer subtypes with specific biological features, prognosis and response to treatment. This classification is increasingly being used to characterize EBC prognosis and adjuvant treatment indication. Therefore, we investigated the association of traditional prognostic factors like age, diameter, grading and lymph-nodal involvement with outcome in each subtype.

Methods. A total of 1024 women undergoing surgery for EBC from Jan 1995 to Sept 2009 were selected for this analysis. Breast cancer subtypes were defined as: Luminal A (ER ≥10%, PgR ≥10%, HER2-, Ki67 ≤14%); HER2 enriched (HER2+, ER and PgR <10%); HER2 luminal (HER2+, ER ≥10%, PgR ≥10%); HER2 enriched (HER2+, ER and PgR <10%); Triple Negative [TN] (HER2-, ER and PgR <10%). Cox proportional hazards models were fitted to study the association of variables of interest with event-free survival (EFS).

Results. A total of 282 (27%) women had Luminal A, 467 (46%) Luminal B, 108 (10%) HER2 luminal, 74 (7%) HER2 enriched and 93 (9%) TN tumours. At median follow-up of 58 months (4-137 months), 37 (13%) Luminal A, 80 (17%) Luminal B, 36 (33%) HER2 luminal, 33 (45%) HER2 enriched, 33 (36%) TN patients developed events. Cox proportional hazard multivariable analysis showed that tumour diameter >20 mm (HR = 3.75, CI 1.50-9.36, p = 0.003) in Luminal A patients and ≥4 positive axillary nodes in Luminal B (HR = 4.09, CI 2.27-7.36, p <0.0001), HER2 luminal/enriched (HR = 3.64, CI 1.85-7.02, p <0.0001) and TN (HR = 3.68, CI 1.61-8.43, p = 0.002) patients were independently associated with EFS. Interestingly, a time-dependent effect of adjuvant chemotherapy was seen in Luminal A tumours, with an initial reduction in the EFS up to 75 months after surgery (HR = 0.26, CI 0.08-0.86, p = 0.03), followed by a potentially detrimental effect beyond that time (p <0.13).

Conclusions. Traditional risk factors retain independent value in subtype-specific fashion in EBC. The integration of molecular classification with traditional factors allows a better definition of risk categories in patients with EBC.
Saggia C.1, D’Agostino F.1, Rossi V.1, Borra G.1, Capitanio C.1, Gaudino E.1, Genestroni S.1, Rigon E.1, Rolla R.2, Bellomo G.2, Alabiso O.1

1Oncologia, AOU “Maggiore della Carità”, Novara; 2Dipartimento di Scienze Mediche, Università del Piemonte Orientale “Amedeo Avogadro”

Background. Tamoxifen, a selective estrogen receptor modulator (SERM), is standard therapy for estrogen-receptor-positive breast cancers (ER+). It is converted into its active metabolites by the cytochromes P450 enzymes, especially CYP2D6. Several reports suggest that polymorphisms of this cytochrome may affect the response to the drug. Primary objective of this study is to investigate the association between genetic variants of CYP2D6 and side effects of tamoxifen in adjuvant setting of breast cancer treatment, in order to clarify the future utility of pharmacogenetic predictive test.

Materials and methods. We collected blood samples from 61 patients receiving tamoxifen as adjuvant therapy for breast cancer ER+. Genotyping for polymorphisms was performed using a new technology based on DNA microarray (BioFilmChip®).

Results. Forty-four out of 61 analyzed patients (72.1%) were classified as extensive metabolizers (EM), 5 (8.2%) as intermediate metabolizers (IM), 8 (14.8%) as ultrarapid metabolizers and 3 (4.9%) as poor metabolizers (PM). This distribution of phenotypes in the analyzed sample was comparable with data reported in literature for unselected populations. With regard to side effects, 34.4% of patients reported hot flashes, 39.3% cramps/muscle pain; 13.1% of patients reported mood disorders, 11.5% headache, 13.1% endometrial thickening, and 11.5% increased weight. The UM phenotypes, compared to EM/IM/PM, more frequently reported weight gain (Fisher’s exact test p = 0.007; difference 38.7%, 95% CI 11.3-67.8%) and two or more adverse reactions (Fisher’s exact test, p = 0.030; difference 41.2%, 95% CI 6-61%).

For all other side effects, with the exception of depression and endometrial thickness, only a trend even not statistically significant difference was observed, probably due to the small UM sample.

Conclusions. Results of our preliminary study show that women with UM phenotype treated with tamoxifen for breast cancer are probably more exposed to side effects. However, further data and long term follow-up are needed to confirm the role of a pharmacogenetic test in the clinical management of these patients.

E15 ACUPUNCTURE AS AN APPROACH TO CONTROL SYMPTOMS OF CLIMATERIC SYNDROME IN PATIENTS WITH BREAST CANCER

Benedetti B.1, Razzini G.1, Artioli F.1, Pezzuolo D.2, Prati G.2, Giovannardi F.2, Scarabelli L.2, Scaltriti L.2

1Division of Medical Oncology, Ramazzini Hospital, Carpi, AUSL Modena; 2Division of Medical Oncology H. Civile di Guastalla, AUSL Reggio Emilia

Background. Hormonal replacement therapy is the standard treatment to manage menopausal symptoms but patients affected by breast cancer cannot receive this therapy.

Breast cancer patients that received adjuvant hormonal therapy or chemotherapy complain of menopausal symptoms in 60-70% of cases; hot flashes and sweating in the night represent the 40% of climacteric symptoms related to adjuvant hormonal therapy or chemotherapy. At present the standard treatment to control climacteric symptoms in patients with breast cancer is self care (psychological help, workout etc.).

Aim. To evaluate the efficacy of acupuncture in patients with breast cancer to control menopausal syndrome and improve quality of life (QoL).

Methods. Climacteric syndrome was evaluated through Greene’s climacteric scale (score >15), hot flashes >15 per day, anxiety and depression syndrome ≥G1. Patients received at least 7 weekly treatments (total 10 sessions). Quality of Life (QoL) was evaluated through Men QoL questionnaire. Climacteric symptoms were evaluated at baseline, after 4 treatments, at the end of treatment and after 6 and 12 months from the end of treatment.

Results. Twenty-five consecutive patients with breast cancer (30% previously enrolled in SoftText trial) were enrolled in the study. Median age was 48 years and all patients received hormonal therapy (tamoxifen and aromatase inhibitors) with or without LHRH analogue. We observed 60% reduction of hot flashes and 50% reduction of menopause-related symptoms at the end of acupuncture treatment.

The effects obtained on vasomotor symptoms are still maintained at 6 months but not at 1 year follow-up. Quality of life was improved with a reduction of anxiety and depression symptoms (>60%).

Conclusions. Acupuncture represents a valid approach to control symptoms of climacteric syndrome in patients with breast cancer. According to Osservatorio Medicina non convenzionali (OMNC) of Emilia Romagna Region we designed a multicentric randomized controlled trial exploring the effectiveness of acupuncture plus self care versus self care alone for breast cancer patients. This study is ongoing.

E16 PATTERNS OF DISEASE RECURRENCE AFTER ADJUVANT TRASTUZUMAB IN HER2-POSITIVE EARLY BREAST CANCER PATIENTS: RESULTS OF VETRA STUDY

Amoroso D.1, Camerini A.1, Gori S.2, Di Marsico R.3, Micheletti A.4, Barni S.5, Allegrini G.6, Baldini E.7, Contu A.8, Puccetti C.1, Valsuani C.1, Siclari O.1, Donati S.1, Tartarelli G.1, Petrella M.C.1, Del Mastro L.9

1Oncologia Medica, Istituto Toscana Tumori, Ospedale Versilia, Lido di Camaiore; 2S.C. Oncologia Medica, Ospedale S. Maria della Misericordia, Perugia; 3Oncologia Medica, Ospedale Civile, Livorno; 4Oncologia Medica, Ospedale S. Chiara, Pisa; 5Oncologia Medica, Ospedale Caravaggio-Treviglio, Treviglio; 6Oncologia Medica, Ospedale Lotti, Pontedera; 7Oncologia Medica, Ospedale Caravaggio-Treviglio, Treviglio; 8Oncologia Medica, Ospedale Lotti, Pontedera; 9Oncologia Medica, Ospedale Campo di Marte, Luca; 1Oncologia Medica, ASLI, Sassari; 2SS Sviluppo Terapie Innovative, IST, Genova

Background. The combination of chemotherapy (CT) plus trastuzumab (T) as adjuvant treatment of early breast cancer (EBC) with HER2 overexpression significantly reduced the risk of disease relapse. Aim of this observational study was to identify disease recurrence patterns and survival data in a population of HER2-positive EBC across Italy.

Methods. 242 consecutive patients with HER2+ EBC receiving adjuvant T from 2006 to 2011 were retrospectively evaluated in 9 different Italian oncology institutions. All patients underwent surgery and received adjuvant T with no restriction of CT.
Results. Population included 54.1% ER+ pts, 36.8% PgR+ pts, 77.3% Ki67>10% pts, 53.3% node-positive pts with a wide majority of poorly differentiated ductal invasive carcinomas. Median follow-up was 56 (range 12-72) months. Overall relapse rate was 10.3% (25/254) with 19/25 (76%) distant and 6/25 (24%) local (i.e., regional and contralateral) recurrences. Distant recurrence sites included liver 36%, lung 16%, brain 16%, bone 24% and lymph nodes 12%. Median recurrence time was 14 (range 1-42) months after T completion. Relapsed patients showed significantly lower PgR mean expression level (p = 0.03) and a similar trend for ER expression levels (p = 0.08). No difference was found as to age, node status, grading or Ki67. All relapsed pts received at least two lines of CT plus T with a median TTP of 11 (range 6-32) months for first-line and a median OS of 19 (range 15-56) months.

Conclusions. The widespread use of T in the adjuvant treatment of HER2+ EBC lowered the relapse rate. Recurrences are mainly visceral and presented early during follow-up.

E17 POLYCOMB GENE EXPRESSION AND SINGLE-NUCLEOTIDE-POLYMORPHISMS (SNPs) IN TRIPLE NEGATIVE BREAST CANCER (TNBC) PATIENTS

Fontana A.1,2, Crea F.3, Ferrari I.1,2, Paolicchi E.3, Bonu E.1,2, De Gregorio V.1,2, Stasi L.1,2, Bartolini I.1,2, Laurà F.1,2, Salvadori B.1,2, Landucci E.1,2, Michelotti A.1,2, Allegrini G.4, Lucchesi S.5, Arrighi G.6, Ghilli M.6, Roncella M.6, Di Paolo A.3, Falcone A.1,2, Danesi R.3

1UO Oncologia Medica II Universitaria, 2Polo Oncologico, Ospedale S. Chiara, AOUP, Pisa and Istituto Toscano Tumori; 4UO Oncologia Medica I, 5UO Oncologia Medica, Az-USL5 di Pisa; 6UO Senologia, AOUP, Pisa

Background. Polycomb group genes (PcGs) are epigenetic modifiers, essential for cancer stem cell self-renewal. In experimental breast cancer (BC) models, PcG members EZH2 and Mel18 act as oncogene and tumour-suppressor-gene, respectively. Previous studies suggested that rs3757441-CC genotype is associated with higher EZH2 expression, while rs708692-GG genotype predicts lower Mel18 expression, both correlated with worse prognosis in cancer patients. Considering the poor outcome of TNBC, the present study aimed at investigating Mel18 and EZH2 gene expression and SNP distribution in TNBC vs other BC subtypes.

Methods. We conducted a gene expression analysis through Oncomine database (oncomine.com) to test Mel18 and EZH2 expression in BC molecular sub-types. Moreover, we compared EZH2 rs3757441-T>C and Mel18 rs708692-G>A genotype distribution among TNBC and other BC subtype, through real-time PCR technique on DNA extracted from blood samples.

Results. Oncomine analysis showed that Mel18 was significantly down-regulated (p = 0.004, fold-change -2.238; 140 patients analyzed, 10 TNBCs) and EZH2 was significantly over-expressed in TNBCs vs other histologies (p = 3.4E-12, fold-change 2.144; 299 patients analyzed, 46 TNBCs). Furthermore, we genotyped 121 samples from BC patients treated at our institution. Main characteristics were: median age 60 years (range 31-81), stage I/II/III/IV respectively in 22/36/18/45 pts, TNBC/HER2+/hormone receptor + and HER2- in 31/26/64 patients. Genotyping analyses were: EZH2 TT/TC/CC variants were 51.6%/45.2%/3.2% among TNBCs and 60/35.6/4.4% among controls; Mel18 AA/AG/GG variants were observed in 41.9%/48.8%/9.7% among TNBCs and in 35.6%/50/14.4% controls. No significant difference in genotype frequencies was observed between case and control groups.

Conclusions. We found Mel18 down-regulation EZH2 over-expression in TNBCs vs other subtypes. Our preliminary analysis doesn't show a significant difference in Mel18 and EZH2 SNPs distribution in BC subtypes. Further studies are needed to better clarify the role of PcGs in TNBC pathogenesis.

We thank Dr. William L. Farrar for providing access to Oncomine data.

E18 PATTERN OF DISTANT RECURRENCE ACCORDING TO THE MOLECULAR SUBTYPES IN WOMEN WITH EARLY BREAST CANCER

Schiprone A.1, Carandina L.1, Indelli M.1, Querzoli P.2, Santini A.1, Da Ros L.1, Nisi C.1, Rocchi A.1, Pedriali M.2, Frassoldati A.1

1Oncology Unit, Azienda Ospedaliero-Universitaria “S. Anna”, Ferrara; 2Department of Experimental and Diagnostic Medicine, Institute of Pathology, Ferrara University

Background. No evidence exists that in early breast cancer patients an intensive follow-up is more beneficial than a minimal one. However, the recent insight into the breast cancer heterogeneity and the availability of new treatments challenge this assumption and induce to reconsider the usual follow-up modalities.

The aim of this study is to investigate the association between molecular subtypes and patterns of distant recurrence in breast cancer.

Materials and methods. We performed a retrospective observational mono-institutional study collecting data regarding 500 early breast cancer patients surgically treated between 1.1.2006 and 31.12.2007. The subtypes were defined as Luminal A (ER/PR >1%, MIB-1 <14%, HER2 negative), Luminal B (ER/PR >1%, MIB-1 >14%, HER2 negative), luminal B-HER2 (ER/PR >1%, MIB-1 >14%, HER2 positive), HER2 (ER/PR <1%, HER2 positive) and Triple Negative (ER/PR <1%, HER2 negative).

Results. Median follow-up time was 58.1 months (range 6.9-72.9). The distant-disease free survival (Figure) and the inci-
dence of first distant recurrence site was significantly different among the subtypes: brain metastasis was more frequent in TN subtype; bone metastasis was more frequent in Luminal subtypes, liver metastasis was more frequent in HER positive subtypes. In Luminal A subtype the earlier sites of metastases were lung and bone (median D-DFS = 31 months), in Luminal B was bone (32 months), in Luminal B-HER2 and HER2 subtypes was liver (18 months for both), in TN subtypes lung (median D-DFS = 18 months). In the multivariate analysis T, ER status, menopausal status and TNM stage were confirmed as independent prognostic factors in terms of D-DFS, and TNM stage only in terms of OS.

Conclusions. Organ-specific metastases may depend on molecular subtype of breast cancer. On this basis, we hypothesize that each breast cancer subtype should undergo a different follow-up program and that this strategy will improve the detection of relapses in a preclinical phase, hopefully amenable of more effective treatments.

E19 ENDOMETRIAL EFFECTS OF TAMOXIFEN AND EXEMESTANE IN EARLY BREAST CANCER: FINAL RESULTS OF A RANDOMIZED PHASE III TRIAL

Principe E., Garrone O., Monteverde M., Occelli M., Bertelli G., Favilla B., Catz Eddie T., Vanella P., Miraglio E., Merlano M.C.

Medical Oncology, Gynecology, ASO S. Croce e Carle Cuneo, South West Wales Cancer Institute Swansea

Background. Tamoxifen (T) has been for a long time the treatment of choice in hormonal receptor positive early breast cancer patients (EBCP). It is known that T has partial estrogen agonistic activity on uterus determining an increase in gynecological symptoms. Long-term T treatment can lead to an increased incidence of endometrial cancer. The availability of aromatase inhibitors (AI) has modified the prescription options in postmenopausal breast cancer patients while remaining the standard of care in premenopausal setting. AI do not mediate their effects through the estrogen receptor potentially conferring tolerability advantages to women particularly in relation to their effects on the endometrium. So far some studies including all the available AI have been published which confirmed the lack of estrogen effects of AI on endometrium compared to T.

In 2001 we started a phase III study comparing T and exemestane (E) in EBCP in order to evaluate the differences in the endometrial changes recorded by transvaginal ultrasound (TVUS).

Materials and methods. Postmenopausal hormonal receptor positive EBCP were randomly assigned to receive T or E. A baseline TVUS was performed and repeated after 6 and 12 months. The primary endpoint, endometrial thickness (ET) was evaluated with T-test.

Results. From 2001 to 2008, 220 patients were enrolled in our department. Patients characteristics were well balanced in each arm. Definitive results are summarized in the Table.

Conclusions. Our results confirmed the data obtained in similar studies. In particular E was associated with significantly less endometrial thickening than T during the projected period of therapy in postmenopausal hormone receptor positive EBCP.

E20 TRASTUZUMAB-INDUCED EARLY CARDIAC DYSFUNCTION ASSESSED BY SPECKLE TRACKING ECHOCARDIOGRAPHY: CORRELATION WITH CHRONIC INFLAMMATION AND OXIDATIVE STRESS MARKERS

Dessì M.1, Mateddu C.1, Orgiano L.1, Piras A.2, Cadeddu C.2, Antoni G.1, Serpe R.1, Mercuro G.2, Mantovani G.3

I Service of Medical Oncology, 2 Cardiovascular Diseases, Department of Internal Medical Sciences, University of Cagliari

Background. Trastuzumab (TZM) was shown to be very effective in patients with breast cancer overexpressing HER-2 in the neoadjuvant, adjuvant and metastatic setting. It has a mild cardiac toxicity which may increase when administered in combination with anthracyclines. The speckle tracking echocardiography (STE), able to assess cardiac mechanics [cardiac torsion movements and the global, circumferential, radial and longitudinal strain (S) and strain rate (SR)], and identify at an early stage left ventricular dysfunction, was used for cardiac monitoring. The present study aimed to assess the STE changes induced by TZM and correlate them with changes of chronic inflammation and oxidative stress markers.

Methods. A phase IV, prospective, non-randomized study was designed: planned sample size 60 patients. Inclusion criteria: 18-70 yrs women with HER-2+ve breast cancer receiving TZM, LVEF ≥55%; ECOG PS score 0-2, no history of cardiac disease. The STE parameters (global, circumferential, radial and longitudinal S and SR) and chronic inflammation (IL-6 and TNF-α)/oxidative stress markers were assessed at baseline, after each three-weekly TZM administration, up to the 8th TZM dose.

Results. In September 2011, 30 patients (mean ± SD age 53 ± 10 yrs) were enrolled and completed the study. A significant reduction of the peak of radial and circumferential SR (p <0.01 and p<0.005) as first sign of systolic dysfunction was observed at the 3rd TZM dose. A significant reduction of the peak of longitudinal SR (p<0.01) was observed at the 4th TZM dose. As for laboratory parameters, TNF-α increased significantly at the 2nd and 3rd TZM dose, whilst the remaining laboratory parameters did not change significantly.

Conclusions. These preliminary results suggest that TZM treatment induces an early preclinical cardiac systolic dysfunction which correlates with an increase of TNF-α. The study is in progress to reach the planned sample size, monitor patients for an adequate follow-up time and eventually select patients candidates for an effective cardioprotective treatment.

This study was funded by AIRC, project number 8679.
E21 PRIMARY SYSTEMATIC THERAPY (PST) WITH DOCETAXEL (D) FOLLOWED BY HIGH-DOSE EPIRUBICIN IN COMBINATION WITH CYCLOPHOSPHAMIDE (EC) PLUS CONCURRENT TRASTUZUMAB (T) FOR STAGE II-III HER-2 POSITIVE BREAST CANCER PATIENTS

Vici P.1, Pizzuti L.1, Mottolese M.2, Sergi D.1, Di Benedetto A.2, Falvo E.3, Botti C.3, Perracchio L.2, Pescarmona E.3, Anzà M.3, Perri P.3, Carpino A.4, Della Giulia M.1, Di Lauro L.1

1Division of Medical Oncology B, 2Pathology Department, 3A Surgery Division, 4Cardiology Division, 5Molecular Medicine Department, Regina Elena National Cancer Institute, Roma

Background. PST with taxanes, anthracycline-containing regimens and T showed a high percentage of pathologic complete response (pCR); T administered concurrently with chemotherapy is more effective, but the combination with taxanes may be at risk of cardiotoxicity. The present study evaluates efficacy and toxicity of T administered concurrently with a sequential regimen of D followed by EC in neoadjuvant setting.

Materials and methods. This phase II single stage trial is enrolling pts with cT2-T4, N0-2, M0, Her-2 positive (IHC 3+ or 2+ amplified) breast cancer. A core biopsy is required prior to treatment start to evaluate hormonal receptors, Ki67, topoisomerase II, Her-2, with re-evaluation of these parameters, whenever possible, at definitive surgery. Blood samples are collected at baseline for evaluation of 9 genetic polymorphisms related to higher risk of developing cardiac toxicity. We are quantitatively evaluating gene copy number by multiple ligand probe amplification (MLPA), PTEN, p-Akt, p-MAPK, and PIK3CA mutations. Patients receive 4 cycles of D (100 mg/m²) plus T (loading dose 8 mg/kg followed by 6 mg/kg), followed by 4 cycles of EC (120/600 mg/m²) plus T, every 3 weeks. Definite surgery is planned at the end of PST, and standard radiotherapy and hormonal adjuvant treatment in case of positive hormonal receptors are given; adjuvant T is given for 6 months. The primary objective of the trial is pCR (absence of invasive tumour cells in the breast and axilla); secondary objectives are cardiac safety, toxicity, disease-free survival. The planned sample size is 42 pts.

Results. To date, 29 pts have been enrolled; median age is 45 years, pre/postmenopausal 22/7, ER and/or PgR positive in 16 patients. We observed 20 pCR (74%, 95% CI 57.5-90.6). Grade 3-4 neutropenia was encountered in 75% of the pts, other toxicities were mild to moderate. No clinical cardiotoxicity was observed.

Conclusions. At preliminary analysis, PST with sequential administration of D followed by EC, given concurrently with T, appears to be very active and safe in stage II-III breast cancer patients.

E22 OVARIAN SUPPRESSION REDUCES THE RISK OF RELAPSE BY IMPROVING AMENORRHEA OCCURRENCE IN PREMENOPAUSAL WOMEN WITH BREAST CANCER

Baretta Z.1, Olopade O.2, Kocherginsky M.3, Ghiotto C.1

1Department of Oncology, Istituto Oncologico Veneto (IOV-IRCCS), Padova: 2Department of Medicine, Center for Clinical Cancer Genetics & Global Health, 3Department of Health Studies, University of Chicago, Chicago, USA

Purpose. To evaluate the impact of treatment-induced amenorrhea (TIA) on breast cancer (BC) recurrence and its frequency in premenopausal women.

Patients and methods. Of 5,791 consecutive BC patients treated at the Istituto Oncologico Veneto (1995-2008), 819 premenopausal women aged ≤50 years at diagnosis who received chemotherapy (CT) and/or luteinizing hormone-releasing hormone agonists (LHRHa) were considered. TIA was defined as the cessation of menses for ≥3 months from the beginning of treatment. TIA status was retrieved from data recorded during the 3-month visits of the first 2 years of follow-up and it was evaluated at 3, 6, 12, 24 months. Due to the time-dependent nature of TIA, statistical analysis was restricted to patients who remained disease-free for the first 24 months.

Results. TIA frequency increased with age (Table 1). Fourteen TIA patterns were identified. Comparing more frequent TIA patterns (2-7, Table 2) with TIA absence (pattern 1), patterns 2 and 6 reduced the risk of relapse by 56% and 54%, respectively (p <0.0001 and p = 0.004), but only pattern 2 increased independently disease-free survival in multivariate analysis (HR = 0.40, p = 0.019). Looking at the age groups, pattern 2 was induced by CT only in 16% and 17% of very young (≤35 yrs) and young (36-40 yrs) patients, respectively, compared with 57% of older patients (41-50 yrs), while 43% of older patients were treated with LHRHa compared with 74% and 73% of very young and young women, respectively. Likewise, 63% and 41% of very young and young patients continued menstruating after CT compared with 4% of older counterpart. Taking together pattern 2 presence and treatment with LHRHa, the risk of relapse was reduced by 45% (p = 0.012) in amenorrheic non-LHRHa-treated patients and by 66% (p <0.0001) in amenorrheic LHRHa-treated patients compared with those non amenorrheic.

Conclusions. The use of LHRHa to increase TIA achievement is warranted in premenopausal patients, mainly in those aged ≤40 years, who rarely experience amenorrhoea after CT.

Table 1 - Achievement of treatment-induced amenorrhea (TIA) in three age groups

<table>
<thead>
<tr>
<th>Time points</th>
<th>≤35 yrs</th>
<th>36-40 yrs</th>
<th>41-50 yrs</th>
<th>Total</th>
<th>Age groups comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months</td>
<td>57 (53%)</td>
<td>106 (60%)</td>
<td>269 (66%)</td>
<td>432 (62%)</td>
<td>0.041</td>
</tr>
<tr>
<td>6 months</td>
<td>63 (59%)</td>
<td>140 (79%)</td>
<td>383 (94%)</td>
<td>586 (84%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>12 months</td>
<td>62 (58%)</td>
<td>137 (77%)</td>
<td>394 (96%)</td>
<td>593 (85%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>24 months</td>
<td>59 (55%)</td>
<td>128 (72%)</td>
<td>393 (96%)</td>
<td>580 (84%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Table 2 - More frequent treatment-induced amenorrhea (TIA) patterns

<table>
<thead>
<tr>
<th>Pattern</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
<th>24 months</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>no</td>
<td>72</td>
</tr>
<tr>
<td>2</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>401</td>
</tr>
<tr>
<td>3</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>14</td>
</tr>
<tr>
<td>4</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>11</td>
</tr>
<tr>
<td>5</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>144</td>
</tr>
<tr>
<td>7</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>yes</td>
<td>27</td>
</tr>
</tbody>
</table>
Background. The aging of the whole population raises the need of an increased attention in the cancer treatment of elderly pts. Thus the senescence influences the capability of tolerating CHT regimens leading to a great number of complications and a possible reduced activity. We recently reported the data of the phase I-II part of the VICTOR study, evaluating the all-oral metronomic CHT regimen with VRL 40 mg fixed dose thrice a week and CAP 500 mg thrice a day continuously as first- or second-line CHT in advanced BC pts (Cazzaniga ME, SABCS 2010). Each cycle was arbitrarily defined to be composed by 3 consecutive weeks. Disease evaluation was planned every 3 cycles. Here we report the results of efficacy and toxicity of this regimen in a group of pts aged ≥70 years.

Patients and methods. From October 2009 to August 2011 we enrolled 18 elderly (≥70 yrs) pts in the phase II part of the VICTOR study. Median age was 76 (70-84), ECOG PS was 0-1 in all patients. Hormone receptor status was ER+/PgR+ in 13 pts (68%), HER2- in 12/18 (66.6%); 6 HER2+ pts couldn’t receive anti-HER2 agents due to underlying cardiac disease. Nine pts (50%) had already received ≥1 CHT regimen for their metastatic disease. Most pts (79%) presented 2 or more metastatic sites at inclusion.

Results. A total of 227 cycles has been delivered (median 9, range 3-24+), observing 3 G3 non-haematological (1.3%, 2 paresthesia, 1 diarrhoea) and 4 G3 neutropenic events (1.7%). No G4 events have been reported. We obtained CR in 1 pt and PR in 5 pts, for an ORR of 30%; SD was described in further 8 pts (44.4%), in all cases of a duration less than 24 weeks.

Conclusions. Our data in the elderly group of advanced BC pts treated with the metronomic combination of VRL and CAP confirm a very good tolerability and a promising activity. The multicenter phase II part of the VICTOR study is still ongoing and will help to assess the role of this combination in the metastatic setting.

E25 RETROSPECTIVE ANALYSIS OF CLINICAL OUTCOME IN EARLY BREAST CANCER PATIENTS WITH SMALL (<1 CM) TUMOUR

Collovà E.1, Porcu L.2, Massari F.3, Furlanetto J.3, Gori S.4, Alabiso I.5, Petrelli F.6, Barni S.6, Saggia C.7, Andreis D.10, Gaudino E.7, Lipari H.8, Santini D.9, Ferzi A.1, Generali D.10

1Oncologia Medica, Ospedale Civile di Legnano; 2Laboratorio di Metodologia per la Ricerca Biomedica, Istituto di Ricerche Farmacologiche Mario Negri, Milano; 3UOC Oncologia Medica, Azienda Ospedaliera Universitaria, Verona; 4Oncologia Medica, Ospedale di Perugia; 5Oncologia Medica, Ospedale Civile, Ivrea; 6Unità Operativa Oncologia Medica, AO Treviglio; 7SC Oncologica, AO Maggiore della Carità, Novara; 8Oncologia Medica, AO Cannizzaro, Catania; 9Oncologia Medica, Università Campus Biomedico, Roma; 10UO Multidisciplinare di Patologia Mammaria, Laboratorio di Oncologia Molecolare Senologica, AO Istituti Ospitalieri di Cremona

Background. Long-term outcome and the role of adjuvant systemic therapy in breast cancer pts with small tumour (<1 cm) remain unclear. Recently a retrospective analysis demonstrated that HER-2 status is an independent, poor prognostic marker in pts with these kind of tumours. The study aimed to analyze the clinical outcome of pts with diagnosis of <1cm early breast cancer, and to identify a subgroup of pts who might benefit from adjuvant therapy.

Methods. All consecutive pts with small tumour (<1 cm), irrespective to nodal and HER-2 status, diagnosed at 9 Italian Medical Oncology Centers between January 2005 and December 2010. Data regarding tumour and clinical characteristics were obtained from pathology reports archived in tumour registry data files and from clinical patients charts.
**Results.** 654 pts met the inclusion criteria for this study. The median age was 60 years (range 40.1-77.8 yrs). Tumour extension and nodal involvement of primary tumour were: T1a 22.6% and T1b 77.4%; N0 90.4%; N1 8%; N2 1%; N3 0.7%. Immunohistochemical characteristic included: ER and/or PR positive 88.3%; ER and/or PR negative 17.9%; HER-2 positive 29.1%. Overall, 19.3% and 84.6% of pts received adjuvant chemotherapy (CT) and endocrine therapy, respectively. Only 6.4% of pts received adjuvant trastuzumab. The rate of adjuvant CT administration varied among the groups: 7.1% in HR+/HER2-; 65.2% in HR+/HER2+; 73.9% in HR-/HER2- and 68.2% in HR-/HER2+. After a median follow-up of 2.4 yrs, we observed 11 relapses of disease and 7 tumour-related deaths.

**Conclusions.** Although the study is retrospective and the follow-up is too short to have statistical differences in terms of outcome between the breast cancer biological subgroups, this analysis showed that small breast cancers have an excellent prognosis and an individualized therapy based on cancer subgroups characteristics should be considered in the decision-making adequate treatment.

**E26 Ki-67 EXPRESSION CAN BE USED TO CHOOSE THE BETTER ADJUVANT CHEMOTHERAPY IN TRIPLE NEGATIVE BREAST CANCER**

Pistelli M.¹, Pagliacci A.¹, Battelli N.¹, Santinelli A.², Berardi R.¹, Cascini S.¹

¹Clinica di Oncologia Medica, ²Anatomia Patologica, AO Ospedali Riuniti, Università Politecnica delle Marche, Ancona

**Background.** Despite consensus regarding increased chemosensitivity in triple negative breast cancer (TNBC), no strong clinical evidence exists to guide the optimal choice of current cytotoxics. Therefore patients may receive adjuvant therapy with anthracyclines containing regimen, taxanes or cyclofosfamide. At present there is no preferred standard adjuvant chemotherapy for TNBC and treatment should be selected as it is for other breast cancer subtypes. The purpose of this study was to identify the prognostic value of Ki-67 among TNBC patients treated with adjuvant chemotherapy.

**Methods.** Patients diagnosed with invasive TNBC were included in the analysis. Patients with stage IV of disease were excluded. We divided our patients into two groups, A and B, on the basis of the level of Ki-67 (group A ≤60%; group B >60%, respectively).

**Results.** 149 patients were included. Median age was 54 years (range 26-83 years). During follow-up, 12% distant metastases and 8.8% local recurrences or second tumours were reported. In the group B, patients were significantly younger (p = 0.03) and (thus) in pre-menopausal status (p <0.01); tumours had a higher incidence of poorly differentiated grading (G3) (p = 0.04), necrosis (p = 0.02) and lymphocytic infiltrate (p = 0.03) while the androgen receptors expression was significantly lower (p <0.01) than in the group A. The 2 groups of patients resulted comparable for all others known prognostic factors (tumour size, lymph node status, type of surgery and adjuvant chemotherapy, intraductal carcinoma or lympho-vascular invasion). The multivariate analysis revealed a better disease-free survival (DFS) in group B when patients received adjuvant anthracyclines containing chemotherapy instead of CMF regimen (p = 0.02; Figure B). In group A, no statistically correlation resulted for DFS when the type of adjuvant chemotherapy regimen was considered (Figure A).

**Conclusions.** TNBC with Ki-67 >60% was associated with a more aggressive clinical and histological features. Ki-67 has prognostic value and it may represent a feasible marker in the clinical practice in order to select TNBC which may obtain a better prognosis administering a more aggressive adjuvant chemotherapy regimen.

**E27 BREAST CANCER RISK: VALUE OF PRECISE FOLLOW-UP REGARDING A SPECIFIC TARGET HIGH RISK POPULATION IDENTIFIED BY GAIL MODEL**

Magnante A.L.¹, Rondinelli R.², Ferrone L.³, Del Bianco S.², Redler A.³

¹Dipartimento di Scienze Radiologiche, Oncologiche e Anatomopatologiche, Radioterapia, Policlinico Umberto I, Università degli Studi di Roma “Sapienza”; ²Unità Funzionale di Oncologia, Casa di Cur A Madonna della Fiducia, Roma; ³Dipartimento di Scienze Chirurgiche, Policlinico Umberto I, Università degli Studi di Roma “Sapienza”

**Background.** The Gail model (GM) is a risk assessment model used in individual estimation of the absolute risk of invasive breast cancer. Although the GM has been validated in several studies, its applicability in the clinical experience remains uncertain. This study provides information for the real value of a precise follow-up regarding a specific target high risk population identified by Gail Model.

**Patients and methods.** The target population under investigation has been identified based on the family history (mother, sister, daughter with breast cancer), age, menarche, age of first birth, biopsy history (atypical hyperplasia), race/ethnicity. For every subject under investigation a detailed genealogical tree has been built. The calculation of the risk is carried out through a dedicated software. High risk women were defined based on the breast cancer risk score over 1.67 (G3). All the women with a breast cancer risk under the cut-off (1.67) received a physical examination every six months, mammography every 12-18 months ± echography. High risk women received: physical examination every six months, echography every six months, mammography every 12 months ± MRI.

**Results.** 550 of 5319 women examined had a lifetime breast cancer risk greater of 1.67. 445 out of 550 completed the recommended precise follow-up. In all 71 breast cancers have been diagnosed in the high risk population so far. Breast cancer histol-
E28 ABBERRANT PROMOTER METHYLATION OF THE KEAP1 GENE IN BREAST CANCER

Barbano R.1, Pasculi B.1, Muscarella L.A.1, la Torre A.1, Trombetta D.1, Murgo R.2, Valori V.M.3, Maiello E.3, Fazio V.M.1, Parrella P.1

1Laboratory of Oncology, 2Breast Unit, 3Department of Oncology, “IRCCS Casa Sollievo della Sofferenza”, San Giovanni Rotondo, FG

Background. The Nrf2/Keap1 pathway is a master regulator of several redox-sensitive genes implicated in resistance of tumour cells against chemotherapeutic drugs. Recent data suggest that epigenetic mechanisms may play a pivotal role in the regulation of KEAP1 expression.

Materials and methods. We determined KEAP1 promoter methylation status in 50 breast cancers (BC), and 6 normal breast tissues (NBT) obtained from reductive mammoplasty. Normal breast tissue adjacent to tumour (NBAT) was available for 45 of the 50 BC cases. In ten cases paired atypical ductal hyperplasia (ADH) and/or ductal carcinoma in situ (DCIS) lesions were available along with NBT and tumour tissues. Promoter methylation analysis was performed using a quantitative methylation specific PCR assay in real time (QMSP).

Results. Methylation levels were significantly higher in BC (median 2.3, IQR 0-17.05) as compared with NBT (median 0, IQR 0-0) (p = 0.0001, Mann Whitney Test). Overall methylation at the KEAP1 promoter region was detected in 38 out of the 50 BC (76%). Similar levels of methylation were detected in normal breast tissues adjacent to tumour (median 5.27, IQR 0-17.05), ADH (median 3.85, IQR 1.57-38.46) and DCIS (median 2.23, IQR 1.27-7.66). Significant differences were observed in normal breast tissues adjacent to tumour (median 5.27, IQR 0-17.05), ADH (median 3.85, IQR 1.57-38.46) and DCIS (median 2.23, IQR 1.27-7.66). Significant differences were observed in normal breast tissues adjacent to tumour (median 5.27, IQR 0-17.05), ADH (median 3.85, IQR 1.57-38.46) and DCIS (median 2.23, IQR 1.27-7.66).

Conclusions. Our results suggest that deregulation of the Nrf2/Keap1 system could play a pivotal role in the carcinogenesis of breast cancer. Studies are in progress to determine whether KEAP1 abnormalities may contribute to disease progression prediction and response to therapy in these patients.

E29 HER-2 ASSESSMENT AND KI-67 LABELING INDEX IN A COHORT OF MALE BREAST CASES: THE INCARE (ICH NETWORK ON CANCER RESEARCH) EXPERIENCE

Masci G.1, Caruso M.2, Losurdo A.1, Salvini P.2, Caruso F.2, Carnaghi C.1, Di Tommaso L.1, Zuradelli M.1

1Laboratory of Oncology, 2Breast Unit

Background. Our experience shows the unequivocal utility of a precise follow-up regarding such kind of risk women (based on Gail Model evaluation) to incisively recognize a significant number of early breast cancer in this selected population.

Conclusions. Our experience shows the unequivocal utility of a precise follow-up regarding such kind of risk women (based on Gail Model evaluation) to incisively recognize a significant number of early breast cancer in this selected population.

E30 PRIMARY CHEMOTHERAPY WITH TAC REGIMEN IN LOCALLY ADVANCED BREAST CANCER (BC): EFFICACY AND TOXICITY IN A SINGLE INSTITUTION EXPERIENCE

Gueli R., Giardina G., Oriani A., Marcon I., Vallini I., Milani K., Pinotti G.

Medical Oncology Unit, Ospedale di Circolo e Fondazione Macchi, Varese

Background. Primary systemic therapy (PST) is used in advanced BC and achievement of pathologic complete response (pCR) is accepted as outcome predictor. TAC regimen has shown good results in adjuvant and metastatic setting, justifying its use as PST. Our aim was to evaluate clinical and pathologic response to neoadjuvant TAC and regimen feasibility.

Materials and methods. From 2004 to December 2011, 42 patients with stage T2-T3, N0-2, M0 invasive BC were treated with TAC regimen.
with TAC (docetaxel 75 mg/m², doxorubicin 50 mg/m², cyclophosphamide 500 mg/m², d1 q21), prophylactic G-CSF plus ciprofloxacin and ovariain function suppression in ER+ve pre-menopausal tumours.

All pts underwent a core-biopsy before PST with evaluation of histological type, grading, ER/PgR/Ki67 and HER2 status. Median age: 43 years. Premenopausal: 32 pts. Median tumour size: 36 mm (range 21-80 mm). Forty pts had infiltrating ductal carcinoma, 2 pts infiltrating lobular carcinoma; 27, 13 and 2 out of 42 pts were respectively G3, G2 and G1. Twenty-four pts were ER and PgR+ve and 16 pts ER and PgR-ve. HER2 was positive (IHC 3+ or FISH positive) in 9 patients. Median Ki67: 45% (4-90%). The number of cycles delivered was 6 in 36 pts, 5 in 1 pt and 4 in 5 pts.

Results. All patients are evaluable for clinical and pathologic response. Ten/42 pts (24%) achieved clinical CR, 30 out of 42 (71%) clinical PR, 2 out of 42 (5%) SD. Nine out of 42 pts (21%) achieved pCR (1 ER/PgR+ve, HER2-ve; 1 ER+ve/PgR-ve, HER2-2ve; 5 ER/PgR-ve, HER-2ve; 1 ER+ve/PgR+ve, HER2-2ve; 1 ER+ve/PgR+ve, HER-2+ve) and 2 out of 42 (5%) minimal residual disease (1 ER/PgR-ve, HER-2 neg; 1 ER/PgR+ve, HER2-2ve).

All patients had G2/3 neutropenia. No febrile neutropenia was observed and dose-intensity was maintained. There were no G3/4 anaemia or piastirinopenia but 2 extra haematological toxicity G3 (nausea and vomiting, 1 adverse reaction to docetaxel).

Conclusions. Our data confirm that TAC is a feasible, safe and highly effective regimen in neoadjuvant setting. Prophylactic G-CSF and ciprofloxacin prevented haematological toxicity complications.

E31 BRCA STATUS, MOLECULAR PROFILE AND CLINICAL VARIABLES IN PRIMARY BILATERAL BREAST CANCERS: A POPULATION-BASED CANCER REGISTRY STUDY

Musolino A.1, Bella M.A.1, Michiara M.1,2, Zanelli P.3, Naldi N.1, Bortesi B.1, Sgargi P.1,2, Camisa R.1, Neri T.M.3, Ardizzoni A.1

1Medical Oncology Unit, University Hospital of Parma, Parma; 2Cancer Registry of Parma Province, Parma; 3Medical Genetics Unit, University Hospital of Parma, Parma

Introduction. Incidence of primary bilateral breast cancer (BBC) is rare and does not exceed 5%. BRCA1/2 mutation carriers diagnosed with breast cancer have a strong life time risk of developing contralateral breast cancer.

Objectives. To address both the proportion of BBC associated with BRCA1/2 germline mutations and the contribution of germline mutations to the clinical features and outcome of these tumours.

Materials and methods. We identified 263 BBC patients from a cohort of 9585 women with a first primary breast cancer systematically collected by the Cancer Registry of Parma Province from 1978 to 2006. Among these, 55 women, unselected for family history, were subjected to BRCA1/2 testing. In addition, 55 unilateral breast cancer pts, which tested negative for BRCA1/2 mutations, were evaluated as control group.

Results. BRCA mutations were detected in 13 (24%) of 55 BBC patients. Family history of breast cancer was identified in 8% of these pts compared with 7% of non-carriers (p = 0.64). Synchronous BBC was significantly rarer in BRCA carriers than in non-carriers. In addition, BRCA-positive pts were younger at diagnosis than BRCA-negative ones. The combination of high histologic grade, ER, PR, and HER2 negativity in both bilateral tumours was more frequent among BRCA-1 positive tumours than BRCA-2 positive and non-BRCA tumours (p <0.001). Taken collectively, BRCA-positive BBC correlated with triple negative status compared to non-BRCA BBC and unilateral breast cancer controls (p <0.001). There were no survival differences between BRCA-positive and non-BRCA tumours.

Conclusions. Our data show that the combination of BBC occurrence and tumour phenotype can provide an efficient model for identifying individuals with high risk for BRCA mutations and support the hypothesis that BBC in BRCA carriers is qualitatively distinct from non-BRCA BBC and from sporadic, unilateral breast cancer. Further studies of incident cases are needed to better define the prognostic value of BRCA mutations.

E32 ATTITUDE OF ITALIAN ONCOLOGISTS ON METASTATIC BREAST CANCER (MBC) MANAGEMENT

Crispino S.1, Labianca R.2, Lorusso V.3, Barni S.4

1Oncologia Medica, Siena, 2OOR, Bergamo, 3Lecce, 4Treviglio-Caravaggio (BG)

Introduction. During the last years, the availability of new drugs produced an advantage in overall survival in MBC. However the real impact of these new therapies has not been established. Today beside many active options for MBC, with an increased number of treatments lines, there is not a standard of treatment or a preferred therapeutic sequence. Treatment choice depends on: histology, molecular profile, tumour burden, site of metastases, previous (neo)adjuvant therapies and patient factors.

Materials and methods. From January to May 2012 a questionnaire has been submitted to specialists during meetings on breast cancer, in order to better understand the attitude of oncologists in the MBC handling in Italy. A total of 183 oncologists (107 female, 71 male, 5 na) filled up a questionnaire regarding:

• the overall survival of women starting from the diagnosis of metastases;
• the number of treatments lines;
• treatments preference (also for monotherapy or polichemotherapy) in first, second-line and subsequent
• the most important endpoint for each line.

Results. The oncologists reported that the median survival of women since the first diagnosis of metastasis is 19-24 months (range 7-36 months) and the median number of chemotherapy line for metastatic setting is 4 (range 2-12).

Most of the oncologists declared that the first and second-line endpoint is progression-free survival (PFS) and about 60% of them chose a combination treatment for the first-line chemotherapy and a monochemotherapy for the subsequent lines. Capecitabine (32%) is the preferred option for third-line treatment.

Conclusions. This survey underlights that for oncologists the number of treatments lines in MBC is now at least 4. Polichemotherapy was the preferred treatment as first-line thera-
py. The feeling on median survival is in line with old literature data. PFS is the most common endpoint for first and second-line reported by oncologists.

E33 HEAT-SHOCK-PROTEIN-90 (HSP90) OVEREXPRESSION, TOPOISOMERASE-2A-COAMPLIFICATION (TOPO2A), AND KI67 OVEREXPRESSION AS PREDICTORS OF PATHOLOGICAL COMPLETE RESPONSE (PCR) FOR PATIENTS RECEIVING NEOADJUVANT CHEMOTHERAPY WITH DOCETAXEL (DOC) AND TRASTUZUMAB (T) FOR HER-2 POSITIVE BREAST CANCER (HER2+ BC)

Furlanetto J.1, Bria E.1, Caliolo C.1, Bonomi M.1, Carbognin L.1, Massari F.1, Sperduti I.2, Brunelli M.3, Brunello E.3, Tortora G.4

1Medical Oncology, University of Verona; 2Regina Elena National Cancer Institute, Roma; 3Department of Pathology and Diagnostics, University of Verona; 4Medical Oncology, University of Verona

Background. According to the available data, neoadjuvant T for locally advanced/operable (LA/O) HER2+ BC has significantly increase pCR and outcome in general. Nevertheless, in light of the concerns related to the potential cardiotoxicity, predictive nomograms are required to identify those pts more likely to benefit, in order to optimize the therapeutic ratio of targeted therapies.

Methods. 24 HER2+ LA/O BC (ICH 3+ or ICH 2+ with amplified FISH) pts, undergone neoadjuvant T-Doc, from 2006 to 2011, were collected. After surgery, pathologic complete response (pCR) according to MDACC (no axillary and nodes involvement at surgery), RMN-based radiological (r) and clinical (c) response, were evaluated, with 95% confidence intervals (95% CI). Potential biomolecular predictors of response [hormonal receptors (HR), TOPO2A amplification, HSP 90 IHC score and Ki-67 proliferation index (cut-off of 15%)] were determined and correlated with activity; a formal comparison between their expression before and after treatment was performed.

Results. pCR was observed in 16.7% (N = 4; 95% CI 1.7-31.5) of pts, CR (c) in 37.5% (N = 9; 95% CI 18.1-56.8), CR (r) in 25% (N = 6; 95% CI 7.6-42.3); 3 out of 4 pts experiencing pCR had also a CR (c) (p = 0.09), while 4 out of 6 pts with RC (r) had also a CR (c). pCR was higher in HR negative pts vs positive (50% vs 5.6% p = 0.03), in TOPO2A amplified vs non amplified (50% vs 12.5%; p = 0.16); and in HSP 90 ICH 3+ tumours vs 2+ (50% vs 14.2%; p = 0.05). After neoadjuvant T-Doc, an increased rate of HR negative status (16.7% vs 25%), a decreased rate of HSP 90 ICH 2-3+ score expression (2+: 33% vs 26.7%; 3+: 20% vs 13.3%; p = 0.08); and a lower Ki-67 proliferation index (30 vs 17.5%; p = 0.005) was observed.

Conclusions. Biomolecular markers such as negative HR status, elevated proliferation index, TOPO2A coamplification and high HSP 90 IHC score may be predictive of response to T-Doc. Additional prospective studies with an adequate statistical power are necessary to validate this hypothesis.

E34 THE RELATIONSHIP BETWEEN ARTHRALGIA AND ACCELERATED BONE LOSS IN EARLY BREAST CANCER (EBC) PATIENTS TREATED WITH UP-FRONT

Background. Aromatase inhibitors (AIs) are standard drugs in adjuvant treatment of hormone responsive early breast cancer (EBC) in postmenopausal women. AIs have a higher incidence of accelerated bone loss and musculoskeletal symptoms (ostalgia, arthralgia, and myalgia).

Aim. The present study investigated the incidence of arthralgia in relationship to bone mineral density (BMD) status in postmenopausal women with EBC scheduled to receive AIs up-front or switch treatment after standard 2-3 years of adjuvant tamoxifen (TAM→AIs). We evaluated both adherence to hormonal adjuvant treatment and supplementary comedinations.

Patients and methods. We reviewed data for 89 patients with hormone receptor-positive EBC: 64 postmenopausal women received up-front AIs for 5 years; 25 patients received TAM→AIs. T-score values were assessed at baseline and then once a year. Osteopenic patients received calcium and vitamin D; osteoporotic patients received also oral bisphosphonates. Arthralgia, generalized bone pain and/or myalgia were recorded every follow-up control using Visual Analog Pain Scale. Musculoskeletal symptoms and patient adherence to supplementary comedinations were monitored.

Results. Most osteopenic or osteoporotic patients reported moderate or severe arthralgia (Figure 1) with an incidence of 17% and 26%, respectively. Supplementary comedinations have improved BMD in 27% of cases (osteopenia→normal, osteoporosis→osteopenia) with an improvement of musculoskeletal symptoms. No patient with a normal baseline BMD (T-score ≥-1) had new-onset of arthralgia and none became osteoporotic during 5 years of follow-up. In addiction, women with osteoporosis at baseline, treated with bisphosphonates, became osteopenic and obtained a partial regression of joint pain symptoms.

Figure 1 - Association between arthralgia and T-score results.
Conclusions. The data suggest that arthralgia is associated to a T-score of less than -1.5 that corresponds to patients at risk of developing osteoporosis during the AIs adjuvant therapy. Comediations with calcium, vitamin D and bisphosphonates reduced musculoskeletal symptoms. Finally, the correct management of treatment-related symptoms might improve patient’s compliance and the adherence to treatment.

E35 PROSPECTIVE STUDY OF POSITRON EMISSION TOMOGRAPHY FOR EVALUATION OF THE ACTIVITY OF TRASTUZUMAB IN HER2 POSITIVE PATIENTS WITH LOCALLY ADVANCED BREAST TUMOURS

Strina C.1, Foroni C.1, Andreis D.1, Zanon V.1, Cappelletti M.1, Bazzola L.1, Milan M.1, Boni E.1, Alevi G.1, Bottini A.1, Ferro F.2, Generali D.1

1U.O. Multidisciplinare di Patologia Mammaria, Laboratorio di Oncologia Molecolare Senologica, A.O. Istituti Ospitalieri di Cremona, Cremona; 2Diagnostica per Immagini e Medicina Nucleare, Casa di Cura Figlie di San Camillo, Cremona

Background. FDg-PET/CT (fluorodeoxyglucose-positron emission tomography/computed tomography) may be useful for response evaluation of anti-cancer treatments using cytotoxic chemotherapy. If target-therapies inhibit cancer cells proliferation, reduction of FDG tumour-uptake should also occur after treatment with molecular targeted drugs. Therefore, FDG-PET/CT can be a promising tool for the evaluation of the target therapies activity. The study aim was to evaluate the role of FDG-PET/CT in assessing anti-tumour activity (tumour and metabolic response) of trastuzumab in breast cancer patients.

Materials and methods. Seventeen female pts with HER2-positive locally advanced breast cancer received a single dose of trastuzumab alone at 8 mg/kg ev in a “window of opportunity” approach. FDG-PET/CT for evaluation of tumour dimension and SUV max (standardized uptake value) as a marker of tumour metabolic activity was performed at baseline and 21 days after the initiation of the treatment. Changes in tumour size and in SUV max were analyzed with the Wilcoxon signed rank test. Relationships between variables were examined using the Spearman’s rank correlation.

Results. Thirty-four FDG-PET/CT were performed in 17 patients. A significant reduction in maximum tumour diameter assessed by PET/CT (median 24-20 mm; p <0.02) was observed: 7 pts (41.2%) achieved a reduction in tumour size; 9 pts (52.9%) showed no changes, and one pt progressed in tumour size. A significant reduction of SUV max (median 8.9-4.2; p <0.002) was observed: 13 pts (76.5%) achieved a reduction of SUV max, 4 pts (23.5%) showed no changes of SUV max which corresponded to no changes in tumour size. Variation in tumour size induced by the treatment was found to be positively correlated with SUV max variation (r = .5, p <0.04).

Conclusions. FDG-PET/CT detected reductions in tumour size and metabolic activity in pts treated with trastuzumab as a window therapy. It was also useful in detecting non-responders patients. Thus, FDG-PET/CT may be useful for the evaluation of molecular targeted drugs, such as trastuzumab.

E36 THE TYROSINE KINASE ERBB2 INHIBITOR LAPATINIB AND THE ANTI-ERBB2 ANTIBODY

E37 BIOLOGICAL MARKERS ASSESSMENT IN RELAPSING BREAST CANCER PATIENTS


IRCCS Azienda Ospedaliera Universitaria San Martino, IST Istituto Nazionale per la Ricerca sul Cancro, Genova

Background. Hormone receptors (HRs) and human epidermal growth factor receptor 2 (HER2) are two important targets to se-
E38 CHEMOTHERAPY IN PREGNANT WOMEN WITH BREAST CANCERS: A SINGLE INSTITUTION EXPERIENCE


Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Catholic University of the Sacred Heart, Rome

Cancer diagnosis in pregnancy occurs in 1:1000 pregnancies; this incidence is likely to rise because childbearing age trend is to postpone. The most frequent malignancies diagnosed during pregnancy are breast cancer, cervical cancer and haematological malignancies. It is often understood that cancer treatment during pregnancy exposes the fetus to adverse effects but in most cases appropriate treatment can be offered to the mother without serious risk for the fetus.

We report the outcome of 5 women treated with chemotherapy for invasive breast cancer during pregnancy in our center over a 3 years period. Median age at diagnosis was 36.8 years (range 34-41). The median gestational age at initial presentation was 18.2 weeks (range 13-27).

Three patients (60%) had surgery at diagnosis (2 breast conserving and 1 mastectomy), 2 (40%) women proceeded with neo-adjuvant chemotherapy. Definitive histology was invasive ductal in 4 (80%), and medullary in 1 case (20%).

Mean tumour size was 2.5 cm (range 1.6-9). Four (80%) were ER+, 2 (40%) were Her2+. 2 (40%) women had involved lymph nodes (range 2-5). All 5 women received anthracycline-based chemotherapy (weekly or every 21 days). None was treated prior to the second three-month-period. A total of 14 cycles of chemotherapy were administered during pregnancy. The mean gestational age at delivery was 35.2 weeks (range 32-36). There were no spontaneous abortions or fetal malformations recorded. One baby was admitted in intensive neonatal care unit for 44 days and discharged in good health. Post delivery, 4 patients (80%) received further chemotherapy and 4 women had radiotherapy. The Her2+ women received trastuzumab for 1 year, the 4 (80%) who were ER+ continue ormonotherapy. All women were alive and clinically well at last review with mean follow-up 27.6 months (range 12-48 months).

Anthracycline-based chemotherapy can be safely administered beyond the first three-month-period. Long term follow-up of these children for potential late toxicities is required.

A multidisciplinary therapeutic approach is required to balance risks and benefits for the mother and the fetus.
Background. Doxorubicin is effective in early breast cancer but concerns about higher incidence of cardiac toxicity due to anthracyclines in older patients (Swain SM, Cancer, 2003) contributed to limit its use in this setting. NPLD is active in advanced disease and has much less cardiotoxicity than doxorubicin.

Methods. In order to explore the feasibility of adjuvant NPLD in terms of cardiac safety, we are conducting a phase II pilot study in high risk EBC pts older than 65 yrs with NPLD 60 mg/m² day 1 plus C 600 mg/m² day 1 q21 for 3 cycles followed by P 80 mg/m² weekly for 9 weeks. Hormonal therapy and radiotherapy post chemotherapy when indicated. Cardiac safety is evaluated by comparison between the basal left ventricular ejection fraction (LVEF) assessed with echocardiogram (ECHO) and LVEF at the end of NPLD + C, after P and every 6 months for 2 years. Cardiac events are defined as appearance of congestive heart failure and/or grade 3-4 LVEF decline, asymptomatic LVEF decline below 50% or an absolute drop >15%.

Results. Up today 17 pts have been enrolled. Main pts characteristics are: median age 74 (range 67-83), ECOG-PS 0/1 = 11/6, basal LVEF >50% in all pts and no relevant cardiac co-morbidities. Basal median LVEF is 60% (range 55%-75%). 48 cycles of NPLD + C have been administered. After NPLD + C the median LVEF is unchanged with a value of 60% (range 58%-70%). No pts had cardiac events as above defined. One patient discontinued NPLD + C after the first cycle for an episode of asymptomatic arrhythmia and one patient had a 10% drop of LVEF above 50%. Toxicities ≥3 were not observed.

Conclusions. These preliminary data suggest the feasibility of adjuvant NPLD + C followed by P in EBC pts. The study is ongoing and a total of 42 pts are planned to better define early and late cardiac events.

E41 ADJUVANT AROMATASE INHIBITORS (AIs) HORMONE THERAPY (HT): WHICH REASONS LEAD THE PATIENTS TO DISCONTINUE TREATMENT? A MONOINSTITUTIONAL ANALYSIS

Mosetti L.1, Sperduti I.2, Fabbri M.A.1, Frittelli P.3, Nelli F.1, Chilelli M.1, Massari A.4, Pompei L.2, Ruggeri E.M.1

1Medical Oncology, Ospedale Belcolle, Viterbo; 2Biostatistics Unit, Regina Elena Institute, Roma; 3Breast Surgery, 4Anatomia Patologica, 5Radiotherapy, Ospedale Belcolle, Viterbo

Background. AIs represent the standard HT for the adjuvant treatment for post menopausal endocrine sensitive early breast cancer (EBC) patients. Although these classes of drugs are well tolerated, a percentage of pts interrupts the treatment because of toxicity. In this setting the switch to other AIs or tamoxifen (T) may represent an option to allow the prosecution of HT. We reviewed the main reasons for interruption of the AIs in our institution from 2006 to nowadays.

Methods. The clinical data of 236 pts affected with EBC has been retrieved. To be considered eligible for analysis, a minimum follow-up time of 6 months was required. Main patients characteristics were: median age 64 yrs (35-89), median follow-up 24 months (6-28). Prior adjuvant chemotherapy: taxanes based: 47 pts, anthracyclines based: 43 pts. 118 pts (49%) had received letrozole (L), 101 (43%) anastrozole (A) and 18 (8%) exemestane (E). An alternative HT (AIs or T) was offered to pts who wanted or needed to interrupt permanently the ongoing drug.

Results. According to the CTC NCIV, arthralgia was the main toxicity observed (26.6%), G1: 19.4%, G2/3 5.5%/1.7%. Overall 24 out of 236 pts (10%) needed the discontinuation of AIs as a result of toxicity. Grade 2 and 3 arthralgia was the main reason for discontinuation in 13/24 pts (54%). No difference in the incidence of arthralgia was noted in pts who had received taxanes or anthracyclines. Headache (N = 2), alopecia (N = 2), G3 itching (N = 2), diffuse skin reaction (N = 1) allergic reaction with hypertensive crisis (N = 1), xerostomia and xerofthalmia (N = 1), insomnia (N = 1) and somnolence (N = 1) were the other reasons for discontinuance. In the multivariate logistic regression analysis, age (65 yrs) and HT represent independent factors associated with the onset of arthralgia (respectively p = 0.006 and 0.008, OR 2.65, CI 95 1.32-5.31). 17/24 pts were switched to E, 5 to T and 1 each to L and A. In pts who switched to another AI we observed a reduction in the severity of arthralgia but not its complete resolution. A complete resolution of symptoms was observed for the other toxicities except for allergic reactions that recurred after switching from L to A. Moreover the patient with the diffuse skin reaction chose the discontinuation of HT.

Conclusions. In our analysis, 10% of pts discontinued AIs due to toxicity. Switching to alternative HT, monitoring the toxicity, represents an option to offer to the pts in order to avoid a premature and permanent interruption of an effective treatment.

E42 CONCURRENT CYCLOPHOSPHAMIDE, METHOTREXATE AND 5-FLUOROURACIL (CMF) AND RADIATION THERAPY (XRT) IN AXILLARY NODE POSITIVE BREAST CANCER (ABCN)


Medical Oncology, Civilian Hospital, Avezzano; Carlo Ferri Foundation, Monterotondo, Roma; Radiation Therapy, Clinical Epidemiology, Geriatrics, Oncology, University of L'Aquila

Background. We ignore the best sequence of chemotherapy-XRT in the adjuvant treatment of ABCN. This phase II study assessed the systemic, cardiac toxicity and efficacy of 4 courses of anthracycline-taxane (AT) chemotherapy, XRT concurrent with CMF, hormonal and targeted therapy in the adjuvant treatment of ABCN.

Methods. 200 ABCN women, were treated, between 03/2002 and 03/2010 with AT, followed by XRT concurrent with 6 courses of CMF. Two courses of dose-dense chemotherapy with ifosfamide, carboplatin, etoposide supported by pegfilgrastim were given to patients with >10 axillary nodes and to patients with triple negative disease. Trastuzumab (T) was given to C-Herb-2 positive (HER+) patients for 1 year. ER+ patients received an aromatase inhibitor (AI) for 5 years. An LH-RH analogue was added, for 5 years, to ER+ premenopausal patients. Adverse effects were graded according to common toxicity criteria of the NCI.

Results. Characteristics: mean number of positive axillary nodes was 4.4, with 52% premenopausal. 74% ER+, 26% triple negative disease and 20% HER+. After a median follow-up of 74 months, the toxicity was as follows: grade 2 and 3 hematological toxicity in 20% of patients, grade 3 cutaneous toxicity in only 1 patient, grade 1 and 2 hepatic toxicity in 14% of patients. No significant reduction of ejection fraction was observed. 10-year disease-free (DFS) and overall survival (OS) were 77%. There was no statistically significant difference in DFS between ER+ and
ER- patients (p >0.05), while OS was better in ER+ patients (p <0.05); premenopausal patients had, also, a better DFS (p <0.005), and OS (p <0.005) of postmenopausal patients. Patients with HER- tumours had a better DFS (p <0.05) compared to patients with HER+, while the difference in OS did not reach statistical significance.

Conclusions. Induction AT, concurrent CMF and XRT and dose-dense chemotherapy, followed by AI, in ABCN resulted in a low level of late cardiac toxicity and excellent local control, DFS and OS. T decreased the risk of death in HER+ patients.

E43 ONCOTYPE-DX: HOW MANY PATIENTS REALLY BENEFIT FROM IT?


U.O.C. Oncologia Medica A, IRCCS, AOU San Martino, Istituto Nazionale per la Ricerca sul Cancro, Genova

Oncotype-DX is one genomic test for selecting which patients will and will not benefit from adjuvant chemotherapy (CT) for early breast cancer (EBC). The implications of sparing patients CT are substantial because of the potential to avoid toxicity that is associated with treatment. On the other hand, this test is expensive and it would be important to establish how many patients really benefit from it.

From October 2011 to May 2012 all new cases of breast cancer were discussed in the Breast Disease Management Team (BDMT) with the presence of medical oncologists, surgeons and pathologists. In this meetings the utility of oncotype-DX was assessed on the basis of the clinical-pathological prognostic factors.

One hundred and thirty-two patients were discussed. Ten patients with ductal carcinoma in situ were excluded from the analysis. Among the remaining 122 cases of carcinoma invasive eight were locally advanced breast cancer candidate for neo-adjuvant CT.

In the 114 EBC, most had T1 (74%), N0 (63%) and hormonal responsive (90%) disease.

Thirty-five patients (31%) were considered at high risk and the BDMT recommended CT for these reasons: N+ (22%), age ≤50 years (15%), T ≥2 cm (12%), hormonal receptor (HR) negative (7%) and HER2+ (3%).

In 63 patients (55%) the risk was considered low and CT was not recommended for the following reasons: HR+ (100%), T <2 cm (43%), N- (33%) and age >70 years (24%).

In the remaining 16 (14%) patients, the risk was defined as intermediate, the role of CT was considered uncertain and then oncotype-DX test was considered useful. Their median age was 46 years (range 40-69). These patients were all highly HR+ and were mostly T <2 cm (87%), N- (68%) and grading 2 (94%). Their median Ki67 labelling index was 19% (range 5-33).

We recommended oncotype-DX test in patients similar to those in which the test was validated but not for all our patients N- and HR+ we considered oncotype-DX useful. Only for 14% of our new EBC patients we recommend oncotype-DX and in all these patients the test could be useful to avoid CT. Therefore we suggest that the budget impact of oncotype-DX may be limited by the selection of patients really needing it.

E44 CLINICAL DECISION-MAKING IN BREAST CANCER (BC): ROLE OF THE MULTIDISCIPLINARY TEAM (MDT) MEETING

Andreis D.1, Zanoni V.1, Foroni C.1, Bazzola L.1, Allevi G.1, Alberio M.1, Ziglioli N.1, Bottini P.1, Olivetti L.2, Bodini M.2, Giardini R.3, Ferrero G.3, Caffaro L.4, Peveri A.4, Martinotti M.5, Antonelli A.6, Galli L.6, Rossi C.6, Generali D.1, Bottini A.1


Background. MDT meeting has become a best practice for treatment decision in BC patients. However, data regarding its frequency, composition and procedures are still limited. This study examines work processes of our BC MDT, to assess concordance between meeting recommendations, evidence-based guidelines and final treatment implementation.

Methods. Face-to-face MDT meeting is performed twice a week at the Cremona BC Care Unit. According to EUSOMA requirements, it comprises a group of professionals with expertise in BC management, and involves 3 phases: a) a clinical data form is made available before the meeting to every MDT member; b) MDT focuses on the patient evaluation to formulate an individually-tailored diagnostic-therapeutic program; c) meeting recommendation is registered, and communicated to/discussed with the patient. MDT prospectively collects data on all cases presented, and holds periodic audits.

Results. From November 2011 to May 2012, 50 consecutive MDT meetings and 487 case presentations were recorded. Mean duration of the meeting was 75 minutes, with a mean of 11 attendees (7 core members). One hundred and fifteen new BC diagnoses have been discussed by MDT (mean of 2.3 new cases per meeting), 43.5% of whom had indications for chemo- and/or hormonal therapy (40.0% in neoadjuvant setting), 54.8% surgery and 1.7% other treatments. Concordance of MDT meeting recommendations with guidelines was in 72 of 115 cases (62.6%, 95% CI 53.1-71.5%). Primary reasons of discordance were eligibility for clinical trials (55.8%), prognostication assessment by gene expression profiling (20.9%), comorbidities (11.6%), pharmacogenetic analysis (4.7%), and other motivations (7.0%).

Twenty-three recommendations (20.0%, 95% CI 11.0-25.6%) have not finally been implemented, due to availability of additional clinical information (65.2%), patient choice (26.1%), and organizational difficulties (8.7%).

Conclusions. MDT meeting is a fundamental approach to BC management and particularly to complex cases requiring integrated and innovative strategies of treatment. Different health and psycho-social professionals are regularly well represented at the meeting. MTD recommendations were fairly concordant with guidelines, rapidly validated, and largely implemented in practice.

E45 SRC TYROSINE KINASE CONTRIBUTES TO LAPATINIB RESISTANCE IN HUMAN BREAST CANCER MODELS

Background. HER2, a member of the HER family, is a transmembrane tyrosine kinase receptor overexpressed in almost 30% of breast cancer patients. Lapatinib is a small molecule HER2 inhibitor approved in metastatic breast cancer patients after trastuzumab failure. Unfortunately, lapatinib resistance is observed even in responding patients. Src is an intracellular kinase involved in tumour growth, angiogenesis and migration and it has been correlated with trastuzumab resistance in human breast cancer cell lines.

Methods. We used different HER2 expressing human breast cancer cell lines: MDA-MB-361, MDA-MB-231 and BT474 (sensitive to lapatinib), JIMT-1 and KPL-4 (acquired resistance to lapatinib). We tested the effects of the Src inhibitor saracatinib (AZD0530), alone and in combination with lapatinib, on cell survival, migration, invasion and signal transduction. We also studied the effects of the combination on nude mice xenografted with JIMT-1 cells.

Results. We observed that the combination treatment of lapatinib and saracatinib is able to inhibit survival, migration and invasion of breast cancer cells in vitro. Moreover, the combination inhibits several signaling transducers such as Src, Akt, MAPK, paxillin and PAK in all tested cancer cell lines. In nude mice xenografted with JIMT-1 cells, the combined treatment reduces tumour growth, prolongs mice survival and strongly decreases the incidence of lung metastases, as revealed through experimental metastasis assays. Interestingly, we observed that in resistant but not in sensitive cells Src preferentially binds EGFR and not HER2. Consistently, EGFR inhibition through cetuximab or RNA interference (siRNA) is able to rescue lapatinib resistance. The combined treatment with lapatinib and cetuximab, moreover, significantly reduces the activation of several intracellular transducers.

Conclusions. Src plays an important role in the development of resistance to lapatinib in breast cancer cell lines, and EGFR may be involved in its activation. These results suggest the development of possible new clinical strategy based on the combination of lapatinib and saracatinib in breast cancer patients resistant to lapatinib.

**E46 CARDIAC SAFETY OF ANTHRACYCLINE-CONTAINING ADJUVANT CHEMOTHERAPY OF EARLY BREAST CANCER: OSCAR/ABC ONGOING, OBSERVATIONAL, MULTICENTRIC STUDY. PRELIMINARY RESULTS**

Ricevuto E.1, Cocciolone V.1, Zilli M.2, Scognamiglio M.T.2, Pistilli B.3, Panotti A.4, Di Menna G.2, Mancini M.6, Cannita K.1, Adinolfi M.I.1, Ferrandina M.G.5, Rota S.1, Santoro A.7

1Medical Oncology, San Salvatore Hospital, University of L’Aquila, L’Aquila; 2Oncologic Clinic, SS Annunziata Hospital and G. Bernabeo Hospital, University G. D’Annunzio, Chieti-Pescara; 3Medical Oncology, Ospedale Civile di Macerata, Macerata; 4Medical Oncology, Mazzini Hospital, Teramo; 5Department of Obstetrics and Gynecology, Catholic University of the Sacred Heart, Roma (Campobasso); 6Medical Oncology, F. Renzetti Hospital, Lanciano (Chieti); 7Medical Oncology, Ospedale Civile di Avezzano, Avezzano (L’Aquila)

Background. OSCAR/ABC is an observational, prospectivemulticenter study aimed at evaluating, in the clinical practice, the relevance of cardiac dysfunction and congestive heart failure induced by “free choice”, selected anthracyclines-containing adjuvant regimens for breast cancer (BC) and to identify at-risk patients.

Patients and methods. Early breast cancer (EB) pts candidate to receive adjuvant anthracycline-containing chemotherapy are currently being enrolled. Data on demographic and clinical characteristics, tumour features and type of adjuvant regimen are centrally registered at the Consorzio Interuniversitario Nazionale per la Bio-Oncologia (CINBO) using an e-CRF. Primary objective is to evaluate the prevalence of cardiac dysfunction, particularly according to risk criteria and in HER2-positive patients. Assessment of cardiac risk involves the evaluation of cardiovascular comorbidities at diagnosis. Cardiac safety and general toxicity on-treatment are evaluated according to NCI criteria. Clinical and instrumental cardiac evaluation (ECG, ecocardiography) are performed at study entry, on-treatment and up to 5 years thereafter.

Results. From September 2010 to May 2012, 8 of 13 Centers are active, with 138 enrolled pts. Out of 121 evaluable pts, 87 (72%) underwent conservative surgery, 34 (28%) mastectomy; sentinel node excision, 84 (52%); axillary dissection, 57 (48%). Tumour features: pT1, 49%; pT2, 44%; pT3, 6%; pT4, 1%; pN0, 41%; pN1, 29%; pN2, 14%; pN3, 16%. Her2-positive BC was detected in 40 pts (33%). Eighteen pts (15%) were ≥65 years. Overall, 42 pts (35%) had cardiovascular comorbidities on treatment at diagnosis, 12% among ≥65 years pts, mainly represented by: hypertension (20% and 50%, respectively), diabetes (3% and 11%, respectively), dyslipidemia (11% and 33%, respectively). A particular analysis will be conducted on Her2-positive pts, candidates for trastuzumab. In this subgroup, 10 pts (29%) had cardiovascular comorbidities on treatment, 12% were also ≥65 years. So far, liposomal anthracyclines have been administered to 13 patients (11%); 21% of HER2-positive pts, 17% of ≥65 years pts, 19% of pts with cardiovascular comorbidity on treatment. Data on cardiac safety are not yet available.

**E47 EFFICACY AND SAFETY OF WEEKLY NON-PEGYLATED LIPOSOMAL DOXORUBICIN CHEMOTHERAPY IN HEAVILY PRE-TREATED METASTATIC BREAST CANCER PATIENTS**

Gandini C.1, Masci G.1, Zuradelli M.1, Guol G.2, Torrisi R.1, Velutti L.1, Giordano L.1, Losurdo A.1, Rota S.1, Santoro A.1

1Department of Medical Oncology and Hematology, Humanitas Cancer Center, Rozzano, Milano; 2Department of Medical Oncology, St. Vincent’s University Hospital, Dublin, Republic of Ireland

Background. Non-pegylated liposomal doxorubicin (NPLD) is indicated in combination with cyclophosphamide as first-line treatment for metastatic breast cancer (MBC). Most of the patients have already received an anthracycline-based chemotherapy in adjuvant setting and subsequently are exposed to a higher risk to develop a cardiac event. According to its low cardiac toxicity profile, NPLD may represent an attractive therapeutic option for these patients. We retrospectively evaluated efficacy and toxicity of weekly NPLD in both heavily pretreated and chemo-naive but elderly or multi-morbidity MBC patients. In some cases weekly NPLD represented a salvage therapy in patients lacking other valid therapeutic options.

Patients and methods. We retrospectively reviewed all the consecutive MBC patients treated with NPLD at our Institution.
Clinical and istopathological data were collected consulting patients charts and computer files. Patients received weekly NPLD at a dose of 20 mg/m² endovenous over 2 hours until progression of disease, clinical deterioration and/or unacceptable toxicity.

Results. Sixty MBC patients were treated at our Institution with weekly NPLD from May 2008 to May 2012. Forty-six patients (median age 60, range 34-93) were evaluable for efficacy and safety: 6 (13%) showed partial response, 13 (28.3%) stable disease for at least 2 months, with a disease control rate of 41.3%. The remaining 27 patients (58.7%) had progressive disease. Ten patients (21.7%) reported an important improvement of cancer-related symptoms. Among the 6 responding patients, 4 (66%) were anthracycline-pretreated. Median duration of treatment was 2.5 months (range 0.7-8.5). Median progression-free and overall survival were 2.99 (range 0.82-16.6) and 7.6 months (range 1.1-43.7) respectively. Grade 3 and 4 adverse events never occurred. Grade 2 neutropenia was observed in 2 patients, grade 1 in one patient. Five patients had grade 2 non-hematological toxicity (asthenia, mucositis, abdominal pain or nausea). No cardiac events were observed.

Conclusions. Weekly NPLD is effective and safe as salvage therapy for heavily pretreated MBC patients and may represent a therapeutic option for elderly patients with poor performance status.

E49 WEEKLY PACLITAXEL AND CARBOPLATIN WITH OR WITHOUT TRASTUZUMAB IN THE FIRST-LINE TREATMENT OF ER POSITIVE METASTATIC BREAST CANCER: RAPID CONTROL OF SYMPTOMS WITH LOW TOXICITY

Sini V., Lanza R., Menghi A., Notarangelo M., Cursano M.C., Mandolini P., Foresi E., Modesti M.
UOC Chirurgia Senologica, Policlinico Umberto I, Roma

Background. Estrogen receptor (ER+) metastatic breast cancer (mBC) with high Ki 67, extended and symptomatic disease, despite the ER status, could benefit more from CT than HT. CT could have the advantage of better and rapid control of disease-related symptoms than HT. Anthracyclines and taxanes are the milestones in BC treatment. Pacitaxel (P), a widely used tubulin-binding agent, seems better in weekly schedule than in the 3-weekly one, probably due to a higher dose-intensity, an antiangiogenic and pro-apoptotic effect of continuous low-dose P.

Aim. The aim of our study is to evaluate a schedule weekly paclitaxel-based in terms of activity, safety and quality of life (QoL) in mBC.

Patients and methods. 28 ER+ mBC female patients, PS ECOG 0 or 1, were enrolled. Twenty-two patients (78.6%) were Her2- and 6 patients (21.4%) were Her2 3+ or Fish amplified. Fifteen patients had only bone metastases, 7 bone and liver, 4 bone liver and lungs (2 patients had pleuric effusion), 2 bone liver lungs and brain (single cerebellar lesion). Symptoms included: bone pain, tremors, asthenia, dyspnea. The treatment was: P 80 mg/m² intravenous (i.v.) and carboplatin at AUC2 i.v. for 3 out of 4 weeks, with or without weekly trastuzumab (4 mg/kg loading dose, then 2 mg/kg) for 3 cycles. Restaging after 3 cycles. Patients with clinical complete response (cCR), clinical partial response (cPR) were eligible to consolidation therapy for further 3 cycles in order to go through HT afterwards. Patients with stable disease (SD) or progression of disease (PD) had to be treated with HT. Primary endpoint was: overall response rate (ORR). Secondary endpoints were: clinical benefit, control of symptoms, safety.

Results. Between Her2+ patients population we obtained 4 cCR (66.6%) and 2 cPR (33.3%), while in Her2- patients we reported 18 cPR (81.8%) and 4 SD (18.2%). No PD was reported. We obtained a rapid control of symptoms, above all on dyspnea and bone pain. The treatment was well tolerated. No grade 4 toxicities.

Conclusions. Therefore, this weekly schedule paclitaxel-based appeared active and safe with rapid and efficacious control of symptoms. Then it seems a feasible therapeutic regimen for mBC.
ES50 Monitoring Tumour Markers CA 15-3 and CEA during First-Line Treatment with Fulvestrant 500 mg in Hormone-Positive (HR+) Metastatic Breast Cancer (MBC): Predictive Value of Treatment Activity and Clinical Outcome?

Palumbo R.1, Bernardo G.1, Riccardi A.2, Tagliaferri B.1, Pozzi E.1, Teragni C.1, Bernardo A.1

1Oncologia Medica II, 2Oncologia Medica III, Università di Pavia, IRCCS, Fondazione Maugeri, Pavia

Background. While previously reported data suggest that both CA 15.3 and CEA are poor prognostic markers of progression of disease during treatment with Fulvestrant 250 mg for MBC, the prognostic value of monitoring response to the higher drug dosage has not been previously evaluated.

Patients and methods. Changes in CA 15.3 and CEA were prospectively monitored monthly in 48 consecutive women with HR+ MBC enrolled into a phase II study and treated with fulvestrant 500 mg 1st-line therapy (i.m. on day 0, then 500 mg on days 14 and 28 and every 28 days thereafter).

Results. All the enrolled patients were evaluable for the study endpoints. The overall clinical benefit rate was 68%, with 3 (6%) complete (CR) and 12 (25%) partial responses (PR), and 18 (48%) stable diseases (SD) lasting >24 weeks. The median PFS was 11 months, median response duration was 9 months.

Conclusions. Our findings suggest that monitoring CA 15.3 and CEA levels during first-line fulvestrant 500 mg therapy could be useful as predictive factors of treatment activity and clinical outcome in patients with HR+ MBC. The rapid decrease of tumour markers in responding patients could reflect the biologically greater effect of higher drug dose.

E51 Multicenter Study in Women with Infracentimetric HER2 Positive Breast Cancer: The Regional Sicilian Experience


1Terapia Integrate in Oncologia, Dip. Patologia Umana, Policlinico Universitario, Messina; 2Oncologia Medica Humanitas CCO, Catania; 3Oncologia Medica Policlinico Universitario, Catania; 4Oncologia Medica Azienda Ospedaliera, Ragusa; 5OM, Catania; 6Oncologia Medica, “La Maddalena”, Palermo; 7Oncologia Medica Ospedale Buccheri-La Ferla, Palermo; 8Fondazione Ist. San Raffaele-G.Giglio, Ospedale di Cefalà; 9Oncologia Medica Garibaldi Nestima, Catania; 10Villa Salus, Messina; 11UOS di Oncologia ASP1 AG, Sciacca; 12Dip. Patologia Umana, sezione di Anatomia Patologica, Messina

Background. Several trials have shown benefit of adjuvant trastuzumab (T) for node-positive and/or supra-centimetric HER2-positive (HER2+) breast cancer (BC) but there are limited data concerning infracentimetric HER2+ tumours. HER2+ disease is relatively uncommon in women with small, early stage BC, accounting for approximately ~10% of the cases. The aim of this study is to identify the pattern of use of T and risk of recurrence in small HER2+ tumours in the Sicilian Region.

Methods. This observational, multicenter, retrospective study was conducted in 11 oncology centers in Sicily during 2005-2011. Multifocal and metastatic tumours were excluded.

Results. Eighty-six cases have been included. Median age was 52.7 years (range 36-77). Tumour stage: T1a 27 (31%) and T1b 59 (69%). Nodal status by sentinel biopsy: node-negative disease 67 (78%). Invasive histological type: ductal 81 (94%), lobular 4 (4.6%) and medullary 1 (1.1%). Histological grade: G1 2 (2%), G2 55 (64%) and G3 29 (34%). The Ki-67 index was ≥13% in 51 (71%). Hormonal receptor status (HR): positive 51 (59.3%). Local treatment: breast conservative surgery and local irradiation 76 (88.3%) and mastectomy 10 (11.6%). Systemic treatment: 32 receiving aromatase inhibitors and 19 received LHHR agonists in combination with tamoxifen. Sixty-three patients (73.2%) received T in combination and/or after adjuvant chemotherapy (mostly anthracycline/taxane-based). Cardiac toxicity: 2 cases of asymptomatic and transient left ventricular ejection fraction decrease below 20% after T. 84/86 patients were evaluable for relapse-free survival (RFS). With a median follow-up of 32.0 months, there were 17 (6.7%) metastatic recurrences, 22 (2.2%) for the non-T treated and 3 (2.5%) in the T-treated. At 60 months, RFS estimates were 83% and 92% in the non-T and T-treated groups (p >0.05), respectively. At 60 months, the RFS estimates in the HR+ and HR- groups were 97.1% and 78% (p = 0.047), respectively.

Conclusions. Our study shows that infra-centimetric HER2+ and HR- tumours are associated with a general poor outcome and T-based therapies are justified in this setting.
E52 PSYCHO-NEURO-ENDOCRINE-IMMUNE SYSTEM (PNEI) INVOLVEMENT AS PROGNOSTIC MARKER IN BREAST CANCER PATIENTS AT 10 YEARS OF FOLLOW-UP

Aragonà M., Chillià F., Muscatello M.R.A., Panetta S., Altavilla G.

Introduction. Because tumour progression is influenced by micro and macro-environment retrospective analysis of the expression of some PNEI and stress parameters, before diagnosis, was evaluated with regard to ten years disease-free (DFS) and overall survival (OS) of breast cancer patients.

Methods. 114 patients hospitalized between 1988 and 1993 for breast lump were studied. All of them had diagnosis of breast cancer. Fifty more patients with benign diagnosis were discarded from the study. During the diagnostic phase, on average 5±3 days before surgery, patients were assessed for prevalence of stressful psychosocial events and depressive mood according to international criteria of DSM-III-R, for neuro-endocrine evaluation (24-hour urine catecholamines, 17-KetoSteroids); plasma cortisol, peripheral lymphocyte phenotype (CD3, CD4, CD8, CD16, CD19, CD25, CD57), immunohistochemical expression of ACTH, beta-END in lymphocytes and NGF-receptor on breast cancer tissues.

Results. At 10 years follow-up, 23 patients were dead within 60±35 months from diagnosis, and 91 were alive: 80 of them were in complete remission and 11 in progression disease; the mean follow-up was of 104.5±40 months. Survival time (DFS and OS) was shorter in patients who had, before diagnosis:

• serious and chronic stressful life events (>3, according to DSM-III-R), DFS: relative risk 2.68; p = 0.05;
• mild depressive mood, adjustment disorder with depressed mood or depression not otherwise specified (NOS), is associated with reduced DFS: p = 0.015;
• low absolute number of circulating NK lymphocytes (CD16+) (p = 0.016);
• decreased diuresis and increased specific weight (>1016 g/cm³) (p = 0.03);
• reduced NGF-R expression in the peri-tumour microenvironment: DFS: relative risk = 2.68, p = 0.033;
• introversion (p = 0.017) and emotional inhibition (p = 0.016).

Conclusions. Our data express the link between psycho-biological PNEI status of patients and the natural history of their breast cancer: mild depression, serious stressful events, introversion and control, diuresis reduction, low NK cells. Focusing attention to micro and macro environment of tumor and PNEI system seems to be necessary for optimal control of growth and neoplastic transformation. This opens new possibilities for therapeutic integrations, both in terms of physical and psychological therapies.

E53 NON-PEGYLATED LIPOSOMAL DOXORUBICIN (MYOCET®) AND CYCLOPHOSPHAMIDE FOLLOWED BY WEEKLY PACLITAXEL WITH (HER 2+) OR WITHOUT (HER 2-) TRASTUZUMAB AS PRIMARY SYSTEMIC THERAPY IN OPERABLE AND LOCALLY ADVANCED BREAST CANCER. PRELIMINARY RESULTS

Rossi D., Pistilli B., Baldelli A.M., Casadei V., Benedetti G., Catalano V., Alessandroni P., Luigi Fedeli S., Giordani P., Graziano F., Latini L., Fiorentini G.

1Oncology Unit, Ospedali Riuniti Marche Nord, Presidio S. Valvatore di Pesaro; 2Oncology Unit, Ospedale Civile Macerata

Background. Schedules with anthracyclines and taxanes are one of the best options for neoadjuvant chemotherapy in breast cancer. Non-pegylated liposomal doxorubicin (NLD) in combination with cyclophosphamide is active and safe as first-line treatment in metastatic breast cancer but we have only few data as primary chemotherapy, especially with concomitant administration of trastuzumab (Theodolou, 2009; Cortes, 2009). The aims of our study were activity, in term of pathological complete response, and safety of a sequential schedule of NLD/cyclophosphamide followed by weekly paclitaxel with or without trastuzumab.

Patients and methods. To date, 31 patients entered the study (13 pts stage IIIA and IIIB, 18 pts stage IIA and IIB). Twenty-five pts are evaluable for clinical and pathological responses (10 pts with stage IIIA and IIIB). Median age was 55.5 years (range 37-71). EGR positive in 23 pts (78% of evaluable pts). High/intermediate Ki 67 in 23 patients. Twenty-one patients without Her2 overexpression (or FISH not amplified) were treated with NLD 60 mg/m² in combination with cyclophosphamide 600 mg/m² every three weeks for 4 cycles followed by weekly paclitaxel 80 mg/m² for 12 courses; 10 patients with Her2 overexpression (or FISH amplified) were treated with the same schedule plus trastuzumab (8 mg/kg for the first administration then 6 mg/kg for the other 3 cycles with NLD and cyclophosphamide; 2 mg/kg/weekly for the following 12 administrations with paclitaxel).

Results. Pathological complete responses were documented in 6 pts (24%): 4 out of 7 evaluable pts with Her2 overexpression (57%) and 2 out of 18 evaluable pts without Her2 overexpression (11%). Overall clinical responses were 91.7%: complete 54.2% (78% in Her2 pts), partial 37.5%. Conservative surgery was performed in 9 pts (36%) and mastectomy in 16 pts (64%). Toxicity was mild: febrile neutropenia in 2 pts (G3-4 neutropenia in 1 pt); G3 vomiting in 1 pt; G3 paresthesia in 1 patient. Only 1 patient experienced an asymptomatic decrease of ejection fraction lower than 50%.

Conclusions. This new sequential schedule with the combination of NLD/cyclophosphamide followed by weekly paclitaxel with trastuzumab seems to be very active despite of the significantly higher rate of patients with ER+ positive disease and 42% of pts with locally advanced cancer. Consistently with previous data, PCR was higher in pts with Her2-overexpression. The study is ongoing to achieve the planned accrual of 43 patients.

E54 FULVESTRANT AFTER FAILURE OF ADJUVANT HORMONAL THERAPY: MULTICENTER RETROSPECTIVE OBSERVATIONAL STUDY

Garrone O., Bighini C., Vaira F., Donadio M., Alabiso O., Folco U., Pastirino G., Carapezza M., Baldini E., Biglia N., Canobbio L., Murielio R., Stevani I., Merlano M., Cerizzo P., Pronzato P.

Medical Oncology S. Croce e Carle General Hospital, Cuneo; IST Genova; Feletetto General Hospital, La Spezia; S. Giovanni Battista General Hospital, Torino; AOU Maggiore della Carità General Hospital, Novara; S. Corona General Hospital, Pietra
Background. Aromatase inhibitors (AI) are superior to TAM in the treatment of hormonal receptor positive metastatic breast cancer (MBC). Fulvestrant (F), an estrogen receptor antagonist demonstrated activity when used after failure of previous TAM or AI.

Objective. To evaluate the position of F in the hormonal strategy sequence in hormonal responsive MBC related to the evolution of adjuvant hormonal therapy (HT).

Materials and methods. MBC patients with disease progression after adjuvant HT or after treatment (CT or HT) for metastatic disease, candidate to receive F at the dose of 250 mg/month (registered in AIFA database) from May 1st 2006 to July 31st 2008. The study registered the HT sequence in clinical practice. Overall 201 patients were collected from 13 Italian centers. Main patients characteristics are summarized in the following Table.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N 201 (%)</th>
<th>Characteristics</th>
<th>N 201 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T size</td>
<td></td>
<td>PgR</td>
<td></td>
</tr>
<tr>
<td>Tis-T1-T2</td>
<td>138 (68.6)</td>
<td>Pos</td>
<td>142 (70.6)</td>
</tr>
<tr>
<td>T3-T4</td>
<td>40 (20)</td>
<td>Neg</td>
<td>33 (16.4)</td>
</tr>
<tr>
<td>T unk</td>
<td>23 (11.4)</td>
<td>Unk</td>
<td>26 (13)</td>
</tr>
<tr>
<td>Nodal Status</td>
<td></td>
<td>Adj CT</td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>54 (26.9)</td>
<td>Yes</td>
<td>105 (51.7)</td>
</tr>
<tr>
<td>N+</td>
<td>120 (59.7)</td>
<td>No</td>
<td>94 (46.8)</td>
</tr>
<tr>
<td>Nx</td>
<td>27 (13.4)</td>
<td>Unk</td>
<td>3 (1.5)</td>
</tr>
<tr>
<td>ER</td>
<td></td>
<td>Adj HT</td>
<td></td>
</tr>
<tr>
<td>Pos</td>
<td>169 (84)</td>
<td>Yes</td>
<td>141 (70.1)</td>
</tr>
<tr>
<td>Neg</td>
<td>12 (6)</td>
<td>No</td>
<td>46 (22.9)</td>
</tr>
<tr>
<td>Unk</td>
<td>20 (10)</td>
<td>Unk</td>
<td>14 (7)</td>
</tr>
</tbody>
</table>

Results. ORR were: CR 2%; PR 7%; SD 43%; PD 41%; NE 7%. Eighty-six patients (43%) had visceral metastases. Median duration of F was 7 months (1-42); 8 patients are ongoing and for 1 patient the duration was unknown. 16, 39 and 56 patients received F as first, second and third-line therapy respectively. For the remaining patients F was administered as more than the fourth-line therapy. The possibility of obtaining a benefit from F did not seem to correlate to the line of treatment.

One of the 2 CR occurred in a patient with visceral disease (lung). Among the patients who progressed under treatment 42% had visceral disease, that was almost the same rate of the whole population. This data suggests that there is lack of correlation between the sites of disease and the probability of benefit. Toxicity was negligible.

Conclusions. More than 50% of the patients benefited from F notwithstanding 73% of them received the treatment as third or more line of HT. This study does not show any correlation between the sites of the metasteses and the treatment results.

E55 ERIEBULIN IN PATIENTS WITH METASTATIC BREAST CANCER IN CLINICAL PRACTICE

D’Alonzo A., Lamberti M., Bighin C., Levaggi A., Giraudi S., Iacono G., Poggio F., Pronzato P., Del Mastro L.
IRCCS San Martino, IST, Genova

Background. Eribulin mesylate (E) is a novel non-taxane microtubule inhibitor approved in Italy since January 2012 for the treatment of metastatic breast cancer (MBC) patients previously treated with at least 3 chemotherapy (CT) regimens. The phase III clinical trial of E in MBC (EMBRACE study) showed improved overall survival for E-treated patients, with a manageable profile of toxic effects. We evaluated safety of E in current clinical practice.

Materials and methods. From January 2012 to May 2012, 12 MBC patients in our institution received E (1.23 mg/m²) administered as a 5-minute intravenous infusion on day 1 and 8 of a 21-day cycle. One patient (8.3%) started the treatment with dose reduction (0.62 mg/m²) because of severe liver dysfunction (total bilirubin: 5.98 mg/dL). All patients were heavily pretreated: the median number of prior CT regimens for MBC was 4 (range 3-6).

Results. The median number of cycles with E was 4 (range 2-7). Neutropenia was the most common clinical grade (G) 3 (2 cases [16.7%]) or 4 (16.7%) adverse event; it caused a delay in E administration of maximum one week. A 20% dose reduction in 3 patients (25%) and a treatment with GCSF in 2 cases (16.7%). The other adverse events were: fatigue (G 1: 33.3%; G 2: 66.7%), liver toxicity (G 1: 83.3%; G 2: 8.3%), and alopecia (G1: 66.7%; G2: 33.3%). In all patients without baseline alopecia, a G1 alopecia with E was observed. Tumour response was assessed in 6 patients: a clinical benefit (SD + PR) was observed in 3 patients. Mean PFS was 3.38 ± 0.32 months. The patient with severe liver dysfunction before E administration obtained a complete recovery of the liver function (bilirubin: 1.06 mg/dL) after 2 cycles.

Conclusions. These preliminary data confirm the utility of E in heavily pretreated MBC patients and suggest the possibility to administer E in patients with severe liver dysfunction.

E56 CLINICAL PRESENTATION IN BRCA1/2 MUTATION CARRIERS: A SINGLE-INSTITUTION EXPERIENCE

Ferrarin I.1,2, Fontana A.1,2, Aretini P.3, Bona E.1,2, Stasi I.1,2, Bartolini I.1,2, Laurà F.1,2, Salvadori B.1,2, Landucci E.4,4, Michelotti A.4,2, Allegrini G.5, Lucchesi S.5, Arrighi G.5, Congregati C.5, Bonci F.5, Rossetti E.5, Fustiano L.5, Roncella M.7, Caligo M.A.8, Bevilacqua G.8, Simi P.8, Falcone A.1,2

1UO Oncologia Medica II Universitaria; 2Polo Oncologico, Ospedale S. Chiara, AOUP, Pisa e Istituto Toscano Tumori; 3Sezione Genetica Oncologica, Divisione di Patologia, Dipartimento di Medicina di Laboratorio e Diagnostica Molleculare, AOUP; 4UO Oncologia Medica I; 5UO Oncologia Medica, Azi-ULS5 di Pisa; 6UO Laboratorio di Genetica Medica, Dipartimento di Medicina di Laboratorio, AOUP, Pisa; 7UO Senologia, AOUP, Pisa; 8Divisione di Anatomia Patologica, Università di Pisa

Background. Genetic testing for BRCA1/2 mutations may be useful for prevention and close surveillance as well for treatments selection in cancer patients.

Methods. Between May 2001 and July 2011 we identified 206 BRCA1/2 mutations carriers: 145 (70%) affected and 61 (30%) unaffected. Of the 145 patients 87 (60%) carried a BRCA1 mutation and 58 (40%) BRCA2 mutation. One hundred and twenty-four patients (85%) were diagnosed with breast cancer (BC) and among them 73 (59%) tested BRCA1-positive and 51 (41%) BRCA2-positive. Bilateral BC was found in 26 (21%) patients (46%
BRCA1, 54% BRCA2). Ovarian tumour was identified in 30 (21%) women (83% BRCA1-positive), while 12 (8%) had breast plus ovarian cancer (92% BRCA1-positive). Other tumours (oesophagus, pancreas, thyroid): 3 (2%) patients.

Results. We obtained clinical and pathological data from 38 BC patients. Median age: 40 years (range 23-65); male/female: 1/37. Histology: ductal carcinoma 32 (84%) patients, lobular 1 (3%) patient, medullary 2 (5%) patients, in situ carcinoma 3 (8%) patients. Most of patients showed stage I BC (19 patients, 50%), while 3 (8%) showed a metastatic spread at the time of diagnosis. Overall 18 (47%) patients had triple negative breast cancer (TNBC), 18 (47%) had hormonal receptor (HR) positive disease, 1 (3%) HER2-positive/HR-negative cancer and 1 was not evaluable. Interestingly, 20 patients were younger than 40 years and among them 11 (55%) had TNBC (91% BRCA1-carriers). Twenty-six patients received neoadjuvant/adjuvant treatments (11 anthracycline-taxane; 8 anthracycline-based; 5 CMF and 2 docetaxel-cyclophosphamide). Among the 7 patients treated with neoadjuvant chemotherapy 2 pCR (ypT0N0) and 5 PR were reported. pCRs were observed in 1 TN and 1 HR-positive BRCA1-carriers, both treated with anthracycline-taxane. Metachronous BC was found in 6 (16%) patients with a median time to diagnosis of 12 years (range 5-22). Prophylactic mastectomy was performed in 4 (10%) patients while 6 (16%) underwent prophylactic bilateral salpingo-oophorectomy.

Conclusions. Our data seems consistent with previous literature. Interestingly the majority of younger BC patients showed a BRCA1-TN phenotype.

E57 PROGNOSTIC MARKERS IN TRIPLE NEGATIVE BREAST CANCER: LESSONS FROM THE CLINICAL PRACTICE

Pagliacci A.1, Pistelli M.1, Battelli N.1, Santinelli A.2, Berardi R.1, Cascinu S.1

1Clinica di Oncologia Medica, 2Anatomia Patologica, AO Ospedali Riuniti, Università Politecnica delle Marche, Ancona

Background. Triple negative breast cancer (TNBC) is a relevant problem because of its relatively poor prognosis, aggressive behaviour and lack of targeted therapies, leaving the chemotherapy as the mainstay of treatment. Unfortunately data about prognostic markers, to predict the risk of recurrence and to select patients for whom chemotherapy is very effective in improving survival, are still lacking. In this retrospective analysis, we investigated the impact of clinical and histological features to identify TNBC with more aggressive behaviour and poor prognosis.

Methods. Patients diagnosed with invasive TNBC breast cancer at our Institution from January 1998 to December 2007 were included in the analysis. Patients with stage IV of disease were excluded.

Results. 149 patients were included. Median age was 54 years (range 26-83 years). During follow-up, 7.4% deaths, 12% distant metastases and 8.8% local recurrences or second tumours were documented. Univariate analysis showed that the following were significant risk factors for breast cancer patients disease free-survival (DFS): tumour size, type of surgery, lympho-vascular invasion and necrosis. A better DFS was related to smaller tumour size (≤2 cm), breast surgical conservation (quadrantectomy), and absence of lympho-vascular involvement or necrosis. Patients age, menopausal status, body mass index, lymph node status, type of adjuvant chemotherapy, grading, Ki-67, intraductal carcinoma and lymphocytic infiltrate were not statistically significant. In the multivariate statistical analysis the significant independent prognostic variables influencing DFS were tumour size (≤2 cm vs >2 cm; p < 0.01), type of surgery (quadrantectomy vs mastectomy; p = 0.04) and lympho-vascular invasion (presence vs absence; p = 0.02).

Conclusions. TNBC is a heterogeneous disease with different biology and clinical behaviour. In our experience patients who underwent mastectomy because of tumour size >2 cm with lympho-vascular invasion showed worse prognosis and higher risk of recurrences than other patients. Unlike other types of breast cancer, the impact of lymph node status and chemotherapy type on TNBC patients survival were not statistically significant.

E58 NON-PEGYLATED LIPOSOMAL DOXORUBICIN (NPLD-MYOCET®) SAFETY PROFILE WITH A NEW SCHEDULE (DAY 1-3) OF ADMINISTRATION

Rondinelli R.1, Magnante A.L.2, Ferrone L.3, Del Bianco S.1

1Unità Funzionale di Oncologia, Casa di Cura Madonna della Fiducia, Roma; 2Dipartimento di Scienze Radiologiche, Oncologiche e Anatomo-Patologiche, Radioterapia, Policlinico Umberto I, Roma; 3Dipartimento di Scienze Chirurgiche, Policlinico Umberto I, Roma

Background. Conventional anthracyclines are active drugs against several solid tumours. NPLD is reported to improve doxorubicin therapeutic index dramatically reducing cardiotoxicity as well as providing comparable antitumour efficacy. The NPLD sole schedule of administration (once q/3 weeks) has been so far employed. Few data exist on the toxicity profile of other schedules. This exploratory pilot safety study was undertaken to investigate whether a new schedule (day 1-3) would be at least as safe as the q/3 weeks schedule so to eventually improve the NPLD therapeutic index.

Patients and methods. Twenty-one patients planned for doxorubicin monotherapy (60-75 mg/m2) have been progressively included. They received NPLD 20-25 mg/m2/die, day 1-3 q/3 weeks. LVEF before starting and every 3 cycles was evaluated. Cardiotoxicity was defined as the appearance of signs or symptoms of CHF and/or LVEF reduction ≥15%. Other toxicities have been evaluated using the NCI toxicity criteria.

Results. Twenty-one patients, 15 females and 6 males have been recruited. Average age was 62 yrs (range 36-83). Tumour types were: 13 breast cancer, 4 soft tissue sarcomas, 2 bladder cancer, 1 pleural mesothelioma, 1 SCLC. Nine patients had previously been pre-treated with chemotherapy (3 with anthracyclines). Sixty-three cycles have totally been administered (median 4, range 1-4). Recorded toxicities have been as follows: no HFS has been found. No significant individual LVEF reduction has been measured. The only G3/G4 event was thrombocytopenia in 1 patient (4%), no platelets transfusions was requested. The other toxicities were: G2 alopecia: 21 (100%); G1/2 neutropenia: 4 (19%), G1/2 thrombocytopenia: 3 (14.3%) G1/2 anemia: 1 (4.7%), G1/2 mucositis: 17 (80.9%).

Conclusions. NPLD has already shown equivalent efficacy but significant less cardiotoxicity than doxorubicin in several comparable studies. Our preliminary safety pilot experience, with a new schedule of administration (d 1-3), has shown an excellent safety profile even on the other known toxicities. If con-
E59 EXEMESTANE AND CYP19A1 GENE POLYMORPHISMS IN EARLY BREAST CANCER

Monteverde M., Lattanzio L., Merlano M., Garrone O., Lo Nigro C.

Laboratory Cancer Genetics and Translational Oncology and Medical Oncology, Oncology Department, S. Croce General Hospital, Cuneo

Background. Estrogens stimulate cell proliferation in breast tumours that express estrogen receptors (ER). The aromatase, enzyme of the P450 cytochrome family, encoded by the gene CYP19A1, catalyzes the synthesis of estrogen through the conversion of androgens C19 (androstenedione and testosterone) in estrogenic aromatic steroid C18 (estrone and 17-β estradiol).

Synthetic aromatase inhibitors (AI) such as letrozole, anastrozole and exemestane have proven efficacy in ER positive early breast cancer patients (EBCP).

Aromatase is expressed in the breast cancer and/or stromal cells surrounding fatty tissue at higher levels than in non-cancer cells.

Statistically significant association was noted between hormone levels and two common polymorphisms in the CYP19A1 gene. Our endpoint was to evaluate the treatment efficacy according to progression-free survival (PFS) and overall survival (OS) discriminating by these two polymorphisms, using KM analysis and log-rank (Mantel-Cox) test.

Patients and methods. The study population is composed by 118 EBCP with a median age of 62 years (range 44-86), treated with AI. The mean follow-up was 80 months (range 24-238). The number of relapsing cases was 9 (8%) and the number of deaths was 8 (7%).

We have studied two regions of the CYP19A1 gene: one localized in exon 10, in the 3′UTR (C1558T, rs10046) and the other in intron 4 (CYP19 IVS4[TCT] +/−, rs28892005). We used a PCR allelic discrimination assay to determine the single nucleotide polymorphism (SNP) and a gene scan analysis to evaluate the TCT ins/del polymorphism in the aromatase gene in DNA extracted from peripheral blood.

Results. From the analyses of the two regions we observed that CYP19 IVS4 shows the following distribution: del/del = 20%, ins/del = 53%, ins/ins = 27%. The CYP19 3′UTR SNP distribution of alleles at position 1558 was: C/C = 30%, C/T = 47%, T/T = 23%.

We are currently correlating these data with PFS and OS. In the final statistical analysis of PFS we observed a not significant correlation with any of the analysed genotypes.

Conclusions. Our results suggest that testing for CYP19A1 polymorphisms could be relevant to discriminate EBCP with different AI treatment outcome.
The possible correlation between NEBC subtypes and prognostic factors is the subject of an ongoing study at our institution.

**E61 EFFECT OF TREATMENT WITH BISPHOSPHONATES IN THE PREVENTION OF SKELETAL EVENTS IN BREAST CANCER PATIENTS WITH OSTEOPOROSIS. CORRELATION WITH SIGNIFICANT BIOLOGICAL PARAMETERS. PRELIMINARY DATA**

Tanca F.M.1, Madeddu C.1, Astara G.1, Massa E.1, Antoni G.1, Ruggiero V.2, Floris C.1, Spiga C.3, Pisano A.4, Gramignano G.2, Mela Q.6, Montaldo L.6, Dettori C.7, Mantovani G.1

1Struttura Complessa di Oncologia Medica I, 2Struttura Complessa di Reumatologia, Azienda Ospedaliero-Universitaria di Cagliari (Presidio di Monzerrato CA); 3Unità Operativa Medicina, Nau- va Casa di Cura Decimomannu (CA); 4Struttura Complessa di Oncologia Medica, Ospedale Policlinico Regionale A. Businco, Ca- gliari; 5Struttura Semplice di Oncologia Medica, Ospedale Nostra Signora di Bonaria, San Gavino Monreale (VS); 6Unità Operativa Odontoiatria Conservativa, Azienda Ospedaliero-Universitaria di Cagliari (Presidio di Monzerrato CA)

**Objectives.** The study aimed to assess the efficacy and safety of zoledronic acid in breast cancer patients with osteoporosis, receiving hormone therapy and at high risk of skeletal events.

**Methods.** Open spontaneous prospective non-randomized phase II study. Eligibility criteria: histologically confirmed estrogen-receptor positive breast cancer; age 18-75 years; stage I-III; adjuvant setting; osteoporosis diagnosis; hormone therapy with tamoxifen ± LHHR analogues or aromatase inhibitors. At baseline all patients underwent the following assessments: DEXA, orthopantomography and dental examination; blood levels of VEGF, IL-8, IL-6, TNF-alpha, lymphocytes sub-populations, bone alkaline phosphatase, osteopontin, vitamin D, PTH, calcium, phosphoremia. Eligible patients were treated with zoledronic acid (5 mg once/year) for two administrations. The evaluations were repeated monthly in year 1.

**Results.** Sixty-nine female patients underwent the preliminary interview and 43 completed the screening: 15 were eligible (4 of them did not give their consent to participate in the study); 6 have already started treatment with zoledronic acid; 5 are currently undergoing the necessary dental treatments. Out of the 15 eligible patients, 3 had stage I, 9 stage IIIA, 2 stage IIIB. 1 stage IIIC; 4 had negative and 11 positive lymph nodes; 12 underwent quadrantectomy + homolateral lymphadenectomy and 3 radical mastectomy; 3 had positive c-erbB2 and received trastuzumab; 14 were in post-menopause and 1 in pre-menopause; 13 received locoregional radiotherapy treatment, 14 received letrozol and 1 tamoxifen + LHHR analogue; 8 received anthracycline-based adjuvant chemotherapy (3 of them in association with taxanes); 4 had already received oral bisphosphonates. The preliminary assessments showed that 4 patients had a significant improvement of the bone mineral density, assessed by DExA, and 2 patients had a stable bone mineral after zoledronic acid. Serum IL-2 values decreased; vitamin D, as well as PTH, calcium and phosphorus values improved compared to baseline after zoledronic acid administration. Osteopontin values increased, probably in line with the bone remodeling related to the treatment administered.

**Conclusions.** The study is ongoing.

**E62 ADJUVANT TRASTUZUMAB (T) IN EARLY BREAST CANCER (BC) PATIENTS. SINGLE INSTITUTION RETROSPECTIVE EVALUATION**

Mariani G.1, Dazzani M.C.1, Bianchi G.V.1, Capri G.1, Cresta S.1, Greco P.2, Materazzo C.2, Piotti P.2, Viggiano V.2, Ricchini F.1, De Braud F.1, Moliterni A.1

1Department of Medical Oncology 1, 2Department of Cardiology, Fondazione IRCCS, Istituto Nazionale dei Tumori, Milano

**Background.** The purpose of the study is to evaluate the outcome of one year of adjuvant (Adj) T after conventional chemotherapy in the clinical practice.

**Methods.** We analyzed the clinical-pathological characteristics and outcome of 210 patients with HER2 positive BC consecutively treated at the Fondazione IRCCS, Istituto Nazionale Tumori from November 2004 to August 2010. HER2 positive was defined as IHC 3+ or HER2 amplification evaluated by FISH or CISH.

T was administered at conventional dose, loading dose 8 mg/kg, 90’ infusion followed by maintenance dose of 6 mg/kg 30’ infusion, at 3-week intervals for 1 year after an integrated program of surgery, neoAdj or Adj chemotherapy. Patients with ER and/or PgR positive tumours received hormonotherapy according to menopausal status or concomitant disease. Radiotherapy when indicated, was completed prior to start T. Adequate cardiac function was necessary to receive T.

**Results.** The median age at the diagnosis was of 51 years (range 28-79), only 10 pts were >70 years old. Almost all pts (94%) were treated with an anthracycline (A) containing regimen and the medium dose of A administered was 234 mg/m2 (range 75-300). Main patients characteristics at diagnosis were:

<table>
<thead>
<tr>
<th>pT1b</th>
<th>pT1c</th>
<th>cT2-</th>
<th>cT3</th>
<th>cT3</th>
<th>pT3</th>
<th>LABC</th>
<th>N0</th>
<th>N &gt;4</th>
<th>Histology</th>
<th>CDI</th>
<th>G3</th>
<th>IV+</th>
<th>ER+/-</th>
<th>PgR</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>40</td>
<td>38</td>
<td>4</td>
<td>49</td>
<td>19</td>
<td></td>
<td>89</td>
<td>72</td>
<td>44</td>
<td>57</td>
<td>47</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The mean number of T administrations was 17 (range 5-18). Treatment was well tolerated without major side effects except for cardiac toxicity (<5%). Only 4 pts of the whole cohort (1.9%) discontinued treatment because of recurrence of disease (local and visceral relapse in 2 pts respectively).

The median follow-up was 57 months (range 18-93) and recurrence rate was 13.8% (29/210). Sites of relapse were viscera (38%), bone and soft tissue (31%). Local recurrence and contralateral BC were detected in 5 and 2 pts respectively. Only 2 pts developed metastases at central nervous system as first site of relapse.

**Conclusions.** The results of our analysis confirm the benefit of Adj T in HER2 positive BC.

**E63 FERTILITY PRESERVATION IN YOUNG EARLY BREAST CANCER: STRATEGIES AND PATIENT PREFERENCES**


IRCCS San Martino, IST, Genova
**Background.** In Italy, approximately 1800 women younger than 39 years are diagnosed with breast cancer (BC) every year. Chemotherapy (CT)-induced loss of fertility is a major concern for these patients. Different strategies are available to attempt to preserve ovarian function. We evaluated feasibility and patient preferences of two different strategies: oocyte cryopreservation (OC) and temporary ovarian suppression with the administration of LHRH analogue (LHRHa) during CT.

**Materials and methods.** From March 2010 to April 2012, 28 BC patients younger than 41 years (median age 38 [range 33-41]) candidates for CT, referred to our institution. They were offered the possibility to reduce the gonadotoxic effects of such treatments by two different strategies. The oncologist proposed both the administration of LHRHa during CT, and a reproductive counselling performed by the gynecologist, where OC was discussed.

**Results.** The majority of patients (25 [89.3%]) accepted to undergo a treatment with LHRHa, started at least 1 week before CT. Nineteen patients (67.9%) refused the reproductive counselling; the reasons for refusal were: previous pregnancies (13 patients [46.4%]) and no desire for children (6 patients [21.4%]). Out of 9 patients (32.1%) that accepted the reproductive counselling, only 3 (10.7%) accepted to undergo OC. The reasons for refusal were: fear of delaying cancer treatment (2 patients [7.1%]), fear of the ovarian stimulation required (1 patient [3.6%]), not eligible for comorbidities (1 patient [3.6%]), low successful rate of the technique (1 patient [3.6%]) and unknown in 1 case (3.6%). The 3 patients underwent a controlled ovarian stimulation with the use of daily injections of recombinant FSH: median length of stimulation was 9 days (range 8-9 days); peak estradiol levels ranged from 280 to 521 pg/mL. An average of 13.3 ± 5.7 oocytes was retrieved, and 8.3 ± 3.1 oocytes cryopreserved per patient.

**Conclusions.** This analysis suggests that the majority of patients (89%) accept the administration of LHRHa during CT and approximately 11% of patients undergoes OC.

### E65 WEIGHT REDUCTION INTERVENTION GROUP BASED ON ACCEPTANCE AND COMMITMENT THERAPY (ACT) FOR BREAST CANCER PATIENTS

Deledda G.1, Mandragona R.2, Mazzi M.1, Goss C.1, Del Piccolo L.1, Bissoli L.2, Fiorio E.2, Lenotti M.2, Parolini V.2, Zorzi M.2, Ballarin G.1, Barutti C.1, Nalini A.4, Zamboni M.3, Molino A.2


**Background.** The weight gain affects 50-96% of breast cancer patients (Rooney and Wald, 2007). The acceptance and commitment therapy (ACT) (Hayes, 1999) has shown to be effective in reducing and maintaining weight (Forman et al., 2009). ACT offers strategies such as acceptance, mindfulness, cognitive defusion, committed action in accordance with values, all increasing psychological flexibility.

The aim is to evaluate the feasibility of a multidisciplinary group intervention promoting a healthy lifestyle based on ACT for breast cancer patients with BMI ≥28.

**Methods.** The intervention consists in a set of eight bi-monthly encounters and six monthly maintenance phase encounters. At the first, eighth and last encounter patients weight is reported and questionnaires on clinical state (RSCL, PWBQ, Distress Thermometer), eating behaviour (TFE-Q-51), psychological flexibility (AAQ-2, Bul’s-eye) are administered.

**Results.** Eleven breast cancer patients attending the oncological out-patient clinic of the Verona General Hospital, with a BMI ≥28 were enrolled in the intervention. The mean age was 56 (SD 6.6); the mean BMI was 35 (SD 7.4). Preliminary baseline data showed high mean scores of physical symptoms, psychological symptoms, quality of life (RSCL: M = 23.86; SD 9.9, M = 25.29; SD 3.4, and M = 3.2 SD 1.2 respectively) and distress level (M = 5.75; SD 2.8). A high degree of acceptance (AAQ2 M = 48.75; SD 14), consistency with the values (Bull’s-eye M = 5.5; SD 1.4) and psychological well being (PWBQM = 72.7; SD 11.3) was observed. Attendance rate was 89% and patients showed a weight loss of 6.8%, corresponding to a mean of 5.4 kg (SD 3.5 kg).
Conclusions. These preliminary data show that patients collaborated actively, despite high initial levels of psychological and physical distress, adhered to the encounters, completed the intervention tasks and achieved the weight loss expected of 5%. The intervention thus seems feasible in the oncological context. These data have to be confirmed for the follow-up maintenance phase and supplemented by a larger sample size.

Essential references

E66 BIOMARKERS FOR EARLY DETECTION OF CHEMOTHERAPY INDUCED CARDIOTOXICITY: A SINGLE CENTER PROSPECTIVE PILOT STUDY IN PATIENTS TREATED FOR EARLY BREAST CANCER (BC)

Giardina G., Oriani A., Gueri R., Bini G., Milani K., Vallini I., Caimi C., Pinotti G.

Medical Oncology Unit, Ospedale di Circolo e Fondazione Macchi, Varese

Background. The use of blood detectable cardiac biomarkers, such as troponin and B-type natriuretic peptide (BNP), has been evaluated in clinical studies but definitive evidence of their diagnostic or prognostic role in predicting oncological treatments induced cardiomyopathy is still lacking.

Methods. In 60 consecutive pts series undergoing anthracycline-based chemotherapy (ABC) ± trastuzumab (T) ± radiotherapy (RT) for BC, we measured, at baseline and every 3 weeks until the end, troponin T and BNP.

Electrocardiogram (ECG) and US-left ventricular ejection fraction (US-LVEF) were done at baseline, chemotherapy end, and supplemented by a larger sample size.

Results. From June to November 2011 we analyzed 60 pts, all female, mean age: 57 yrs (range 31-87). Thirty-eight were in post-menopause; 15 were smokers.

Five received ABC alone, 8 ABC, RT and T, 8 ABC and T, 7 ABC and RT, 32 RT and endocrinotherapy (ET).

In anamnesis: left ventricular hypertrophy (1 pt), supra-ventricular tachycardia (1 pt), ischemic disease (2 pts), valvular disease (1 pt), hypertension (13 pts), dyslipidemia (8 pts).

Thirty-one had positive cardiological family history.

Ten pts had BNP alteration (median value: 131 pg/mL, range 101-219 pg/mL, normal range 0-100 pg/mL): 5 treated with RT plus ET, 1 with ABC, 2 with ABC plus paclitaxel and RT, 2 with ABC plus T.

Three pts had troponin T alteration (0.06 ng/mL, 0.07 ng/mL, 0.08 ng/mL; normal value <0.06 ng/mL): 1 treated with RT and ET, 1 with ABC plus paclitaxel, 1 with ABC, T and RT.

All alterations were unrelated each others and with ECG or US-LVEF. All pts were asymptomatic; no treatment changes have been done.

One pt had US-LVEF marked reduction (37.5%) during RT and ET, with no biomarkers changes.

Conclusions. The pts small number and treatments heterogeneity make impossible to derive conclusions. The cardiac biomarkers predictive role is still unclear: further large clinical trials with longer follow-up are needed.

Moreover, clinical studies are required to define optimal time of serum biomarkers measurement in potential cardiotoxic treatments.

E67 CHROMOSOME 17 POLYSOMY IMPLICATION IN BREAST CANCER PATIENTS WITH HER-2/NEU PROTEIN EXPRESSION IN ABSENCE OF HER-2/NEU GENE AMPLIFICATION

Giotta F.1, Addati T.2, Mattioli E.2, Caponio M.A.2, Rubini V.2, Bruno A.1, Simone G.2, Petroni S.2

1Medical Oncology Department, 2Anatomic Pathology Unit, National Cancer Research Center, Istituto Tumori “Giovanni Paolo II”, Bari

Background. Beside HER-2 gene amplification, a subset of breast cancer patients presents different genetic alterations, such as chromosome 17 polysomy (increased copy number of chromosome 17). Abnormalities of chromosome 17 are important molecular genetic events in human breast cancers. The reported incidence of chromosome 17 polysomy, as estimated by FISH, ranges from 5 to 50%. Previously published data showed that polysomy of Chr17 may lead to HER-2 protein overexpression and that these cases may be associated or not with HER-2 gene amplification.

Aim. We analyzed clinical behaviour in a subset of 25 polisomic tumours which showed HER-2/neu protein expression in absence of HER-2/neu gene amplification in FISH.

Methods. Twenty-five patients with invasive breast carcinoma overexpressing HER-2/neu protein but without HER-2/neu gene amplification (FISH test) were selected between 177 polisomic cases (from 2007 to 2009). Immunohistochemical staining for estrogen (ER), progesteron (PgR) receptors and Ki-67 (MIB-1) was performed in all cases. Follow-up data of 18 out of 25 patients were available.

Results. All 25 patients had diagnosis of ductal invasive breast cancer. 18 out of 25 were grade III and 7 were grade II. Only 4 out of 25 cases did not express ER, whereas 8 out of 25 were negative to PgR. Regarding to MIB-1, only 3 cases showed a low kinetic activity (cut-off ≤20%). Three of these patients were treated with adjuvant chemotherapy including anthracyclines followed by trastuzumab for 52 weeks. After a median follow-up of 48 months 2 patients are disease-free, while the remaining patients relapsed on bone.

Conclusions. Conflicting results (Downey et al., Clin Cancer Res, 16: 1281-1288, 2010; and Kaufman et al., J Clin Oncol, 25: 1009, 2007), but also the recent study by Bartlett et al. (Lancet Oncol, 11: 266-274, 2010) indicate that large prospective clinical trials are necessary to validate whether patients showing increased CEP17 indeed show a better response to HER2-targeted therapies and anthracyclines, also in the absence of HER2 amplification.

E68 HER-2/NEU OVEREXPRESSION AS POTENTIAL PROGNOSTIC FACTOR IN SMALL SIZE BREAST CARCINOMA (pT1N0M0)

Petroni S.1, Asselti M.1, Bruno A.2, Giannone G.1, Marzano A.L.1, Giotta F.2, Simone G.1

Aim. To evaluate if HER2 gene amplification is related to tumor size in small breast cancer with HER2 protein overexpression, as many studies show a relationship between small tumor size and HER2 amplification.

Methods. We analyzed 120 cases of breast cancer (BC) with HER2 protein overexpression and without HER2 gene amplification (FISH test) treated at the Oncological Unit of St. Maria Hospital (Bari, Italy) from 2007 to 2009. All the cases were retrospective.

Results. Among the 120 BC cases, 32 had HER2 protein overexpression without HER2 gene amplification and a tumor size of 0.1-0.5 cm (pT1a). The HER2 gene amplification was found in 28/39 cases (72%) of the patients who had small size tumors (pT1a, pT1b, pT1c).

Conclusions. Our data suggest that HER2 gene amplification is related to tumor size in BC, as shown in other studies.
Background. Patients with primary breast cancer pT1a-bN0M0 have generally a favourable prognosis. However relapse occurs up to 25% of cases so it is necessary to identify bio-pathological and bio-molecular parameters in order to administrate target therapy. The aim of this retrospective study was to identify prognostic factors and predictive factors associated with clinical outcome.

Methods. 292 women (median age 61 years) with pT1N0M0 breast cancer observed from 2004 until 2010, entered in the study. 187/292 tumours (64%) were pT1c, whereas 105 (36%) were pT1a-b. ER, PgR, Ki-67 status were evaluated using immunohistochemistry (IHC); HER-2/Neu protein expression was investigated by IHC (HercepTest, DAKO), HER-2/Neu gene status was assessed by FISH and scored according to FDA guidelines.

Results. There was no statistical significance for HR expression in two subsets (pT1ab VS pT1c; \( \chi^2 \) p = 0.897). A high proliferative activity was detected in 75.7% and 24.3% respectively for pT1c and pT1a-b (t-test, p = 0.002). HER2/Neu was positive (IHC, FISH) in 22/187 (11.8%) cases of pT1c and in 9/105 (8.5%) cases of pT1a-b; the proliferative activity index was high in both HER2/Neu + subset (t-test, p = 0.985). Follow-up data (mean FU 56.3 months, range 9-108 months) were available in 22/31 patients HER2/Neu + (8 pT1a-b, 14 pT1c). Two relapses (9.1%) were observed: the first (pT1b, G3, high Ki-67 treated only with radio-therapy), recurred both locally and on visceral sites; the second patient (pT1c, G2, high Ki-67 treated only with hormonal therapy) showed a triple negative biological features on a re-biopsy performed on liver metastases.

Conclusions. We observed that different Ki-67 expression, in two subsets (pT1a-b vs pT1c), is associated with tumour size and this difference is lost in HER2/Neu positive cases regardless of tumor size (t-test, p = 0.985). We concluded that HER2/Neu overexpression/amplification could represent a significant marker of high risk of relapse and could be a prognostic and predictive factor also in pT1N0M0 breast cancer.

E69 EFFICACY, SAFETY AND COST-EFFECTIVENESS (CE) ANALYSIS OF LENOGRASTIM (L) VERSUS PEGFILGRASTIM (P) IN MANAGEMENT OF CHEMOTHERAPY RELATED NEUTROPENIA (CRN) IN NON-METASTATIC BREAST CANCER (BC) PATIENTS

Papa A.1, Rossi L.1, Zoratto F.1, Tomao F.2, Ricci F.3, Giordani E.1, Spinelli G.P.1, Lo Russo G.1, Basso E.1, Verrico M.1, Zaccarrelli E.1, Stati V.1, Rinaldi G.1, Tomao S.1

1Department of Medical-Surgical Sciences and Biotechnologies, Oncology Unit, S.M. Goretti Hospital, Latina, University of Rome “Sapienza”; 2Department of Obstetrics and Gynecology, University of Rome “Sapienza”; 3Department of Surgery, S.M. Goretti Hospital, Latina

Background and aims. CRN is associated with mortality, morbidity, costs and chemotherapy delays and reductions. This retrospective study was conducted to determine efficacy, safety and cost of a single injection of P (6 mg) compared with daily L (263 μg), in primary prophylaxis of CRN in non-metastatic BC patients.

Methods. Fifty women (median age 54 years) underwent median 6 (range 4-8) chemotherapy doses with anthracyclines ± taxanes. At every cycle, 28 pts received daily L (median 5 injections, days 5-9), while 22 pts single P on day 2. Incidence of G3/G4-CRN, bone pain (BP: NRS ≥7) and CE were evaluated.

Results. In overall population, G3/G4-CRN incidence was 93% in L versus 64% in P; two and three febrile CRN (FCRN) occurred with L and P. During first and last cycle of chemotherapy, G3/G4-CRN was 28.5% and 11% in L, while 23% and 0% in P. In FEC100 (10 L vs 9 P): G3/G4-CRN was 30% in L versus 78% in P. In TAC/AC+T (18 L vs 13 P): G3/G4-CRN was 100% in L versus 46% in P. At first and last cycle of FEC100: G3/G4-CRN was 20% and 0% in L versus 22% and 0% in P. At first and last cycle of TAC/AC+T: G3/G4-CRN was 33% and 17% in L versus 23% and 0% in P. CT reduction was observed in 35.7% in L versus 41% in P. 18.2% of pts in P had BP vs 35.7% in L. In Italy, cost of 1 P injection was about 1489.00 euros compared with about 655.00 euros for 5 L injections.

Conclusions. In TAC/AC+T, P was more effective than L to prevent CRN especially at last cycle, despite the major costs. In FEC100, L was satisfactory with good CE profile. At first cycle there is no difference between L and P compared to CRN in both chemotherapy subgroups. No difference was found about safety and chemotherapy reduction.

E70 CLINICAL IMPLICATIONS OF USE OF DIFFERENT ANTI ESTROGEN RECEPTOR ANTIBODIES SP1, 6F11 AND 1D5 IN BREAST CANCER

Bogina G., Lunardi G., Sapino A.*, Marconi M., Coati F., Cassandrini P., Zamboni G.

Dipartimento Oncologico, Ospedale Sacro Cuore Don Calabria, Negrar (VR); *Dipartimento Scienze Biomediche e Oncologia Umana, Università di Torino

Introduction. Estrogen receptors (ER) are powerful predictors of breast cancer response to endocrine-therapy. In addition, the benefit of chemotherapy is significantly higher in patients with ER negative as compared to positive breast cancer. Therefore it is of paramount importance to use reliable assays for determining ER status, in order to assure an adequate therapy for patients.

The aim of this study was to compare the clinically validated anti ER antibodies (SP1, 6F11 and 1D5) in breast carcinoma cases to evaluate whether this could generate possible differences in the therapeutic management of patients.

Materials and methods. We selected 66 cases of breast cancer with different range of positive cells: <1% ER negative; 1%-9% low ER positive; 10%-50% intermediate ER positive; >50% highly ER positive. Each case was immunostained with the three antibodies.

Results. 1D5 antibody was less sensitive than SP1 and 6F11: 26, 20 and 21 negative cases respectively.

In nine cases there were differences in endocrine-therapy indications, particularly eight 1D5 negative cases showed SP1 and/or 6F11 low positivity. These cases were prevalently G3, PR negative or low-positive, with high Ki67 and positive HER-2.

Conclusions. We demonstrated higher sensitivity of anti-ER SP1 and 6F11 antibodies compared to 1D5. However, cases negative with anti-ER 1D5 showed low positivity with SP1 and 6F11 and were also related to others biological features associated to
endocrine-resistance. The ER values obtained by these three antibodies had not implication in chemotherapy indications.

E71 INCREASED LONG-TERM SURVIVAL IN ELDERLY WOMEN WITH METASTATIC BREAST CANCER, CHEMOTHERAPY NAÏVE, TREATED WITH THREE LINES OF SEQUENTIAL CHEMOTHERAPY PRE-PROGRAMMED

U.O. Oncologia Medica, A.O. Bolognini, Seriate (BG)

Background. To evaluate the efficacy and tolerability of sequential single agent chemotherapy pre-programmed in women older than 70 years, chemotherapy naïve, with advanced breast cancer, HER2 negative status.

Methods. We accrued fifteen patients aged between 70 and 78 years, ECOG PS 1-2; distant sites of metastases were: liver (8 patients), liver and lung (4 patients) and 3 patients with lung metastases. All patients underwent cardiac doppler ultrasound with EF >60%. Every patient was treated with a sequential chemotherapy program consisting of three drugs prescribed for a minimum of 6 cycles or until clinical progression; the schedule included 6 cycles of epirubicin 60 mg/m² every 3 weeks; 6 cycles of weekly paclitaxel 60 mg/m² and 6 cycles of gemcitabine 1000 mg total on day 1 and 15 every 4 weeks. Instrumental staging was not scheduled until the end of the treatment or until clinical progression.

Results. Six patients had paresthesias G2 after the sequence with taxanes, 5 patients had thrombocytopenia G2 during the administration of gemcitabine, two patients with clinical progression had to perform instrumental restaging before the end of the program and so they discontinued treatment for confirmation of PD.

Conclusions. The sequence was completed by almost all patients (except the two patients with progression) without particular problems. This sequence was highly tolerated and at the end of the program 9 patients had SD and 4 patients had PD. We assessed the quality of life of these patients with an internal survey carried out by our team of psychologists and there were no data to justify any deterioration of the psychological state during the sequential treatment. The sequential approach with a single chemotherapy drug pre-planned can be a viable alternative to the treatment of metastatic breast cancer obtaining a good local control of disease, increasing long term survival and improving quality of life.

E72 NEOADJUVANT CHEMOTHERAPY FOR OPERABLE BREAST CANCER IN DAILY CLINICAL PRACTICE: ROLE OF THE MULTIDISCIPLINARY TEAM

Claps M.¹, Amoroso V.¹, Bianchi A.², Grisanti S.¹, Consoli F.¹, Filipini L.², Ragni F.³, Simoncini E.¹
¹Oncologia Medica, ²Centro Senologico, ³2a Chirurgia, Azienda Spedali Civili di Brescia

Background. Neoadjuvant chemotherapy (NACT) is increasingly prescribed in women with operable breast cancer (OBC). Coordination is essential for a good standard of care. We aimed to evaluate the outcome of patients treated with NACT in our daily practice, focusing on the role of the breast multidisciplinary team (MDT).

Methods. We retrospectively assessed 48 patients with stage II or stage III breast cancer treated with NACT since 2004. The chemotherapy regimens were anthracycline-based or anthracycline and taxane-based, with the addition of trastuzumab in cases of HER2 positivity. Patients characteristics were compared using χ² test and Fisher’s exact test.

Results. The referral for NACT has been increased since the establishment of the breast MDT at our hospital in 2010: 18 patients were treated from 2004 to 2009 (on average, 3 patients per year), and 30 patients have been treated since 2010 (on average, 10 patients per year). Clinical and pathologic parameters, such as age, clinical stage, ER positivity, HER2 positivity, and pCR rate were not significantly different in the two considered time periods. Nine out of 40 evaluable patients (22%) achieved a pCR after NACT. The rate of pCR was 2.9-fold greater in clinical stage II compared with clinical stage III tumours. 2.4-fold greater in tumours with Ki67 >20%, and 1.9-fold greater in ER-negative tumours, even though these differences did not reach statistical significance. At a median follow-up of 17 months, 8 recurrences and 3 deaths from breast cancer were reported.

Conclusions. NACT is more frequently recommended when all OBC patients, at any clinical stage, are primarily assessed by the MDT. The overall rate of pCR observed in our daily practice is similar to that of published clinical trials. This data set is available for further translational research.

E73 MONITORING OF CARDIOTOXICITY WITH ULTRA-SOUND LEFT VENTRICULAR EJECTION FRACTION (US-LVEF) IN HER-2 POSITIVE BREAST CANCER (HER2+VEBC) PATIENTS TREATED WITH ADJUVANT TRASTUZUMAB (T): A SINGLE CENTER EXPERIENCE

Oriani A., Giardina G., Vallini I., Milani K., Pinotti G.
Medical Oncology Unit, Ospedale di Circolo e Fondazione Macchi, Varese

Background. Cardiotoxicity is a well known anticancer agents side-effect. Cardiac injury early detection is crucial since it may facilitate therapeutic measures avoiding lasting damages. Adjuvant trastuzumab provides substantial benefits to HER2+ve BC pts, however it is potential cardiotoxic. Strict, prolonged cardiac monitoring is of crucial importance.

Patients and methods. We evaluated 127 consecutive HER2+ve BC pts treated with anthracycline based chemotherapy (ABC) and adjuvant T (January-December 2011). US-LVEF was evaluated at baseline and thereafter every 3 months until treatment end. Cardiotoxicity was defined according to CTCAE-NCI-2.0 and NYHA class.

Median age: 53 years (range 30-85); 98% female. 17% treated with right mastectomy; 22% with left mastectomy; 26% with right quadrantectomy; 26% with left quadrantectomy; 1.5% with bilateral mastectomy; 2.3% with bilateral quadrantectomy, 3.2% with other surgical approaches.

Results. All pts were ABC pre-treated and had normal US-LVEF before T. Ninety-one received also endocrinotherapy, 86 radiotherapy (RT). In 21 T was done concomitant with RT. Sev-
entity (55%) had positive cardio-vascular anamnesis: hypertension (21%), foramen ovalis pervious (1.5%), mitral prolapse (0.8%), atrium paroxystic tachycardia (0.8%), dyslipidemia (6%), myocardial infarct not Q (0.8%), abdominal aorta aneurysm (0.8%), heart conduction system disease (2.3%).

T was discontinued due to US-LVEF reduction (>10% of baseline value) in 6 pts (4.7%), restarted in 1 after US-LVEF recovery. All were treated with angiotensin converting enzyme inhibitors and beta-blockers.

Patients characteristics: 1 male, 5 female, median age 62 yrs (range 38-73), 4 had positive cardiological anamnesis, 4 did RT concomitant to T, 4 T with endocrinotherapy.

Conclusions. In our retrospective study, US-LVEFs were done by different clinicians and different instruments. There is concern that outside clinical trials, cardiotoxicity observed rates may be increased due to less strict selection criteria and toxicity monitoring. Our cardiotoxicity incidence (4.7%) agrees with other studies even if long-term cardiac follow-up is essential to understand real incidence and natural history of T preceded by ABC related cardiotoxicity.

E74 THE ROLE OF BODY MASS INDEX (BMI) ON CHEMOTHERAPY RELATED AMENORREA (CRA) IN PREMENOPAUSAL BREAST CANCER (BC) PATIENTS TREATED WITH ADJUVANT ANTHRACYCLINE, CYCLOPHOSPHAMIDE (AC) AND TAXANE (T)

Basso E.1, Rossi L.1, Tomao F.2, Papa A.1, Zaccarelli E.1, Zoratto F.1, Verrico M.1, Giordani E.1, Spinelli G.P.1, Lo Russo G.1, Strudel M.1, Caruso D.1, Rinaldi G.1, Perrone Congedi F.1, Tomao S.1

1Department of Medico-Surgical Sciences and Biotechnologies, Oncology Unit, University of Rome, Latina; 2Department of Gynecology and Obstetrics, Roma

Background. Amenorrhea often occurs during chemotherapy. The rate of CRA depends on patient age and chemotherapy regimen. These side effects might reduce fertility, cause sexual dysfunction, bone loss and menopausal symptoms in many women. In this retrospective study we analyzed incidence of CRA in premenopausal BC patients and influence of their BMI in disappearance of menstrual cycle (MC).

Methods. We evaluated incidence of CRA in 24 premenopausal BC patients, 43 median age years, treated with adjuvant ACxT. Overall population (OP) had regular MC and nobody began hormone therapy at the same time. BMI was evaluated in all women.

Results. Ten patients received AC, 6 TAC, 8 AC+T. In 22 patients CRA occurred during CT: 90% in AC group vs 83% in TAC vs 100% in AC+T. In 82% of OP amenorrhea appeared during the first three cycles of CT. CRA occurred within the first two doses of treatment in 14/22 patients: 66.7% of AC group vs 80% of TAC vs 50% of AC+T. MC reappeared at the end of CT in 32% of patients with a median age of 40 years. In OP, 58% had BMI <24.9, while 42% had BMI >25%. In AC+T group 7 pts had BMI <24.9 (83% experienced amenorrhoea) vs 3 pts with BMI >25 (all occurred amenorrhoea). MC reappeared in 1 pt with BMI <24.9, TAC group: 3 patients had BMI <24.9 (2 experienced amenorrhoea) vs 3 had BMI >25 (3 appeared amenorrhoea). AC+T: 4 patients had BMI <24.9 vs 4 with BMI >25, everybody experienced amenorrhoea. MC reappeared in 3 patients: 1 with BMI <24.9 and 1 with BMI <25 in TAC; 1 pt with BMI >25 in AC+T.

Conclusions. In our study, incidence of CRA was extremely high and there are no differences between subgroups. In TAC amenorrhoea occurred earlier than in other groups. MC reappeared at the end of CT in younger patients. BMI did not influence CRA incidence.

E75 SINGLE ILEUM METASTASIS AS A FIRST SIGN OF BREAST CANCER: A CASE REPORT

Volpatto R., Biaggi G.1, Bertoldo E.1

SC Oncologia, Ivrea Hospital, ASL TO4, Ivrea (TO); *SOC Oncologia, Santo Spirito Hospital, Casale Monferrato (AL)

Breast cancer is the most frequent malignancy in women. The most common sites for breast cancer metastases are bone, lungs, liver, pleura and central nervous system. However, although other sites have been reported, solitary metastasis to the gastrointestinal tract is extremely uncommon.

Metastatic involvement of the upper gastrointestinal tract from breast cancer has been reported in autopsy series as occurring in more than 15% of patients, usually associated with extensive systemic spread; clinical manifestations from such metastases have been described in less than 1% of cases. Lobular infiltrating carcinoma seems to have a different metastatic pattern than ductal type, with an apparent predilection for the gastrointestinal tract.

We here report the case of a 72-year-old woman with isolated ileum metastasis from breast cancer, associated with small bowel perforation and intestinal obstruction, as the first sign of metastatic spread. The patient underwent an ileum resection in the year 2008 and then received chemotherapy with vinorelbine 25 mg/m² intravenously on day 1 and 8 every 3 weeks (11 cycles), resulting in a partial response and a clinical benefit. Pathological and immunohistochemical study of the small-bowel intestinal confirmed the diagnosis of metastasis from lobular carcinoma of the breast, which was corroborated by breast biopsy.

The patient was treated with vinorelbine because chemotherapy with anthracyclines was refused by the patient and for ECOG performance status: 3.

The patient is alive now with ECOG performance status: 0. She is in hormonal therapy with stable disease.

The literature revealed only few cases of breast cancer metastatic to the small-bowel, therefore, patients with known breast cancer, particularly of the lobular histological type, presenting specific or less specific abdominal symptoms or signs such as microcytic anemia, should be endoscopically explored or make an abdominal CT in order to detect possible metastases of the primary breast tumour.

E76 TOXICITY AND SAFETY OF ADJUVANT DOCEFIXEL, EPIRUBICIN AND CYCLOPHOSPHAMIDE CHEMOTHERAPY IN EARLY BREAST CANCER: THE TEC REGIMEN


Background. The use of taxanes and anthracyclines in the adjuvant treatment of primary breast cancer is well established, with benefit in disease-free and overall survival. Several studies demonstrated that the adding of taxanes to anthracyline-based therapy improves the outcome in combined or sequential sched-
u. Nowadays, the TAC (docetaxel, doxorubicin and cyclophosphamide) regimen is a standard treatment in node-positive and node-negative high risk early breast cancer. We know that doxorubicin and epirubicin are equivalent, but at similar doses epirubicin appears to have a better side effects profile than doxorubicin in terms of myelosuppression and cardiotoxicity. We present here a retrospective study of TEC (epirubicin) regimen in adjuvant setting, largely used in clinical practice.

Methods. Pre o postmenopausal women, with stage I-III breast cancer, PS ECOG 0-2 and normal left ventricular ejection fraction were eligible. A chemotherapy regimen of docetaxel 75 mg/m², epirubicin 60, 75 or 90 mg/m² and cyclophosphamide 600 mg/m² was administered, with or not G-CSF primary prophylaxis, every three weeks for 6 cycles. The primary endpoints were toxicity and safety; secondary endpoints were DFS and OS.

Results. Thirty-three consecutive female patients were enrolled from 2008 to 2010. The average age was 57 years. The 85% of the population completed the treatment with a average of 5.58 cycles per patient. An average reduction of about 15% was registered while a deleted dose was necessary in the 24% of cases. Just 5 patients interrupted the treatment prematurely: two for adverse reaction to docetaxel, one for relapse disease, one for diagnosis of second tumour, just one for febrile neutropenia. In our study the percentage of hospitalization for febrile neutropenia, of emesis or another side effect, was very low, about 4%. No cardiotoxicity or death related treatment was seen.

Conclusions. TEC regimen with epirubicin 60 mg/m² is feasible, well tolerated and effective adjuvant chemotherapy in breast cancer, as compared with TAC scheme, with acceptable and manageable toxicity and with good QoL.

E75 PRIMARY PROPHYLAXIS WITH PEGYLATED G-CSF IN EARLY BREAST CANCER IN ADJUVANT CHEMOTHERAPY WITH TEC SCHEDULE (DOCETAXEL, EPIRUBICIN, CYCLOPHOSPHAMIDE) AT HIGH RISK OF NEUTROPENIA. AN INSTITUTIONAL EXPERIENCE


Background. The effectiveness of chemotherapy in the adjuvant setting is directly related to its dose-density and dose-frequency. Neutropenia and febrile neutropenia represent the main cause of dose reduction and/or delay of chemotherapy. The prophylactic use of growth factors (pegylated or not) in high-risk protocols is widely used in clinical practice. Studies show that the primary endpoints were toxicity and safety according to NCI common toxicity criteria.

Results. The incidence of neutropenia G1-G2 was 13.5% and neutropenia G3-G4 was 18.4%. Anyway 24.1% of patients received a second different G-CSF type at failure of the pegylated form, so the 95% of patients completed the chemotherapy without reduction of the dose to baseline and about the 96% concluded the treatment without delay of dose. So the percentage of febrile neutropenia was very low, about the 2.5%, and just in 3.1% of cases was necessary the hospitalization.

Conclusions. In our experience, despite avoid of the international guidelines, the sequential use of two different types of G-CSF pegylated and not was necessary in the ¼ of population due to the adverse effect of neutropenia with the maintenance of dose-density, dose-frequency and good QoL. So we suppose that about 25% of patients are non-responders to pegylated G-CSF maybe due to biological and/or genetic factors not yet known, and prospective studies need to demonstrate the presence of predictive factors.

E78 “THE TRASTUZUMAB DAY”, AN ORGANIZATION TO IMPROVE ONCOLOGY RESOURCES ALLOCATION: A SINGLE CENTER EXPERIENCE WITH TRASTUZUMAB


Medical Oncology Unit, Ospedale Civile di Guastalla, AUSL Reggio Emilia

Background. Trastuzumab, a monoclonal antibody that blocks HER2 receptor, improves the survival of women with HER2 positive early and advanced breast cancer when given with chemotherapy. It is also indicated, in combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma, who have not received prior treatment for metastatic disease. The aim of this study was to show how a careful organisation within an oncology day hospital will lead to a considerable reduction of costs in the management of breast cancer and metastatic gastric cancer whenever you use trastuzumab.

Methods. We collected data about patients treated with trastuzumab for 24 months. From January 2010 to June 2011, trastuzumab administration took place on any day of the week. From August 2011 we created the “Trastuzumab Day”, the administration takes place only one day a week.

Results. From January 2010 to December 2011, 95 patients were treated with trastuzumab (30 in 2010 and 65 in 2011). The total cost was 366,157 euros in 2010, and 541,607 euros in 2011. The real cost of therapy (the sum of the real cost of single patient without surplus) was 323,973 euros in 2010 and 517,748 euros in 2011. The cost of the drug discarded was 42,184 euros in 2010 and 23,859 euros in 2011. The difference, despite the greater number of patients in 2011, originated from a better organization of trastuzumab administration in a single day. We observe that the percentage of discarded medication was reduced (11.52% in 2010 and 4.41% in 2011). In 2011 there was an increase in the trastuzumab doses (351 vs 227) and in the number of patients treated (65 vs 30) with a reduction of discarded drug equal to 43.44% (equivalent in 18,324 euros).

Conclusions. Improving the organization with a planning in a single day of high cost chemotherapy is an easy and cheap way to save money.
**Session F • Genitourinary tumours**

**F1** PRIMARY, SECONDARY, AND QUALITY-OF-LIFE ENDPOINT RESULTS FROM THE PHASE 3 AFFIRM STUDY OF ENZALUTIMIDE (MDV3100), AN ANDROGEN RECEPTOR SIGNALING INHIBITOR


*Department of Medical Oncology, San Camillo-Forlanini Hospitals, Rome

**Background.** Enzalutimide-proposed INN (MDV3100) is a novel androgen receptor (AR) signaling inhibitor (ARSI) which inhibits: 1) binding of androgens to AR, 2) AR nuclear translocation, and 3) association of AR with DNA. Enzalutimide (MDV3100) showed antitumor activity in a phase 1-2 trial enrolling pre- and post-docetaxel castration-resistant prostate cancer (mCRPC) patients. The AFFIRM trial evaluated whether enzalutimide (MDV3100) could provide clinical benefit to men with post-docetaxel metastatic mCRPC.

**Methods.** In this double-blind, multinational phase 3 study in patients with mCRPC who had received 1-2 lines of therapy, including prior docetaxel-based chemotherapy, patients were randomized 2:1 to enzalutimide 160 mg/day or placebo. Treatment with corticosteroids was optional. Patients randomized was stratified by baseline ECOG and mean brief pain inventory score. The primary endpoint was overall survival (OS); other efficacy endpoints included radiographic progression-free survival (rPFS), time to PSA progression (TTPP), soft tissue objective response (PR+CR), PSA response (≥50% decrease), and quality of life (QoL) response (≥10 point improvement in FACT-P global score).

**Results.** 800 patients were randomized to enzalutimide and 399 to placebo with median OS of 18.4 months vs 13.6 months (HR = 0.631) and respective median treatment durations of 8.3 and 3.0 months. The treatment groups were well balanced with a significant proportion of patients having >20 bone lesions (24.5% enzalutimide vs 20.6% placebo). Efficacy results are presented in the Table.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Enzalutimide</th>
<th>Placebo</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS, median</td>
<td>18.4 months</td>
<td>13.6 months</td>
<td>0.631 (0.529, 0.752)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>rPFS, median</td>
<td>8.3 months</td>
<td>2.9 months</td>
<td>0.404 (0.350, 0.466)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>TTPP, median</td>
<td>8.3 months</td>
<td>3.0 months</td>
<td>0.248 (0.204, 0.303)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>PR+CR</td>
<td>25.1%+3.8%</td>
<td>2.9%+1.0%</td>
<td>-</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>PSA response</td>
<td>54.0%</td>
<td>1.5%</td>
<td>-</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>QoL response</td>
<td>43.3%</td>
<td>17.8%</td>
<td>-</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>

The most common enzalutimide adverse events, with incidences higher than placebo respectively, were fatigue (34% vs 29%), diarrhea (21% vs 18%), and hot flushes (20% vs 10%). Grade ≥3 events of interest occurring in enzalutimide vs placebo were cardiac disorders (0.9% vs 2%), fatigue (6% vs 7%), seizure (0.6% vs 0%), and LFT abnormalities (0.4% vs 0.8%, respectively).

**Conclusions.** Enzalutimide was generally well tolerated, significantly prolonged OS, slowed disease progression, improved response rate and improved QoL in men with mCRPC post-docetaxel.

**F2** TUMOUR VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) AND VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTORS (VEGFR) POLYMORPHISMS AND CLINICAL OUTCOME IN ADVANCED RENAL CELL CARCINOMA PATIENTS RECEIVING FIRST-LINE SUNITINIB

Bianconi M.1, Scartozzi M.2, Faloppi L.1, Loretelli C.2, Burattini L.2, Bittoni A.2, Del Prete M.1, Francoletti M.2, Giampieri R.2, Montironi R.3,3, Causini S.2

1Postgraduate School in Medical Oncology, Polytechnic University of the Marche Region, Ancona; 2Clinic of Oncology, Ospedali Riuniti, Ancona; 3Institute on Pathological Anatomy, Polytechnic University of the Marche Region, Ancona

**Background.** The introduction of novel treatments has radically changed the approach to the treatment of metastatic renal cell carcinoma (mRCC). Currently TKIs directed against the VEGF pathway are the therapeutic strongholds. However, criteria for treatment selection are largely lacking. In this study we assessed the role of VEGF and VEGFR polymorphisms, in the prediction of the clinical outcome in mRCC patients.

**Methods.** Forty-one formalin-fixed paraffin-embedded tissue blocks from mRCC patients receiving first-line sunitinib were tested for VEGFA, VEGFC and VEGFR-1, 2, 3 single nucleotide polymorphisms (SNPs). SNPs results were correlated with progression-free survival (PFS) and overall survival (OS).

**Results.** Forty-one patients with metastatic renal cell carcinoma were available for our analysis. All patients received sunitinib as first-line treatment with standard schedule, dose reduction was applied in patients with grade 3 and 4 toxicities. Median PFS was of 8.22 months, while median OS was of 32.13 months. VEGF A rs833061 polymorphism resulted statistically significant in PFS (17 months for CC + CT vs 4 months for TT; p = 0.0001) and OS (36 months for CC + CT vs 8 months for TT; p = 0.0040). VEGF A rs699947 was statistically significant for PFS (17 months for AA + AC vs 4 months for CC; p = 0.0001) and OS (36 months for AA + AC vs 11 for CC; p = 0.0059). VEGF A rs2010963 was significant in PFS (17 months for GG vs 5 for GC vs 3 for CC; p = 0.0186). VEGFR3 rs6877011 was significant in PFS (12 months for CC vs 4 for CG; p = 0.0221) and OS (36 months for CC vs 17 for CG; p = 0.0052).

**Conclusions.** In our analysis patients with TT polymorphism of rs833061, CC polymorphism rs699947 and CC polymorphism of rs2010963 seem to have a worse PFS and OS in first-line. VEGF-A gene polymorphisms are probably connected with the control of the neoangiogenesis, maybe controlling vasculature normalization. Patients with CG polymorphism of rs6877011 seem equally to have a poor impact of first-line therapy. VEGFR-3 seems to be involved in vessels sprouting and architecture.

**F3** ANTIANGIOGENIC AGENTS ARE INEFFECTIVE TO INCREASE COMPLETE RESPONSE RATE IN mRCC: A META-ANALYSIS

Forty-one formalin-fixed paraffin-embedded tissue blocks from mRCC patients receiving first-line sunitinib were tested for VEGFA, VEGFC and VEGFR-1, 2, 3 single nucleotide polymorphisms (SNPs). SNPs results were correlated with progression-free survival (PFS) and overall survival (OS).

**Results.** Forty-one patients with metastatic renal cell carcinoma were available for our analysis. All patients received sunitinib as first-line treatment with standard schedule, dose reduction was applied in patients with grade 3 and 4 toxicities. Median PFS was of 8.22 months, while median OS was of 32.13 months. VEGF A rs833061 polymorphism resulted statistically significant in PFS (17 months for CC + CT vs 4 months for TT; p = 0.0001) and OS (36 months for CC + CT vs 8 months for TT; p = 0.0040). VEGF A rs699947 was statistically significant for PFS (17 months for AA + AC vs 4 months for CC; p = 0.0001) and OS (36 months for AA + AC vs 11 for CC; p = 0.0059). VEGF A rs2010963 was significant in PFS (17 months for GG vs 5 for GC vs 3 for CC; p = 0.0186). VEGFR3 rs6877011 was significant in PFS (12 months for CC vs 4 for CG; p = 0.0221) and OS (36 months for CC vs 17 for CG; p = 0.0052).

**Conclusions.** In our analysis patients with TT polymorphism of rs833061, CC polymorphism rs699947 and CC polymorphism of rs2010963 seem to have a worse PFS and OS in first-line. VEGF-A gene polymorphisms are probably connected with the control of the neoangiogenesis, maybe controlling vasculature normalization. Patients with CG polymorphism of rs6877011 seem equally to have a poor impact of first-line therapy. VEGFR-3 seems to be involved in vessels sprouting and architecture.

Dipartimento di Scienze Radiologiche, Oncologiche e Anatomia-Pathologiche, Day Hospital Oncologico B, Sapienza, Università di Roma

Background. Antiangiogenic agents (AAs) have reported greater activity compared to IFNα with an increase of PFS and ORR. Despite these advances, complete response (CR) to therapy is rare. We meta-analyzed the incidence of CR in pts treated with AAs compared to IFNα alone (RR = 1.6, p = 0.14); if only phase III RCTs were considered, the RR was 1.7 (95% CI 0.9-3.4; Q = 3.6, p = 0.30; I² = 17.2%) with a trend for significance (p = 0.08). No differences were found when AAs were compared to IFNα alone (RR = 1.6, p = 0.14). Among AAs, sunitinib reported the highest RR for CR (2.7; 95% CI 1.3-5.3) with a trend for significance (p = 0.088).

Conclusions. Even if AAs reported greater activity in terms of PFS and ORR, they didn’t increase the curative rate of metastatic disease. Probably other biologic factors than angiogenesis may influence the CR in mRCC.

### Table F3

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Therapy</th>
<th>Control</th>
<th>Phase of study</th>
<th>Type of study</th>
<th>N of pts</th>
<th>Incidence of CR (%)</th>
<th>AAs 95% CI</th>
<th>Control 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yuang et al.</td>
<td>2003</td>
<td>Bevacizumab 10 mg</td>
<td>Pbo</td>
<td>2</td>
<td>RCT</td>
<td>116</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Escudier et al.</td>
<td>2007</td>
<td>Bevacizumab 3 mg</td>
<td>Pbo</td>
<td>3</td>
<td>RCT</td>
<td>649</td>
<td>1.3</td>
<td>0 – 2.7</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>+ IFN</td>
<td>IFN</td>
<td></td>
<td>RCT</td>
<td>750</td>
<td>3.3</td>
<td>1.2 – 5.3</td>
<td>1.2</td>
</tr>
<tr>
<td>Motzer et al.</td>
<td>2007</td>
<td>Sunitinib</td>
<td>IFN</td>
<td>3</td>
<td>RCT</td>
<td>731</td>
<td>3.4</td>
<td>1.3 – 5.5</td>
<td>1.3</td>
</tr>
<tr>
<td>Rini et al.</td>
<td>2007</td>
<td>Bevacizumab + IFN</td>
<td>IFN</td>
<td>2</td>
<td>RCT</td>
<td>189</td>
<td>0</td>
<td>0</td>
<td>1.1</td>
</tr>
<tr>
<td>Escudier et al.</td>
<td>2009</td>
<td>Sorafenib</td>
<td>IFN</td>
<td></td>
<td>RCT</td>
<td>435</td>
<td>0.3</td>
<td>0.1 – 1.2</td>
<td>0</td>
</tr>
<tr>
<td>Sternberg et al.</td>
<td>2010</td>
<td>Pazopanib</td>
<td>Pbo</td>
<td></td>
<td>RCT</td>
<td></td>
<td>Total</td>
<td>1.9</td>
<td>1.1 – 2.6</td>
</tr>
</tbody>
</table>

### Table F4

<table>
<thead>
<tr>
<th>P Group</th>
<th>Cleveland clinic</th>
<th>French</th>
<th>Heng</th>
<th>MSKCC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pts (%)</td>
<td>PFS (mos)</td>
<td>p</td>
<td>Pts (%)</td>
</tr>
<tr>
<td>Good</td>
<td>20</td>
<td>NR</td>
<td>&lt;0.001</td>
<td>6</td>
</tr>
<tr>
<td>Intermediate</td>
<td>37</td>
<td>15.3</td>
<td>0.008</td>
<td>81</td>
</tr>
<tr>
<td>Poor</td>
<td>43</td>
<td>10.2</td>
<td>0.008</td>
<td>13</td>
</tr>
</tbody>
</table>

Background. Outcomes of pts treated with three TTs for mRCC have not been well characterized. Survival data as well as existing prognostic criteria in this population were evaluated.

Methods. Patients with clear-cell mRCC who received 3 TTs were included. A questionnaire was sent to main Italian centers involved in the treatment of mRCC. Demographic data, history of RCC, type and length of first, second and third lines were collected. Values of serum Hb, PLT, neutrophils, LDH and Ca, ECOG-PS, previous RT and number of metastatic sites >2 before the start of third-line were evaluated. Cleveland Clinic, French, Heng, and MSKCC scores and relative survival were calculated.

Results. Following the screening of 1905 pts, 252 (13%) with 3 TTs were identified. The median age was 60 yrs (range 52-68), 73% were male, 96% had nephrectomy and 38% were metastatic at diagnosis. At first-line, the Motzer class was good, intermediate, and poor in 48%, 47% and 5% of pts, respectively. The median OS from the start of third-line was 14.3 mos (95% CI 10.1-18.6). Rate and survival by prognostic group according to each classification are reported in the Table below. When prognostic factors were considered separately, at the univariate analysis ECOG-PS ≥2, Hb <LLN, LDH >1.5 ULN, Ca >ULN; PLT

### Table F4

<table>
<thead>
<tr>
<th>P Group</th>
<th>Pts (%)</th>
<th>PFS (mos)</th>
<th>p</th>
<th>Pts (%)</th>
<th>PFS (mos)</th>
<th>p</th>
<th>Pts (%)</th>
<th>PFS (mos)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>20</td>
<td>NR</td>
<td>&lt;0.001</td>
<td>6</td>
<td>NR</td>
<td>0.008</td>
<td>32</td>
<td>17.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intermediate</td>
<td>37</td>
<td>15.3</td>
<td>0.008</td>
<td>81</td>
<td>14.3</td>
<td>0.008</td>
<td>62</td>
<td>15.2</td>
<td>0.008</td>
</tr>
<tr>
<td>Poor</td>
<td>43</td>
<td>10.2</td>
<td>0.008</td>
<td>13</td>
<td>9.1</td>
<td>0.008</td>
<td>6</td>
<td>5.5</td>
<td>0.008</td>
</tr>
</tbody>
</table>

Motzer et al. 2007 Sunitinib IFN 3 RCT 750 1.2 0 – 2.6
Escudier et al. 2009 Sorafenib IFN 2 RCT 189 0 1.1 0 – 3.7
Rini et al. 2007 Bevacizumab + IFN IFN 3 RCT 731 3.4 1.3 – 5.5 1.3 0 – 2.7
Escudier et al. 2009 Sorafenib IFN 2 RCT 189 0 1.1 0 – 3.7
Sternberg et al. 2010 Pazopanib Pbo 3 RCT 435 0.3 0.1 – 1.2 0

Background. Antiangiogenic agents (AAs) have reported greater activity compared to IFNα with an increase of PFS and ORR. Despite these advances, complete response (CR) to therapy is rare. We meta-analyzed the incidence of CR in pts treated with AAs compared to IFNα alone (RR = 1.6, p = 0.14); if only phase III RCTs were considered, the RR was 1.7 (95% CI 0.9-3.4; Q = 3.6, p = 0.30; I² = 17.2%) with a trend for significance (p = 0.08). No differences were found when AAs were compared to IFNα alone (RR = 1.6, p = 0.14). Among AAs, sunitinib reported the highest RR for CR (2.7; 95% CI 1.3-5.3) with a trend for significance (p = 0.088).

Conclusions. Even if AAs reported greater activity in terms of PFS and ORR, they didn’t increase the curative rate of metastatic disease. Probably other biologic factors than angiogenesis may influence the CR in mRCC.
>ULN; Neu >ULN, and sites of disease >2 had negative prognostic role. Multivariate analysis shows an independent prognostic role only for ECOG-PS ≥2 (HR = 1.8; 95% CI 1.1-2.8), Hb <LLN (HR = 1.8; 95% CI 1.2-2.6) and neu >ULN (HR = 2.1; 95% CI 1.2-3.8). Patients were stratified in 3 groups according to the presence of none, 1 or ≥2 prognostic factors. The median OS was 20.3, 13.6 and 7.8 months, respectively (p <0.0001).

Conclusions. Current nomograms are able to predict survival in patients with mRCC before the third-line with TT. Neutrophils, platelets and ECOG-PS were the most important prognostic factors.

F5* PROGRESSION-FREE SURVIVAL (PFS) AND OVERALL SURVIVAL (OS) IN PATIENTS RECEIVING 3 TARGETED THERAPIES (TTS) FOR METASTATIC RENAL CELL CARCINOMA (mRCC)

Lacovelli R.1, Verzoni E.2, Recine F.3, Santoni M.4, Di Lorenzo G.5, Ortega C.6, Masini C.7, Giganti M.O.8, Lorusso V.9, Procopio G.10

1Oncology Unit, Sapienza University of Rome; 2San Camillo-Forlanini Hospital, Rome; 3AO Ospedali Riuniti, Università Politecnica delle Marche, Ancona; 4Dipartimento di Oncologia Medica, Università Politecnica delle Marche, Ancona; 5Università Federico II, Napoli; 6Istituto per la Ricerca e la Cura del Cancro, Candido; 7Medical Oncology Division, Azienda Ospedaliero Universitaria, Policlinico di Modena; 8Niguarda Ca’ Grande Hospital, Milan; 9Pol Oncologico PO Vito Fazzi, Lecce; 10Foundation IRCCS, National Institute of Tumours, Milan

Background. In recent years, TTS have improved the prognosis of mRCC patients. In spite of a not negligible number of pts receiving 3 TTs in clinical practice, no TTs have been evaluated as third-line. Aim of this study is to investigate the clinical outcome in pts who received 3 TTs.

Patients and methods. Patients with clear-cell mRCC who received 3 TTs were included. A questionnaire was sent to main Italian centers involved in the treatment of mRCC. Demographic data, history of RCC, type and length of first, second and third-line were collected; MSKCC risk class was calculated before first-line treatment were allowed on study until the target accrual at a significance level of 5%. Patients who underwent any other interest, a minimum targeted accrual of 47 pts in the sunitinib pretreated group was to be pursued in order to reach 90% power with documented progression after first-line treatment. Primary endpoint, a 6-mo PFS rate of 20% unacceptable (p = 0.01), for TKI>TKI→mTOR and TKI→mTOR→TKI or sunitinib (SU)-sorafenib (SO)-everolimus (EV) and SU-EV-SO. Median PFS, OS and time to strategy failure (TTSF: from start of first to end of third-line) were estimated with the Kaplan-Meier method with 95% CI and curves were compared with log-rank test. The study had the ethical approval.

Results. 1905 pts were screened and 252 pts (13%) were treated with 3 TTs. The median age was 60 yrs (range 52-68), 73% were male, 96% underwent nephrectomy and 38% were metastatic at diagnosis. At first-line, the Motzer class was good, intermediate, and poor in 48%, 47% and 5% of pts, respectively. PFS for type and line of therapy are reported in the Table. The TTSF was 36.4 (30.5-42.2) vs 30.6 (26.5-34.6) mos (p = 0.11), and the OS was 52.1 (41.6-62.6) vs 36.3 (31.2-41.4) mos (p = 0.01), for TKI>TKI→mTOR and and TKI→mTOR→TKI, respectively. TTSF for SU-SO-EV was 36.5 vs 30.4 mos for SU-EV-SO (p = 0.011). When stratified by ECOG-PS before third-line or baseline MSKCC, TS maintained its independent prognostic role (p = 0.002 and p = 0.004, respectively).

Conclusions. Only few patients received 3 lines of TTs. The sequence sunitinib-sorafenib-everolimus was associated with a better TTSF and OS as compared to the sequence sunitinib-everolimus-sorafenib.

Therapy First-line Second-line Third-line

<table>
<thead>
<tr>
<th>Therapy</th>
<th>% PFS</th>
<th>% PFS</th>
<th>% PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sunitinib</td>
<td>60</td>
<td>31</td>
<td>8</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>25</td>
<td>35</td>
<td>28</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bevac+FN</td>
<td>11</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Everolimus</td>
<td>0</td>
<td>30</td>
<td>55</td>
</tr>
<tr>
<td>Temsirolimus</td>
<td>2</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Other</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

F6* TEMSIROLIMUS AS SECOND-LINE TREATMENT FOR ADVANCED RCC: A PHASE II TRIAL BY THE ITALIAN KIDNEY CANCER GROUP (GIR) (mTOR TRIAL)


Regina Elena Cancer Institute, Rome; University of Naples Federico II; Ospedale Policlinico Universitario, Rionero in Vulture; Arcispedale S. Maria Nuova, Reggio Emilia; Azienda Ospedaliera C. Poma, Mantova; Istituto Scientifico S. Raffaele, IRCCS, Milano; Azienda Ospedaliera Santa Maria degli Angeli, Pordenone; USL 9, Ospedale Misericordia, Grosseto; Azienda Ospedaliera S. Paolo, Polo Universitario, Milano; Ospedale Unico Versilia, Livorno; Ospedale Belcolle, Viterbo

Background. The mammalian target of rapamycin (mTOR) kinase is an essential regulator of growth and response to hypoxic and metabolic stress and a well established therapeutic target in renal cell carcinoma (RCC). The mTOR inhibitor temsirolimus (CCI-779, Torisel®) is the first-line treatment of choice for RCC patients with poor-risk features. Preclinical and clinical evidence indicates that mTOR inhibitors may be effective in controlling RCC growth, even after resistance to agents targeting the VEGF/VEGFR axis ensues. Thus we designed a multicenter phase II trial to assess the activity and safety of temsirolimus as second-line treatment for advanced RCC patients.

Methods. This was an open-label, multicenter, phase II trial of temsirolimus (25 mg/wk i.v.); administered to advanced RCC pts with documented progression after first-line treatment. Primary endpoint was PFS rate at 6 months. Tumour response was assessed every 8 weeks. Considering a 6-mo PFS rate of 20% unacceptable (p = 0.01) and a 6-mo PFS rate of 40% (p = 0.40%) of interest, a minimum targeted accrual of 47 pts in the sunitinib pretreated group was to be pursued in order to reach 90% power at a significance level of 5%. Patients who underwent any other first-line treatment were allowed on study until the target accrual in the sunitinib pretreated group was met.

Results. From May 2009 to January 2012, 76 pts were enrolled (median age 67 yrs, range 36-86; M/F: 58/18; ECOG PS 0/1/2: 51/19/6); first-line therapy included sunitinib (60 pts), bevacizumab (8), sorafenib (3), cytokines (2), or other (3). With 18/57 evaluable patients free from progression at 6 mos in the
sunitinib pretreated group the primary endpoint was met. Median PFS was 4.0 mos (95% CI 2.7-5.3) and 4.6 mos (95% CI 2.8-6.5) in the overall (N = 71) and sunitinib pretreated (N = 57) populations, respectively; OS in the same groups was 13.7 mos (95% CI 9.1-18.3) and 14.6 mos (95% CI 8.9-20.3), respectively. Six out of 71 pts (8%) had PR and 33/71 (46%) had SD as their best response. Toxicity (N = 68) was mild with G3 anemia, neutropenia and thrombocytopenia in 2, 1, and 1 pt, respectively; G3 hyperglycemia and G3 hypertriglyceridemia in 2 and 7 pts, respectively; G4 hypercholesterolemia in 2 pts; G3 stomatitis in 5 pts; G3 asthenia in 3 pts; G3-4 pulmonary toxicity in 2 pts; G3 diarrhea in 2 pts; G3 cutaneous rash in 1 patient. Only 1 hypersensitivity reaction occurred during temsirolimus infusion. Treatment compliance was good, with <10% of weekly administrations omitted and 15/67 (22%) pts requiring dose reductions (to 20 mg/wk and 15 mg/wk in 11 and 4 pts, respectively). Mean number of weekly administrations received was 15.

Conclusions. Temsirolimus is an active and well tolerated second-line treatment for advanced RCC, particularly in sunitinib pretreated pts, and may constitute a suitable therapeutic option in this setting.

F7 DURABLE RADIOLOGIC AND CLINICAL DISEASE STABILITY BEYOND PSA PROGRESSION IN PATIENTS WITH METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (mCRPC) TREATED WITH ABI-RATERONE ACETATE (AA)


The Royal Marsden Hospital and The Institute of Cancer Research, Sutton, United Kingdom; The Institute of Cancer Research and Royal Marsden Foundation Trust, Sutton, United Kingdom; The Institute of Cancer Research, Sutton, United Kingdom; The Institute for Cancer Research and Royal Marsden Hospital, Sutton, United Kingdom; Royal Marsden Hospital, Dublin, Ireland; The Institute of Cancer Research and Royal Marsden NHS Foundation Trust, Sutton, United Kingdom; Royal Marsden NHS Foundation Trust, London, United Kingdom; Royal Marsden Hospital and Institute of Cancer Research, Sutton, United Kingdom; Institute of Cancer Research, London, United Kingdom; The Royal Marsden Hospital, Sutton, United Kingdom; The Institute for Cancer Research and Royal Marsden Foundation Trust, Sutton, United Kingdom

Background. AA, a potent oral CYP17A1 inhibitor is approved for treatment of mCRPC with a survival advantage of 4.9 months. In clinical practice, response evaluation remains challenging for pts with mCRPC. CTC conversion from CTC ≥5 to CTC <5 with treatment predicts for improved overall survival in mCRPC. We hypothesized that pts continue to have durable disease stability beyond PSA progression on AA.

Methods. Prostate specific antigen (PSA) responses, radiological responses and CTC conversion rates were retrospectively analysed in pts treated on AA at our institution. CTCs, PSA and imaging were obtained at predefined time points during these studies. Radiological and PSA progression were defined by standard Prostate Cancer Working Group Criteria II. Clinical progression consisted of worsening disease related pain, skeletal events or declining performance status. Pearson’s chi-squared test and the Kaplan-Meier method were used for this analysis.

Results. 141 patients [ECOG performance status 0-2; median age: 69.7 (range 44.7-87.1); 85 post-docetaxel, 56 pre-docetaxel] received AA. The median duration of clinical and radiological stable disease (SD) was 16.8 months (N = 55) and 5.6 months (N = 75) in patients with a baseline CTCs count of ≤5 cells/7.5mls and ≥5 cells/7.5 mls respectively. In the 105 patients with documented PSA progression on AA there was a median 5.7-month delay in detecting radiological and/or clinical progression (95% CI 4.2-8.4; range 0.3, 35.6 months). Radiological and clinical SD of ≥1 year, ≥2 years and ≥3 years on AA was observed in 43/141 (30.5%), 21/141 (14.9%) and 12/141 (8.5%) respectively.

Conclusions. Radiological and clinical disease stabilization beyond PSA progression is maintained in a high proportion of mCRPC patients treated with AA. Future studies should evaluate whether continued AA treatment beyond PSA and radiological progression can impact outcome.

F8 OVERALL SURVIVAL (OS) IN METASTATIC RENAL CELL CARCINOMA (mRCC) SEQUENTIALLY TREATED WITH DIFFERENT TARGETED THERAPIES (TTs): RESULTS FROM A LARGE COHORT OF PATIENTS

Procopio G., Verzoni E., Iacovelli R., Testa I., Grassi P., Garanzini E., De Braud F.

Fondazione IRCCS, Istituto Nazionale Tumori, Milano

Introduction. Targeted therapies (TTs) have improved survival in patients with mRCC. However the optimal therapeutic strategy is not entirely shared. This study was performed to assess the overall survival (OS) in a consecutive series of mRCC patients receiving TTs.

Methods. Baseline characteristics and outcomes of 336 patients were collected from the database of IRCCS Istituto Nazionale Tumori of Milan. The main characteristics of patients were: ECOG PS 0/1/2 186 (55%)/131 (39%)/19 (6%); clear-cell histology 291 (87%); previous nephrectomy 293 (87%). According to Motzer criteria, 32% of patients showed low risk, 48% intermediate and 20% had poor prognosis. Overall, 167 (50%) patients received one TT, while 116 (34%), 42 (13%) and 11 (3.3%) received 2, 3 and 4 TTs, respectively. Altogether, 245 (73%) patients received sorafenib (So), 212 (63%) sunitinib (Su), 33 (10%) a bevacizumab regimen and 73 (22%) other TTs, including everolimus, temsirolimus and axitinib. The uni- and multi-variate analyses for OS were carried out by means of Cox proportional hazard regression analysis.

Results. At a median follow-up of 43 months, 199 patients (57%) were dead. The median OS was 24 months (95% CI 20.0-27.0) and the 5-year OS was 24.6% (95% CI 18.7-30.8). In univariate analyses, there were no differences in the hazard ratios (HR) for sorafenib followed by sunitinib compared to sunitinib followed by sorafenib (HRSU/SO-SO = 1.16; 95% CI 0.57-2.33) or compared with other therapies (HR Other sequential th./SO-SU = 1.21; 95% CI 0.78-1.88; p = 0.674).

In the multivariate analysis, no difference in OS was reported as follows the regulation used (Su/So vs So/Su; p >0.05 or bevacizumab regimen) as compared to Su and/or So used sequentially (p >0.05). The ECOG PS, nephrectomy status, Fuhrman grade and previous cytokines treatments are independent predictive factors of outcome (p <0.01).

Conclusions. These efficacy data suggest that TTs improve OS in mRCC without any statistical difference when using different sequences. No cross-resistance between different TTs was documented.
F9 SAFETY OF ABRATERONE ACETATE (AA) IN PATIENTS WITH CASTRATION RESISTANT PROSTATE CANCER (CRPC) AND CONCOMITANT CARDIAC RISK FACTORS

Verzioni E., De Braud F., Testa I., Stagni S., Villa S., Valdagni R., Garanzini E., Procopio G.

Fondazione IRCCS, Istituto Nazionale Tumori, Milano

Introduction. Abiraterone acetate (AA) is an inhibitor of extraovarian androgen biosynthesis that prolongs overall survival in CRPC patients who have received a chemotherapy including docetaxel. The most common adverse events related to AA therapy were fluid retention, hypertension, hypokaliemia and cardiac disorders. No safety data are available in patients with concomitant cardiac disease.

Methods. Metastatic CRPC patients were enrolled in this prospective study if they were also suffering from a concomitant controlled cardiovascular disease. AA 1000 mg per day and prednisone 5 mg bid were administered orally until grade 3-4 adverse events (AE) or disease progression. The primary endpoint was the safety profile while the secondary endpoints were progression-free survival and PSA response.

Results. From April to September 2011, 46 CRPC patients with concomitant cardiovascular disorders have been treated with AA. Main patients characteristics were: median age 71 years (range 57-81); baseline mean PSA value 40 ng/mL (6.32-995); most common sites of disease were bone (33 pts, 81%), lung (13 pts, 33%) and liver (6 pts, 15%). No safety data are available in patients with concomitant cardiac disease.

Conclusions. Treatment with AA was feasible and well tolerated also in patients suffering from cardiac comorbidities and risk factors for cardiovascular disease.

F10 UPDATED SAFETY RESULTS OF A LARGE ITALIAN EARLY-ACCESS PROGRAM (EAP) WITH CABAZITAXEL PLUS PREDNISONE (CBZP) IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (mCRPC) PATIENTS WHO PROGRESED DURING OR AFTER DOCEFAXEL THERAPY

Di Lorenzo G.1, Gasparro D.2, Marchetti P.3, Boccardo F.4, Martoni A.5, Carteni G.6, Fornarini G.7, Baldazzi V.8, Dogliotti L.9, Messina C.10, Sisani M.11, Braarda S.12

1Azienda Ospedaliera Universitaria, Policlinico Federico II, Napoli; 2Azienda Ospedaliera Universitaria di Parma; 3Azienda Ospedaliera S. Andrea, Roma; 4Istituto Nazionale per la Ricerca sul Cancro, Genova; 5Policlinico Sant’Orsola Malpighi, Bologna; 6Azienda Ospedaliera A. Cardarelli, Napoli; 7Azienda Ospedaliera Universitaria Careggi; 8Azienda Ospedaliera Universitaria San Luigi, Orbassano; 10Azienda Ospedaliera Ospedali Riuniti, Bergamo; 11Presidio Ospedaliero San Donato, Arezzo

Background. A significant percentage of mCRPC patients, progressed on docetaxel therapy, have a long life expectancy and are candidates for additional treatments. In TROPIC trial patients who progressed during or after docetaxel had a significant OS advantage and clinical benefit with CbzP compared to mitoxantrone (MP). Benefits observed supported a global EAP.

Methods. We report the safety results of the first 90 patients entered into EAP and treated with CbzP, out of 232 patients enrolled by 25 Italian centers between Jan and Aug 2011

Results. Patients characteristics were median age 70 years (≥75 years, 22.2%); ECOG-PS 0-1, 97.8%; median number of previous docetaxel cycles 8 (median cumulative docetaxel 675 mg/m²); 14.1% received 675 ± 900 mg and 40.0% ≥900 mg of docetaxel. Median time from last docetaxel dose to first CbzP dose was 5.29 months including any other chemotherapy treatment. At the time of analysis 50% of patients had received 4 cycles of CbzP.

Thirty-three patients discontinued mainly due to PD (42.4%), AEs (related/not related, 27.3%), investigator’s (3.0%)/patients decision (18.2%) and others (9.1%). AEs resulting in CbzP discontinuation (10.0%) are mainly fatigue, pyrexia and haematological disorders. A total of 57 patients were still on treatment. In discontinued pts, CbzP has been delayed in 24.2% while a dose reduction occurred in 21.2% of patients.

Most common G 3/4 AEs were leukopenia (25.6%), neutropenia (48.9%), anaemia (6.7%), diarrhoea (1.1%), asthma (3.3%) and fatigue (5.6%). One death occurred during the study period in a heavily pretreated pt who received 33 cycles of docetaxel.

Conclusions. This preliminary safety analysis suggests the good tolerability of cabazitaxel, in terms of haematological as well as non-haematological AEs even in heavily pretreated patients according to the previous experience of Italian Centers in the TROPIC trial. This is remarkable because of the increased similarity of the patients populations treated in the EAP and daily clinical practice. Results of the extended Italian cohort will be presented.

F11 PROGNOSTIC VALUE OF PERIOSTIN EXPRESSION IN HUMAN PROSTATE CANCER

Nuzzo P.V.2, Rubagotti A.1,2, Zinoli L.1,2, Ricci F.1, Salvi S.1, Boccardo S.1,2, Truini M.1,2, Boccardo F.1,2

1IRCCS San Martino University Hospital, IST National Cancer Research Institute, Medical Oncology B, Genoa; 2University of Genova, Department of Internal Medicine, School of Medicine Genoa

Background. Prostate cancer (PCa) has become the most common malignancy among men. Many studies have focused on researching proteins of the extracellular matrix (ECM) for identifying novel tumours markers. Periostin (POSTN), an ECM protein produced by fibroblasts, seems to play a relevant role in human carcinogenesis.

Purpose. To investigate POSTN expression in PCa tissue specimens and in normal peritumoral specimens, in order to confirm its role in carcinogenesis and to evaluate its putative prognostic value also as a function of its compartmentalization.
Methods. POSTN expression in PCa cells and peritumoral stroma was immunohistochemically evaluated in a cohort of 90 patients undergoing retropubic prostatectomy by an immunoreactive score (IRS) based on the intensity of immunocoloration and the quantity of stained cells. The correlation with clinical pathological data and the risk of biochemical relapse and death was investigated on a retrospective basis.

Results. Both stromal and epithelial POSTN expression were significantly increased in tumour tissues as compared to normal tissues (p <0.000 and p = 0.001). In tumour tissues, stromal expression was significantly higher than epithelial expression (p = 0.003). A significant correlation between POSTN epithelial expression and capsular penetration was found (p = 0.03). At a median follow-up time of 134.4 months (range 33.7-178.2), 44 patients progressed and 19 died. While a high stromal (IRS value = 12, corresponding to the 75° percentile) POSTN expression was significantly associated with a shorter overall survival (p = 0.008), a low epithelial score (IRS ≤2, also corresponding to the 75° percentile) was significantly correlated with a shorter PSA-free survival (p = 0.04). The patients showing both a high stromal expression (IRS = 12) and a low epithelial expression (IRS ≤2) constituted a subgroup with shortest PSA-free (p = 0.004) and shortest overall survival (p = 0.002).

Conclusions. Our findings suggest that POSTN might play a relevant role in prostate tumorigenesis. They should be regarded as explorative and should be confirmed in a much larger set, also in order to better understand the different role of POSTN associated with its different compartmentalization.

F12 CABAZITAXEL PLUS PREDNISONE (CBZP) IN METASTATIC CASTRATION-RESISTANT PROSTATE CANCER (mCRPC) PATIENTS PREVIOUSLY TREATED WITH DOCETAXEL (D): EFFICACY AND SAFETY RESULTS FROM EARLY-ACCESS PROGRAM (EAP) SINGLE SITE EXPERIENCE


University Federico II, Genitourinary Cancer Section and Rare Cancer Center, Naples

Background. In the phase 3 TROPIC trial, mCRPC pts previously treated with D had a significant survival and clinical benefit with CbzP, a new tubulin-binding taxane, compared with mitoxantrone plus prednisone. The clinical benefits observed supported a global EAP, allowing pts with mCRPC to have access to Cbz prior to its commercial availability and providing safety and efficacy data in the real life population. We report the safety and efficacy results of 32 consecutive pts treated with CbzP in a single Italian center.

Methods. Patients recruited from a single center between March and December 2011 received Cbz 25 mg/m² IV q21 and prednisone 10 mg daily until disease progression, unacceptable toxicity, physician/pt decision or death. Biochemical and tumour response were assessed before cycle 6 and 12. Pain response was assessed in symptomatic pts before each cycle.

Results. Thirty-two pts were analyzed; median age was 67 years (≥75 years, 18%); 68.8% of pts had one previous D regimen and 31.2% ≥2 regimens, 93.8% had ECOG PS 0-1; median number of CbzP cycles was 8; 43.7% had pain at treatment initiation with a median PSA value of 85 ng/mL. All pts had bone metastases, 68% had visceral disease (visceral and nodes). The most common grade 3/4 adverse events (AEs) were neutropenia (64.5%) leukopenia (45.2%), and febrile neutropenia (9.7%, 3 pts). G3/4 diarrhea was reported in 1 patient. Efficacy results are reported in the Table.

<table>
<thead>
<tr>
<th>PSA response by Gleason (PSA decline &gt;50%)</th>
<th>6 cycles (N 32 pts)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA decline ≥50%</td>
<td>17 (53%)</td>
</tr>
<tr>
<td>PSA decline &lt;50%</td>
<td>15 (47%)</td>
</tr>
<tr>
<td>Progression</td>
<td>0</td>
</tr>
<tr>
<td>Tumour response (RECIST)</td>
<td>22 patients</td>
</tr>
<tr>
<td>PR + SD</td>
<td>19 (61.4%)</td>
</tr>
<tr>
<td>PD</td>
<td>3 (13.6%)</td>
</tr>
<tr>
<td>1 previous D regimen (17 pts)</td>
<td>6 (23%)</td>
</tr>
<tr>
<td>2-3 previous D regimen (15 pts)</td>
<td>5 (20.8%)</td>
</tr>
<tr>
<td>Pain response</td>
<td>14 patients</td>
</tr>
</tbody>
</table>
Conclusions. Our results indicate a high activity of cabazitaxel in terms of PSA, tumour and pain responses in all subgroups of pts analysed; cabazitaxel shows globally a good and manageable safety profile in daily clinical practice.

F13 HYPERTENSION IS THE MOST RELEVANT RISK FACTOR FOR CONGESTIVE HEART FAILURE (CHF) DURING SUNITINIB THERAPY IN GIST AND RENAL CELL CARCINOMA (RCC)


Fondazione del Piemonte per l’Oncologia, Istituto per la Ricerca e la Cura del Cancro, Candiolo (TO)

Sunitinib is associated with increased risk of CHF (Richards, JCO, 2011). CHF known predictor is a history of hypertension (Chu, Lancet, 2007). An early left ventricular ejection fraction (LVEF) decline recognition, sunitinib interruption and appropriate antihypertensive therapy are the only effective treatment for CHF prevention. Aim of this project was to enhance our ability to identify patients at risk to develop CHF. Between July 2007 and March 2012, 57 consecutive patients, median age 65 years (41-82) affected by either GIST (24) and RCC (33) were treated with sunitinib. In all patients, two expert cardiologists longitudinally studied LVEF at baseline, after 3 months, and every 6 months until progression or permanent sunitinib discontinuation. We prospectively recorded the following patients features: cardiovascular history, blood pressure, NYHA class, renal function, antihypertensive therapy. We searched correlations between CHF and patients features. Results were assessed with paired Student’s t-test and Chi-square test. Predictors of CHF were searched by means of logistic regression analysis. At baseline, we found 39 patients (68%) with hypertension. On sunitinib, 24 (42%) patients developed hypertension or worsened a preexisting one. We observed 9 patients (15%) with all-grade CHF and 3 (5%) with high-grade CHF (NYHA III-IV). In 24 patients (42%), we prospectively showed a median ≥10% LVEF reduction compared to baseline value (p <0.001). Predictor of ≥10% LVEF decline was the development of worsening of preexisting hypertension (p = 0.015) regardless of optimal antihypertensive therapy based on ACE inhibitors and/or beta-blockers. No difference was found between patients on sunitinib 50 mg 4 wks on/2 wks off and patients on sunitinib 37.5 mg every day (p = 0.75). Since only an early identification and treatment of patients at risk to develop CHF may reduce this complication, we suggest that worsening or progression or permanent sunitinib discontinuation. In total, 291 patients (9.2%) had a PS 2. 181 were in the experimental arm: 15.5% received chemotherapy (CHT) with cabazitaxel and 84.5% hormonal therapy (HT) with abiraterone acetate (45.3%) or MDV3100 (39.2%). 110 pts were in the control arm and received mitoxantrone (30%) or placebo (70%). In the overall cohort the HR for OS was 0.758 (95% CI 0.574-0.999, p = 0.049), no significant heterogeneity was observed (Q = 0.510; p = 0.774; I² = 0%). The subgroup analysis revealed that the HR for pts treated with CHT was 0.81 (95% CI 0.477-1.373, p = 0.434) and HR for pts treated with HT was 0.739 (95% CI 0.534-1.023, p = 0.068).

Conclusions. In this meta-analysis, we demonstrated a significant improvement in OS also for CRPC patients with a PS = 2 treated with second-line therapy after docetaxel failure compared with control patients. Considering the small number of pts with PS = 2 included in the trials, it is not possible to find out the best treatment option for this subgroup of patients.

F15 INCIDENCE OF ANEMIA WITH SORAFENIB (SO) AND SUNITINIB (SU) IN ADVANCED SOLID TUMOURS: A POOLED ANALYSIS OF 6 TRIALS

Maspero F, Petrelli F, Cabiddu M, Borgono K, Ghilardi M, Cremenesi M, Barni S.

Medical Oncology Division, A.O. Treviglio-Caravaggio, Treviglio

Introduction. Anemia is a common event associated with advanced cancer and linked both to neoplastic disease and oncological treatments. We described in a published meta-analysis of 24,310 patients affected by solid tumours, that the addition of targeted therapies to standard treatment increased by 7% the risk of all grades anemia (p = 0.09). Now we analyse the risk of anemia in patients treated with So and Su as single agent therapy.

Materials and methods. We searched PubMed for published, randomized, controlled, phase II and III trials (RCTs), and we have performed a pooled-analysis to calculate the incidence of anemia associated with So and Su. Relative risk (RR) with 95% confidence interval has been calculated to quantify the burden of anemia in these patients.

Results. Six studies have been selected, for a total of 2802 patients analysed. Four trials included Su and 2 So. Comparison
Arms were placebo in 3 trials, no therapy in 1 trial, axitinib in 1 trial and bevacizumab/INF or bevacizumab/temsirolimus in 1 trial. The overall incidence of anemia was 44% in experimental vs 34% in control arms (incidence difference 9.8%; p ≤0.0001). The RR was 1.19 (p = 0.02) (Figure 1). The risk is significant only for low grade anemia (G 1-2: incidence 42%) with RR = 1.19 (p <0.0001). A meta-regression was performed to calculate the weight of median treatment duration on anemia risk and the results is significant (p = 0.00046).

**Conclusions.** Sunitinib and sorafenib are associated with an high incidence of anemia events. The risk is increased by about 20% compared with control arms and it increases the longer is the duration of treatment. We think that this information is particular useful in kidney cancer patients which often are affected by anemia. The oncologists should pay attention to this hematological toxicity to prevent worsening of patients quality of life.

**F16 ABIRATERONE THERAPY SIGNIFICANTLY DECREASES BONE RESORPTION IN METASTATIC CASTRATE RESISTANT PROSTATE CANCER PATIENTS WITH PROGRESSIVE DISEASE TO DOCETAXEL AND Zoledronic ACID TREATMENT**

Vignani F.1, Tucci M.1, Buttigliero C.1, Bertaglia V.1, Fiori C.2, Porpiglia F.2, Scagliotti G.1, Berruti A.1


**Introduction.** Abiraterone acetate (AA), a strong inhibitor of androgen biosynthesis, is efficacious in the management of metastatic castration-resistant prostate cancer (mCRPC) with progressive disease to docetaxel therapy. More than 80% of CRPC patients have bone metastases and the effect of abiraterone therapy on bone turnover is not known.

**Purpose.** The present study was undertaken to assess the effect of AA on bone turnover markers and correlate these changes with antitumour activity. We present here preliminary results on early changes after 3 months of treatment.

**Experimental design.** mCRPC patients received AA 1,000 mg daily with prednisone 5 mg twice a day in 28-day cycles, the treatment was planned to be continued till progression. All patients had disease progression after docetaxel and were on zole-dronic acid therapy which was commenced at least 6 months before starting AA. Serum alkaline phosphatase (ALP), as a marker of bone formation, and serum c-telopeptide (CTX), as a marker of bone resorption, were measured every 3 months together with serum PSA. Circulating tumour cells (CTC) count was also prospectively assessed at baseline and after 3 months.

**Results.** Twenty-four patients have completed the 3 months evaluation. A decrease in serum PSA levels (≥30%) was observed in 11 patients (46%). Seventeen patients were evaluable for CTC count, 15 patients had detectable CTC and 11 showed a reduction in CTC count. A significant decrease in CTx values was observed: mean 1.18 (95% CI 0.7-1.6) and 0.86 ng/mL (95% CI 0.4-1.2) at baseline and at 3 months respectively (p <0.04). ALP showed a non-significant increase, mean 212 (95% CI 125-300) and 304 ng/mL (95% CI 170-438) at baseline and at 3 months respectively (p = 0.1).

**Conclusions.** These preliminary results suggest that in mCRPC patients with disease progression to chemotherapy and zoledronic acid, abiraterone therapy decreased significantly bone resorption. The increase of ALP suggests that bone repair may be a possible mechanism. Updated data will be presented at the meeting.
1994 to 2011: since DOC was introduced into our clinical practice in 2003, we separately evaluated two periods (P1: 1994-2002; P2: 2003-2011). We limited our search to male pts to avoid the bias due to the incidence of BM from breast cancer.

Results. 490 males with BM were referred to our ORDs (P1 = 241 pts; P2 = 249). The most frequent recognized primary tumour was lung cancer, with a similar percentage of BM for P1 and P2 (58.9 vs 60.6%). Concerning PC we collected a series of 9 pts with BM: 2 pts in P1 and 7 in P2 (0.8% and 2.8%, respectively). All but 2 pts had a CRPC. 6 pts developed BM during or after a DOC-based chemotherapy and 1 before first-line DOC start.

The median interval from the PC diagnosis and the achievement of CRPC was 25 mos (range 5-84) while the appearance of BM was documented after 0-111 mos (median 36) from diagnosis. The median survival after BM was 8 wks (range 1-54).

Conclusions. Our data appear to confirm that: 1) the BM from PC pts are more frequent than in the past; 2) this finding could be related to a survival improvement due to DOC introduction in the clinical practice.

F18 DOES A PATIENTS’ SELECTION STRATEGY ON THE BASIS OF ANGIOGENETIC BIOMARKERS INCREASE THE BENEFIT OF TARGETED AGENTS FOR ADVANCED RENAL CELL CARCINOMA (ARCC) PATIENTS? INTERACTION AND POWER ANALYSIS OF RANDOMIZED TRIALS (RCTs)

Massari F.1, Maines F.1, Pilotto S.1, Bonomi M.1, Giannarelli D.2, Melisi D.1, Brunelli M.2, Martignoni G.2, Tortora G.3, Bria E.1

1Medical Oncology d.U., 2Department of Pathology and Diagnostics, Azienda Ospedaliera Universitaria Integrata (AOUI) and University of Verona; 3Biostatistics, Regina Elena National Cancer Institute, Rome

Background. To increase the therapeutic ratio of sorafenib, pazopanib and bevacizumab in ARCC, several studies analyzed angiogenesis-related biomarkers (soluble VEGF and VEGF-receptors, VEGF polymorphisms, IL-8 polymorphisms and VHL mutations) as putative predictors of benefit. To assess how much a biomarker-based approach can affect the sample size of a trial in ARCC, a power analysis was conducted.

Methods. Hazard ratios (HR) for survival with 95% confidence intervals (CI) for overall survival were extracted and cumulated according to a random-effect model from RCTs. A sensitivity analysis according to ‘biomarker-selection’ approach and to ‘unselected’ fashion was accomplished in order to test for interaction. Testing for heterogeneity was performed as well.

Results. Three RCTs (1987 patients) reported treatment effect according to a featured biomarker; the attrition rate for the survival analysis according to the molecular analysis was 45% (range 20-60%). Although taking into account the wide difference in the analyzed biomolecular profiles (heterogeneity p = 0.002), a significant interaction according to strategy (‘biomarker-selected’ versus ‘unselected’) was found (p = 0.025). Indeed, the HR for overall survival in the ‘biomarker-selection’ approach was 0.60 (95% CI 0.40-0.89; p = 0.013), while in the ‘unselected’ sample was 0.90 (95% CI 0.80-1.00; p = 0.06), supporting a differential effect of these drugs when administered according to a predictive phenotype. From a clinical trial design perspective, if targeting these expected survival differences, with a power 80%, and an alpha-error 0.05, the required events would be:

<table>
<thead>
<tr>
<th>Patients</th>
<th>Expected survival difference</th>
<th>Required events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unselected</td>
<td>HR 0.90</td>
<td>2382</td>
</tr>
<tr>
<td>Biomarker-selected</td>
<td>HR 0.60</td>
<td>126</td>
</tr>
</tbody>
</table>

Conclusions. Although considering the large attrition and the heterogeneity in both the selected biomarkers and drugs, patients selection according to a biomolecular classifier may offer an important perspective for clinical trial design in RCC, and shorten the gap between clinical research and current practice.

F19 EFFECTS OF HEDGEHOG SIGNALING INHIBITION BY NVP-LDE 225 ON TUMOUR GROWTH AND INVASION OF HUMAN RENAL CANCER CELLS


Dipartimento di Oncologia ed Endocrinologia Molecolare e Clinica, Università degli Studi Federico II, Napoli

Introduction. Multiple lines of evidence support the idea that Hedgehog (Hh) signaling plays a role in the maintenance and progression of renal cell cancer (RCC). Therefore, the inhibition of the Hh pathway has been proposed as an interesting therapeutic approach for this cancer. NVP-LDE 225 is an oral specific Smo antagonist, that leads to dose-related inhibition of Hh-and Smo-dependent tumor growth.

Methods. In this study we used a wide panel of human RCC cell lines, including cells with acquired resistance to sunitinib, a multiple tyrosine kinase inhibitor (TKI) approved as a first-line for treatment of RCC patients. We tested the efficiency of the Smo-inhibitor NVP-LDE 225 on proliferation, migration, invasion and signal transduction of RCC cells.

Results. In most of the RCC cells, stimulation with recombinant Sonic Hedgehog (rShh) moderately induced proliferation and activation of the Hh pathway. MTT assays demonstrated that NVP-LDE 225 inhibits cell growth in a dose-dependent manner (IC50 ~ 2 microM). The expression of Gli1, the main transcription factor downstream to the Hh pathway, was reduced by treatment with the drug. Moreover, NVP-LDE 225 could modulate migration and invasion capability of RCC cells, particularly those resistant to sunitinib. Indeed, in presence of the drug, RCC cells showed reduced migration capabilities compared to untreated cells. As a confirm, the expression/activation of some factors involved in the migration pathway, such as N-cadherin and paxillin, were induced by rShh. In vitro specific assays suggested that NVP-LDE 225 could modulate migration and invasion capability of RCC cells, particularly those resistant to sunitinib. Indeed, in presence of the drug, RCC cells showed reduced migration capabilities compared to untreated cells. As a confirm, the expression/activation of some factors involved in the migration pathway, such as N-cadherin and paxillin, were induced by rShh. In vitro specific assays suggested that NVP-LDE 225 could modulate migration and invasion capability of RCC cells, particularly those resistant to sunitinib. Indeed, in presence of the drug, RCC cells showed reduced migration capabilities compared to untreated cells. As a confirm, the expression/activation of some factors involved in the migration pathway, such as N-cadherin and paxillin, were induced by rShh. In vitro specific assays suggested that NVP-LDE 225 could modulate migration and invasion capability of RCC cells, particularly those resistant to sunitinib. Indeed, in presence of the drug, RCC cells showed reduced migration capabilities compared to untreated cells.

Conclusions. Our results showed that NVP-LDE 225 has a specific role in regulating migration and invasion, rather than proliferation, of RCC cells. In order to confirm the effect of NVP-LDE 225 on in vivo tumour growth and metastatic process, an experiment in nude mice xenografted with RCC cells is ongoing.
F20 SEQUENTIAL USE OF TREATMENT OPTIONS IN ADVANCED RENAL CELL CARCINOMA (RCC): A RETROSPECTIVE ANALYSIS OF 42 CASES

Derosa L.1, Galli L.1, Fontana A.1, Antonuzzo A.1, Ciani C.1, Marconcini R.1, Biasco E.1, Farnesi A.1, Orlandi F.1, Fontana E.2, Falcone A.1,3

1Division of Medical Oncology 2, Azienda Ospedaliero-Università Pisan, Istituto Toscana Tumori, Pisa; 2Division of Medical Oncology, Azienda USL 6 of Livorno, Istituto Toscana Tumori; 3University of Pisa

Background. The best sequence of targeted therapy options has not been sufficiently defined and also the significance of cytokine (Cy) in TKI (sorafenib-So, sunitinib-Su) and mTOR era. The objective of this study was to describe the clinical activity of sequence options in second-line treatment.

Methods. Retrospective study of 42 patients receiving TKI or everolimus (EV) treatment after progression on first-line therapy. Sequence of targeted treatment consisted of a Cy-TKI-sequence (N = 20; Cy-So, N = 12; Cy-Su, N = 8), TKI-TKI-sequence (N = 15; Su-So, N = 11; So-Su, N = 4) or a TKI-EV-sequence (N = 7; Su-EV, N = 7). We measured response to treatment (RECIST 1.0). Progression-free survival (PFS) and overall survival (OS) were determined using the Kaplan-Meier method.

Results. Treatment groups did not significantly differ by gender, MSKCC prognostic group, or ECOG PS. Best response to second-line included CR (Su: N = 2, sequential therapy after Cy), PR (So: N = 3, after Cy) and SD (EV: N = 5, after TKI; TKI: N = 13; So: N = 5 after Cy, Su: N = 3 after So, N = 5 after Cy). The estimated second-line PFS was 5.2 months for EV and 5.86 months for So sequential therapy after Su, 6.56 months for So sequential therapy after So, 6.54 months for Su sequential therapy after So, and 6.56 months for Su sequential Cy. The estimated OS was longer for the group of patients receiving the Cy-TKI-sequence (49.87 months; 95% CI 16-26 for the group Cy-So and 40.36 months; 95% CI 16-26 for the group Cy-Su) and TKI-EV sequence (40.72 months; 95% CI 32-48) than for those receiving the TKI-TKI sequence (33.36 months, 95% CI 21-62) and Su-So (16.32 months, 95% CI 13-37). The TKI-TKI group was characterized by a relatively short first-line PFS (6.12 months of the Su-So group to 12.37 So-Su compared to 12.8 months of the TKI-EV group) which may in part explain the observed OS difference.

Conclusions. Common sequence treatment options may have comparable efficacy in terms of PFS and response. The observed differences in OS await further confirmation in prospective randomized trials.

F21 QUALITY OF LIFE AND LONG-TERM FIRST-LINE TREATMENT WITH SUNITINIB AS INDEPENDENT PROGNOSTIC FACTORS OF OUTCOME IN PATIENTS WITH METASTATIC RENAL CARCINOMA (mRCC): A PROSPECTIVE ANALYSIS

Sottotetti F.1, Bernardo A.1, Palumbo R.1, Tagliaferri B.1, Teragni C.1, Pozzi E.1, Quaquarini E.1, Azzara M.1, Riccardi A.2

1IRCCS Fondazione S. Maugeri, UO Oncologia Medica 2; 2Divisione di Oncologia, Università degli Studi di Pavia

Background. The management of treatment-related toxicities and preservation of an optimal quality of life (QoL) in patients receiving new biological agents for mRCC remains a challenging issue, especially for drugs with a proven correlation between exposition and position. Poor compliance because of toxicity is often a major limiting factor for long-term treatment with these drugs, reducing the possibility of achieving the best possible response. We elsewhere reported results of a prospective phase II study performed to assess activity and safety of sunitinib as first-line therapy in mRCC patients. Here we show the final updated results concerning QoL and prognostic factors analysis.

Patients and methods. Thirty-five consecutive pts were accrued from January 2007 to December 2010. Progression-free survival (PFS) and overall survival (OS) were calculated with Kaplan-Meier method; univariate and multivariate analysis were performed to identify potential prognostic factors; QoL was assessed by FACT-G score every 2 cycles.

Results. With OS data updated at December 2011, the median follow-up was 36 months (range 12-61). Thirteen (36%) partial responses (PR) and 19 stable diseases (53%) lasting >3 months were documented by RECIST criteria, for a global clinical benefit of 88%. Toxicities were expected and manageable: fatigue (42%), thrombocytopenia (25%), hand foot syndrome (15%), anemia (10%), hypertension (8%), neutropenia (5%), hypothyroidism (60%). Univariate analysis tumour grading, serum LDH and treatment duration were associated with better PFS and OS. On multivariate analysis duration of sunitinib treatment and maintenance of high QoL scores significantly correlated with longer OS (p = 0.02 and 0.03 respectively).

Conclusions. Our data suggest that patients who conserve high QoL scores and therefore receive a prolonged treatment are those exhibiting the best therapeutic outcomes, although the observed benefit could reflect a selection based on good performance status and more favorable disease biology. In the clinical practice, the possibility to modulate treatment doses and schedules on the basis of individual tolerance allows to achieve the best possible response in each patient.

F22 SUNITINIB IN ADVANCED RCC: COST-EFFECTIVENESS EVALUATION BASED ON CLINICAL PRACTICE

Trojniak M.P.1, Palozzo A.C.1, Imbevaro S.2, Rescigno P.2, Jirillo A.2

1Oncology Pharmacy Department, 2Evaluation and Introduction of New Drugs in Cancer Therapy Unit, Istituto Oncologico Veneto IRCCS, Padua

The approval trials have established sunitinib, multi-targeted TKI, a standard treatment in patients with metastatic RCC. RCTs may fail to show relevant clinical benefit in wider population and routine use, as certain patient subtypes are under-represented, notably those with poorer prognostic factors and pretreated.

The data were collected through national registry Onco-AIFA as part of the mandatory surveillance. RCC patients receiving sunitinib once daily, on schedule 4/2, between 2007 and 2011, had been checked prospectively for toxicity, clinical outcomes and length of treatment. Based on the difference in effectiveness in PFS between approval RCT and clinical practice, a new price adjusted for effectiveness has been calculated.

A total of 106 patients (64 years, M 70/F 36) were reviewed, 77% had prior nephrectomy and 74% were treatment-naïve. At
first evaluation we found 28% partial responses, 25% stable diseases, 45% progressions and one discontinuation due to toxicity. The median PFS and OS were 7 and 13 months, respectively. Among 79 RCC patients with metastases (mets) at first diagnosis, 63% had lung mets, 21% pts had liver mets, 21% had bone mets and 9% had brain mets. Cox regression model showed in subgroups analysis significantly worse survival prognosis in males, brain and liver mets, ECOG PS=1, non-clear cell histology and non-prior nephrectomy. Sorafenib treatment after progression on sunitinib (33% pts) did not improve OS. Grade 3 thrombocytopenia, neutropenia, mucositis and HFS caused dosage reductions. Effectiveness adjusted price was 3.87 euro/mg as opposed to the ex-factory price of 2.46 euro/mg proportionally to the difference of PFS form RCTs (11 months) and that form clinical practice oncology (7 months).

The results show that sunitinib clinical benefit in RCC patients was gained in selected responders, but in overall the effectiveness was nearly half of that reported in the approval RCTs. Evaluating cost-effectiveness ratio, price should be at least 36% lower than actual ex-factory price based on net clinical benefit achieved in real life practice.

**F23 OUR EXPERIENCE OF ABIRATERONE ACETATE (AA) PLUS PREDNISONE IN PATIENTS WITH PROGRESSIVE METASTATIC CASTRATION RESISTANT PROSTATE CANCER (mCRPC) AFTER FAILURE OF DOCETAXEL BASED CHEMOTHERAPY IN COMPASSIONATE USE PROGRAM (CUP)**

Accettura C.1, Giampaglia M.1, Leo S.1, Chiuri V.E.2, Licchetta A.1, Petrucci L.1, Gambino A.1, Lupò L.1, Saracino V.1, Lorusso V.1

1U.O. Oncologia Medica “Vito Fazzi” Hospital, Lecce; 2U.O. Oncologia “A. Panico” Hospital, Tricase (Lecce)

**Background.** A proportion of mCRPC overexpress androgen synthetic enzymes and are dependent on androgens for growth. Abiraterone acetate is a potent, selective, and orally bioavailable small molecule inhibitor of CYP17, an enzyme that catalyzes two key serial reactions in androgen and estrogen biosynthesis. The most common adverse events related to AA therapy were fluid retention, hypertension, hypokaliemia.

**Methods.** AA plus prednisone was studied in pts with mCRPC who had progressed on docetaxel based chemotherapy. Patients received, prior to commercial availability in compassionate use program (CUP), oral AA 1000 mg QD and prednisone 5 mg BID in 30 day cycles until disease progression, death or unacceptable toxicity.

**Results.** From June 2011 in our Oncology Department, 23 pts with metastatic CRPC were screened and 18 treated. The median age was 63 years (47-80) and median PSA baseline 384 ng/mL (56-4258). Prior systemic therapy included at least 2 lines of hormone therapy in all patients. Moreover 9 pts received one, and 9 two lines of chemotherapy respectively. Sites of metastases were bone only in 9 pts (50%), bone and lymph nodes in 3 (17%), bone and visceral in 4 (22%), and bone and soft tissue in 2 (11%). Of 18 pts treated, 14 were evaluable, 2 are too early, 2 lost to follow-up, 9 pts (64%) remained on treatment for 2-3 months (mos) and 5 (36%) for 4-7 months. At 2 mos, 4 of 14 pts (29%) achieved a decline in PSA ≥50% from baseline and 1 pt in subsequent cycles. Seven pts (50%) had reduced pain during the first 2 months of treatment and 1 pt had partial response in liver metastases. AA with regard to toxicity has shown a favorable safety profile: no toxicity related to mineralocorticoid excess.

**Conclusions.** AA plus prednisone was feasible and well tolerated and has demonstrated PSA declines and improvements in pain control in pts with mCRPC after failure of docetaxel based chemotherapy.

**F24 ASSESSMENT OF EMERGING MOLECULAR PATHWAYS IN METASTATIC CLEAR CELL RENAL CARCINOMA**

Maines F.1, Massari F.1, Zampini C.2, Brunelli M.2, Martignoni G.2, Bria E.1, Sava T.3, La Russa F.3, Molino A.3, Tortora G.1

1Medical Oncology d.U., 2Department of Pathology and Diagnostics, 3Medical Oncology d.O., Azienda Ospedaliera Universitaria Integrata (ADU) and University of Verona

**Background.** Several molecular markers and signaling pathways have been proposed as predictors of poor prognosis and drug-responsiveness in patients with localized renal cell carcinoma (RCC), while less data are available in mRCC. We sought to investigate some markers, in particular the loss of chromosomes 3p, 9p (-9p) and 14q, in patients with mRCC who received targeted therapies, doing some correlations with clinical parameters.

**Materials and methods.** From a database containing 91 patients, affected by mRCC, either on the resected primary tumour or on the metastases, and treated with at least one target therapy, we evaluated the -9p, -14q and -3p in the first 23 patients for whom an immediate surgical paraffin block was available. Clinical parameters and outcomes were extracted from a single-institution kidney cancer database. We performed an interphase FISH analysis using a telomeric-specific probe mapping on the chromosome 9p, 14q and 3p telomeres and a centromeric probe mapping on chromosome 9 and 3. The presence of single fluorescent signal in more than 40% of the nuclei was interpreted as “deletion”. The relationship between cytogenetic results and clinical variables, including tumour size, histological grade and MSKCC score, were retrospectively assessed using chi-square test.

**Results.** 3p, 9p and 14q were found deleted in 18/23 (78%), 8/18 (44%) and 9/15 (60%) primary tumours and in 17/18 (94%), 3/17 (17%) and 3/17 (17%) metastases respectively; wild-type in 2/23 (8%), 1/18 (5%) and 3/15 (20%) primary tumours and in 2/18 (11%), 2/17 (11%) and 1/17 (5%) metastases respectively; not evaluable in the remaining. -9p was observed in 20% G1-2 versus 58% G3-4 (p = 0.05) and in 40% of pT1-2 versus 46% pT3-4 (p = 0.06). -9p was not observed in cases with Metz score favorable versus 64% with intermediate/poor score.

**Conclusions.** -9p is significantly observed in carcinomas with pT3-4 and high grading and shows a trend in further stratifying patients with different MSKCC risk group. While more cases are under evaluation, this study suggests that integration of molecular and clinical data could greatly improve the prognostic classification of mRCC.

**F25 HIGH DOSE CONTINUOUS INTRAVENOUS INFUSION IL-2 (HD-civ-IL-2) IN METASTATIC RENAL CELL CARCINOMA (mRCC): STILL AN OPTION?**

**Background.** Targeted therapy has markedly improved the prognosis of mRCC but chronic treatment is needed to maintain benefit. A relatively short treatment with HD-civ-IL-2, instead, may provide in some patients long-lasting responses.

**Materials and methods.** From April 2001 to September 2011, we treated 21 mRCC patients, 16 males and 5 females, with HD-civ-IL-2, according to West schedule (18 MU/m² days 1-5 q14 x 4). Predominant metastatic sites were: lung (14 pts), lymph nodes (7 pts) and liver (3 pts). Four pts were pretreated: 3 with TK and 1 with m-tor inhibitors. All pts had excellent PS and 15/21 had no comorbidities: the remaining pts presented mild hypertension, associated with type II diabetes in 1 patient.

**Results.** Patients were followed for 1-116 mos (median 6). Fourteen pts completed the 4 planned cycles, while 7 stopped after 1-2 cycles for rapid progressive disease. Overall, treatment resulted in 10 progressions, 2 complete remissions (1 after surgery of a small residual lesion), 4 partial remissions, and 5 stable diseases. The median duration of response was 12.5 months (3-60) with the 2 CR pts still NED after 4 and 1 year, respectively. Major toxicities were due to capillary leak syndrome and consisted primarily of G3 hypotension, associated with fever and anuria in 14 pts. All side effects recovered rapidly after the end of treatment. Finally, 2 out of the 4 pts previously treated with targeted therapy experienced severe non-fatal cardiac toxicity (myocardial infarction in 1 case and atrial fibrillation with rapid ventricular response in the other).

**Conclusions.** In selected mRCC pts HD-civ-IL-2 may provide long-lasting responses, avoiding the need of chronic treatment. However, the complexity of the treatment in the acute phase and the lack of predictive factors of response, makes difficult to select pts to whom offer this opportunity.

**F26 CORRELATION BETWEEN URINARY TRACT CANCER (UTC) AND DIABETES: A CASE CONTROL STUDY**

Pazè E., Brusa F., Consito L., Ciuffreda L.
SC Oncologia Medica I, AOU S. Giovanni Battista, Torino

There is growing interest in correlation between glycemic metabolism and cancer development. Diabetes has been associated with increased incidence of breast, liver, pancreas, colon and urinary tract/bladder cancer. Hypoglycemic drugs may have both protective and causative tumour effect and increased insulin secretion together with its metabolic pathways seems to be involved in cancer growth.

We studied incidence of diabetes in a group of 145 UTC patients with stage II-IV disease who were diagnosed and treated at our Institution between 2005 and 2009. We postulated a direct cancerogenic effect of diabetes on bladder tissue and in order to prove this we did a comparison with a group of lung cancer patients matched according to age and gender.

Data concerning patients characteristics, smoking (smoking habit was not known for every patient) and diabetes incidence are shown in Table 1.

**Conclusions.** In our case-control study we did not detect any difference in diabetes incidence between UTC patients, lung cancer patients and a control population.

**F27 OBSERVATIONAL CROSSOVER STUDY OF CABAZITAXEL AND ABIRATERONE ACETATE IN METASTATIC, DOCETAXEL-REFRACTORY, CASTRATION-RESISTANT PROSTATE CANCER**

Bracarda S.¹, Sisani M.¹, Hamzaj A.¹, Marroccolo F.¹, Del Buono S.¹, De Angelis V.²
¹Ospedale San Donato, Arezzo; ²Ospedale S. Maria della Misericordia, Perugia

**Background.** In recent years both cabazitaxel (Cbz) and abiraterone acetate (AA) showed to be efficacious treatment options for patients with metastatic, docetaxel-refractory, castration-resistant prostate cancer (mDR-CRPC). However, no data exist for patients treated with both these drugs. Aim of our study was to analyze these data in a real world scenario.

**Materials and methods.** Intention-to-treat (ITT) analysis of activity data deriving from all consecutive patients with mDR-CRPC treated in our unit with prednisone plus Cbz, AA or both.

**Table 1 F26**

<table>
<thead>
<tr>
<th>M/F</th>
<th>Born before 1930</th>
<th>Born 1931-1940</th>
<th>Born 1941-1950</th>
<th>Born after 1951</th>
<th>Active smokers</th>
<th>Former smokers</th>
<th>Never smokers</th>
<th>Diabetes</th>
<th>No diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>UTC pts</td>
<td>117/28</td>
<td>19</td>
<td>61</td>
<td>53</td>
<td>12</td>
<td>28</td>
<td>80</td>
<td>17</td>
<td>28</td>
</tr>
<tr>
<td>Lung ca pts</td>
<td>117/28</td>
<td>19</td>
<td>61</td>
<td>53</td>
<td>12</td>
<td>48</td>
<td>60</td>
<td>4</td>
<td>24</td>
</tr>
</tbody>
</table>

**Table 2 F26**

<table>
<thead>
<tr>
<th>UTC patients</th>
<th>Lung cancer pts</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>24</td>
<td>19</td>
</tr>
<tr>
<td>No diabetes</td>
<td>88</td>
<td>93</td>
</tr>
<tr>
<td>Never smokers</td>
<td>16</td>
<td>4</td>
</tr>
</tbody>
</table>
Primary endpoint of the study was median progression-free survival (mPFS), evaluated according to Prostate Cancer Working Group 2 (PCWG2) criteria.

**Results.** Here we report characteristics and activity data of 42 patients, 8 treated with Cbz, 24 with AA and 10 with both drugs. The median age of our study population was 70.5 years (range 55-82), median Gleason score 8 (4-9) and median ECOG PS 0 (0-3); visceral disease was present in 28 cases (66.7%). The mPFS, according to Kaplan-Meier method (KM), was 4.7 months (mos) for patients treated with Cbz, not reached for cases treated with AA and 6.7 mos for cases treated with both agents. Of the 10 patients treated with both drugs, 6 received a sequence Cbz-AA and 4 a sequence AA-Cbz for an overall median PFS of, respectively, 6.7 and 4.6 mos.

**Conclusions.** In our limited experience, both Cbz and AA confirmed an intriguing activity in the mDR-CRPC setting. Moreover, both drugs seem to be active also in a sequential use. These data should be verified in large size prospective studies to avoid potential selection biases.

---

**F28 A MODEL OF INTEGRATED PSYCHO-ONCOLOGICAL INTERVENTION FOR PATIENTS WITH TESTIS CANCER**


**Psycho-oncological Service, *Medical Oncology Department, San Vincenzo Hospital, Taormina**

**Introduction.** The multifaceted therapeutic approach for testis neoplasms determines important clinical psycho-emotional triggers that require specific psycho-oncological interventions. In young pts orchidectomy gives rise to a range of issues related to sexuality, gender identity and body image; medical treatment involves a period of psychophysical “fatigue” relevant on a personal level and impacts on patients quality of life; furthermore, follow-up period also reactivates the dysphoric dimension for a considerably long period of time following the diagnosis. Based on such premises, our Psycho-oncological Service has developed a project for pts with testicular cancer to ensure the care of the “psycho-emotional response” in all phases of treatment, in order to avoid iatrogenic neurosis and to enable the processing of disease experience during the follow-up period.

**Patients and methods.** The project includes two distinct phases simultaneously developing: a) group psychotherapy for patients in follow-up and b) psychological therapy during diagnosis and treatment through clinical interventions for individuals and family.

The therapeutic group met over six months, once every two weeks. Two psychologists coordinated each group meeting to facilitate verbal dealing, sharing of experiences and containment of emotions among participants.

To date, forty-six pts with testicular cancer are still followed up by Psycho-oncological Service. As to psychological care by means of clinical interviews, 115 individual psychological interviews, 42 individual sessions of psychotherapy and 45 psychological familial interviews have been conducted.

**Observations and preliminary results.** Mood disorders are present in almost all pts undergoing adjuvant chemotherapy; anxiety symptoms persist even after many years (up to 12) in those pts who did not receive psychological therapy from the treatment starting (diagnosis prior to the implementation of Psycho-oncological Service in our Hospital); less detection of anxiety symptoms in pts treated psychologically from the early stages of treatment; better management of dysphoria in pts treated with radiotherapy.

More wide and detailed data will be reported in final release of extensive work.

---

**F29 A CASE OF HEMATOPOIETIC PROGENITOR AND STEM CELLS (HPSC) MOBILIZATION WITH PLERIXAFOR IN TESTICULAR CANCER PATIENT TREATED WITH HIGH DOSE CHEMOTHERAPY (HDCT)**

De Blasio A.1, Rossi L.2, Zoratto F.2, Papa A.2, Pacilli M.1, Ortu La Barbera E.1, Coppetelli U.1, Zappone E.1, Carbone A.3, Tomao S.2

1*Haematology Unit, S.M. Goretti Hospital, Latina; 2Department of Medical-Surgical Sciences and Biotechnologies, Oncology Unit, S.M. Goretti Hospital, “Sapienza” University of Rome, Latina; 3Department of Medical-Surgical Sciences and Biotechnologies, Urology Unit, “Sapienza” University of Rome, Latina

**Introduction.** Plerixafor, CXCR4 antagonist, induces rapid release of HPSC from bone marrow into peripheral blood; it is approved for autologous HPSC mobilization in multiple myeloma and non Hodgkin’s lymphoma patients. This is a case report of successful plerixafor use in advanced testicular cancer patients treated with HDCT.

**Case report.** In January 2011, testis embryonal carcinoma was diagnosed in a 33-year-old patient. Staging CT scan showed a lung micronodule of unknown significance and pre-surgery markers were altered (IS Stage: pT2cN0cM0; S1). Patient underwent orchiectomy followed by 3 cycles of cisplatin-etoposide. Before chemotherapy β-HCG was 86 mUI/mL, while dFP was 135 ng/mL, after 3 cycles were 3.06 mUI/mL and 2.05 ng/mL respectively but revaluation CT scan showed new not typable lung micronodules. Additional 3 cycles of cisplatin-etoposide were given but subsequent PET demonstrated lung disease progression and increase of tumour markers occurred. Then patient started HDCT with etoposide (300 mg/m2), carboplatin (250 mg/m2) and ifosfamide (1500 mg/m2) (ICE) but inadequate number of HPSC was not mobilized following stimulation with granulocyte colony stimulating factor (G-CSF). In an attempt to reach target quantity of CD34+ plerixafor was used. Following a cycle of cyclophosphamide (4000 mg/m2) whit support of G-CSF, plerixafor was administered at a dose of 24 mg/die in eleventh and twelfth day with increase in circulating CD34+. 5 x 10^6 CD34+ cells/kg body weight were harvested over 2 consecutive days. Meantime, revaluation PET showed lung and abdominal disease progression and β-HCG value increased (88 mUI/mL). HDCT with ICE plus paclitaxel (175 mg/m2) was administered. Autologous peripheral blood stem cell transplantation was performed in the seventh day. Therapy has been discreetly tolerated and complete hematological recovery was obtained on the fortieth day. At first biochemical and radiological control there was reduction of β-HCG but uptake of PET was significant. At four months after transplantation HDCT was discontinued.

**Discussion.** In patients suffering from advanced germ cell cancer, plerixafor with G-CSF may be an innovative option for HPSC mobilization to investigate during HDCT.
F30 IMPACT ASSESSMENT OF THE REGIONAL GUIDELINES PUBLISHED IN 2009 ON PROSTATE CANCER AND METHODS FOR MONITORING THEIR SYSTEMATIC IMPLEMENTATION


Department of Oncology Network Piedmont and Valle d’Aosta; *Cancer Epidemiology, AOU San Giovanni Battista in Turin-CPO Piedmont

Introduction. Prostate cancer (PC) is a major public health problem. In many countries the incidence of PC has increased in recent decades, while the mortality rate is basically stable over time. The regional guidelines (GL) on PC have been prepared by the Cancer Commission and the Center for cancer prevention in the context of the Regional Oncological Network (RON) in order to favor some changes in the management of the disease. The drafting of the GL started in 2005, and it was published in 2009.

Objectives. The main objective of the project was the definition of rules for the dissemination of regional guidelines, and the development of methods for the systematic monitoring of their adoption.

Materials and methods. The spread of the regional guidelines has occurred through placement on web sites, mailing the printed document, organization of seminars for presentation and discussion at the Regional Cancer Poles, Case Management Services (CAS) and other services of the RON. Subsequently, we used data from routinely collected health databases to define several indicators (at regional level) including: PC incidence and mortality, PSA exams, prostate biopsies, CAS and Interdisciplinary Care Group (GIC) visits, radical prostatectomies. We then evaluated the time trends of these indicators (with an approach before-after) to assess long-term impact of the GL implementation.

Results. For several indicators related to the initial diagnostic steps (mainly due to opportunistic screening, an activity not recommended by the GL) we observed a progressive decrease starting from 2005. The analysis of the visits carried out in 2009 at CAS and GIC shows that these were made in about 10% only of patients with newly diagnosed PC, a figure unchanged from the previous year and probably linked to the traditional management of the patient at diagnosis done by the urologists.

Conclusions. The current health records (in- and particularly out-patients records) can be an important source of information for monitoring the implementation of some recommendations of the GL.

F31 RECHALLENGE TREATMENT WITH DOCETAXEL IN ELDERLY PATIENTS WITH CASTRATION-RESISTANT PROSTATE CANCER: OUR EXPERIENCE

Iaculli A., Cotroneo G., Duluc M., Galdy S., Rodà G., Bonassi L., Nastasi G.

U.O. Oncologia Medica, A.O. Bolognini di Seriate (BG)

Background.Docetaxel is the current standard of care in castration-resistant advanced prostate cancer, basing on the results of large phase III trials (TAX327, SWOG9916). Most patients respond to first-line docetaxel and complete treatment, experiencing disease progression during the follow-up. In daily practice some patients discontinue treatment not because of a disease progression, but for the occurrence of manageable side-effects; most of them have a good PS and require further treatment. Until the introduction of new effective drugs, no second-line options were available; previous phase II studies and experiences evaluated the role of a docetaxel-based rechallenge treatment in responders, suggesting the feasibility and clinical efficacy.

Patients and methods. From March 2010 to February 2012, 9 elderly patients (median age 76, range 75-83) with mCRPC (5 bone, 3 lymph node and/or local relapse, 1 lung), with clinically, biochemically or radiologically progressing disease after a first-line docetaxel treatment (median of 5 cycles; 4-8), underwent a re-treatment (maximum 8 cycles; 3-8; total 42); all patients had a biochemical and clinical-symptomatic progression.

Results. We observed 2 biochemical responses (>50% decrease in PSA), 4 minor biochemical responses (30-50% decrease), 1 stable disease (<30% decrease), 2 biochemical progressions; a clinical benefit (pain relief), was observed in 6 patients. Median number of cycles to best biochemical response was 4. Treatment was well tolerated, with 5 grade 3/4 neutropenia, 8 grade 3 stomatitis, 2 grade 3 neuropathy; most common toxicities were mild nausea, diarrhea and stomatitis.

Conclusions. In our experience, rechallenge treatment with docetaxel is feasible and well tolerated, with clinical and biochemical efficacy, even in elderly and pretreated; G-CSFs may ameliorate treatment compliance. An accurate selection is required, to balance clinical goals and QoL parameters. Such strategy, beyond effective second-line options, could be symptoms palliation, disease control and delay of a second-line. No statements are possible on survival endpoints; a large European retrospective study is ongoing, but prospective, randomized trials are needed.

F32 BRCA2 GERMLINE VARIATIONS AND HEREDITARY PROSTATIC CANCER

Adami F., Carbonardi F., Cengarle R., Pisanelli M.B., Rabbi C., Cavazzini G., Cavello P.

Medical Oncology and Hematology Department, Mantua; Genetic Service, Cremona

Men with a father or brother with prostate cancer are twice as likely to develop prostate cancer as men with no affected relatives. The risk increases with increasing number of affected relatives, such that men with 2 or 3 first-degree relatives affected have a 5-fold and 11-fold increased risk of prostate cancer, respectively.

Dominantly inherited susceptibility is the cause of 5-10% of the prostate cancer cases. Among patients with early onset disease, 30-50% may carry a germline mutation in a prostate cancer susceptibility gene. No such gene has yet been identified, but several chromosome loci likely to comprise such genes have been detected.

In 1996, a genome-wide search with linkage analysis resulted in the mapping of a prostate cancer susceptibility gene to chromosome 1q24-25. This gene, named HPC1 (hereditary prostate cancer gene 1), was linked to prostate cancer in one-third of the 79 North American and 12 Swedish families studied. Linkage to HPC1 is more prevalent in families with early onset prostate cancer and is more easily detected in large families with many affected members. Recently a prostate cancer susceptibility gene
was indeed located to the long arm of the X chromosome (Xq27-28). The gene, named HPCX, accounted for 15-16% of the North American and up to 41% of the Finnish hereditary prostate cancer cases analysed. The risk of prostate cancer for male carriers of mutations in BRCA1 or BRCA2 is increased three-fold compared with those who are not carriers.

In our family we performed BRCA2 germline variations: C125 A/G, Tyr42Cist and C6665 A/G, Tyr2222cyst.

Conclusions. Our results suggest an important role for BRCA2 mutations in prostatic disease. A correct surveillance in the BRCA2 carriers males including PSA annual evaluation and annual urologic examen.

F33 BLADDER CANCER: CT UROGRAPHY VERSUS CYSTOSCOPY: DIAGNOSTIC YIELD AND LIMITS

Capalbo E.1,2, Peli M.1,2, Lovisatti M.1,2, Cosentino M.1,2, Berti E.2, Kluzer A.2, Cariati M.2

1School of Specialization of Diagnostic and Interventional Radiology, University of Study Milano; 2Department of Science Diagnostic, UOC of Diagnostic and Interventional Radiology, Hospital San Carlo Borromeo, Milano

The purpose is to evaluate diagnostic accuracy of CT urography (UTC) versus cystoscopy in diagnosis of bladder cancer.

From January 2010 to December 2011, 169 patients consecutively with suspicion bladder cancer performed both cystoscopy and CTU. We calculated sensitivity, specificity, diagnostic accuracy, positive predictive value (PPV) and negative predictive value (NPV) and κ Cohen’s coefficient. We evaluated also that contrastographic phase is more diagnostic in patients with bladder cancer.

CT urography sensitivity, specificity, diagnostic accuracy, PPV and NPV were of 96.3%, 86.4%, 92.8%, 92.9% and 92.7% respectively and a good concordance with κ Cohen = 0.8413. We had 8 false positives, described by histology as wall thickening with inflammation meaning, and 4 false negatives described as millimeter cancer (2-3.5 mm). In the 106 positive UTC, the arterial phase has a higher diagnostic accuracy than other acquisition phases, identifying 93.4% of bladder lesions, only in 7 patients (6.6%) with vegetating lesions, mean size 1.8 cm, localized on the lateral and postero-lateral wall mostly on the right, the arterial phase was not diagnostic.

CT urography is an accurate examination in evaluation of bladder cancer, among acquisition phases, the arterial is the best diagnostic phase, but today the gold standard diagnostics is cystoscopy.

F34 NON-PEGYLATED LIPOSOMAL DOXORUBICIN IN PROSTATE CANCER PATIENTS REFRACTORY TO HORMONE THERAPY. OUR EXPERIENCE

Carnicelli P., Mogavero A., De Filippo M., De Luca P., Citera M., Barzelloni M.L.


Introduction. Prostate cancer is one of the most common cancers in men (15% of human cancers) after their 50s years. For patients unsuitable for radical treatment the first choice of treatment is hormone therapy. In the cases with patients refractory to hormone therapy, chemotherapy can be used as therapeutic strategy, even if the chemosensitivity of prostate cancer is rather low. Among the active ones there are platinum, anthracyclines and taxanes drugs.

Methods. Between January 2010 and January 2012 we have observed several cases with patients refractory to hormone therapy. Twenty of these patients, average age 74 years (range 60-82) with a PS 0-1, with a diagnosis of adenocarcinoma of the prostate refractory to hormone therapy, progressing after two lines of chemotherapy (docetaxel in first-line and vinorelbine second-line), with an average Gleason score at diagnosis of 7 (range 6-9), an average PSA of 245 ng/mL (range 55.00-2100 ng/mL), an average LDH 800 U/L (range 187-1856 U/L), an average Hb 10.9 g/dL (9.2-13.7 g/dL), all with measurable disease (regional lymph node or lung metastases) were treated, after signing informed consent for off-label, with the non-pegylated liposomal doxorubicin dose of 75 mg/m² every 21 days for a total of 6 cycles. The toxicities were grade 1/2, only for 3 patients there was a G3 neutropenia and anemia G3 in 1 patient.

Results. The response to chemotherapy was assessed on measurable lesions on the performance of PSA. The results obtained were as follows: 3 RP instrumental, 14 SD instrumental and 3 PD instrumental. In 12/20 patients we obtained a reduction of the PSA ≥50%, in 5/20 patients, the PSA has remained unchanged and in 3/20 patients there was an increase in the PSA ≥25%.

Conclusions. The data of the literature shows that the non-pegylated liposomal doxorubicin is an active drug in vitro in cells of prostate cancer refractory to hormone therapy. The clinical results obtained with our little experience are the same as the data of the literature. It is also important to point out the tolerance to the treatment in all the elderly patients who have received many chemotherapy lines.
**G1* THE EUROPEAN IPILIMUMAB EXPANDED ACCESS PROGRAMME (EAP): EFFICACY AND SAFETY DATA FROM THE ITALIAN COHORT OF PATIENTS WITH PRETREATED, ADVANCED MELANOMA**

Ascierto P.A.1, Chiarion Sileni V.2, Del Vecchio M.3, Altomonte M.4, De Galittis F.5, Ridolfi L.6, Cognetti F.7, Testori A.8, Bernengo M.G.9, Queirolo P.10

1Istituto Nazionale per lo Studio e la Cura dei Tumori, Fondazione Pascale, Napoli; 2Istituto Oncologico Veneto, Padova; 3Istituto Nazionale Tumori, Milano; 4Policlinico Le Scotte, Siena; 5Istituto Dermopatico dell’Immacolata, Roma; 6Istituto Scientifico Romagnolo per lo Studio e la Curac dei Tumori, Meldola; 7IFO, Istituto Regina Elena, Roma; 8Istituto Europeo di Oncologia, Milano; 9A.O.U. San Giovanni Battista, Torino; 10Istituto Nazionale per la Ricerca sul Cancro IST, Genova

**Purpose.** Ipilimumab was the first agent approved for the treatment of unresectable or metastatic melanoma that showed an overall survival benefit in a randomised phase III trial. Here, we evaluate the safety and efficacy of ipilimumab treatment outside of clinical trials in patients enrolled in the EAP in Italy.

**Methods.** Ipilimumab was available upon physician request for patients aged ≥16 years with unresectable stage III/IV melanoma who had either failed systemic therapy or were intolerant to ≥1 systemic treatment and for whom no other therapeutic option was available. Ipilimumab 3 mg/kg was administered intravenously every 3 weeks for 4 doses. Tumour assessments were conducted at baseline and after completion of induction therapy using immune-related response criteria. Patients were monitored for adverse events (AEs), including immune-related AEs, within 3 to 4 days of each ipilimumab dose using Common Terminology Criteria for Adverse Events v.3.0.

**Results.** In total, 848 Italian patients participated in the EAP from June 2010 to April 2012 across 53 centers. Of these 848 patients, data are currently available for 563 patients. With a median follow-up of 3 months, the disease control rate among 468 evaluable patients was 31.4%, including 7 patients with a complete response, 51 with a partial response and 89 with stable disease. As of April 2012, median progression-free survival and overall survival were 3.1 months and 6.2 months (range 0.1-22.7 months), respectively. In these 18 pts, we compared median progression-free survival and overall survival between the two techniques was low (Cohen kappa 0.36; CI 95% 0.17-0.55). Of the 18 pts with SD according to RECIST, a total of 13 (72%) pts were reevaluated to responder (8 PR, 44%) and non-responder (5 PD, 28%) groups, while only in 5 cases SD was confirmed using CHOI criteria. Median PFS and OS for SD RECIST pts were 8.3 and 22.7 months, respectively. In these 18 pts, we compared median PFS and OS of responders (CR + PR, N = 8) vs non-responders (SD + PD, N = 10) according to CHOI criteria. PFS was 11.2 vs 7.9 (p = 0.05), and OS 23.3 vs 15 months (p = 0.21).

**Conclusions.** Our analysis suggests that CHOI criteria may be helpful to define response, according to both RECIST and CHOI criteria.

**G2* SUPERIORITY OF CHOI VS RECIST CRITERIA IN EVALUATING OUTCOME OF ADVANCED SOFT TISSUE SARCOMA (STS) PATIENTS TREATED WITH SORAFENIB**

De Santis R.1, Bertuzzi A.F.1, Magnoni P.2, Giordano L.3, Gasco M.3, Lutman R.2, Santoro A.3

1Department of Medical Oncology and Hematology, 2Department of Radiology, 3Biostatistic Unit, Humanitas Cancer Center, Istituto Clinico Humanitas, IRCCS, Rozzano, Milan

**Background.** Objective tumour response may be underestimated by RECIST criteria, since biological agents can cause metabolic response (necrosis) not related to tumour size. For this reason, CHOI criteria were designed to evaluate both tumour density and size. We compared CHOI and RECIST criteria in evaluating response to sorafenib in patients with advanced STS, treated within a phase II trial. The objective was to compare CHOI and RECIST criteria and to relate response to progression-free (PFS) and overall survival (OS).

**Patients and methods.** Sixty-one advanced STS patients received sorafenib 400 mg twice daily for progressive or relapsed disease after anthracycline-based chemotherapy. Treatment was continued until progression or major toxicity. Contrast-enhanced CT was performed every 3 months. Thirty patients were evaluable for response, according to both RECIST and CHOI criteria.

**Results.** A total of 30 patients were included in the analysis. According to RECIST, we observed 1 (3%) complete response (CR), 1 (3%) partial remission (PR), 18 (60%) stable diseases (SD) and 10 (34%) progressive diseases (PD) at 3 months. According to CHOI, we observed 1 (3%) CR, 10 (34%) PR, 5 (16%) SD and 14 (47%) PD. The agreement between the two techniques was low (Cohen kappa 0.36; CI 95% 0.17-0.55). Of the 18 pts with SD according to RECIST, a total of 13 (72%) pts were reevaluated to responder (8 PR, 44%) and non-responder (5 PD, 28%) groups, while only in 5 cases SD was confirmed using CHOI criteria. Median PFS and OS for SD RECIST pts were 8.3 and 22.7 months, respectively. In these 18 pts, we compared median PFS and OS of responders (CR + PR, N = 8) vs non-responders (SD + PD, N = 10) according to CHOI criteria. PFS was 11.2 vs 7.9 (p = 0.05), and OS 23.3 vs 15 months (p = 0.21).

**Conclusions.** Our analysis suggests that CHOI criteria may be helpful to define response, according to both RECIST and CHOI criteria.
Purpose. In the registrational phase III trial of ipilimumab, patients who progressed after initially responding to ipilimumab treatment could subsequently receive additional ipilimumab therapy with the same treatment regimen (reinduction). Here, we describe efficacy and safety data from the Italian subgroup of patients in the EAP who received reinduction with ipilimumab outside of a clinical trial setting.

Methods. Ipilimumab was available upon physician request for patients aged ≥16 years with life-threatening, unrespectable stage III/IV melanoma who failed or did not tolerate previous treatments and for whom no therapeutic option was available. Induction therapy with ipilimumab was 3 mg/kg every 3 weeks for 4 doses. Patients who progressed after stable disease (SD) lasting ≥3 months or an initial partial response (PR) or complete response (CR) were eligible for reinduction therapy at the same dose/schedule. Tumour assessments were conducted at baseline and after completion of induction therapy using immune-related response criteria. Patients were monitored for adverse events (AEs), including immune-related AEs, within 3 to 4 days of each ipilimumab dose using Common Terminology Criteria for Adverse Events v.3.0.

Results. Of 848 patients participating in the EAP in Italy, 59 received reinduction treatment. After a median follow-up of 10 months, the disease control rate among 26 reinduced patients with data available was 100%, comprising nine patients with a PR and 17 with SD. Overall, only two reinduced patients died as a result of disease progression, after 11 and 13 months. As of April 2012, median overall survival for patients that received reinduction therapy had not yet been reached. In total, 57% patients reported grade 1/2 AEs. Grade 3/4 AEs were reported by 15% patients, but only considered drug-related in one patient. AEs were generally reversible with treatment as per protocol-specific guidelines.

Conclusions. Considering available data, reinduction with ipilimumab resulted in durable objective responses and/or stable disease. No new types of toxicities occurred during reinduction and most events were mild-to-moderate.

G4* TIME TREND INFLUENCE OF SOCIOECONOMIC STATUS ON SURVIVAL, BRESLOW THICKNESS, TIME FROM ONSET OF SYMPTOMS AND SURGICAL RESECTION IN STAGE I-II PRIMARY CUTANEOUS MELANOMA

Mandalà M.1, Imberti G.2, Piazzalunga D.3, Lucisano G.4, Merelli B.1, Marchesi L.2, Gianatti A.5, Labianca R.1, Ansaloni L.3, Tondini C.1

1Medical Oncology, 2Dermatology, 3Surgery, 4Pathology, Ospedali Riuniti Bergamo; 5Epidemiology, Mario Negri Sud

Objective. To investigate the time trend influence of socioeconomic status (SES) on Breslow thickness (BT) and survival in patients with stage I-II primary cutaneous melanoma (PCM).

Patients and methods. Pathologic and sociodemographic characteristics of prospectively collected, consecutive pts diagnosed with PCM between November 1, 1998, and July 31, 2009 were evaluated. We categorized SES into 3 levels: low (manual employees and skilled/unskilled workers, including farmers, with primary education level), middle (non-manual employees and clerks with middle education level), and high (professionals, executives, administrators, and entrepreneurs with tertiary education). We divided the representative years between 2000 and 2009 into three-year periods: 2000-2002, 2003-2005 and 2006-2009. In the multivariate analysis models the following variables were tested: SES, marital status, sex and age.

Results. A total of 1274 available patients were analyzed. Overall a progressive decrease of BT and ulceration's rate was observed (Table 1). In the first four-year period, gender and age correlated with BT and ulceration [m vs f OR (95% CI): 1.66 (1.10-1.52) and (>60 vs ≥60 OR (95% CI): 2.08 (1.35-3.20), respectively. In the second and third four-year period only SES correlated with Breslow thickness [low vs high OR (95% CI): 2.32 (1.27-4.26), middle vs high OR (95% CI): 2.26 (1.28-4.00)], respectively. Overall the median time from onset of symptoms and surgical resection decreased for high and middle but not for low SES patients. SES correlated with symptoms (Table 2). Finally compared with high SES, the risk of melanoma-related death, adjusted for age and sex, was 7 times higher (hazard ratio 7.44; 95% CI 3.27-16.93) in patients with low SES living alone.

Conclusions. Our data for the first time demonstrates that BT and survival decreased over time but not for low SES patients. These pts should be considered the optimal target for future prevention campaign.

Table 1 - Time trend BT and ulceration's rate decrease in stage I-II primary cutaneous melanoma

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N. Group</td>
<td>417</td>
<td>442</td>
<td>415</td>
<td></td>
</tr>
<tr>
<td>Breslow_r (median)</td>
<td>0.60</td>
<td>0.50</td>
<td>0.45</td>
<td>0.0002</td>
</tr>
<tr>
<td>(Q1-Q3)</td>
<td>(0.32-1.35)</td>
<td>(0.30-1.25)</td>
<td>(0.21-0.92)</td>
<td></td>
</tr>
<tr>
<td>Ulcer, N. (%) No</td>
<td>308</td>
<td>354</td>
<td>340</td>
<td>0.014</td>
</tr>
<tr>
<td></td>
<td>(77.58)</td>
<td>(83.69)</td>
<td>(85.00)</td>
<td></td>
</tr>
<tr>
<td>Ulcer, N. (%) Yes</td>
<td>89</td>
<td>69</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(22.42)</td>
<td>(16.31)</td>
<td>(15.00)</td>
<td></td>
</tr>
</tbody>
</table>

Table 2 - SES and time from onset of symptoms and surgical resection

<table>
<thead>
<tr>
<th>OR stepwise Effect</th>
<th>OR</th>
<th>Lower CL</th>
<th>Upper CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>SES1 low vs high</td>
<td>1.57</td>
<td>1.11</td>
<td>2.24</td>
</tr>
<tr>
<td>SES1 middle vs high</td>
<td>1.53</td>
<td>1.12</td>
<td>2.10</td>
</tr>
<tr>
<td>Gender M vs F</td>
<td>0.68</td>
<td>0.51</td>
<td>0.89</td>
</tr>
</tbody>
</table>

G5* RE-SURGERY FOR RECURRENT GLIOBLASTOMA: PROGNOSTIC FACTORS FOR OUTCOME

Poggi R.1, Ermanni M.2, Franceschi E.1, Fioravanti A.3, Andreoli A.3, Pozzati E.3, Bacci A.4, Occhilupo P.1, Degli Esposti R.1, Lombardo L.1, Bartolini S.1, Crisi G.3, Brandes A.A.1

1Medical Oncology Department, Bellaria-Maggiore Hospital, Azienda USL, Bologna; 2Department of Neurosciences, Statistic and Informatic Unit, Azienda Ospedaliero-Universitaria, Padova; 3Neurosurgery Department, 4Neuroradiology Department, Bellaria-Maggiore Hospital, Azienda USL, Bologna; 5Neuroradiology Department, Azienda Ospedaliero-Universitaria, Parma

Introduction. Treatment options for glioblastoma at recurrence are various in despite of the limited efficacy. Surgical re-
section has been used both for confirmation of recurrent disease as well as for debulking in order to provide relief of symptoms. Therefore, the role of surgical resection for recurrent glioblastoma has not been completely clarified.

Methods. A retrospective analysis was made for glioblastoma patients followed between 01/2005 and 06/2010. Eligibility criteria for the study were: age ≥18 years; PS 0-2; chemotherapy at disease progression after RT/TMZ, availability of data regarding second progression.

Results. 232 patients with recurrent glioblastoma (mean age 52 years, range 18-77 years, MGMT methylated/unmethylated 62 [37.6%]/103 [62.4%]) were evaluated. At progression after RT/TMZ, 102 patients (44%) were treated with re-surgery followed by chemotherapy, and 130 patients (56%) with chemotherapy alone. Overall survival from first surgery was 22.4 months (95% CI 20-24.7), being 25.8 months (95% CI 20.6-31) in patients who received second surgery at recurrence, and 18.6 months (95% CI 17-20.1; p = 0.003) in patients treated without surgery. However, in multivariate analysis no significant effect of re-surgery was found (p = 0.11) being age (p = 0.001), MGMT methylation (p = 0.002) and PFS6 (p = 0.0001) the only significant prognostic factors. Moreover, median time between first and second surgery was 13.1 months, being significantly longer in patients with MGMT methylated than in patients MGMT unmethylated (19.3 vs 13 months; p = 0.001).

Conclusions. Our data suggested that second surgery may have a limited impact in the clinical course of recurrent glioblastoma patients. MGMT methylation status, as well other clinical factors (i.e. age) remain the major prognostic determinants of the outcome.

G6* CAUSES OF DELAY IN DIAGNOSIS AND TREATMENT OF SOFT TISSUE SARCOMAS (STS): A PROSPECTIVE ITALIAN STUDY


Gruppo Piemontese Sarcomi

Background. STS are 1% of malignant tumours in adults. Rarity, heterogeneity in presentation, low expertise in primary care physicians (PCP) or in general hospitals, organization problems in specialized centers may cause a delay in both diagnosis and treatment. Aim of this study is to acknowledge the barriers to optimal care and the consequences of the delay on prognosis.

Patients and methods. Patients with STS of the extremities, trunk, retroperitoneum treated and followed from 1999 to 2011 were included.

Time and pattern of symptoms onset, anatomic site, tumour volume, patients age, gender and home; interval between diagnosis and surgical treatment or neoadjuvant chemotherapy; time to start of adjuvant RT or CT were considered.

Results. 449 adult patients (53% F, 47% M, median age 55 years) were followed for a median time of 116.38 months. 65.7% of STS were at the extremities, 17.6% retroperitoneal, 16.7% at the trunk wall. Median volume at diagnosis was 8 cm for trunk and extremities, 15 cm for retroperitoneum. Commonest histologies: liposarcoma 18.2%; leiomyo 16.8%; mixofibro 13.6%. Increasing mass, pain and abdominal discomfort were the main revealing signs of disease. Median time of delay were: from onset of symptoms to first medical visit 68 days for trunk and extremities, 82 for retroperitoneum; 104 days from symptoms to histological diagnosis; 129 days from symptoms to start of therapy. Time to surgery after definitive diagnosis was 12 days in extremities and 21 in abdomen. Adjuvant CT started 22 days after surgery for extremities, 25 in trunk, 35 in retroperitoneum. RT initiated after 78 days. Longer delay in treatment led to worse prognosis: MS 89.95 months if delay was >3 months; 190.40 months if wait was <3 months (p = 0.007).

Conclusions. Misdiagnosis or inadequate approach in general hospitals and late referral to specialized centers are 75% of the causes of wasted time. Organization problems at the referral Center concur for 25% of delay. Guidelines implementation among PCP and general hospitals is necessary.

G7 EFFICACY AND SAFETY OF IPILIMUMAB IN PATIENTS WITH PRETREATED, MUCOSAL MELANOMA: EXPERIENCE FROM ITALIAN CLINICS PARTICIPATING IN THE EUROPEAN EXPANDED ACCESS PROGRAMME (EAP)

Del Vecchio M.1, Simeone E.2, Chiarion Sileni V.3, Nuzzo C.4, Rinaldi G.5, Testori A.6, De Gallitis F.7, Queirolo P.8, Marconcini R.9, Maio M.10

1Istituto Nazionale Tumori, Milano; 2Istituto Nazionale per lo Studio e la Cura dei Tumori, Fondazione Pascale, Napoli; 3Istituto Oncologico Veneto, Padova; 4IFO, Istituto Regina Elena, Roma; 5AUP Policlinico Paolo Giaccone, Palermo; 6Istituto Europeo di Oncologia, IEO, Milano; 7Istituto Dermopatico dell’Immacolata, Roma; 8Istituto Nazionale per la Ricerca sul Cancro IST, Genova; 9AOU Pisana “Spedali Riuniti di Santa Chiara”, Pisa; 10Policlinico Le Scotte, Siena

Purpose. Mucosal melanoma is an extremely rare and aggressive malignancy associated with a poor prognosis. Because of its rarity and the challenges associated with each anatomical location, mucosal melanoma often remains undetected until it is at an advanced stage, when effective treatment options are limited. The EAP provided an opportunity to assess the activity and safety of ipilimumab in patients with mucosal melanoma outside of controlled clinical trials from the EAP in Italy.

Methods. Ipilimumab was available upon physician request for patients aged ≥16 years with stage III (unresectable) or stage IV skin, ocular or mucosal melanoma, who had failed or did not tolerate previous treatments and for whom no therapeutic option was available. Patients were treated with ipilimumab 3 mg/kg every 3 weeks for 4 doses. Tumour assessments were conducted at baseline and after completion of induction therapy using immune-related response criteria. Patients were monitored for adverse events (AEs), including immune-related AEs, within 3 to 4 days of each scheduled visit using Common Terminology Criteria for Adverse Events v3.0.

Results. Of 848 Italian patients participating in the EAP, 70 (8.2%) had mucosal melanoma. Of these, data are available for 50 patients. With a median follow-up of 2.5 months, the disease control rate among 39 evaluable patients was 23.1%, including one patient with a complete response, two patients with a partial
response and six with stable disease. As of April 2012, median progression-free survival and overall survival among patients with mucosal melanoma were 3.9 months and 6.2 months (range 1.5-19.9), respectively. In total, 40.0% patients reported an AE of any grade, most of which were drug-related (32.0%). Grade 3/4 AEs were reported by 18.0% patients and considered drug-related in 12.0%. AEs were generally manageable and most resolved with treatment as per protocol-specific guidelines.

Conclusions. Results from the EAP suggest that ipilimumab is active in some patients with mucosal melanoma and warrants further investigation in prospective clinical trials.

G8 EXPRESSION OF THYMIDINE PHOSPHORYLASE AND CYCLOOXYGENASE-2 IN MELANOMA: CLINICOPATHOLOGICAL CORRELATIONS

Poletto E.1, Pascoletti G.1, Minisini A.M.1, Iacono D.1, Rihawi K.1, Intersimone D.2, Spizzo R.3, Driol P.1, Di Loreto C.2, Pasini G.6, Polselli A.7, Foca F.1, Rengucci C.8, Gentili G.1, Faedi M.2

1Department of Medical Oncology, 2Department of Pathology, Azienda Ospedaliero-Universitaria di Udine; 3Department of Experimental Oncology 1, CRO Aviano

Background. Several studies have demonstrated an increase of vascular structures in malignant melanoma. Neovascularization can be enhanced by several factors. Among them thymidine phosphorylase (TP) and cyclooxygenase 2 (COX-2) have been reported to play a role.

Methods. The expression of TP and COX-2 were evaluated through immunohistochemistry in a series of 78 primary cutaneous melanomas diagnosed between 2000 and 2004. Expression of TP and COX-2 through mRNA and Western Blotting analysis were also evaluated in several melanoma cell lines (SKMEL28, A375P1, TMX, DM14, MeWo, M14, COLO38, 1259CL, EC6LCP, patient 1 and patient 2). Mann-Whitney test, Chi-Square test and Kaplan-Meier method were used for statistical analysis.

Results. TP expression and COX-2 expression were considered positive in 25 cases (32%) and 22 cases (28.2%) respectively. TP-positive melanomas showed lower mitotic rate (median 0 vs 2; p = 0.008), smaller thickness (median 0.73 mm vs 2.6 mm; p = 0.01) and absence of lymphovascular invasion (p = 0.04). COX-2 positive melanomas showed higher mitotic rate (1 vs 3.5; p = 0.01) and higher thickness (3.0 mm vs 1.2 mm; p = 0.03).

Median follow-up was 7.6 years. COX-2 expression was associated with reduced DFS (p = 0.01). COX-2 positive cases showed a trend for reduced survival while TP was not correlated with OS.

COX-2 expression was detected in 4 of 11 melanoma cell lines both by mRNA and Western Blotting analysis. We showed a correlation between mRNA and protein level expression. We also detected TP mRNA expression in some cell lines, but mRNA levels were much lower than COX-2 mRNA expression and we did not detect protein expression in any tested cell lines.

Conclusions. Our study shows that TP expression is associated with more favorable prognostic factors (thin melanoma, low mitotic count and absence of lymphovascular invasion) while COX-2 expression is associated with poor prognostic factors (thicker melanoma and high mitotic count).

G9 IS MGMT STATUS REALLY A PREDICTIVE MARKER IN GBM IN THE CLINICAL PRACTICE?

Dall’Agata M.1, Melegari E.2, Gamboni A.3, Dazzi C.4, Cerasoli S.5, Pasini G.6, Polselli A.7, Foca F.1, Rengucci C.8, Gentili G.1, Faedi M.2

1UBSC IRCCS Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST); 2DH Oncocinematoogic Cesena, IRCCS IRST; 3Oncologia, AUSL Faenza; 4Oncologia, AUSL Ravenna; 5Anatomia Patologica, AUSL Cesena; 6Oncologia, AUSL Rimini; 7Oncologia, AUSL Cattolica; 8Laboratorio di Bioscienze, IRCCS IRST, Meldola (FC)

Background. Malignant gliomas (GBM) are the most common types of malignant primary brain tumours. In despite of progresses made in treatment, the median survival is between 12 and 15 months.

EORTC/NCIC trial (2005) showed that radiotherapy (RT) plus concomitant temozolomide (TMZ), followed by up to six cycles of adjuvant TMZ increased the median survival (OS) from 12.1 to 14.6 months, with a median follow-up of 28 months.

The MGMT (O6-methyl guanine-DNA methyl transferase) is implied in tumoral resistance, because interferes with the therapeutic effects of chemotherapy alkylating agents such as TMZ. The methylation of MGMT, resulting in gene silencing, is associated with better prognosis.

Aim. To retrospectively evaluate the correlation between MGMT status and survival for patients with GBM treated between 2008 and 2011 in Area Vasta Romagna.

Materials and methods. MGMT methylation status was available for 47 patients with newly diagnosed GBM. They were all treated with RT+ concomitant TMZ, followed by adjuvant TMZ for most of them.

Results. Median age was 61 years (range 35-73); 31 males and 16 females. Median follow-up was 32 months (7-69), median survival was 21 months (16-23).

Twenty-three patients were MGMT unmethylated, 24 were methylated. In the first group median OS was 19 months (16 NE) (not evaluable), whereas in the second group was 23 (14-NE) (p = 0.87).

We also analyzed OS correlated to MGMT status and number of cycles of TMZ (<6 versus ≥6) and only to TMZ treatment.

Conclusions. Our data showed that MGMT methylated improved OS as reported in the literature. Prolonged TMZ treatment increases significantly survival both in MGMT methylated and in unmethylated: 76% of patients were alive at 24 months from diagnosis versus 11%.

One question remains open: is MGMT methylation status or prolonged TMZ treatment to influence patients survival?
We will update our analysis for AIM Congress considering some important prognostic factors like performance status, radical surgery and the increase of our cases.

G10 PROTEOMIC PROFILE MODIFICATIONS INDUCED IN MALIGNANT MELANOMA CELLS BY THE CURCUMIN ANALOGUE COMPOUND D6


Istituto di Chimica Biomolecolare, CNR, Sassari; *Porto Conte Ricerche Srl., Alghero (SS)

Malignant melanoma (MM) is one of the most aggressive cancers that affect humans for which, in the advanced stages, there is no effective therapy: search for new compounds able to control it is therefore essential.

We have already demonstrated that an hydroxylated biphenyl compound ((3E,3*E)-4.4'-((5,5',6,6'-tetramethoxy-[1,1'-biphenyl]-3,3'-diyl) bis(but-3-en-2-one)), called D6, structural analogue of curcumin, showed a strong antitumor activity on MM cells (about ten times more than curcumin itself) both in vitro and in vivo. The mechanisms of action of this compound are not clear yet, but it inhibits cancer cells growth and induces apoptosis through the mitochondrial intrinsic pathway.

In order to investigate the modifications of protein expression following the treatment of MM cells with D6 we performed a proteomic analysis on a primary MM cell line (LB24Dagi) treated or not with 10 μM D6. GelC-MS/MS techniques (in-gel tryptic digestion followed by liquid chromatography-tandem mass spectrometry) were performed to extract and identify all the proteins characterizing the proteome profile for each sample. Upon data analysis, a total of 984 different proteins were identified with high confidence. A comparison between the proteomic profiles of D6 treated and untreated samples was carried out according to spectral counting protein abundance estimation, and 62 proteins were detected as differentially expressed (27 over-expressed and 35 under-expressed in the D6 treated samples). Observing the top ten up-regulated molecules in the D6 treated cells we noted that most of them belong to the heat shock protein (HSP) family while, among the top ten down-regulated molecules, the majority are involved in the protein translation machinery. HSPs have a protective function in stress conditions but they also have an essential role in the apoptosis regulation that is one of the mechanisms by which D6 causes cell growth inhibition. A pathway analysis is now ongoing by using the ingenuity pathway analysis (IPA) software in order to shed light on the molecular pathways involved in the D6 antitumoral activity.

G11 IMATINIB MESYLATE IN DESMOPLASTIC SMALL ROUND CELL TUMOUR

Bertuzzi A.1, Bisogno G.2, Carli M.2, Ferrari A.3, Comandone A.4, Gasco M.1, De Sanctis R.1, Gnocchi C.6, Santoro A.1

1Humanitas Cancer Center, Milan; 2Clinica di Onco-Ematologia Pediatrica, Padova; 3Fondazione IRCCS, Istituto Nazionale dei Tumori, Milano; 4Presidio Sanitario Gradenigo, Turin; 5Novartis Farma, Origgio

Introduction. Desmoplastic small round cell tumour (DSRCT) is a very rare and aggressive mesenchymal neoplasia with an extremely poor prognosis. The typical translocation t (11;22) determines the overexpression of PDGFRα and β, responsible of clinical stromal fibrosis reaction constantly detected in abdominal lesions. We investigated the role of imatinib, as tyrosine kinase inhibitor of PDGF-R, in DSRCT.

Patients and methods. From August 2005 to June 2009 we enrolled patients with histologically proven diagnosis of DSRCT, refractory to conventional treatment. Inclusion criteria comprised immunohistochemical positivity of imatinib targets (PDGFRα and β). Treatment consisted of imatinib 400 mg p.o. daily. Primary endpoint of the study was objective response rate. Secondary endpoint was safety and tolerability assessment.

Results. Of the 13 enrolled patients, 8 pts were evaluable for response (4 screening failure and 1 never treated). Median age was 20 years (range 9-32). M/F ratio was 3/1. ECOG PS was 0 in 6 patients. Median time from diagnosis was 24.5 months (range 6-148). 75% of pts had metastastic disease. The primary site was abdominal-pelvic for all patients. PDGFRα and β were expressed with an heterogeneous intensity pattern. Objective responses at first radiological evaluation at 3 months were: stable disease in one pt (12.5%) and progressive disease in 7 (87.5%) patients. Treatment-related adverse events were G1-2 nausea/vomiting, fatigue and periorbital oedema.

Conclusions. In our limited case series, imatinib showed no efficacy in the treatment of DSRCT pts unresponsive to conventional therapy, in despite of molecular-based selection of patients. Probably to identify responder pts, it is necessary a more complex evaluation comprehension of both levels of expression and activation of PDGFRα and β. Furthermore, enrolled pts were affected by advanced refractory disease, probably less responsive to target therapies. It would be hopeful a global effort to define a new combined approach based on the association of conventional chemotherapy and biological drugs.

G12 EFFICACY AND SAFETY DATA FROM PATIENTS WITH ADVANCED MELANOMA AND BRAIN METASTASES PARTICIPATING IN THE EUROPEAN IPILIMUMAB EXPANDED ACCESS PROGRAMME (EAP) IN ITALY

Quierolo P.1, Simeone E.2, De Gallitis F.3, Di Guardo L.4, Di Giacomo A.5, Marconcini R.6, Ferraresi V.7, De Rosa F.8, Guida M.9, Stragliotto S.10

1Istituto Nazionale per la Ricerca sul Cancro IST, Genova; 2Istituto Nazionale per lo Studio e la Cura dei Tumori, Meldola; 3Istituto Tumori Giovanni Paolo II, IRCCS, Bari; 4Istituto Oncologico Veneto, Padova

Introduction. Patients with melanoma brain metastases have a very poor prognosis and are usually excluded from melanoma clinical trials. The EAP provided an opportunity to evaluate the feasibility of ipilimumab treatment in this patient population outside of a controlled clinical trial in Italy.

Purpose. Ipilimumab was available upon physician request for patients aged ≥16 years with unresectable stage III/IV
melanoma, including those with asymptomatic brain metastases, who had either failed systemic therapy or were intolerant to ≥1 systemic treatment. Induction therapy with ipilimumab was 3 mg/kg every 3 weeks for 4 doses. Tumour assessments were conducted at baseline and after completion of induction therapy using immune-related response criteria. Patients were monitored for adverse events (AEs), including immune-related AEs, within 3 to 4 days of each ipilimumab dose using Common Terminology Criteria for Adverse Events v.3.0.

Results. Of 848 patients with advanced melanoma participating in the EAP in Italy, 144 (17%) had asymptomatic brain metastases. Of these, data are available for 84 patients. With a median follow-up of 3 months, the disease control rate among 74 evaluable patients was 16.2%, comprising four patients with a partial response and eight with stable disease. As of April 2012, median progression-free survival and overall survival among patients with brain metastases were 2.5 months and 3.8 months (range 0.1-16.1), respectively. In total, 50.0% patients reported an AE of any grade, most of which were drug-related (40.5%). Grade 3/4 AEs were reported by 28.5% patients and considered drug-related in 15.5%. The most common grade 3/4 drug-related adverse events were diarrhoea (N = 3; 3.6%) and liver dysfunction (N = 3; 3.6%). AEs were generally reversible with treatment as per protocol-specific guidelines.

Conclusions. Ipilimumab shows activity in patients with advanced melanoma metastatic to brain, with safety results consistent with what has been previously reported for ipilimumab.

G13 SEQUENTIAL COMBINATION OF LOW DOSE CHEMO-MODULATING TEMOZOLOMIDE (TMZ) WITH FOTEMUSTINE (FM) IN METASTATIC MELANOMA (MM). A PHASE II STUDY

Guida M.*, Cramarossa A.§, Petrillo P.*, Albano A.*, Tommasi S.*, Piscotti S.*, Aieta M.+, Traversa M.§, Ridolfi R.+, Colucci G.* on behalf of GOIM (Gruppo Oncologico Italia Meridionale) and IMI (Italian Melanoma Intergroup)

*Department of Medical Oncology, 1Department of Radiology, 2Department of Sperimental Oncology, National Cancer Research Center, Bari; 3Department of Medical Oncology, Ospedale Civile, Taranto; 4Department of Medical Oncology, National Institute of Cancer, Rionero in Vulture (PZ); 5Immunotherapy Unit, National Cancer Institute of Romagna (IRST), Meldola (FC)

Background and purpose. MM is a chemoresistant cancer with poor prognosis. Further progress is likely to come from novel targeted antiBRAF therapy, available for about 50% of mutated pts, and from immunotherapeutic agents such as the monoclonal antibody ipilimumab, at present available only in some countries. Preclinical and clinical experiences support the concept that continuous exposure to an alkylating agent can effectively deplete cells of the DNA repair enzyme O6-methylguanine DNA methyltransferase (MGMT), the primary mechanism of tumour resistance to chemotherapeutic agents. Our study was finalized to verify this hypothesis using a sequential combination of low dose chemo-modulating TMZ) and FM. Primary endpoints were safety and tumour response evaluation.

Methods. Fifty-three consecutive MM pts were enrolled in the study. The majority of them (80%) were enrolled before the targeted therapy era and the BRAF status is not available. The main characteristics included: median age 56 years (21-79); ECOG PS 1 (0-2); number of disease sites: 1 in 30%, 2 in 27%, >2 in 43%; M status: M1a 9%, M1b 21%, M1c 70% with 5 pts having brain metastases. The following schedule was used: oral TMZ 100 mg/m2 d 1 and 2; FM i.v. 100 mg/m2 d 2, 4 h after TMZ. The regimen was repeated every 3 weeks for a maximum total of 9 cycles. Tumour assessments using RECIST criteria were conducted at baseline and then every 3 cycles.

Results. Fifty-two pts are evaluable for toxicity and 51 for clinical assessment (1 withdrew consent; 2 early). The median number of treatment cycles administered was 7 (range 2-9). There were 13 (25%) responses (1 CR and 9 PRs) with a median duration of 7 months, and 23% of stable disease. Median progression-free survival was 6 months and median overall survival 11+ months (range 2-35+ months). Drug-related toxicities ≥G3 included thrombocytopenia (10%), neutropenia (6%), anemia (2%), and hepatopathy (2%). Approximately 75% of the pts were treated without dose reduction. Two patients (4%) discontinued therapy because of toxicities.

Conclusions. Sequential combination of low dose TMZ and FM demonstrated a high activity in our patient population with an acceptable and easily manageable toxicity. This schedule could therefore represent a good alternative for patients not eligible for targeted therapy or in whom previous targeted therapies failed. The study of the correlation between MGMT level and clinical outcomes is ongoing.

G14 2-HYDROXYGLUTARATE (2HG) CONCENTRATION IN SERUM AND URINE FROM PATIENTS WITH GLIOMAS: A CASE-CONTROL STUDY CORRELATED WITH IDH-1/2 GENE STATUS

Lombardi G.1,6, Corona G.2, Farina P.1, Zustovich F.1, Bertorelle R.3, Della Puppa A.5, Gardiman M.1, Magro C.1, Diamanti O.1, D’Avella D.7, Tofolli G.2, Zagonel V.1

1Medical Oncology, Istituto Oncologico Veneto, IRCCS, Padua; 2Experimental and Clinical Pharmacology Unit, Department of Molecular Oncology and Translational Medicine, National Cancer Institute, Aviano; 3Molecular Immunology and Oncology, Venetian Oncology Institute, IRCCS, Padua; 4Neurosurgery Department, Azienda Ospedaliera di Padua, Padua; 5Pathology Department, Neurological Sciences, Padua Hospital, University of Padua, Padua; 6Department of Surgical Sciences, Oncology and Gastroenterology, 7Neurosurgery Department, University of Padua

Background. IDH-1/2 mutations are prognostic markers in gliomas. These mutations result in the production of 2HG. We investigated whether 2HG produced by IDH-1/2 mutant gliomas accumulates in patients serum and urine and whether this accumulation can be used to assess IDH-1/2 mutation status.

Methods. We prospectively studied PTS with intracranial gliomas and measurable disease on brain-MRI. All pts had a partial surgical resection or a recurrent disease. The resected tissues were analyzed for IDH-1/2 mutational status; subsequently, in absence of chemotherapy and after 3 weeks from a prior surgery, a serum sample and 24 hour-urine collection were taken from consecutive pts. 2-HG concentrations were determined by liquid chromatography tandem mass spectrometry. The statistical significance of the difference in the level of 2-HG between the PTS with IDH-1/2 mutated and control group were evaluated by non-parametric Mann-Whitney test.
**Results.** We analyzed 13 pts with IDH-1 mutated and 13 pts with IDH-1/2 wild-type; 2 pts with low-grade glioma and 24 pts with high-grade glioma; 10 females and 16 males. In all pts we analyzed the mean 2HG concentration in serum (S_2HG) and urine samples adjusted for urine creatinine (U_2HG). The results are shown in Table 1. We found significant differences in mean U_2HG, and in mean S_2HG/U_2HG in patients with or without IDH mutated. No statistically significant associations of tumour volume and U_2HG, of tumour volume and S_2HG were found in all pts and in pts with IDH1 mutated.

**Conclusions.** U_2HG and S_2HG/U_2HG might be used as markers to differentiate between gliomas with and without IDH mutated. No associations were found between tumour volume and U_2HG and S_2HG, indicating that 2HG might not be utilized as marker to monitor tumour growth.

However, a larger number of samples need to be analyzed to draw final conclusions.

| Table 1 |
|-------------------|-------------------|------------------|
|                | IDH wild-type     | IDH mutated      | p     |
| U_2HG (ng/mL)   | 7.49 ± 3.87       | 5 ± 3.08         | 0.03  |
| S_2HG/U_2HG     | 86.42 ± 38.74     | 112.74 ± 73.19   | 0.26  |
| S_2HG (ng/mL)   | 13.96 ± 7.54      | 23.83 ± 9        | 0.005 |

**G15 EFFICACY AND SAFETY OF IPILIMUMAB IN PATIENTS WITH PRETREATED, OCULAR MELANOMA: EXPERIENCE FROM ITALIAN CLINICS PARTICIPATING IN THE EUROPEAN EXPANDED ACCESS PROGRAMME (EAP)**

Maio M.1, Chiarion Sileni V.2, Pilla L.3, Nicoletti S.V.L.4, Di Guardo L.5, Queirolo P.6, De Giullitiss F.7, Mandalà M.8, Guida M.9, Ascierto P.A.10

1Policlinico Le Scotte, Siena; 2Istituto Oncologico Veneto, Padova; 3Ospedale S. Pietro, Centro S. Raffaele del Monte Tabor, Milano; 4Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, Meldola; 5Istituto Nazionale Tumori, Milano; 6Istituto Nazionale per la Ricerca sul Cancro IST, Genova; 7Istituto Dermopatico dell’Immacolata, Roma; 8Ospedali Riuniti di Bergamo; 9Istituto Tumori Giovanni Paolo II, IRCCS, Bari; 10Istituto Nazionale per lo Studio e la Cura dei Tumori, Fondazione Pascale, Napoli

**Purpose.** Ocular melanoma is a rare malignancy with an incidence of 5.3-10.9 cases per million per year (Papastefanou and Cohen, J Skin Cancer, 2011). Currently, the treatment of metastatic ocular melanoma is limited by the lack of an effective systemic therapy. The EAP provided an opportunity to assess the activity and safety of ipilimumab in patients with ocular melanoma outside of a controlled clinical trial in patients from the EAP in Italy.

**Methods.** Ipilimumab was available upon physician request for patients aged ≥16 years with stage III (unresectable) or stage IV skin, ocular or mucosal melanoma, who had failed or did not tolerate previous treatments and for whom no therapeutic option was available. Patients were treated with ipilimumab 3 mg/kg every 3 weeks for 4 doses. Tumour assessments were conducted at baseline and after completion of induction therapy using immune-related response criteria. Patients were monitored for adverse events (AEs), including immune-related AEs, within 3 to 4 days of each scheduled visit using Common Terminology Criteria for Adverse Events v3.0.

**Results.** Of 848 Italian patients participating in the EAP, 83 (9.8%) had ocular melanoma. Of these 83 patients, 55 have data available. With a median follow-up of 3 months, the disease control rate among 46 evaluable patients was 34.8%, including 3 patients with a partial response and 13 with stable disease. As of April 2012, median progression-free survival and overall survival among patients with ocular melanoma were 2.9 months and 5.9 months (range 0.3-21.3), respectively. In total, 63.6% patients reported an AE of any grade, most of which were drug-related (47.3%). Grade 3/4 AEs, which were reported by 20.0% patients, were only considered drug-related in 5.4%. AEs were generally manageable and most resolved with treatment as per protocol-specific guidelines.

**Conclusions.** Safety and early efficacy results are similar to experience in other melanoma populations, thus suggesting that treatment of ocular melanoma with ipilimumab warrants further investigation in prospective clinical trials.

**G16 CIRCULATING TUMOUR CELLS IN SOFT TISSUE SARCOMAS PATIENTS**

Vincenzi B.1, Rossi E.2, Zoccoli A.1, Iuliani M.1, Pantano F.1, Frezza A.M.1, Silletta M.1, Tonini G.1, Zamarchi R.2, Santini D.1

1Università Campus Bio-Medico, Roma; 2Istituto Oncologico Veneto IRCCS, Padova

**Introduction.** Soft tissue sarcomas (STSs) are a heterogeneous group of highly malignant mesenchymal tumours with only few recognised prognostic and predictive factors. Circulating tumour cells (CTCs) are considered a prognostic marker classically associated with poor prognosis in epithelial solid cancer patients. The purpose of this study was to explore the possibility to detect CTCs in blood samples of STSs metastatic patients.

**Methods.** Patients with histologically confirmed STSs and known metastases treated at Campus Bio-Medico Hospital of Rome from June 2011 to February 2012 were included. Blood was collected from patients who progressed on previous chemotherapy (first, second or third-line). All patients signed informed consent before phlebotomy. CTCs were assessed with CellSearchSystem (Veridex, USA). After immunomagnetic enrichment with an anti-Epcam-antibody, cells were labelled with anti-Ck8/18/19 and anti-CD45 antibodies to distinguish between epithelial cells and leukocytes. Wilcoxon rank sum test was used to test for associations between CTC assay results and specific histotype, number of previous treatments, number and localization of metastatic disease sites.

**Results.** Twenty-three patients with metastatic STSs were evaluated. CTCs were detectable in 10/23 (43%) patients with CTC counts in the range of 0-4 cells/7.5 mL. The median number of CTCs was significantly lower in patients with only one site of metastasis compared to those with two or more metastatic sites (0 vs 2; p = 0.003). There was no statistically significant difference (p = 0.210) in median CTC counts between patients who received only a first-line regimen (0, range 0-4) vs patients who previously received more anticancer therapies (1, range 0-3). Finally, no statistically significant correlation was identified between the number of CTCs and the histological grading evaluated according to the FNCLCC grading system (p = 0.468).

**Conclusions.** To our knowledge this is the first detection of circulating Epcam/Ck8/18/19+ cells in STSs patients, even if the
identified circulating cells could be epithelial cells due to direct tumour invasion of the blood vessel from the surrounding tissue or tumour cells at the moment of mesenchymal-epithelial transition.

G17 USE OF [11C]-METHIONINE POSITRON EMISSION TOMOGRAPHY IN THE MANAGEMENT OF PRIMARY AND RECURRENT GLIOMAS

Santoni M.1, Bittoni A.1, Paccapelo A.1, Polonara G.2, Nanni C.3, Trignani R.4, Cardinali M.5, Castelluccio P.3, Burattini L.1, Fanti S.3, Rychlicki F.4, Berardi R.1, Cascinu S.1

1Department of Medical Oncology, 2Department of Neuroradiology, Polytechnic University of the Marche Region, Ospedali Riuniti Umberle I-G. M. Lancisi - G. Salesi, Ancona; 3Department of Nuclear Medicine, S. Orsola-Malpighi University Hospital, Bologna; 4Division of Neurosurgery, Radiotherapy Unit, Polytechnic University of the Marche Region, Ospedali Riuniti-Umbert, Azienda Ospedale-Università, Padova

The development of efficient methods to assess tumour response in glioma patients remains a major challenge in clinical neuro-oncology. Aim of this study is to assess whether 11C-methionine positron emission tomography (11C-MET PET) has a clinical significance in the management of glioma patients.

A total of 249 11C-MET PET scans were performed on 53 patients with histologically proven primary gliomas (16 grade II, 15 grade III, and 22 grade IV). Functional imaging with PET was compared with concurrent MRI or CT scans.

In this study, 11C-MET PET registered high sensitivity and specificity in the detection of malignant progression in low grade glioma patients and the assessment of post-surgery status in both low and anaplastic gliomas. Moreover, 11C-MET PET expresses its maximum potential in earlier disclosing recurrence during the long-term follow-up of glioblastoma (GBM) patients, with a relevant impact on therapeutic course and survival of these patients. Thus, the overall survival (OS) of GBM patients followed by 11C-MET PET serial controls and parallel CT or MRI scans resulted significantly increased (29.24 vs 17.39 mos) as compared to patients who underwent CT or MRI scans alone. In conclusion, combined 11C-MET PET and CT or MRI scans may improve the management of primary and recurrent gliomas, showing a significant clinical impact on the outcome of GBM patients.

G18 DOES TIME FROM LAST TEMOZOLOMIDE TO RECURRENT HAVE A ROLE IN RECURRENT Glioblastoma?

Franceschi E.1, Agati R.2, Poggi R.1, Dall’Occa P.1, Bartolotti M.1, Di Battista M.1, Marucci G.3, Girardi F.1, Ermani M.4, Brandes A.A.1

1Medical Oncology Department, 2Neuroradiology Department, Bellaria-Maggiore Hospital, Azienda USL, Bologna; 3Section of Pathology M. Malpighi, Department of Haematology and Oncological Sciences L. and A. Seragnoli, Bellaria Hospital, University of Bologna; 4Department of Neurosciences, Statistic and Informatic Unit, Azienda Ospedale-Univerità, Padova

Purpose. Since temozolomide in combination with radiotherapy (RT/TMZ) became a new standard for newly diagnosed glioblastoma, the scenario at recurrence became less defined. Moreover, the role of prognostic and predictive factors for the second treatment has not been clarified.

Methods. A retrospective analysis was made for glioblastoma patients followed between 01/2005 and 06/2010. Eligibility criteria for the study were: age ≥18 years; PS 0-2; chemotherapy at disease progression after RT/TMZ, availability of data regarding second progression.

Results. 232 patients with recurrent glioblastoma [mean age 52 years, range 18-77, MGMT methylated/unmethylated 62 (37.6%)/103 (62.4%)] were evaluated. At progression after RT/TMZ, 102 patients (44%) were treated with surgery followed by chemotherapy, and 130 patients (56%) with chemotherapy alone. Chemotherapy consisted in TMZ rechallenge 5/28 in 80 patients (34%), nitrosoureas in 120 patients (52%), experimental treatments in 32 patients (14%). DFS-6 calculated from 1st to 2nd PD was 22% (95% CI 16.3-26.9%). Time from the last adjuvant TMZ treatment to recurrence (TTR) was shorter in patients treated with nitrosoureas (2.6 months) than in patients treated with TMZ (9.8 months, p < 0.00001). Univariate analysis showed that longer TTR (p = 0.007) and type of chemotherapy (TMZ vs nitrosoureas p = 0.033) were both significantly correlated with PFS. Only TTR showed an effect on PFS (p = 0.07) in multivariate analysis. Median OS from recurrence was 8.6 months (95% CI 7.4-9.8), and 11.3 months (95% CI 9.5-13), 7.4 months (95% CI 6.3-8.5), and 7.1 months (95% CI 4.6-9.8), with TMZ, nitrosoureas, or other treatments, respectively. TTR and type of chemotherapy at recurrence were significantly correlated with OS (p = 0.026 and p = 0.016) in univariate but not in multivariate analysis.

Conclusions. As in other cancer types (i.e. ovarian cancer), TTR seems to be promising as a predictive factor for PFS obtained with treatments for recurrence and could be useful in patients stratification. TMZ rechallenge seems more useful than nitrosoureas if TTR is longer.

G19 BONE METASTASES IN SOFT TISSUE SARCOMA PATIENTS: A SURVEY OF NATURAL HISTORY, PROGNOSTIC VALUE AND TREATMENT OPTIONS

Vincenzi B.1, Frezza A.M.1,3, Schiavon G.2,11, Santini D.1, Dileo P.3, Silletta M.1, Bertoldo F.3, Badalamenti G.3, Baldi G.4, Zovato S.7, Berardi R.8, Tucci M.9, Tirabosco R.10, Whelan J.3, Tonini G.1

1Department of Medical Oncology, Università Campus Bio-Medico, Roma; 2Breast Unit, Royal Marsden Hospital, London; 3University College of London Hospital, London Sarcoma Service, London; 4Department of Medicine, Università di Verona, Verona; 5Department of Medical Oncology, Policlinico P. Giaccone, Palermo; 6Department of Medical Oncology, Ospedale Santa Chiara, Pisa; 7Department of Medical Oncology, Istituto Oncologico Venero, Padova; 8Department of Medical Oncology, Università Politecnica delle Marche, Ancona; 9Department of Medical Oncology, Ospedale Giovanni XXIII, Bari; 10Department of Pathology, Royal National Hospital Paediatric Hospital, London; 11Department of Medical Oncology, Daniel den Hoed Cancer Center, Erasmus University Medical Center, Rotterdam

Background. Given the limited data currently available in the literature, we surveyed the natural history of bone metastases in patients affected by soft tissue sarcoma (STS).
Methods. This multicenter retrospective observational study evaluated 135 patients affected by STS with bone metastases who presented between 2001 and 2011. The following data were recorded for all patients: primary tumour histological subtype, characteristics of bone metastases (onset, number, site), type of treatment received (surgery, radiotherapy, bisphosphonates), type and frequency of skeletal related events (SRE), and disease outcome.

Results. The most represented histological subtypes were leiomyosarcoma (27%), angiosarcoma (13%), and spindle cell sarcoma (8%). The spine was the most common site for bone involvement (51%), followed by hip/pelvis (20%), long bones (15%), and other sites (14%). In 27% of cases, bone metastases were present at the time of diagnosis. Fifty-four (40%) patients developed SREs and the median time to first SRE (if developed) was 4 months (range 1-9 months). The most common SRE was the need for radiotherapy, occurring in 28% of patients, followed by pathological fracture (22%). Median survival after bone metastases diagnosis was 6 months (range 1-14 months). The occurrence of a SRE was associated with decreased overall survival (p = 0.04). A subgroup analysis revealed that bisphosphonates significantly prolonged median time to first SRE (5 versus 2 months; p = 0.002). Conversely, bisphosphonates did not determine an improvement in terms of overall survival, even if a favourable trend was identified (median: 7 versus 5 months, respectively; p = 0.105).

Conclusions. This study illustrates the burden of bone disease from STS and supports the use of bisphosphonates in this setting.

G20 DIMENSION OF RESIDUAL CT SCAN MASS IN HODGKIN’S LYMPHOMA (HL) IS A NEGATIVE PROGNOSTIC FACTOR IN PATIENTS WITH PET NEGATIVE AFTER CHEMO ± RADIOTHERAPY

Magagnoli M.1, Lopci E.2, Latman F.R.3, Mazza R.1, Rodari M.2, Marzo K.2, Bramanti S.1, Giordano L.4, De Vincenzo F.1, Chiti A.2, Balzarotti M.1, Santoro A.1

1Department of Medical Oncology and Hematology, 2Nuclear Medicine Department, 3Biostatistic Unit, 4Department of Radiology, Humanitas Cancer Center, Istituto Clinico Humanitas, Rozzano, Milan

Background. Positron emission tomography (PET) with 2-[18F]fluoro-2-deoxy-D-glucose (18F-FDG) currently represents the mainstay for response assessment in HL, as defined by revised response criteria (Cheson, 2007). PET negativity is mandatory to define complete remission (CR), independently from the persistence of residual masses at computed tomography (CT) scan. Nevertheless, some reports suggest a slightly worse prognosis among patients with CT scan residual masses. The aim of this study was to evaluate the unfavorable predictive value of residual CT scan masses in HL pts with PET negative at the end of treatment.

Material and methods. The present analysis was retrospectively conducted in 105 pts with negative PET at the end of first or second-line treatment, at our institution, from February 2004 to February 2009. Post-treatment restaging included CT and PET in all patients. Inclusion criterion was complete remission demonstrated by PET, as per 2007 response criteria, independent of the presence of residual masses on CT. Twenty millimeters in maximum diameter was considered the cut-off for a significant residual mass on CT. No patient received further therapy after restaging PET. Primary study outcome was disease-free survival (DSF) for PET-/CT- vs PET-/CT+ patients.

Results. Main clinical characteristics: median age 58 years, males 62, B-symptoms 25, bulky disease 41, prior radiotherapy 57. Seventy-four pts were evaluated after first-line treatment program, while 31 pts after salvage therapy program. In 76 pts, residual CT scan mass (PET-/CT scan+) of at least 2.0 cm in the largest diameter was assessed. Fifty-seven had only one site residual mass, while 19 pts had more than one site. Considering the whole series, with a median follow-up of 45 months, 23 pts relapsed, nine patients died and 94 are alive without disease.

The five-year DSF for PET-/CT scan- vs PET-/CT scan+ pts was 89.4% and 68.7% respectively (p = 0.053). The prognostic impact of residual mass at CT scan had a correlation with the dimension of the residual itself in a continuous fashion: the larger is the mass, the lower the DSF: HR 1.03 (1.01, 1.05) p = 0.007. This difference is even more pronounced when a cut-off of 4 cm in the largest diameter of the residual mass is applied: in patients with a mass diameter ≥ vs <4 cm, DFS is 50% vs 82% respectively (HR 3.25; CI 1.5, 7.04; p = 0.029). Among all the other prognostic factors analyzed (number of masses, first vs salvage treatment program, sex, bulky disease, B-symptoms), no correlation with DSF or overall survival (OS) emerged.

Conclusions. In our study we observe a significant difference in DFS among PET negative pts with or without CT scan residual masses after therapy for HL. This difference is more significant when the residual mass is larger than 4 cm. Thus, although PET is the main tool in response definition, CT scan maintains an important role and cannot yet be abandoned. The role of consolidation radiotherapy in these cases should be focused.

G21 IPILIMUMAB IN PREVIOUSLY TREATED METASTATIC MELANOMA: EXPERIENCE OF THE ISTITUTO NAZIONALE TUMORI DI MILAN

Di Guardo L.1, Del Vecchio M.1, Martinetti A.1, Sottotetti E.1, Pusceddu S.1, Canova S.2, De Braud F.1, Pilla L.1

1Medical Oncology I, Fondazione IRCCS, Istituto Nazionale dei Tumori, Milano; 2Medical Oncology, San Gerardo Hospital, Monza

Background. The incidence of melanoma in the US is increasing faster than any other type of cancer in men and more than any other type of cancer, except lung cancer, in women. Iplimumab, a novel CTLA-4 inhibitor, is under investigation for the treatment of metastatic melanoma. Results of a randomized phase III clinical trial comparing ipilimumab vs control showed a first-ever OS benefit for patients with previously treated metastatic melanoma. The objective of this study was to assess the disease control rate (DCR) and objective response rate (ORR) as a measure of the antitumour effect of ipilimumab in patients with melanoma which had progressed in despite of one previous standard chemotherapy

Patients and methods. Since July 2010 we have identified, for ipilimumab-based therapy “as compassionate use”, 86 patients affected by previously treated advanced melanoma. Patients characteristics: 43M/43F; median age 55 (range 27-80); ECOG PS 0-1(100%). In most of the pts the disease stage was M1c (91%) and had received only one previously chemotherapy (59%). In 15 pts the treatment was not administered for early rapid disease progression and for the appearance of symptomatic brain. According to guideline phase III trial the induction or re-
induction phase consisted in 3mg/kg i.v. every 3 wks for 4 administrations. The first radiological assessments were performed after 4 weeks at the end of treatment and then every 3 months.

**Results.** We observed 14 SD >6 months, 1 PR and 1 CR. In two patients treatment was started at the hospital near home. Four pts did the re-induction. Data regarding PFS, response duration and OS will be shown at the completion of the patients disease re-evaluation.

**Conclusions.** Our data suggest a certain clinical activity and a significantly good tolerability profile with rash being the main side effect. This expanded access trial is currently ongoing and will go on until the Italian registration of ipilimumab. Shortly we will provide the pending data regarding all the treated patients.

**G22 TREATMENT WITH TEMOZOLOMIDE AND RADIOThERAPY FOLLOWED BY TEMOZOLOMIDE UNTIL PROGRESSION IN A SELECTED POPULATION OF PATIENTS WITH NOT RADICALLY RESECTED HIGH GRADE GLIOMAS**

Spinelli G.P.1,2, Lo Russo G.1,2, Stati V.1, Rossi L.1, Rinaldi G.1, Zoratto F.1, Basso E.1, Giordani E.1, Papa A.1, Fontana A.3, Miscusi M.1, Frati A.1, Minozzi M.1, Tomao S.1,2

1Department of Medical-Surgical Science and Biotechnology, University of Rome “Sapienza”; 2Distretto ASL di Aprilia, Oncology Unit, University of Rome “Sapienza”; 3OCU Radiotherapy, S. Maria Goretti Hospital, Latina

**Introduction.** In spite of the important progress in the treat-ment of tumours, high grade gliomas (HGGs) remain a poor prognosis neoplasm, especially when patients are not radically resected. We reported the results of the treatment of a selected population of newly diagnosed HGGs, with standard schedule of radiotherapy (RT) + temozolomide (TMZ) followed by TMZ until progression.

**Patients and methods.** Between January 2008 and January 2010, 14 newly diagnosed HGG patients with median age of 50.6 years (range 27-75 yrs) were enrolled at Oncology Unit of S. Maria Goretti Hospital in Latina. All patients were not radically resected and had ECOG PS = 0. Furthermore patients were selected according to O6 methyl-guanine-DNA-methyl transferase (MGMT) promoter methylation status and only methylated patients were included. After surgery, patients were assigned to receive standard treatment with TMZ (75 mg/m2) concomitant with radiotherapy and chemotherapy. Temozolomide administered was 6.19 (range 1-23). The OS in patients with TMZ was 14.8 months (range 4-24) and in patients with partial removal, the OS was 6.35 (range 2-17).

**Results.** One-year overall survival (OS) and progression-free survival (PFS) rate were 85.7% and 71.4% respectively. Two-year OS rate was 70% and two-year PFS rate was 10%. A total of 108 cycles of adjuvant TMZ were administered (range 1-16). For each patient the average number of treatment cycles was 9. The most frequent side effects observed were haematological toxicity and fatigue. Thrombocytopenia (G2-G3) was observed in 42% of patients, neutropenia (G2-G3), fatigue (G2-G3) and nausea (G2-G3) in 30%, 32% and 25% of patients respectively.

**Conclusions.** In spite of the small number of patients, our experience suggests a manageable safety profile and an excellent efficacy of the use of TMZ until progression in a selected population of patients with HGGs not radically resected and with a good ECOG PS. These data also confirm the literature knowledge, underlining the prognostic positive impact of MGMT promoter methylation in patients with HGG.

**G23 PATTERNS OF CARE AND SURVIVAL IN A RETROSPECTIVE ANALYSIS OF PATIENTS WITH GLIOBLASTOMA MULTIFORME: A MONOINSTITUTIONAL EXPERIENCE**

Taibi E., Sanò M.V., Ali M., Chiarenza M., Di Marco R., Fallica G., Aiello R.A., Caruso M.

Department of Medical Oncology, Humanitas Centro Catanese di Oncologia, Catania

**Introduction.** Glioblastoma is the most common primary brain tumour accounting for 60% of malignant gliomas. The conventional treatment of GBM consists of maximal surgical resection followed by radiation therapy and chemotherapy. Temozolo-mide is considered as the standard treatment.

**Purpose.** To report the toxicity and overall survival in 72 patients with GBM (operated or not) treated at our institution.

**Materials and methods.** From October 2005 to end April 2012, 72 patients, affected by GBM, have been enrolled (31F/46M; M/F 1.48). The median age was 54 years (range 18-79); in 28 of the patients (37.36%) surgery resulted in complete removal, partial removal occurred in 29 (37.66%) and 20 (25.9%) were inoperable. Thirteen (16.88%) patients received temozolomide after RT alone and 64 patients (83.11%) received concomitant and sequential TMZ. Concurrent TMZ was started at 75 mg/m2/day for 28 consecutive days. Adjuvant TMZ was given at 150 to 200 mg/m2/day for 5 days every 28 days. Toxicities were defined using CTCAE v3.0.

**Results.** The most common toxicities included nausea, lym-phopenia, neutropenia, hypertransaminasemia, but no instances of grade 3 or higher. Only 3 patients discontinued therapy prior to a PD of disease: 1 allergy (1 cycle), 1 for cardiotoxicity (2) and 1 for skin toxicity (3). The median number of cycles of temozolomide administered was 6.19 (range 1-23). The OS in patients radically operated was 14.8 months (range 4-24) and in patients with partial removal, the OS was 6.35 (range 2-17).

**Conclusions.** This present study provides analysis of current patterns of clinical practice and outcomes for patients with glioblastoma. OS in this small cohort of patients was comparable to that treated with current standard of care therapy.

**G24 FOTEMUSTINE AS SECOND-LINE THERAPY IN ELDERLY PATIENTS WITH RECURRENT OR PROGRESSIVE GlioBLASTOMA**

Burattini L.1, Santoni M.1, Scoccianti S.2, Detti B.2, Paccapelo A.1, Bili G.2, Berardi R.1, Cascinu S.1

1Department of Medical Oncology, Polytechnic University of the Marche Region, Azienda Ospedaliero-Universitaria, Ospedali Riuniti Umberto I-G.M. Lancisi-G. Salesi, Ancona; 2Radiotherapy Unit, Azienda Ospedaliera Universitaria Careggi, Firenze
The present study aims to assess the feasibility and the effectiveness of a second-line fotemustine (FTM) chemotherapy in elderly patients with confirmed glioblastoma (GBM). From 2005 to 2012, 37 patients with progressive GBM after radiotherapy plus concomitant and/or adjuvant temozolomide, age older than 65 years, and a median Karnofsky performance score of 80, were treated with 70-100 mg m² of FTM every week for 3 consecutive weeks and then every 3 weeks (70-100 mg m²) till progression. In this study, median time to progression was 41 months. Progression-free survival at 6 months was 35.13%. Median overall survival from the start of FTM chemotherapy was 7.63 months, with a median overall survival from primary diagnosis of 23.64 months. The most frequent grade 3-4 intervention-related adverse events were thrombocytopenia (18.9%) and neutropenia (16.2%). This study demonstrates that FTM has therapeutic efficacy as second-line chemotherapy in elderly GBM patients, with a manageable and mainly haematological safety profile.

G25 TREATMENT OF ANAPLASTIC ASTROCITOMAS (AA) WITH RADIOOTHERAPY (RT) PLUS TEMOZOLOMIDE (TMZ): A SINGLE INSTITUTION EXPERIENCE

Brugnara S.1, Nagliati M.2, Magri E.2, Pulcrano G.3, Colorusso E.3, Valduga F.1, Caldara A.1, Frisinghelli M.1, Vecchia A.1, Dipasquale M.1, Caffo O.1, Russo L.1, Moroso S.1, Soini B.1, Murgia V.1, Barbareschi M.4, Chiolfi F.3, Galligioni E.1

1Oncology, 2Radiotherapy, 3Neurosurgery, 4Pathology, Ospedale Santa Chiara, Trento

Purpose/Objective. Although the evidence for the benefit of adding TMZ to RT is limited to glioblastoma patients, there is currently an increased tendency toward a combined RT+TMZ approach also in AA patients. We report here our experience with RT+TMZ in a group of AA patients treated in our institution, looking to clinical outcome, in term of overall survival (OS) and disease-free survival (DFS).

Materials and methods. Data were retrospectively collected on a consecutive series (Jan 2004 to Dec 2009) of 18 AA patients (12 Males, 6 Females, median age 48 years, range 29-79), treated in our institution with radical radiotherapy and concomitant chemotherapy (temozolomide 75 mg/m²) followed by adjuvant TMZ (200 mg/m² 5q28) for 6 cycles. Out of the 18 pts, 17 received surgical resection (12 radical surgery, 5 subtotal surgery), and 1 diagnostic biopsy only. Patients were grouped according to the recursive partitioning analysis (RPA) classes as follows: class I 6 pts, class II 5 pts, class III 3 pts, class IV 3 pts, class VI 1 pt.

Results. Median OS was 40 mos (range 3-101) and median DFS was 22 mos (range 1-83) for all patients. Among those treated with radical resection, median OS was significantly increased (p = 0.04) compared to those treated with partial resection only. The median OS for each RPA class subgroup was 82 mos for class I, 58 mos for class II, 13 mos for class III, 38 mos for class IV and 2 mos for the pt in class VI. No severe or unexpected toxicity was reported.

Conclusions. Even if limited by the small sample size and the lack of a control group, our results seem to suggest that the combined treatment is feasible in AA pts and may possibly contribute to a prolonged control of the disease. Definitive results however may arise only from prospective randomized trials.

G26 COMPASSIONATE USE OF BEVACIZUMAB AND IRINOTECAN IN PATIENTS WITH GLIOBLASTOMA MULTIFORME, PROGRESSING AFTER A FIRST AND/OR A SECOND-LINE CHEMOTHERAPY: OUR EXPERIENCE

Cariello A.1, Gamboni A.2, Verlicchi A.1, Casanova C.1, Freier E.2, Mazza V.1, Cenni P.3, Minguzzi N.4, Cerasoli S.5, Guiducci G.6, Cruciani G.1, Dazzi C.3

1Dipartimento di Oncologia, Ospedale Santa Maria delle Croci, Ravenna; 2Servizio di Oncologia, Ospedale degli Infermi, Faenza; 3Neuro-Radiologia, 4Radioterapia, Ospedale Santa Maria delle Croci, Ravenna; 5Anatomia Patologica, 6Neurochirurgia, Ospedale Bufalini, Cesena

The standard of care for the treatment of newly diagnosed glioblastoma multiforme (GBM) is surgical resection, followed by concurrent chemo-radiation therapy with temozolomide, and 6 months of maintenance chemotherapy with temozolomide. Despite the survival benefit associated with this management of GBM, the majority of patients relapse within 2 years, and there is no defined standard of care when tumour progresses. Encouraging results derive from the use of antiangiogenic drug bevacizumab associated with irinotecan. From 2009 to 2012 we have treated 16 patients affected with GBM or anaplastic glioma, who relapsed after standard chemo-radiation treatment. Patients were registered in a program of compassionate use of bevacizumab and irinotecan and gave written informed consent. Median age was 63 years (range 35-72). All of the patients were required to have a minimum Karnofsky performance status score of 50%, normal kidney and adequate bone marrow function to be eligible for treatment. Bevacizumab 10 mg/kg was administered associated with irinotecan 125 mg/m², both every 2 weeks. Objective response was evaluated with gadolinium-MRI every 8 weeks. A median of 8 courses were administered (median 3-21+) and one patient is still ongoing. Nine out of 16 patients (56%) required irinotecan dose reduction due to diarrhea and/or thrombocytopenia, whereas no symptomatic intracranial bleeding was observed. Tumour control was achieved in 68.5% (11/16) patients. In our experience the combination of irinotecan and bevacizumab appeared safe and provided clinical benefit in patients affected by recurrent GBM.

G27 COMBINED RADIO-CHEMOTHERAPEUTIC TREATMENT IN MULTIFORM GLIOBLASTOMA: EVALUATION OF TOXICITY, OVERALL SURVIVAL AND MGMT METHYLATION STATUS

Burattini E., Pavese I., Satta F., Coiro G., Todi F., Pellegrino A., Palumbo B., Gentile P.C.*, Di Palma M.

Oncology and *Radiotherapy Departments, S. Pietro Fatebenefratelli Hospital, Rome

Introduction. In multiform glioblastoma (MG) the combined radio (RT) and chemotherapy (CT) with temozolomide (TMZ) increases the overall survival. The mechanism of action of the TMZ resides in the alkylation of the DNA, position 06 of the guanine: such damage comes in normally by the 06-methyl guanine-DNA methyl transferase (MGMT). The MGMT is implicated in the tumoral resistance since it is partially able to invalidate the effect of the alkylant agents on the 06-guanine.
Methods. Between March 2009 and April 2012, 29 pts with MG were treated with combined RT and CT with TMZ.
All pts (18 males, 11 females) had a PS 0-2 (ECOG). The median age was 53 years (range 25-76).
Radical surgical resection, partial surgical resection and biopsy were performed in 12, 14 and 3 pts respectively.
The MGMT methylation status was: 14 pts had MGMT methylated; 11 had MGMT non-methylated and 4 had MGMT unknown.
All pts received TMZ 75 mg/m²/die for 6 weeks with concurrent brain radiotherapy (total dose 60 Gy). After the combined radiochemotherapy, all pts started CT with TMZ 200 mg/m².

Results. The main toxicities were: fatigue (G2), 75% (22/29); nausea (G2), 41% (12/29); vomit (G1), 20% (6/29); stipsis (G2), 20% (6/29); sleepiness (G1-2), 41% (12/29); anemia (G1-2), 13% (4/29); leukopenia (G1), 17% (5/29).
80% of pts experienced symptom-related disease improvement.
At the median follow-up of 36 months (range 4-36), the median overall survival (OS), for all pts, was 18 months (range 4-36).
OS for MGMT methylated group was 21 months (range 13-36).
OS for MGMT non-methylated group was 6 months (range 4-13).
OS for MGMT unknown group was 9 months (range 5-13).

Conclusions. We conclude that our experience confirms the good tolerability and the improved survival with combined radiochemotherapeutic treatment in MG. Moreover it is important to know the MGMT methylation status in order to obtain the best results. The pts with MGMT non-methylated should be included in clinical trials.

G28 LONG-TERM PROGNOSTIC SIGNIFICANCE OF RESPONSE IN MULTIPLE MYELOMA AFTER STEM CELL TRANSPLANTATION
*Haematology and Bone Marrow Transplant Unit, Azienda Ospedaliera BMM, Reggio Calabria; *The National Research Council (CNR), Reggio Calabria

Background. Multiple myeloma is largely an incurable malignant plasma cell neoplasia; however, the landscape of its treatment is rapidly changing and the use of novel combination regimens improves response rates and increases overall survivals. High-dose chemotherapy followed by autologous haematopoietic stell cell transplantation (HSCT) remains an integral component of upfront treatment strategy but in despite of the improvements, myeloma remains incurable and long-term survival appears elusive.

Methods. For establishing the true effect of different response categories in patients with multiple myeloma (MM) treated with high-dose melphalan (HDM) and autologous peripheral blood stem cell transplantation (APBSCT), we evaluated, after a median follow-up of 41 months, 151 patients, mean age 55 ± 8 years, with MM who received a transplant between 1994 and 2006.

Results. Overall survival (OS) at 9 years was 91% in complete response (CR) patients, 43% in near complete response (nCR), 10% in partial response (PR) groups. Significant differences in OS and event-free survival were found between CR and nCR groups (p = .019 and p < .001, respectively), between CR and PR groups (p < .001 and p < .001), or between nCR and PR groups (p < .001 and p < .001). We observed a plateau phase in OS after 12 years; 70% patients (16 patients) in the CR group are alive at 16 years.

Conclusions. MM achieving CR after HDM and APBSCT is a central prognostic factor. The relapse rate is low in patients with >9 years of follow-up, possibly signifying a cure for patients in CR.

G29 CAN ELDERLY PEOPLE AFFECTED BY NON-HODGKIN LYMPHOMA HAVE ANTHRACYCLINES-BASED CHEMOTHERAPY? A RETROSPECTIVE ANALYSIS
Di Nardo P., Rossi S., Signorelli D., Astone A., Pozzo C., Bagalà C., Schinzari G., Barone C.
Divisione di Oncologia Medica, Università Cattolica Del Sacro Cuore, Roma

In elderly population non-Hodgkin lymphoma (NHL) is a frequent disease. Treatment options for these patients are often conditioned by comorbidities; in particular, fear of anthracyclines cardiotoxicity leads to under-power chemotherapy. In recent years, some Authors suggested that anthracyclines-based regimens (both liposomal and not) are safe and effective in elderly population. The present retrospective study includes NHL patients treated in a single institution with and without anthracyclines; clinical results are analyzed comparing elderly (>70 years) and not-elderly population.
Sixty-eight patients affected by indolent (16%) or non-indolent (84%) NHL who were candidate for an anthracyclines-based chemotherapy were included. According to proper prognostic index, 22%, 46% and 32% of patients had a good, intermediate or poor prognosis, respectively. 37% of patients were older than 70 years. 57% of patients had two or more significative comorbidities. In the whole population median overall survival (OS) was 34 months; no significative difference was observed between elderly and not elderly patients who underwent anthracyclines-based regimens (OS 38 months), while the OS of elderly patients not treated with anthracyclines was significantly lower (20 months, p = 0.0002). 94% of elderly patients who underwent an anthracyclines-based regimen reported symptoms relief and an upgrade of performance status (ECOG).
Randomized trials are difficult in elderly and/or impaired patients, who represent an important fraction of NHL patients in practice. This study was aimed to implement our knowledge on feasibility of such an important drug as doxorubicinc in NHL, through a comparative analysis of a retrospective study.
Our data suggest that anthracyclines-based chemotherapy produces a significative improvement in OS even in elderly or impaired patients. Comorbidities and age don’t seem an absolute contraindication to anthracyclines-based chemotherapy.
**Session H • Gynaecological tumours**

**H1* THE PUTATIVE DNA/RNA HELICASE SCHLAFEN-11 SENSITIZES CANCER CELLS TO DNA DAMAGING AGENTS**

Zoppoli G.1,2, Regairaz M.1, Leo E.1, Reinhold W.C.1, Murialdo R.2, Pommier Y.1, Ballestrero A.2

1Laboratory of Molecular Pharmacology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland; 2Department of Internal Medicine (DiMI), AOU IRCCS San Martino IST, Genoa

DNA damage is the main mechanism of action of most of the currently used anti-cancer therapies. These include topoisomerase I and II inhibitors, alkylating agents, DNA synthesis inhibitors, and ionizing radiation (IR). Upon DNA damage, cancer cells can either undergo cell cycle arrest and DNA repair, or death, usually induced by apoptosis. The molecular determinants of cancer response to DNA damage-based therapy are, however, still poorly understood. Here we show that high expression levels of a single gene, Schlafen-11 (SLFN11), sensitize cancer cells to multiple types of DNA damaging agents. We identified SLFN11 by correlating the expression of more than 17,000 genes characterized by microarray analysis in the NCI-60 panel of cancer cell lines with the in vitro toxicological profile of four topoisomerase I inhibitors. We then found that SLFN11 expression is positively correlated with the response to the vast majority of DNA damaging compounds tested in the NCI-60. Using siRNA-based silencing and clonogenic assays, we demonstrated the causal relationship between SLFN11 expression and cytotoxic activity of topoisomerase I and II inhibitors and alkylators, but not of mitotic poisons or kinase inhibitors. Next, we analyzed SLFN11 expression in ovarian and colorectal cancers and normal corresponding tissues from The Cancer Genome Atlas (TCGA) database, and observed that SLFN11 has a wide expression range in those tumours (Figure 1A). We also observed that high SLFN11 expression independently predicts overall survival in a group of ovarian cancer patients treated with cisplatin-containing regimens (Figure 1B). The identification of SLFN11 as a key-player in cancer cell response to these agents has strong translational implications in clinical oncology, since SLFN11 expression could be used as a biomarker to predict cancer response to most currently used treatments.

*The present work was presented in part as a poster at the AACR Annual Meeting 2012, Chicago IL, USA.*

---

**H2* EFFICACY AND SAFETY OF NEOADJUVANT TIP (PACLITAXEL, IFOSFAMIDE, AND CISPLATIN) CHEMOTHERAPY IN LOCALLY ADVANCED SQUAMOUS CELL CERVICAL CARCINOMA FOLLOWED BY RADICAL SURGERY. A SINGLE INSTITUTION EXPERIENCE**

Scandurra G.1, Scibilia G.2, Banna G.L.1, Lipari H.1, D’Agata G.2, Scollo P.2

1Servizio di Oncologia Medica, 2Unità Operativa Ostetricia e Ginecologia, Dipartimento Materno Infantile, Azienda Ospedaliera Cannizzaro, Catania

**Background.** The management of locally advanced squamous cell cervical carcinoma includes chemoradiotherapy or neoadjuvant cisplatin based chemotherapy followed by surgery, that may offer specific advantages and a better potential activity.

**Purpose.** To evaluate efficacy and safety of TIP neoadjuvant chemoregimen in patients affected by local advanced squamous cell cervical carcinoma.

**Materials and methods.** July 1997-December 2011 were treated at our institution 165 patients with locally advanced squamous cell cervical carcinoma of whom 143 are evaluable.

Regimen: ifosfamide 5000 mg/m² ev, day 1 i.v. in 24 h; Mesna 5000 mg/m² ev day 1 i.v. in 24 h; paclitaxel 175 mg/m² ev day 2; cisplatin 75 mg/m² ev day 2; every 3 weeks for a total of three courses.

Tumour extension was assessed clinically and by abdominal MRI, PET WB and 3D ultrasound at baseline and after three courses.

The operable patients after TIP chemotherapy underwent radical hysterectomy and pelvic lymphadenectomy.

Median age 53 (range 24-79 yrs), clinical FIGO stage Ib 2, 2 pts (1%); Ib, 59 pts (41%); IIb bulky, 68 pts (48%); III-IV, 14 pts (10%); histological subtype SCC, 138 pts (96%) and adenocarcinoma, 5 pts (4%).

**Results.** After neoadjuvant chemotherapy 132 pts (92%) underwent surgery.

Post-chemotherapy pathological response was pCR 25 pts (19%), PR1 16 pts (12%), PR2 80 pts (61%), SD 10 pts (7%), PD 1 pt (1%).

Median number of courses of TIP administrated was 3 (range 1-3). Treatment was delayed or withdrawn in 22 pts (16%).
Cervical cancer (CC) and breast cancer (BC) are the most frequent female malignancies in Uganda (incidence 45.6/100,000; 23.4/100,000 respectively). The 5-yr cancer survival is poor (19% and 45% respectively) because of lack in screening programs and public health facilities.

**Aim.** Oncology for Africa is an Italian non-profit organization that cooperates in Uganda. Two missions were held in order to assess the sustainability of a screening campaign; the first was held in January 2011 at the Nsambya Hospital in Kampala and the second one was held in January 2012 at the St. Joseph’s Hospital in Kitgum (Northern Uganda). The effectiveness of the campaigns was also analyzed in different subsets of population: urban and rural areas.

**Methods.** One month before the starting of the campaigns, informative brochures and radio ads were addressed to female population living in Kampala and in Kitgum districts. The CC and BC screening campaigns were performed by 1 expatriate gynecologist, 1 expatriate pathologist, 1 Ugandan medical doctor and 6 nurses, according to the local methods (VIA test for gynecological inspection and breast palpation-BP). Suspected cases were sent for II level examinations to the referral Hospitals. Specific database were set up.

**Results.** A total of 2,772 women were screened (median age 36.0), belonging to any religion, with a median accrual of 49 pts/die in Kampala and 188 pts/die in Kitgum. The major findings are reported in the Table.

<table>
<thead>
<tr>
<th></th>
<th>Kampala (urban area)</th>
<th>Kitgum (rural area)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Abnormal findings by:</td>
<td>pts 884</td>
<td>pts 1888</td>
</tr>
<tr>
<td>VIA test</td>
<td>9.8</td>
<td>3.9</td>
</tr>
<tr>
<td>Breast examination</td>
<td>3.4</td>
<td>0.7</td>
</tr>
<tr>
<td>II level examination</td>
<td>38</td>
<td>25</td>
</tr>
<tr>
<td>Precancer lesions</td>
<td>33</td>
<td>25</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>0.22</td>
<td>0.21</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>0.11</td>
<td>0.10</td>
</tr>
<tr>
<td>Compliance of population</td>
<td>84</td>
<td>98</td>
</tr>
</tbody>
</table>

**Conclusions.** A screening campaign is affordable regarding women compliance, effectiveness of sensitization and training of the local medical and paramedical staff. The percentage of precancerous and cancer lesions do not differ in the two subsets of population, however a larger employment of II level analyses occurred in Kampala. The reason is unclear, but we have to consider that VIA test is more operator-depending than PAP test, not in use in developing countries. Our findings also indicate a 4-fold higher incidence of cancer compared with the official data.

These descriptive results would sensitize to the growing incidence of female cancer in Africa and stimulate collaboration with Sub-Saharan Health Units in ameliorating their standard of care.

**H4** ROLE OF PEGYLATED LIPOSOMAL DOXORUBICIN IN THE MANAGEMENT OF OVARIAN CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED TRIALS

Staropoli N., Ciliberto D., Salvino A., Botta C., Tassone P., Tagliaferri P.

Medical Oncology Unit, Campus “Salvatore Venuta”, Magna Gracia University and Tommaso Campanella Cancer Center, Catanzaro

**Introduction.** Ovarian cancer is the third leading cause of cancer-related death in women. Since 2003, the gold standard treatment for this malignancy is represented by the association of carboplatin and paclitaxel. However, there is still no agreement on the therapy for recurrent or progressed ovarian cancer. One of the most commonly used options in this setting is pegylated liposomal doxorubicin (PLD) based regimen, currently not available. The aim of this meta-analysis is to evaluate the activity of PLD in randomized studies.

**Methods.** Clinical trials were selected by searching “Pubmed” database and abstracts from major cancer meetings. We considered the January 2000-January 2011 time frame. Primary endpoint was overall survival (OS), secondary endpoints were progression-free survival (PFS) and response rate (RR). Hazard ratios (HRs) of OS and PFS, with confidence intervals, odds-ratios (ORs) of RR, and risk ratios of grade 3–4 toxicity rates, as presented in retrieved studies, were extracted and used for current analysis. Meta-analysis was carried out by the fixed effect model for survival endpoints and random effect model for RR and toxicity.

**Results.** Twelve randomized trials for a total of 3827 patients were selected and included in the final analysis. The analysis showed in the PLD group a minimal benefit in terms of PFS (pooled HR 0.89; 95% CI 0.81-0.97). Regarding OS there is not a significant advantage (pooled HR 0.9; 95% CI 0.81-1.01) for PLD. The analyses on RR showed no difference between the two groups (OR for RR 0.99, 95% CI 0.62-1.58). Among toxicities, anemia and neutropenia were more frequent in the alternative treatment group but the difference was not significant. Thrombocytopenia was more frequent in the PLD group (0.74, 95% CI 0.35-1.60) even if it doesn’t reach a statistical significance.

**Conclusions.** When compared to other schedules, PLD-containing regimens do not improve OS whether the advantage in terms of PFS is marginal. New ad hoc approaches, in the era of targeted therapy, are eagerly awaited.
Volta E., Zucchini G., Bernardi A., Martoni A.A.

Medical Oncology Unit, S. Orsola-Malpighi University Hospital, Bologna

Purpose. The aim of this study was to evaluate the clinical utility of 18F-FDG-PET in the detection of recurrent OC as compared with computed tomography (CT) in asymptomatic patients with increased Ca125 levels as only sign of recurrence.

Patients and methods. This was a retrospective analysis of 21 patients with suspected recurrent OC who had previously undergone primary radical debulking surgery and had received platinum-based neoadjuvant or adjuvant chemotherapy for ovarian cancer. In all patients the suspect of first recurrence was a rise of Ca125 levels during follow-up in absence of disease-related symptoms. Diagnostic CT and 18F-FDG-PET were subsequently performed and results of the two diagnostic techniques were compared.

Results. Diagnostic CT was performed in 19 out of 21 patients and revealed recurrence in 13 patients, providing a sensitivity of 68% and a positive predictive value (PPV) of 100%. 18F-FDG-PET was performed in all 21 patients and identified disease recurrence in all cases, showing a sensitivity and a PPV of 100%. After detection of recurrence all patients received chemotherapy which consisted in a platinum-based regimen in 17 cases. Five patients could also undergo debulking surgery of recurrent disease: after chemotherapy hyperthermic intraperitoneal chemotherapy was performed in 3 patients, whereas before chemotherapy one patient underwent para-aortic and retroperitoneal lymphadenectomy and one patient underwent abdominal mass dissection. One patient with mediastinal lymph node metastases received bilateral internal mammary lymph nodes radiation therapy (RT) after chemotherapy.

After a median follow-up of 67.3 months, 81% of patients experienced disease progression and 55% died. Disease progression and death rates were higher in patients who did not undergo cytoreductive surgery of recurrent disease (p = 0.22 and p = 1.0 respectively).

Conclusions. 18F-FDG-PET showed a greater ability to identify recurrent OC compared to conventional CT imaging in asymptomatic patients with rising Ca125 levels, providing a diagnostic accuracy of 100%. Moreover 18F-FDG-PET resulted helpful in optimizing treatment strategies, allowing selection of candidates for site-specific treatments like cytoreductive surgery and RT.

H6* OVARIAN CANCER IN ELDERLY PATIENTS: A RETROSPECTIVE ANALYSIS FROM A SINGLE INSTITUTION

Giuliani J., Marzola M., Frassoldati A.

Clinical Oncology Unit, S. Anna University Hospital, Ferrara

Background. The aim of this study was to evaluate the outcome of the elderly patients with ovarian cancer in daily clinical practice.

Materials and methods. We retrospectively analyzed all consecutive elderly patients evaluated by our Institution from January 2007 to August 2010. An univariate analysis for overall survival (OS) was estimated according to the Kaplan-Meier method, censoring surviving patients at the time of last follow-up.

Results. Among 153 patients affected by gynaecological malignancies, 32 out of 64 patients with ovarian cancer were elderly (≥65 yrs). At last follow-up, 20 patients (62.5%) were alive and 12 patients (37.5%) were deceased. Median OS was 19.05 months (range 1.02-67.01). Median age was 73.50 years (range 65-85). Seventeen patients (53.1%) were “young-old” (65-74 years old), 14 patients (43.8%) were “old-old” (75-84 years old) and 1 patient (3.1%) was “oldest-old” (≥85 years old). In the subgroup of “young-old” patients there were less “high malignant potential” (64.3% vs 70.0%) and grade 3 ovarian cancers (84.6 vs 90.0%), less advanced stages (III-IV: 64.7 vs 86.7%), higher number of optimal surgical procedures (50.0 vs 30.0%) and more frequent use of chemotherapy (82.4 vs 66.7%). Single agent carboplatin was administered in 81.8 vs 77.8% of “young-old” and “old-old” patients, and average number of lines was 2 vs 1. Other characteristics were similar in the two subgroups. By the univariate analysis there was no statistical significance difference in OS (p = 0.393) between the two subgroups, with only a positive trend for young-old patients (Figure 1).

Conclusions. The incidence of ovarian cancer in elderly patient is high in the clinical practice. In old- and oldest-old patients the characteristics of disease are more frequently worse, and optimal treatment strategy is less frequently applied. The management of patients by multidisciplinary team is needed to better individualize the treatment approach.

H7 CHILDHOOD TRAUMATA IN 108 PATIENTS SUFFERING FROM FEMALE CANCER: A CASE-CONTROL STUDY

Tavella K.1, Miraglia Raineri A.2, Faravelli C.2, Villanucci A.1, Casale S.2, Fei L.3, Vannini L.1, Amunni G.4

1Unit of Medical Gynaecologic Oncology, Department of Oncology, 2Department of Psychiatry, 3Department of Neurology and Psychiatry AOU-Careggi, Florence; 4University of Studies of Florence

Figure 1 - Univariate analysis for OS considering “young-old” and “old-old” patients.
Background. A substantial body of research investigated the association between stress-related psycho-social factors and cancer outcomes. Chida Y (2010) suggests that stress-related psychosocial factors have an adverse effect on cancer incidence, poorer survival and mortality. This study was aimed at: a) exploring whether adverse childhood events are associated with an increased risk factor for cancer vulnerability during adulthood; b) examining whether life events are an aspecific risk factor for breast, endometrial and ovarian cancers.

Methods. A total of 108 oncological patients suffering from breast cancer (N = 29), ovarian cancer (N = 30) and endometrial cancer (N = 49) were compared with 104 controls matched for sex, age and education. Early life events were studied by using a semistructured face to face interview (Florence Psychiatric Interview, Faravelli et al., 2001).

Results. The oncological group reported a greater number of traumatic events compared with a control group. Moreover loss and separation from parents during the first 15 years of life seem to be associated in a statistically significant way (p < 0.001) with the appearance of cancer in the adulthood. Finally, differences between specific site-disease subgroups (breast, ovarian and endometrial cancers) and control groups were also statistically significant (p < 0.001).

Conclusions. Childhood adverse life events are commonly reported as risk factors for mental disorders. Our results seem to point out that such a risk exists also for oncological patients. Patients childhood history seems to be important for the cancer vulnerability. Considering the traumatic history in clinical assessment and investigating recent life events may be also important.

H8 F-18 FDG PET/CT METABOLIC TUMOUR VOLUME PREDICTS OUTCOME IN PATIENTS WITH DISSEMINATED EPITHELIAL OVARIAN CANCER

Gallicchio R.1,2, Capobianco A.1, Capacchione D.1, Giacomobono S.1, Nardelli A.2, Bozza G.1, Sirignano C.2, Troiani L.1, Impota G.1, Tempone A.1, Nappi A.1, Aieta M.1, Storto G.1

1IRCCS, CROB, Rionero in Vulture; 2Institute of Biostructures and Bioimages, CNR, Naples; 3Department of Biomorphological and Functional Sciences, University “Federico II”, Naples

Aim. Post-operative follow-up and treatment for patients with disseminated epithelial ovarian cancer (EOC) represent a clinical challenge being the therapy mostly ineffective and the quality of life poor. We evaluated the prognostic significance of the quantitative assessment by standardized uptake value (SUVmax) and metabolic tumour volume (MTV) on F-18 FDG PET/CT in patients complying with primary peritoneal carcinosis from ovarian cancer.

Materials and methods. Twenty-three patients (mean age 53±14 years) with epithelial ovarian cancer underwent F-18 FDG PET/CT for a restaging 4 ±1 months after the complete surgical pelvic intervention, being diagnosed a carcinosis (before adjuvant chemotherapy). The maximum standardized uptake value and the metabolic tumour volume (cm3; 42% threshold) were registered on the five most hypermetabolic peritoneal lesions. Patients were categorized into two groups according to SUVmax and MTV median values and followed up 15±3 months thereafter. Main events such as re-intervention, evidence of newly discovered distant metastases (not peritoneal) or death constituted surrogate end-points. PET/CT results were then compared to the disease outcome (overall survival, OS).

Results. Global mean SUVmax was 9.11±2.6 and global mean MTV was 7.17± 6 cm3. The median SUVmax value was 9.3 and median MTV value was 3.6 cm3. 4/23 patients (17%) underwent second-look re-intervention whereas 4/23 (17%) showed newly discovered distant metastases and 7/23 (30%) died. The Kaplan-Meier survival analysis for SUVmax did not show a significant difference in OS between the two groups (p = 0.07; HR = 0.2, log-rank test). Interestingly, survival analysis for MTV showed a significant better OS in patients presenting a tumour burden above the median value as compared to those having less than 3.6 cm3 (p = 0.009; HR = 8.5, log-rank test). Apart from chemosensitivity, the higher the MTV the better the response to adjuvant therapy.

Conclusions. The quantitative assessment by MTV rather than SUVmax on F-18 FDG PET/CT may be helpful for stratifying patients presenting carcinosis from EOC in order to implement appropriate therapeutic regimens sparing aggressive approaches.

H9 PEGYLATED LIPOSOMAL DOXORUBICIN IN OVARIAN CANCER TREATMENT: A MONOINSTITUTIONAL EXPERIENCE. DO WE STILL NEED IT?

Staropoli N., Salvino A., Ciliberto D., Botta C., Tassone P., Tagliaferri P.

Medical Oncology Unit, Campus “Salvatore Venuta”, Magna Graecia University and Tommaso Campanella Cancer Center, Catanzaro

Background. Ovarian cancer (OC) is the sixth most common cancer in women. Currently, carboplatin/paclitaxel represents the cornerstone of front-line treatment. Conversely, the scenario for recurrent or progressed disease is not well established. For platinum-sensitive patients the best therapeutic option is represented by rechallenge with a platinum-based regimen. Instead, for platinum-refractory patients, therapy with pegylated liposomal doxorubicin (PLD), currently not available, is considered one of the best options. The aim of this mono-institutional exploratory analysis is to evaluate the impact of PLD on OC patient survival.

Patients and methods. We performed a retrospective analysis on 108 patients with diagnosis of OC followed by our Institution between 2001 and 2011. Eighty patients were in stage III/IV and 55 had received a second-line treatment. A subgroup of 35 patients was treated with PLD in presence of recurrent or progressed disease, while 20 patients were never treated with this agent. Both groups underwent a mean of 3 treatment lines and were prognostically balanced with a median follow-up of 60 months. Survival analysis and correlations between patients baseline characteristics and toxicities were evaluated by Kaplan-Meier curves and log-rank test statistics.

Results. Patients treated with PLD showed a median overall survival of 45 months compared with 65 months of any other therapy [HR 2.50 (0.95-6.67; p = 0.06)]. Furthermore, median progression-free survival was 6 months in patients treated with PLD and 10 months in patients treated with any other therapy [HR 1.75 (0.94-3.34; p=0.07)]. No advantage was showed with PLD in platinum-refractory patients when compared with any other therapy.
other chemotherapy \([30 \text{ vs } 32 \text{ months}; \, \text{HR} = 1.16 \, (0.31-4.34; \, p = 0.81)]\). Moreover, our analysis provided evidence for a trend to worse survival in elderly patients treated with PLD \([\text{HR} = 1.23 \, (0.33-4.57; \, p = 0.75)]\). No differences in term of response-rate or toxicities were observed between the different groups.

**Conclusions.** Our findings suggest minor activity of PLD in clinical practice, in particular in refractory/elderly patients. However further studies are needed.

**H10 CYTOREDUCTIVE SURGERY AND HYPERTHERMIC INTRAPERITONEAL CHEMOTHERAPY (HIPEC) FOR ADVANCED OVARIAN CANCER: EARLY EXPERIENCE OF A SINGLE INSTITUTION**

Bagnoli P.\(^1\), Gasco M.\(^2\), Bertuzzi A.F.\(^2\), Deraco M.\(^3\), De Sanctis R.\(^2\), Cauchi C.\(^2\), Santoro A.\(^2\), Quagliuolo V.\(^1\)

\(^1\)Department of Surgery, \(^2\)Department of Medical Oncology and Hematology, Humanitas cancer Center, Istituto Clinico Humanitas, IRCCS, Rozzano (Milano); \(^3\)Department of Surgery, National Cancer Institute, Milan

**Background.** Abdominal cytoreductive surgery (CRS) with hyperthermic intraperitoneal chemotherapy (HIPEC) represents a combined therapeutic approach reserved to a limited subset of patients affected by peritoneal carcinomatosis. The surgical procedure comprises total peritonectomy and removal of all resectable disease followed by HIPEC. In our Institution we have explored CRS + HIPEC in 11 patients with peritoneal carcinomatosis from different types of cancer.

**Patients.** Since February 2011, 6 advanced pretreated EOC (epithelial ovarian cancer) pts were enrolled. The median age was 59 years (range 40-71), ECOG PS was 0 in 4 pts, 1 in 1 pt and 2 in 1 patient. Median PCI (peritoneal carcinomatosis index) was 4.5. Three pts were platinum-sensitive (relapsed after 12 months after completion of adjuvant chemotherapy). The remaining 3 pts received CRS/HIPEC following upfront surgery and adjuvant chemotherapy.

**Results.** Complete removal of all macroscopic disease (CCR-0) was performed in all pts, total peritonectomy in 1 case, enteric resection with protective ileostomy in 3 cases. Intraperitoneal cisplatin 25 mg/m\(^2\)/L and doxorubicin 7 mg/m\(^2\)/L at 41-2°C were administered. Mean length of hospital stay was 14 days and in Intensive Care Unit 3 days. No peri-operative severe adverse events were observed. No pts received post-operative chemotherapy. Of the 6 pts treated, one relapsed 2 months after CRS/HIPEC; three are disease-free at 11, 10 and 5 months respectively; in the last two cases, follow-up is only 2 months from the procedure.

**Conclusions.** In our beginning experience, CRS followed by HIPEC could be a promising, safe and feasible therapeutical opportunity in ovarian peritoneal carcinomatosis. Considering the cost-effectiveness ratio, it should be reserved to carefully selected pts in order to obtain a real benefit in terms of progression-free survival. Optimal timing of CRS/HIPEC in the natural history of EOC should be further investigated.
Session L • Health Technology Assessment

L1 READABILITY ASSESSMENT OF INFORMATION AND CONSENT FORMS FOR CANCER CLINICAL TRIALS IN ITALY

McMahon L.1, Defraia S.2, Demartini P.3, Ragazzini A.4, Raisi E.5, Ranchicchio P.6, Sottile R.7 on behalf of Gruppo Italiano Data Manager (GIDM)

1UOC Oncologia Medica, AULSS 9, Treviso; 2Dipartimento Oncologia Medica, Università di Cagliari; 3SC Oncologia Medica 2, AOU S. Giovanni Battista, Torino; 4IRCCS Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST), Meldola (FC); 5UO Oncologia Clinica, Azienda Ospedaliero-Universitaria, Ferrara; 6Divisione di Oncologia Medica, Ospedale Careggi, Firenze; 7Dipartimento di Oncologia, Azienda Ospedaliero-Universitaria di Udine

Introduction. The signed informed consent form represents an absolute requirement for voluntary consent to participation in clinical trials as prerequisite key for the ethical conduct of research and evidence of the subject’s consent to participation. How much patients really understand and comprehend of the information and consent forms (ICFs) has often been debated and readability standards have been suggested to improve their comprehensibility.

Methods. A sample of 114 ICFs administered to Italian cancer patients for phase II-IV trials in the 2007-2012 period were examined. All ICFs had been approved by the referring Ethical Committee. To determine their readability score the Gulpease index was used. Developed in 1988 and validated for Italian, the scale is automated in Microsoft Word and it is based upon two linguistic variables: the length of the word and of the sentence (mean number of words per phrase). Results range from 0 to 100, where 100 indicates the highest readability and 0 the lowest. The advisable reading score for most documents should be in the 60-70 range.

Results. Mean number of pages of the 114 assessable ICFs was 10.3 (2.5-27.5); those for industry funded trials (N 47, 41.2%) are significantly longer than those for investigator initiated trials (N 67, 58.8%) with mean number of pages of 15.4 and 6.7 respectively (p <0.0005). Significantly higher is also the number of pages of the ICF when comparing international (N 50, 43.9%) to national trials (N 64, 56.1%) with mean number of pages of 15.1 vs 6.5 (p <0.0005). The mean Gulpease Index readability score of the 114 ICFs is 41 (30-67) irrespective of valuable variables. Only one ICF (0.87%) met the >60 desirable readability value.

Conclusions. ICFs for cancer trials have poor readability scores, seem far too complex, too long to be read and understood by an average study participant. Every effort should be made to obtain a truly informed consent assessing the ICF readability prior to study activation.

L2 WHEN THE CANCER PATIENT NEEDS HOSPITAL ADMISSION: THE CHANGING ROLE OF MEDICAL ONCOLOGY WARDS


S.C. Oncologia, Azienda USL della Valle d’Aosta, Aosta

Background. An inpatient medical oncology ward is available in 20.2% of the oncology centers in Italy. However its use has not been properly described and seems quite heterogeneous. Although intended as a specialist ward with the principal aim of performing complex treatments, it is increasingly used for supportive treatments in pts with cancer and associated medical conditions.

Methods. We aimed at describing the admissions to a medical oncology inpatient service within a 2-year period with respect to pts characteristics, their malignancies, and outcome of admission. The medical records of 672 consecutive admissions were reviewed.

Results. 672 admissions of 455 patients were analyzed. Median age was 68 (range 26-92); 298 (44.3%) were ≥70; 381 (56.7%) were males. The most common primaries were gastro-intestinal (28.4%), lung (24.1%) and hematological malignancies (21.4%). The admission was programmed in 174 cases (25.9%) and was urgent in 498 (74.1%). The most common reason for admission (79.6%) was the occurrence of symptoms: dyspnea in 12.9%, pain in 12.6%, fever in 11.8%, digestive/abdominal symptoms in 17.1%, neurological symptoms in 11.8%, cardiovascular symptoms in 2.5%, systemic symptoms in 10.9%. Chemotherapy was administered during hospital stay in 130 cases (19.3%), an invasive procedure was performed in 224 (33.3%) while medical treatment alone was given in 382 cases (56.8%). The majority of the hospitalizations resulted in discharge to home (60.6%); 176 patients died (26.5%) and 87 (11.0%) were transferred to hospice or other hospital departments.
Conclusions. Inpatient care is an important part of the activity of medical oncologists. Urgent admissions of symptomatic patients is becoming the prevalent role of the oncology wards. This represents a clear shift from the previous intended aims. Also, taking care of pts at the end of life is increasingly part of the ordinary clinical management. These features should lead to organizational and cultural efforts aimed at improving knowledge and expertise accordingly.

### Table L3

<table>
<thead>
<tr>
<th>Drug Type</th>
<th>Cancer Type</th>
<th>PFS in RCT (months)</th>
<th>PFS in Clinical Practice Oncology (months)</th>
<th>Ex-factory (euro /1mg)</th>
<th>Adjusted Price (euro /1mg)</th>
<th>Effectiveness</th>
<th>Difference in priceDiscount proposal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sorafenib</td>
<td>Kidney</td>
<td>5,5</td>
<td>3,2</td>
<td>0,16</td>
<td>0,09</td>
<td>44%</td>
<td></td>
</tr>
<tr>
<td>Sorafenib</td>
<td>Liver</td>
<td>5,5</td>
<td>3,0</td>
<td>0,16</td>
<td>0,09</td>
<td>44%</td>
<td></td>
</tr>
<tr>
<td>Erlotinib</td>
<td>NSCLC</td>
<td>2,2</td>
<td>2,0</td>
<td>0,48</td>
<td>0,44</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>Sunifilin</td>
<td>Kidney</td>
<td>11,0</td>
<td>7,0</td>
<td>3,87</td>
<td>2,46</td>
<td>36%</td>
<td></td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Colorectal</td>
<td>4,1</td>
<td>3,0</td>
<td>2,08</td>
<td>1,52</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>Lung adenoca</td>
<td>2,9</td>
<td>1,8</td>
<td>3,02</td>
<td>1,87</td>
<td>38%</td>
<td></td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Colorectal</td>
<td>10,6</td>
<td>6,3</td>
<td>3,36</td>
<td>2,00</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Breast</td>
<td>11,8</td>
<td>7,9</td>
<td>3,36</td>
<td>2,25</td>
<td>33%</td>
<td></td>
</tr>
<tr>
<td>Panitumumab</td>
<td>Colorectal</td>
<td>2,0</td>
<td>1,9</td>
<td>4,22</td>
<td>4,01</td>
<td>5%</td>
<td></td>
</tr>
</tbody>
</table>

The post marketing study allows for assessment of response outcomes in real life practice in order to verify both effectiveness and safety in general population testing external validity of the randomized trials. This kind of assessment lacks in approval RCTs, further emphasizing the importance of observational investigations in clinical practice. The price should be based on net clinical benefits achieved in real life practice as more appropriate in evaluating cost-benefit balance.
L5 EVALUATING CANCER PREVALENCE IN CAMPANIA THROUGH GENERAL PRACTITIONERS MEDICAL CHARTS. A FEASIBILITY PILOT STUDY

Arpino G1, Cammarota S2, Crispo A3, De Angelis C1, Montella M4, Tommaselli G5, Savignano L4, Perrone V4, Pizzi C4, De Placido S1

1Dipartimento di Endocrinologia e Oncologia Molecolare e Clinica, Università di Napoli “Federico II”; 2Centro Interdipartimentale di Ricerca in Farmacoeconomia e Farmacoutilizzazione (CIRFF), Università di Napoli “Federico II”; 3UO Epidemiologia INT “Fondazione Pascale”, Napoli 4, Consorzio “Campania Medica”

Background. Data on cancer prevalence, incidence and mortality in Campania and South Italy are very sparse due to the almost complete lack of cancer registries. However, epidemiology data on cancer are critical for health and economic planning, especially in these undeveloped areas. This is a pilot study evaluating the feasibility and reliability of cancer prevalence in Campania by analyzing medical records of general practitioners (GPs) serving in this region.

Methods. Overall 584,405 individuals, the 15% of Campania adult population, 276,512 men and 307,533 women, distributed throughout the territory of Campania were included in the study. Relevant clinical information were extracted from electronic clinical charts of the 474 GPs belonging to the Regional Consortium “Campania Medica”. Data on cancer prevalence of “Campania Medica” Consortium (A), was compared to data of “Registro Tumori di Napoli” (B) and updated data on Italian prevalence from the “Associazione Italiana Registro Tumori” (Italy) (C).

Results. As shown in Table 1, the numbers of cancers registered in Consortium “Campania Medica” database were 11,341, 4693 men and 6648 women, with an age range between 18 and 84 years. Among those 2730 (23%) have been diagnosed for less than 2 years, 3509 (31%) from 2 to 5 years, 3614 (32%) from 5 to 10 years, 549 (5%) from 10 to 15 years, 119 (1%) from 15 to 20 years and 820 (7%) more than 20 years. Overall, Campania Medica prevalence data are comparable to cancer prevalence observed in “Registro Tumori di Napoli” and “Italy”.

Conclusions. Data from this pilot study show that extracting data from GPs charts may provide reliable information for the cancer prevalence in their patient population. Moreover, if the number of patients is relevant, as in this study, the GP prevalence may be representative of the overall cancer prevalence for the area served by the GPs. Sensibilizing GP community to improve cancer information recording in their medical charts is critical as it may become a tool to evaluate epidemiology of cancer and corroborate information of cancer registries where present.

<table>
<thead>
<tr>
<th>From diagnosis</th>
<th>Men</th>
<th>Women</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2</td>
<td>1236</td>
<td>1994</td>
<td>3230</td>
</tr>
<tr>
<td>2-5</td>
<td>2679</td>
<td>3506</td>
<td>6185</td>
</tr>
<tr>
<td>5-10</td>
<td>4196</td>
<td>5747</td>
<td>9943</td>
</tr>
<tr>
<td>10-15</td>
<td>4347</td>
<td>5665</td>
<td>10012</td>
</tr>
<tr>
<td>15-20</td>
<td>4338</td>
<td>6132</td>
<td>10470</td>
</tr>
<tr>
<td>&gt;20</td>
<td>4338</td>
<td>6183</td>
<td>10521</td>
</tr>
<tr>
<td>Total</td>
<td>4693</td>
<td>6648</td>
<td>11341</td>
</tr>
</tbody>
</table>

Table 1

L6 DIFFUSION OF “STANDARD DI PRODOTTO” OF ONCOLOGY AND HEMATOLOGY CENTERS OF PIEMONTE AND LIGURIA

Perrotto E.*, Porcile G.^

*Outcomes S.a.s.; ^ARS Liguria

The “Standard di prodotto” is a management tool based on a comparison between the performance values achieved from its
structure in the delivery of its services and the “standard values” of other equivalent structures operating in the area or region (benchmarks) established based on best available scientific evidence or, if such there be, in the opinion of experts.

With the support of the company Outcomes Sas and the financial contribution of B.U. Novartis Oncology, the regional Standard di prodotto for the Centers of Oncology and Hematology was developed to provide managers of hematology-oncology centers of Piedmont and Liguria the concrete opportunity to:

* define “quality criteria” and “system indicators” considered essential to measure and evaluate the performance of an oncology or hematology center and monitor their performance in a structured manner using the tools that were developed and shared with a multidisciplinary path, inter-and intra-regional;
* make use of a tool that would allow the managers to compare the performance levels of its structure with the gold standard summary of the performances of other equivalent structures;
* place the “outcomes of quality” for their actions, to manage its fundamental logical structure evidence based in assessing the relationship between the absorbed resources and the results obtained.

The project has been developed since the first half of 2009 involving in parallel two distinct regions, Piedmont and Liguria with the various project activities and training provided.

Each of the two working groups composed of multi-disciplinary, multi-center physicians (oncologists and hematologists), nurse coordinators (DH and/or hospitalization onco-hematology) and pharmacists (engaged in the management of personalized chemotherapies) has over time helped to select, refine and test field in its own “short list” of several indicators related to the specific quality requirements which they consider crucial (accuracy, appropriateness, clarity, fairness, empathy, responsiveness, and safety) creating de facto two pilot systems different but increasingly converging that are briefly described in the Table.

### Quality criteria

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Indicators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accuracy in information management</td>
<td>Cases of medical records do not meet minimum requirements compared to shared/Total records checked</td>
</tr>
<tr>
<td>Cases of nursing folders do not comply with the requirements agreed minimum/Total folders nursing controlled</td>
<td></td>
</tr>
<tr>
<td>Accuracy in the preparation of therapies</td>
<td>Cases of non-compliant therapies discarded in production/Total therapies controlled</td>
</tr>
<tr>
<td>Appropriateness of therapeutic choice</td>
<td>Cases of suspected impropriety in relation to agreed criteria/Total patients treated</td>
</tr>
<tr>
<td>Clarity of information</td>
<td>Perception of the patient</td>
</tr>
<tr>
<td>Correctness in prescribing therapy</td>
<td>Cases of incorrect prescriptions/Total prescriptions controlled</td>
</tr>
<tr>
<td>Empathy</td>
<td>Perception of the patient</td>
</tr>
<tr>
<td>Timely start of adjuvant therapy after surgery</td>
<td>Suspected untimeliness than maximum times shared/Total patients treated</td>
</tr>
<tr>
<td>Security during the therapy giving</td>
<td>Cases of accident (encoded) in the therapies giving/Total treatments given</td>
</tr>
</tbody>
</table>

### Results

The study included 23 patients with a median age of 66 years (range 42-85). Eighteen subjects (78%) had a LC, 3 (13%) a CRC and 2 (9%) another gastrointestinal cancer. CSCs were obtained from liver metastases in 6 cases (25%), lung nodule in 2 cases (8%), lymph node in 3 cases (12.5%) and pleural, peritoneal or pericardial effusion in 13 cases (54%). The procedure was repeated in 1 patient. CSCs were successfully isolated in 15/23 patients (65%). The highest rate of CSCs isolation was obtained with neoplastic effusion. Failure in CSCs isolation was due to inadequate material (7 cases) or sample loss (1 case). CSCs sensitivity assay was successfully performed in 7 patients (30%), with a median of 15 drugs or combinations tested (range 5-28) and a median time required for results of 51 days (range 37-75).

### Conclusions

Our data indicate that CSCs isolation and in vitro sensitivity assay are feasible in 30% of patients. A phase II trial exploring the efficacy of the procedure will start soon.

## L7 CONTINUITY OF CARE FOR CANCER PATIENTS: AN INNOVATIVE MULTIDIMENSIONAL MODEL IMPROVING HEALTH SERVICE

Posca T.1, Lattuada S.1, Manachino D.1, Torazzo R.1, Francese B.2, Borasio G.3, Sartori S.3, Ferrari P.1, Sicuranza M.R.2, Perugini L.4, De Marino E.1

1S.C. Oncologia, 2C.O.C.A., 3Servizio di Psicologia, 4Servizio Sociale, Ospedale S. Andrea, ASL VC, Vercelli

### Background

Modern welfare program for cancer patients has to ensure continuity of care which is concerned with quality of care over time. Traditionally, continuity of care is idealized in patients’ experiences of a continuous caring relationship with an identified health care professional. For providers in vertically integrated systems of care, the contrasting ideal is the delivery of a “seamless service” through integration, coordination and the sharing of information between different providers. As patients’ health care needs can now only rarely be met by a single professional, we developed a multidimensional model of continuity to accommodate the possibility of achieving both ideals simultaneously. Our model is based on three important aspects: discharge, case-management, multidisciplinary team working.
Methods. We considered discharge an interactive-provider process starting at the time of hospitalization. Oncologist plans care pathways while a nurse, appointed case manager, knows needs and social problems talking with patients and family. Within three days program is formalized in medical records. Care giver activates a multidisciplinary team made by primary care physician, home care nurse, care giver, social aid and psycho-oncologist. Team check and burden home care plan defined in letter of discharge arranged with oncologist and case manager, who organize educational meetings and interviews, recording events and outcomes. We compared mean length of hospitalization and patient praise-releases of the same period in two years, 2010-2012.

Results. From January to September 2011 we activated 75 processes, 74/75 (97%) were completed; 100% formalized. In the same period mean length of hospitalization was 10.36 days in 2010 and 8.72 days in 2011 (-16%); patient praise-releases 5 in 2010 and 11 in 2011; no patient lost at follow-up.

Conclusions. Discharging process is a milestone in continuity of care. Our multidimensional model shows that a good integration and organization between providers is cost-effective and is appreciated by patients because of positive impact on quality of life and relationship.

L9 COMPARISON OF COSTS AND RESOURCES NEEDED FOR ORAL (CAPECITABINE) AND INFUSION (5-FLUOROURACIL/FOLINIC ACID) CHEMOTHERAPY (CHT) ADMINISTERED BY CENTRAL VENOUS DEVICES: AN OPPORTUNITY TO RESHAPE ONCOLOGICAL DAY HOSPITAL ACTIVITY

Giaquinta S., Pini S., Melotti B., Di Fabio F., Martoni A.A.
Medical Oncology Unit, S. Orsola-Malpighi Hospital, Bologna

Introduction. The introduction of new drugs or formulations in clinical practice requires the demonstration of advantages in terms of efficacy, tolerability and costs. At the same efficacy and tolerance, treatment choice should consider costs, compliance and patients preference. In colorectal cancer treatment, both in adjuvant and in advanced setting, standard medical treatment for many years was based on infusional 5-fluorouracil (5-FU) and folinic acid modulation. In last years some randomized clinical trials demonstrated similar efficacy and tolerability profile of capecitabine (cape), an oral fluoropyrimidine, and 5-FU.

Methods. The aim of this two phases (retrospective/perspective) observational study is to compare cape based regimens to 5-FU based regimens in terms of total management costs. The chemotherapy regimens considered were: monotherapy 5-FU intravenous continuous infusion (De Gramont), 5-FU and oxaliplatin (Folfox), monotherapy capecitabine, capecitabine and oxaliplatin (xelox).

Results. In the retrospective phase were enrolled 83 patients: 57 (68.7%) males, 26 (31.3%) females; median age 69 years (range 37-87); median ECOG-PS 0 (range 0-2); stage II 13 (15.7%), III 26 (31.3%), IV 44 (53%). Eight (9.6%) patients received De Gramont, 21 (25.3%) cape, 22 (26.5%) Folfox and 32 (38.6%) Xelox. Median and range courses were respectively: 11 (2-12); 6 (3-11); 11 (2-12); 6 (2-10). In the group of patients treated with 5-FU based regimens CVC were placed in 27/30 (90%) pts, while in the group treated with cape in 4/53 (7.5%) patients. The main chemotherapy grade 3-4 side effects were comparable in pts that received oral or infusion CHT except for extravasation of oxaliplatin occurred in 3 pts who received Xelox regimen without CVC. The main CVC side effects were: deep vein thrombosis in 3 pts and accidental remove in 1 patient.

Conclusions. Preliminary data of retrospective phase of this study show that chemotherapy toxicity is comparable in pts that received oral or infusion CHT and CVC side effects were not so many as we expected. Further analysis about costs and quality of life will be available.
Testore F.¹, Graziano P.², Milanese S.¹, Colombo M.², Toffano A.M.⁶

¹SOC Oncologia, ²SOC Farmacia Ospedaliera, Ospedale Cardi- nal Massaia, Asti

Since 10/2010 in the SOC Oncologia of the Cardinal Massaia Hospital there is a new professional figure, the clinic pharmacist.

We share a project with the Hospital Pharmacy to assess the efficacy of a new professional figure in improving oncological drugs and supportive therapies management.

The main functions of the Clinic Pharmacist are:

- creation and update of the Clinic Drug Manual;
- drug storage management, elimination of surplus, and daily medications uploading and downloading;
- patient medication dispensation on discharge;
- file F compilation for expensive medications;
- cooperation in managing high cost infusional therapies by grouping them in specific days;
- retrieval of no longer needed high cost oral biological drugs and individual repackaging for further dispensation to new patients;
- over-the-counter drugs distribution management.

The 2011 economical analysis shows the following data:

<table>
<thead>
<tr>
<th></th>
<th>2009</th>
<th>2010</th>
<th>2011</th>
<th>2010/2011 difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-related costs (€)</td>
<td>3,953,277</td>
<td>4,829,835</td>
<td>4,566,442</td>
<td>-5.45%</td>
</tr>
<tr>
<td>Total clinic costs (€)</td>
<td>6,991,083</td>
<td>7,201,650</td>
<td>7,094,229</td>
<td>-1.49%</td>
</tr>
<tr>
<td>Production total value (€)</td>
<td>4,104,080</td>
<td>4,177,836</td>
<td>4,725,679</td>
<td>+13.11%</td>
</tr>
</tbody>
</table>

Discussion. As compared with previous years, in which we experienced a constant increase in drug-related costs, proportional to increased activity, for the first time in 2011 we registered a decrease in global pharmaceutical expenditure, which had an impact on total Oncology expense, in despite of an increase (+13.11%) in clinical activity.

Specifically, the pharmaceutical savings totalled € 263,392, while the project cost was € 12,000, financed by the SOC with Clinical Research grant-related funds.

Conclusions. Effective alternatives to therapy rationing, especially expensive therapies, can be found by improving therapeutic activity organization and drug management; the Clinic Pharmacist has a central role in a rational and economically sound organization, while respecting in full patients expectations to find a reasonable therapeutic approach to their disease.
Session N • Oncology nursing

N1* THE CAREGIVER AS A PROTAGONIST IN ONCOLOGIC DAY HOSPITAL: AN INVESTIGATION ON CUSTOMER SATISFACTION

Clementi S.1, De Maria B.1, Paradiso R.2, Lorenzi E.3, Zingaro M.1, Irenze G.1, Zatta L.1, Vietti Ramus G.1

1Oncologia Medica, Ospedale San Giovanni Bosco, 2Oncologia Medica, Ospedale Valdese, 3Oncologia Medica, COES Ospedale San Giovanni Battista, Torino

Cancer affects not only the patient’s life, but also the person who attends to the patient. The main point of reference for a patient are the caregivers (CG). This study is aimed to evaluate the initial expectations the CG have towards services provided (‘the expected’) and then their satisfaction after 30-45 days of actually experiencing said service (‘the observed’) in some Oncological Day Hospitals (DH) in Turin.

From January to July 2009 in 3 Turin DH the CG received and responded to 2 anonymous questionnaires. The first was aimed at the expectations of the CG and the second at their satisfaction after 30-45 days. The responses were analyzed and compared.

One hundred and forty questionnaires on expectations and 104 on satisfaction were assessed. There was no significant difference in sample distribution between the first and second questionnaires and among the 3 DH. Ninety-four percent of the CG were family members, predominantly women (69%). In about 2/3rds of the cases they had additional support. The accessibility to DH facilities, services and timetables were considered appropriate. Access to DH in the morning was preferred. The Psychologist was the most appreciated additional service. The CG generally presumed a DH treatment should last at least one year (78%). They expected mostly healing (76%), but then also expected to be notified the true diagnosis (88%); was communicated and understood the true diagnosis in 86% of cases. The CG expected (71%) and noted (82%) a significant change in their daily lives by their support to the patient. Communication was judged well: the information investigated were deemed complete by the majority of CG (a deficiency on home therapies). The Oncologist was the main reference for health information (82%), the Nurse for organizational ones (60%), and the Family Doctor was not considered important. The knowledge of law 104/92 improved in for organizational ones (60%), and the Family Doctor was not considered important. The knowledge of law 104/92 improved in

Methods. Eighty patients were admitted in the study. The median age of the patients was 65 years (range 36-82). Twenty-eight were male, fifty-two female (M/F ratio = 0.53). Median ECOG was 1 (range 0-2). Patient whose ECOG was from 3 to 4 were excluded. Our fall-risk assessment instrument (FRAI) applied by oncology nurses was a home-grown tool (a Conley scale integrated with the clinical categories identified by Evans in 2001) that included the following 1 point variables: history of falls, motor deficits, cognitive impairment, dysuria or incontinence, use of psychotropic and/or opioid analgesic drugs, number of drugs >4, visual impairment, pathologies of the feet. A high risk for falling was determined by having ≥2 risk variable present (score ≥2). Standard safety interventions for low risk patients (score 1) were place sign to indicate wet floor hazard, secure locks on beds and wheelchairs, keep floors clutter/obstacle free, place call ring and frequently used objects within patient reach, orient patients to surroundings, evaluate patient’s ability to interpret information. For high risk patients additional interventions were use a red arm band as flagging system, remain with patient while toileting and bedside sitting, observe/round every hour, advice patient and his family about fall risk, and if taking anticoagulants, regarding increased risk of bleeding with injury and ensure that the patient with sensory deficits wears personal glasses and hear aids.

Results. Our FRAI documented a consistent percentage of high risk of falling patients (65%), a marked use of opioids (21%) and polypharmacy >4 (26%) and despite what, no patient fell in Day Hospital during the study.

Conclusions. The FRAI applied by our oncology nurses seems to reduce the incidence of falls.

N3* QUALITY OF LIFE AND BURDEN IN CAREGIVERS OF CANCER PATIENTS: SEVERAL VARIABLES NEED TO BE CONSIDERED

Garotti P.L.*, Morini E.*, Dall’Agata M.**, Prati S.**, Faedi M.**

*Department of Psychology, University of Bologna; **Oncoematological Day Hospital of Cesena, IRRCS Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori, Meldola (FC)

Background. The disease of a relative triggers complex and stressful circumstances that threaten the family unity and balance. As the disease progresses, one of the relatives takes on him/herself great part of the so-called “burden of care”.

Caregivers’ skills, characteristic, and quality of life are directly related to his/her burden. Several Authors enlightened the importance of caregivers’ burden, needs and quality of life assessment. Few efforts, however, capture the multidimensional nature of cancer caregiving task and few of them include all more important dimensions of burden and needs: informational, daily activity, financial, emotional, social support, caregiving skills, communication needs.
The aim of this work is to identify socio-demographic characteristics of caregivers' burden and to evaluate the association between burden and caregiver’s quality of life.

Methods. We studied 30 caregivers (mean age 50.4; 64% women, 36% men; 40% spouses, 40% sons, 10% sisters, friends and others) of patients with different malignant diseases: glioblastoma, breast cancer, colon-rectal, prostate cancer and "other" tumours. The implementation of this trained nurse based project, presented in 2011, we found that perceived by physicians, i.e. mainly of technical nature in the latter’s opinion, mainly of assistance nature according to nurses. Since May 2010 to March 2012, so-rafenib was administered to 26 patients (5 F, 21 M, median 73 years, range 46-83) 13 affected by kidney cancer and 13 by HCC. Patients performed medical examination, were educated by trained nurses to the proper use of dermatologic support creams. A photographic study of cutaneous toxicity was undertaken from the baseline to the completion of treatment. Moreover ad hoc questionnaires were administered to explore 1) skin barrier potentially damaging activities of daily living, 2) the effects of TKI toxicities on QoL and adherence to TKI and suggested dermatologic support too.

Results. Only 2 patients interrupted TKI for G2 skin toxicity and 1 patient had only reduced the dose by 25%. Two patients, treated in 2011, affected by advanced renal cancer had already begun treatment at another center but with recurrent suspensions by not well managed dermal toxicity. The proper nurse approach reduced the severity of skin toxicity with a better QoL.

Conclusions. The implementation of this trained nurse based management, with the administration of dermatologic support creams, of ad hoc questionnaires, is highly effective in reducing severity and duration of HFSR allowing to continue treatment properly without interruptions and with appropriate dose intensity.

N4* A SUCCESSFUL PROJECT TO COORDINATE NURSES AND PHYSICIANS IN THE MANAGEMENT OF HAND FOOT SKIN REACTION WITH INOPERABLE RCC, ADVANCED AND METASTATIC RENAL CARCINOMA TREATED WITH SORAFENIB. A MONOINSTITUTIONAL DAY-HOSPITAL EXPERIENCE

Introduction. Sorafenib, a multitargeted kinase inhibitor, has improved treatment of advanced renal cell carcinoma and inoperable RCC. Unfortunately sorafenib is commonly associated with cutaneous toxicity frequently named hand-foot skin reaction (HFSR). A multidisciplinary approach (nurses and physicians) is necessary for better compliance.

Proposal. The tyrosine kinase inhibitor toxicity may reduce dose intensity and QoL. Patient’s proper education to the use of dermatologic support creams allows a better management of HF- SR-TKI-related. In the past project, presented in 2011, we found very useful a nurse based management of HFSR sorafenib related, so we wanted to support further this approach.

Materials and methods. Since May 2010 to March 2012, sorafenib was administered to 26 patients (5 F, 21 M, median 73 years, range 46-83) 13 affected by kidney cancer and 13 by HCC. Patients performed medical examination, were educated by trained nurses to the proper use of dermatologic support creams. A photographic study of cutaneous toxicity was undertaken from the baseline to the completion of treatment. Moreover ad hoc dermatologic support creams allows a better management of HF-SR-TKI-related. In the past project, presented in 2011, we found very useful a nurse based management of HFSR sorafenib related, so we wanted to support further this approach.

Results. Only 2 patients interrupted TKI for G2 skin toxicity and 1 patient had only reduced the dose by 25%. Two patients, treated in 2011, affected by advanced renal cancer had already begun treatment at another center but with recurrent suspensions by not well managed dermal toxicity. The proper nurse approach reduced the severity of skin toxicity with a better QoL.

Conclusions. The implementation of this trained nurse based management, with the administration of dermatologic support creams, of ad hoc questionnaires, is highly effective in reducing severity and duration of HFSR allowing to continue treatment properly without interruptions and with appropriate dose intensity.

N5* THE NURSE IN ONCOLOGY: AN ALLY TO THE PHYSICIAN, A SUPPORT TO THE PATIENT

Verzé A.1, Ibrahim T.2, Rosti G.3, Amoroso D.4, Maiello E.5, Astone A.6, Badalamenti G.7, Cecchini I.8, Fregosi S.8, Tedaldi R.9

1AOI, Verona; 2U.O. Oncologia, AUSL Forlì; 3Ospedale Civile, Treviso; 4Ospedale Versilia, Lido di Camaiore; 5Casa Sollievo della Sofferenza San Giovanni Rotondo, 6Policlinico A. Gemelli, Roma; 7AO Universitaria Policlinico Paolo Giaccone, Palermo; 8GfK Eirusko; 9IRST, Meldola

Background. Good cooperation between physicians and nurses requires a multidisciplinary approach. Cooperation issues might imply assistance’s deficit in terms of quality, safety and efficacy for patients. In oncology, the nurse is an important professional, and acts as a complement the oncologist. He/she plays an important role by providing the patient with information, explanations and psychologic support, as well as by cooperating with the physician in managing everyday’s clinical practice. The present survey is aimed to assess the perception by oncologists of the nursing staff activity, comparing it with statements made by the same nurses. Furthermore, the nurses’ knowledge of problems concerning bone metastases and their treatment with bisphosphonates was also assessed.

Methods. As part of a project by Novartis, implemented by GfK Eirusko, between January and February 2012 an online survey was submitted to 200 oncologists selected throughout the country. The interviewed physicians were asked to indicate nurses of the Oncologic Unit available to take part in the survey, so to obtain a matching sample. Among these, 200 names were randomly chosen to receive questionnaires.

Results. A total of 200 interviews was collected for each target, with an average of 2 interviews per center. (Participating centers average features: 10 seats at Day Hospital, 21 beds for in-patients). The results showed that 93% of the interviewed nurses manages oncologic patients regardless of tumor’s type; 60% of them declares to be fully informed about the diagnosis of the patients he/she manages. 96% of nurses declare to feel in need of attending professional refresher courses. The activity performed by nurses was found to be, in a statistically significant degree, different from that perceived by physicians, i.e. mainly of technical nature in the latter’s opinion, mainly of assistance nature according to nurses.
N6 NUTRITION IN CANCER PATIENTS: A WORK IN PROGRESS

Terpin R.1, Agostini S.2, Calligaris M.3, Di Camillo E.1, Driol P.1, Foghin L.1, Gon S.1, Miceli B.1, Fontana R.1, Perlazzi R.1, Russo F.1, Stacul A.1, Zandigiacomo L.1, de Pangher Manzini V.1

ASS 2 ‘Isontina’, 1SOC di Oncologia, 2Servizio di Dietetica, 1Distretto Basso Isontino, Gorizia

Discussion. The performed survey shows that the oncologist tends to underestimate the ‘relational’ aspects of the nurse’s role, characterizing his/her activity mainly as of practical/technical quality. The findings indicate that, in the specialized field of oncology, the integration between physicians and nurses, as well as the training of the latter, should be given greater attention and should be better organized, in order to provide the patient with an improved and more complete management.

N7 SELF EVALUATION OF SUBJECTIVE TOXICITY ACCORDING TO THE COMMON TOXICITY CRITERIA IN BREAST CANCER PATIENTS UNDERGOING ADJUVANT CHEMOTHERAPY: PRELIMINARY ANALYSIS OF AN ONGOING PROSPECTIVE STUDY OF THE RETE ONCOLOGICA PIEMONTESE


Background and purpose. In cancer patients enrolled in clinical trials, treatment-related toxicities are collected by interview and by assigning a grade of severity according to systems like the Common Toxicity Criteria (CTC) for adverse events. We sought to evaluate the feasibility of collecting 10 selected subjective chemotherapy-related toxicities by the use of a self administered questionnaire.

Methods. Prospective, multicenter, single cohort study in patients undergoing adjuvant chemotherapy for early breast cancer. The questionnaire was administered after the first and the third cycle of chemotherapy. For each toxicity (nausea, vomiting, constipation, anorexia, taste alterations, diarrhea, fatigue, pain, neuropathy and dyspnea) the definitions of grade of severity were translated into Italian and rephrased into questions. Patients were asked to choose the definition that better represented the worst toxicity experienced after chemotherapy. Day of onset with respect to the day of the last cycle of chemotherapy and total duration in days were also requested. We present a preliminary analysis on approximately half of the 600 patient that we plan to enroll.

Results. 572 questionnaires were distributed to 305 patients as of May 12th 2012. All questionnaires were returned by patients. Of the returned questionnaires 489 (85%) contained complete information. In 83 incomplete questionnaires, the most frequent omission regarded the occurrence of a specific toxicity (nausea 17, vomiting 24, constipation 17, anorexia 15, taste alterations 24, diarrhea 20, fatigue 20, pain 26, neuropathy 31, dyspnoea 34). When a toxicity was reported, all the subsequent questions were answered in most cases. A comparison between toxicities collected by questionnaires and those extracted from the medical records of the patients is ongoing.

Conclusions. Self evaluation of adjuvant chemotherapy-related toxic effects according to the Common Toxicity Criteria, is feasible in the clinical practice and potentially time saving. The study is ongoing.
N8 PATIENT CENTRIC ONCOLOGY: WHAT ONCOLOGISTS THINK, WHAT NURSES DO

Astone A.¹, Rosti G.², Verzè A.³, Amoroso D.⁴, Maiello E.⁵, Badalamenti G.⁶, Tedaldi R.⁷, Cocchini I.⁸, Fregosi S.⁹, Ibrahim T.⁷

¹Università Cattolica, Policlinico A. Gemelli, Roma; ²Ospedale Regionale, Treviso; ³AOI Verona; ⁴Ospedale Versilia, Lido di Camaiore; ⁵Casa Sollievo della Sofferenza, San Giovanni Rotondo; ⁶AO Universitaria Policlinico Paolo Giaccone, Palermo; ⁷Centro di Osteoncologia, IRCCS IRST Meldola; ⁸GfK Eurisko

Background. In oncology, the nurse is an important professional and acts as a complement to the oncologist. He/she plays an important role by providing patient with information, explanations and psychological support and cooperates with the physician in managing everyday’s clinical practice. The present survey aims at assessing the perception by oncologists of the nursing staff activity, comparing it with statements made by nurses themselves. Furthermore, the nurses’ knowledge of bone metastases and their treatment with bisphosphonates was assessed.

Methods. As part of a project by Novartis, implemented by GfK Eurisko, between January and February 2012, an online survey was submitted to 200 oncologists selected throughout the country. The interviewed physicians were asked to indicate nurses of their Oncologic Unit available to take part in the survey, so to obtain a matching sample. Among these, 200 names were randomly chosen to receive questionnaires.

Results. A total of 200 interviews was collected for each target, with an average of 2 interviews per centre. Participating centres had an average of 10 DH seats and 21 beds for in-patients. The results showed that 93% of the interviewed nurses manages oncologic patients regardless of the tumor type; 60% declares to be fully informed about the patients’ diagnosis; 96% feels in need of attending professional refresher courses. With regard to bone metastases, 36% does not feel informed about treatment with bisphosphonates. The activity performed by nurses was found to be different from that perceived by physicians, i.e. mainly of technical nature in the latter’s opinion, mainly of assistance nature according to nurses.

Working time dedicated by nurses: physicians’ perception vs nurses’ replies

<table>
<thead>
<tr>
<th></th>
<th>In the opinion of:</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>physician nurse</td>
<td>(z - test)</td>
</tr>
<tr>
<td>Psychological assistance to the patient</td>
<td>37% 53%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Explanation of the treatment program</td>
<td>19% 44%</td>
<td>0.0000</td>
</tr>
<tr>
<td>Blood sample collection</td>
<td>79% 69%</td>
<td>0.0022</td>
</tr>
<tr>
<td>Chemotherapy administration</td>
<td>92% 64%</td>
<td>0.0000</td>
</tr>
<tr>
<td>Management of adverse events</td>
<td>57% 8%</td>
<td>0.0000</td>
</tr>
<tr>
<td>Management of mucositis and stomatitis</td>
<td>40% 12%</td>
<td>0.0000</td>
</tr>
<tr>
<td>Paperwork proceedings</td>
<td>34% 62%</td>
<td>0.0000</td>
</tr>
<tr>
<td>Attending refresher courses</td>
<td>24% 9%</td>
<td>0.0000</td>
</tr>
</tbody>
</table>

Discussion. The survey shows that oncologists tend to underestimate the ‘relational’ aspects of the nurse’s role, characterizing his/her activity mainly as of practical/technical quality. The findings indicate that the integration between physicians and nurses, as well as the training of the latter, should be given greater attention and should be better organized, in order to provide the patient with a fully integrated management.

N9 ANXIETY AND INSOMNIA: RESULTS FROM A NURSE BASED SURVEY IN A DAY HOSPITAL SETTING AT HUMANITAS CENTRO CATANESE DI ONCOLOGIA

La Rocca R., Licciardello P., Caccamo F., Todaro F.M., Di Mauro G., Ali M., Clementi S., Fallica G., Taibi E., Sanò M.V., Aiello D.

Department of Medical Oncology, Humanitas Centro Catanese di Oncologia, Catania

Introduction. Anxiety represents, in oncology, the main symptom of a series of disorders which have, however, clinical characteristics, prognostic and therapeutic different from each other. Anxiety disorders are characterized constant thoughts of the disease, re-enactments of intrusive imagery, similar to what occurs after a catastrophic event or a violent trauma, can rapidly escalate to more serious issues responses such as anticipatory nausea and insomnia and can lead to more serious issue such as Post-Traumatic Stress Syndrome (PTSD). Data from a presentation to the Clinical Oncological Society of Australia’s Annual Scientific Meeting in 2010 suggest that around 25 percent of cancer patients meet the criteria for an anxiety disorder. Data from literature reported that 30-50% percent of cancer patients is affected by insomnia, accompanied to constant worry for the disease and for the future, difficulties in interpersonal relationships due to the sense of shame, diversity and inadequacy.

Methods. Eighty patients have been enrolled in the survey during a period of 4 months. The median age of the patients analyzed was of 65 years (range 36-82). Twenty-eight of eighty patients were male, fifty-two were female, (M/F ratio = 28/52 = 0.53). Median ECOG was 1 (range 0-2). Patients affected by non-hematologic malignancies receiving chemotherapy were included in this study. ECOG 3-4 patients were excluded from this study.

Results. The assessment of anxiety and insomnia has been done directly by the nurse with a standardized questionnaire and has documented the considerable rates of 71% and 56%.

Conclusions. Anxiety and insomnia are a commonly neglected problem among the cancer population. The specialist intervention (psychological support, psychotherapy and, if necessary, psychological and pharmacotherapy) represents a mode of action essential for their treatment of anxiety and insomnia. This nurse based survey documents frequencies above the data reported in the literature particularly for anxiety but also for insomnia and encourages us to draw a study comparing cognitive-behavioral therapy vs pharmacotherapy.

N10 NURSING FOLLOW-UP OF G-CSF ACUTE TOXICITY

Astori A., Bosio S., Papini S., Cavalleri M.E., Maspero F., Petrelli F., Cavallari M., Bergonovo K., Cremonevi M., Ghilardi M., Barni S.

Medical Oncology Division, A.O. Treviglio-Caravaggio, Treviglio

Background. Myeloid growth factors (G-CSFs) stimulate the neutrophils production, reduce the incidence of febrile neutropenia (FN) and also the delay of the chemotherapy, but with some side effects. Within a plan ‘of continuum of care’, our project was to evaluate the safety and the compliance of G-CSFs treatment (as primary prevention), during domiciliary therapy.
Methods. After 10 days from the first course of the G-CSFs, all the patients were asked by phone to report side effects, number of vials and time of treatment.

Results. Twenty-six patients were evaluated, mean age 65.7 years (range 34-84), 18 with elementary or middle school education. Nine patients out of 26 assumed pegfilgrastim, the others were treated with filgrastim. The patients treated with filgrastim received a mean of 3 daily injections of filgrastim (range 2-5). Seven of the 26 patients experienced adverse effects that they correlated to the treatment with filgrastim (4 out of 7) or filgrastim (3 out of 7); 3 patients experimented bone pain, 1 hypotension and 3 asthenia. Three patients benefited of non steroidal anti-inflammatory drugs for G-CSFs side effects. Adverse events were comparable between pegfilgrastim and filgrastim. A total of 19 patients, 6 of those assumed analgesic medications as prevention, had not shown side effects.

Conclusions. The administration of both forms of G-CSFs, pegfilgrastim and filgrastim, was safe and manageable. In our survey only 27% of patients that received the treatment have mild side effects that can be controlled by analgesics.

Although the use of G-CSFs was not associated with many adverse events, side effects must be discussed with the patient who can easily treat them with non steroidal anti-inflammatory drugs. G-CSFs treatment represents an effective therapy that simultaneously reduces the neutropenia and the risks of infection after chemotherapy. This treatment is convenient, safe and feasible at home. Overall the compliance was good.

N11 SURVEY IN MEDICAL ONCOLOGY DEPARTMENT OF “VITO FAZZI” HOSPITAL ABOUT EVALUATION OF NURSES’ BURNOUT SYNDROME AND POSSIBILITY TO HAVE PSYCHOLOGICAL TRAININGS

Visconti A. ¹, Dell’Atti A. ¹, Saracino V. ¹, Lorusso V. ¹

¹U.O. Oncologia Medica “Vito Fazzi” Hospital, Lecce

Background. The nurses working in Oncology Department, are often affected by anxiety, stress and depression, because oncological patients which are very fragile, both physically and psychologically can easily involve them emotionally. This may cause a state of working distress which can interfere in the helping relationship. Moreover the decline of motivation and loss of positive attitude may lead nurses to burnout syndrome. The aim of this study was to demonstrate that the previous assumptions may be incorrect.

Methods. A questionnaire was distributed to 20 nurses, who worked at least for one year in the oncology department from 01/10/2010 to 31/10/2010. Of these nurses, 16 were women and 4 men, with median age of 38.2 years (range 26-53 years).

The first part of the questionnaire focuses on the Italian version of Maslach Burnout Inventory (22 items) that identifies three different components [emotional exhaustion (EE), depersonalization (D), personal gratification (PG)] and indicates the criteria for the critical threshold: the second part deals with psychological individual and group interventions.

Results. The results from the questionnaire were as follows: EE point value was 18; D point value was 13.3; PG point value was 29.6. Comparing these values to the interpretation scale, we can state that the degree of burnout defined as exhaustion is moderate, whereas the degree of depersonalization as well as satisfaction with life are high.

Conclusions. Although the questionnaire was administered to a scant number of nurses, our results suggest that oncological nurses suffer from burnout in a percentage less than expected, and that their psychological and physical distress doesn’t affect their job gratification and life satisfaction. However having adequate psychological trainings and support, as well as living in the best possible working environment may help to avoid psychological distress.

N12 TEAM TRAINING AND IMPROVEMENT IN MEASURING PAIN IN ONCOLOGICAL DAY HOSPITAL (DH) PATIENTS

Cabiddu M., Borgenovo K., Ghilardi M., Cremonesi M., Petrelli F., Maspero F., Barni S.

Medical Oncology Division, A.O. Treviglio-Caravaggio, Treviglio

Introduction. Patients are often reluctant to communicate the pain they feel. We evaluated in our Day Hospital any discrepancies between the pain score measured by an oncologist and a nurse. Then we tried to improve the detection of pain by team training.

Materials and methods. From January 2010 to February 2011 we evaluated 154 patients (total DH admissions: 1546). Pain was measured by both an oncologist and a nurse using the Pain Visual Analogic Scale (VAS). The discrepancies were defined by at least 2 points of difference on the VAS score. On May 2011 we explored the possible cause of discrepancy and we organized meetings with oncologists and nurses to discuss this problem.

From July to December 2011 we performed a new evaluation of discrepancies between pain evaluation in 194 patients for a total of 979 DH admission.

Results. The characteristics of the two samples of patients were similar; the oncologists and nurses involved were the same too. In the first survey the following discrepancies were observed: in 9.4% of admissions the VAS score recorded by the oncologist was greater than that registered by the nurse; in 33.8% of admissions the opposite was noted. Overall the concordance between VAS score oncologist/nurse was of 56.8%.

In the second survey the concordance reached 81%, with only 9% and 9.6% of discrepancies between the two measurements, with VAS score greater in nurse and oncologist evaluation, respectively.

Conclusions. Our results appeared to confirm the reluctance of patients to reveal their pain, especially to the oncologist. The oncologists are more focused on chemotherapy than on supportive care, and pain measurement is performed so fast that the patient is brought to minimize the real entity of pain. The pain measurement can be also altered by emotional involvement of both oncologist and nurse: our team training was useful to improve patient’s care and pain’s management.


U.O. Oncologia Medica, A.O. Bolognini di Seriate (BG)
Background. The use of central venous access systems is common in oncology. The main indications are: chemotherapy regimens continuously infused administration of vesicant drugs, hydration and parenteral nutrition, pain management, with infusion pump systems, recovery of venous access in patients with poor vascular bed, etc. Nowadays, several types of central venous catheter (CVC) are available with different characteristics. The CVC may lead to various complications in the short and long term; however few data are available in the literature.

Aim. The main purpose of this perspective no randomized trial, that was initiated on 1 January 2011, is the creation of a care pathway for positioning, management and removal specifically of the PORT-a-Cath, a fully implantable device. Objectives of the study: 1) recording the number of PORT-a-Caths implanted in our hospital per year, 2) percentage of infections, thrombosis or any other complications per each 1000 days of device-implantation, 3) improving information and training for each patient. To achieve this goal we created a database and we elaborated a notebook to give to each patient.

Results. From 01/01/2011 to 31/03/2012 were enrolled 43 patients. For each PORT-a-Cath implanted, the data related to its management at every access to hospital have been collected by the nurse in 100% of cases. In addition, each patient received a notebook to record every use or any malfunction of the catheter. After about 9 months of median follow up, just a PORT-a-Cath was removed for allergic reaction. In any case, we have no recorded cases of infection, thrombosis or any other complication, early or late.

Conclusions. This is the first study in the world which wants to study prospectively the early and late complications of central venous catheters, specifically those of the PORT-a-Cath. Preliminary results of our trial show that the PORT-a-Cath is a type of catheter really manageable with a risk of complications very low and with very high patient’s compliance, being a fully implantable device.

N14 EFFICACY OF NURSE BASED ASSESSMENT BY EXTRAVASATION SCORE IN CANCER PATIENTS TREATED WITH CHEMOTHERAPY IN HUMANITAS CENTRO CATANESE DI ONCOLOGIA: THE “GOLIATH PROGRAM”

Caccamo F.1, Mazzamuto L.1, Ciancittò R.1, Iannino F.1, Ali M.1, Clementi S.1, Sanò M.V.1, Taibi E.1, Scandurra G.2, Aiello R.A.1

1Department of Medical Oncology, Humanitas Centro Catanese di Oncologia, Catania; 2U.O. Oncologia Medica, P.O. Cannizzaro, Catania

Introduction. Prevention is the best nursing strategy to face complication of extravasation because sometimes the use of antidotes can be less effective. The following conditions involve increased risk of extravasation: obesity, diabetes, mental impairment, lymphedema, previous administration.

Methods. 100 patients have been enrolled. Median age of patients was of 58 years (range 17-81). M/F ratio = 0.19. Median ECOG was 1 (range 0-2). Patients affected by malignancies admitted to chemotherapy regimen were included in the study. Patients with central venous access were excluded from this study. According to data from literature we assigned a score ranging from 1 to 3 to each condition to stratify the patients in different risk levels: diabetes 1 point, obesity 1 point, previous chemotherapy cycles greater >1 1 point, one arm lymphedema 1 point, both arms lymphedema 2 points, mental deficiency 3 points. Scores less than or equal to 2 identify normal-risk, scores between 3 and 4 distinguish a high-risk, scores 5 and up very high-risk. Normal-risk needs standard preventive procedures (suitable peripheral access, normal saline preinjection flushing), high-risk requires also vigilance on venous flow with frequency equal to 7-10 minutes. Very high-risk requires vigilance on venous flow with frequency equal to 5 minutes or less. A port-a-cath placement would be desirable in very high-risk patients with long-term chemotherapy regimens.

Results. The assessment made by extravasation score documented normal-risk (91%), high-risk (8%), very high-risk (1%). Median extravasation score was 0.5 (range 0 to 4). Median chemotherapy cycles administered was 7 (range 1 to 38). Only one case of extravasation occurred in a high-risk patient in the study period despite 350 chemotherapy cycles administrated resulting in 0.28% of treatments versus 1% of the best data from literature.

N15 USING ICE CHIPS REDUCES ORAL MUCOSITIS IN PATIENTS UNDERGOING CHEMOTHERAPY WITH EPIDOXORUBICIN


Oncologia, Istituto Dermopatico dell’Immacolata, Roma

Oral side effects remain a major source of illness despite the use of a variety of agents to prevent them. One of these side effects is oral mucositis (mouth ulcers). The ice chips technique works by constricting the blood vessels in the mouth, has the advantage of being cheap and low-tech and is adequate for bolus types of chemotherapy. The aim of this study was to assess the effect of oral cryotherapy on the development of oral mucositis related to infusion of bolus epidoxorubicin.

The nurse-team enrolled 50 patients (42 F/8 M; age 37-79 yrs), who were being treated with bolus epidoxorubicin for breast cancer (42) and for prostate cancer (8). The schedules of epidoxorubicin were: FEC (26%), EC (40%), epirubicin (18%), TEC (16%). Patients swirled ice chips in their mouth for 10 minutes prior to the injection of epirubicin, during the infusion and for 10 minutes afterward. Following therapy the patients responded to a questionnaire reporting the degree of ice chips therapy and duration of mucositis. Grade 1-2 oral mucositis according to the NCI-CTC v3 mucositis scale was observed at 7 and 14 days in 13 patients (26%). The questionnaire showed a different incidence of stomatitis: 15 patients (30%) had grade 1, 13 (26%) grade 2 and none had grade 3 or 4 mucositis. Besides 20 (40%) patients did not like the ice chips technique and 15 (30%) believed that the technique was useless.

In conclusion cryotherapy (ice chips) showed some benefit in preventing stomatitis to epidoxorubicin and nurses’ awareness of how cryotherapy can affect patients and options for resolving problems will enable them to provide a higher standard of individualized care.

N16 PERIPHERALLY INSERTED CENTRAL CATHETER IN ADULT ONCOLOGY PATIENTS: A SINGLE CENTER RETROSPECTIVE EXPERIENCE

Grifoni R., Angiolini C., Centineo D., Vergioli M., Wirtz V., Borgia C., Ribecco A.S., Fiorello L.

Medical Oncology Unit, Oncology Department, Ospedale Santa Maria Annunziata, Azienda Sanitaria, Firenze
**Purpose.** To evaluate a single center Medical Oncology Unit experience in peripherally inserted central catheter (PICC) implantation and to correlate patient-related characteristics with safety and efficacy of the procedure.

**Materials and methods.** We retrospectively evaluated 343 adult cancer patients who underwent PICC insertion in our Institution. From April 2009 to April 2012 a total of 360 silicone, single lumen (4 Fr), valved Groshong® device was inserted. The procedure was undertaken by a trained nurse in an aseptic outpatient setting, through an upper arm vein and with ultrasound guide. Patients’ characteristics are summarized in Table 1.

### Table 1

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Patients (N = 343)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian race, N (%)</td>
<td>337 (98.2%)</td>
</tr>
<tr>
<td>Female, N (%)</td>
<td>247 (72%)</td>
</tr>
<tr>
<td>Age, yr, median (range, yr)</td>
<td>62 (19-89)</td>
</tr>
<tr>
<td>Solid malignancy, N (%)</td>
<td>327 (95.3%)</td>
</tr>
<tr>
<td>breast cancer</td>
<td>128 (39.1%)</td>
</tr>
<tr>
<td>gastroenteric cancer</td>
<td>93 (28.4%)</td>
</tr>
<tr>
<td>urogenital cancer</td>
<td>45 (13.8%)</td>
</tr>
<tr>
<td>other cancers</td>
<td>61 (18.7%)</td>
</tr>
<tr>
<td>Hematologic malignancy, N (%)</td>
<td>16 (4.7%)</td>
</tr>
<tr>
<td>• Hodgkin lymphoma</td>
<td>1 (3.2%)</td>
</tr>
<tr>
<td>• non-Hodgkin lymphoma</td>
<td>15 (93.7%)</td>
</tr>
<tr>
<td>Fit upper arm/arms, N (%) - two arms</td>
<td>238 (69.4%)</td>
</tr>
<tr>
<td>- one arm</td>
<td>100 (29.1)</td>
</tr>
<tr>
<td>- none arm</td>
<td>5 (1.5%)</td>
</tr>
<tr>
<td>Right upper arm insertion site, N (%)</td>
<td>241 (71.3%)</td>
</tr>
<tr>
<td>Catheterized insertion vein, N (%) - basilic</td>
<td>281 (83.2%)</td>
</tr>
<tr>
<td>- brachial</td>
<td>42 (12.4%)</td>
</tr>
<tr>
<td>- cephalic</td>
<td>15 (4.4%)</td>
</tr>
</tbody>
</table>

Details about different PICC uses are summarized in Table 2. The main indication for PICC implantation was chemotherapy infusion in patients with advanced disease. The vascular device underwent standard weekly maintenance flushing when not used.

### Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (N = 343)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood sampling, N (%)</td>
<td>343 (100%)</td>
</tr>
<tr>
<td>Chemotherapy setting, N (%)</td>
<td>332 (96.8%)</td>
</tr>
<tr>
<td>• adjuvant/neoadjuvant treatment</td>
<td>127 (38.3%)</td>
</tr>
<tr>
<td>• advanced disease</td>
<td>205 (61.7%)</td>
</tr>
<tr>
<td>Necrotizing drugs, N (%)</td>
<td>122 (36.7%)</td>
</tr>
<tr>
<td>Continuous chemotherapy infusion</td>
<td>84 (25.3%)</td>
</tr>
<tr>
<td>Exclusive supportive care, N (%)</td>
<td>11 (3.2%)</td>
</tr>
</tbody>
</table>

**Results.** We observed a good patients’ compliance with a complication rate of 26.8%. We reported a high incidence of reaction to dressing plasters (38%) but a small incidence of major complications such as infection (4.3%), venous thrombosis/phlebitis (15.2%) and catheter occlusion (17.4%). Other minor complications (intolerance reaction, spontaneous retraction, fracturing) occurred 23 times. The median number of catheter insertion per patient was 1 (range 1-3) with a median life span of 13 weeks (range 1-62 weeks). PICC was removed, because of complications, in 3.5% of cases, and at the end of a treatment in 194 patients.

**Conclusions.** Patients with cancer require repeated venous punctures for a wide variety of medical exams and treatments. PICC is a reliable long term vascular access that conjugates treatment needs, good patient’s quality of life and intermediate complications rate with a sustainable cost. The results of this study will guide a departmental prospective evaluation with regard to patients’ selection criteria and resources optimization. The potential correlation between complication risk factors and advanced disease will be presented at the meeting.

**N17 NURSING MANAGEMENT OF CHEMOTHERAPY-RELATED ADVERSE REACTION AND TOXICITY: A NURSING CALL**


*Istituto Oncologico Veneto, IRCCS, Padova

**Background.** Chemotherapy is a core component of cancer care. Patients frequently receive such treatment as outpatients and are often required to manage side effects at home without direct support from oncology health professionals. Moreover chemotherapy toxic effects put patients at risk of developing a number of symptoms which, if not identified in the early stages, can be serious, life-threatening and can make their quality of life worse. Some of these symptoms and some adverse reaction appear during the chemotherapy administration in the hospital.

**Aim.** The aim of the study is not only to continue the nursing care started in the hospital but also to strengthen the relationship between patient and nurse.

**Materials and methods.** This project tries to realize a model of nursing, treatment and management of chemotherapy-related adverse reactions and toxicities that patients present during the drug administration in the Day Hospital. Indeed, the day after the event, the nurse will call the patient at home to get information about his health, paying attention to present symptoms and signs that the patient can still refer. Moreover the nurse will give information and educate the patient for a faster decrease of present symptomatology or will contact a physician for medical instructions.

**Results.** A total of 42 calls have been made to 42 patients. 79% of patients are female and 21% are male. 83% presented a chemotherapy-related adverse reaction and 17% a chemotherapy-related toxicity with grade ≥2 (CTCAE v. 3.0). The call to home helped a lot 84% of patients; it gave a real benefit to 55%; it was appreciated a lot from 52% and very much from 43%. 95% of patients helped a lot 84% of patients; it gave a real benefit to 55%; it was appreciated a lot from 52% and very much from 43%. 95% of callers did not find any difficulties during the call. The project is ongoing.

**Conclusions.** These partial results confirm that home monitoring of patients’ adverse reactions and toxicity is very useful; furthermore patients feel secure in the knowledge that their symptoms are closely monitored and self-confident in their own care management.

**N18 RANDOMIZED CONTROLLED CLINICAL PILOT TRIAL OF PROPOLIS FOR PREVENTION OF ORAL MUCOSITIS IN ADULT PATIENTS RECEIVING CHEMOTHERAPY FOR BREAST CANCER: PRELIMINARY RESULTS**

Piredda M., Vincenzi B., Facchinetti G., Stan I., Armento G., Tonini G., De Marinis M.G.

Università Campus Bio-Medico, Roma
Oral mucositis is a clinically important, dose-limiting and costly adverse effect of chemotherapy. Standard chemotherapy (doxorubicin and taxane based) regimens for breast cancer can cause important oral mucositis. Available evidence cannot recommend any proven effective treatment for this specific cancer population.

Propolis is a natural substance with many biological properties (anti-inflammatory, antimicrobial, antifungal, antiviral, anti-oxidant, immunomodulatory and anesthetic), relatively cheap and non-toxic. A dry extract of propolis has been proven effective in reducing the severity of oral mucosa diseases and pharyngeal inflammations, and reducing oral ulcers in patients diagnosed with recurrent aphthous stomatitis.

This pilot study aims to evaluate safety, tolerability and preliminary clinical efficacy of a dry extract of propolis with a minimum 8% of galangin for the prevention of chemo-induced stomatitis in patients diagnosed of breast cancer receiving chemotherapy.

Ethical approval has been obtained from the Ethical Committee and written informed consent will be obtained from willing participants.

Patients will be randomized to receive: either a dry extract of propolis with a minimum 8% of galangin 8-10 mg/kg/day plus mouth rinsing with sodium bicarbonate (intervention group; N = 20) or mouth rinsing with sodium bicarbonate (control group; N = 20). The intervention will last for 2 weeks starting on the first day of chemotherapy.

The incidence and severity of stomatitis will be evaluated using the National Cancer Institute Scale (NCI-CTCAE) version 4.0 (NCI 2009). Stomatitis will be evaluated at baseline, after 5, 10, 15 and 21 days of treatment. In the same days, oral pain will be evaluated and use of opioids will be reported. Compliance with treatment, tolerability of propolis and potential adverse effects will also be recorded.

SPSS software (version 17.00) will be used for statistical analysis. The comparison between groups in terms of rate and severity of stomatitis will be performed. Descriptive analysis will be performed using uncorrected chi-square test and the corresponding p value will be considered statistically significant if <0.05.

The study is under way and preliminary results will be presented in October. Results from this pilot study will be used to plan a multicenter randomized controlled trial aimed to test the efficacy of propolis for stomatitis prevention.

N20 ANTIBLASTIC DRUGS EXTRA VASATION: PREVENTION AND MANAGEMENT PROCEDURE


SOC di Oncologia, Ospedale di Gorizia, ASS2 “Isontina”

Background. Antiblastic drugs extravasation is an infrequent but sometimes dangerous event. So, it’s mandatory to adopt all preventive measures useful to reduce the risk of extravasation, and to have an easy procedure in every department dedicated to antiblastic drugs infusion.

Methods. 1. Clarification of the nurse role in prevention, education/involvement of the patient, modality of infusion, early detection and management of extravasation. 2. Classification of the antiblastic drugs based on their tissue damage potentiality. 3. Description of general and specific measures for extravasation. 4. Extravasation kit. 5. Some drafts for the patient information, description of general and specific measures for extravasation.

Results. Nurses can consider the opportunity of an infuse-agent in every patient with an inadequate venous asset, must inform the patients before the start of the infusion about the risk of extravasation, describe the alarming symptoms of the incident, proceed in a standard manner in the choice of the best site of the infusion and in the follow-up of the patient. Antiblastic drugs have been classified into five categories in a decreasing order of hazard: vesicants with DNA linkage (necrotizing), vesicants without DNA linkage, irritants, possible irritants, non-vesicants.

The general measures to adopt in every case of extravasation independently from the type of drug and the specific, physical and pharmacological measures to adopt in case of extravasation of some dangerous drugs (anthracyclines, taxanes, vinca alkaloids) have been listed. Moreover, a kit for extravasation with all drugs and tools required for any incident has been prepared. Finally,
some drafts have been compiled for information and consensus to the infusion with vesicant drugs, for the registration of any extravasation event, for the extravasation follow-up.

Comment. In case of extravasation the nurse and the doctor can quickly recognize the type of drug extravasated, specify the hazard of the incident, and adopt the appropriate physical and pharmacological measures. By learning how to effectively recognize extravasation and becoming familiar with the local, standardized, up-to-date procedure for dealing it, nurses play a pivotal role in cutting the incidence of extravasation and helping to minimize the complications, raising the standard of care in cancer therapy.

N21 ANTINEOPLASTIC CHEMOTHERAPY: FROM THE MEDICAL PRESCRIPTION TO THE PATIENT. COMPARING THE NEGRAR EXPERIENCE TO THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY/ONCOLOGY NURSING SOCIETY (ASCO-ONS) CHEMOTHERAPY ADMINISTRATION SAFETY STANDARD


Oncologia Medica, Ospedale Sacro Cuore Don Calabria, Negrar (VR)

Background. The risk of toxicity is particularly high concerning the administration of antineoplastic agents. Severe toxicity for the patients could result not only as a consequence of a wrong prescription but even as a consequence of a wrong preparation or administration. Despite these high risks there are few standards for safe administration. Only recently, the ASCO plus ONS published specific guidelines to meet this need for the safe administration of chemotherapy particularly in the outpatient setting (JCO 2009; 27: 5469).

Methods. Since March 2009 in our Oncology Unit we are exploiting a standardized informatics system for the prescription, preparation and administration of chemotherapy in the outpatient setting also including oral drugs. This E-system, named LOG80, is in agreement with the ASCO-ONS guidelines. As the process itself involves many professional caregivers (nurses, physicians and any practitioner licensed for drug preparation) our E-system included the medical prescription by the physician, the preparation of any drug exclusively at the Pharmacy Unit, and the administration of any drug to patients by trained nurses. Chemotherapy drugs are labelled immediately after preparation thus allowing a complete identification through a bar-code.

Findings. Our E-system proved a valid tool for reducing errors. From its introduction into practical use to date we have never registered errors at any level from the prescription to the administration of chemotherapy, particularly thanks to the bar-code which certified a total correspondence patient/drug and the pathway of chemotherapy as a whole. Moreover, we recorded every treatment, patients were performed to, in a specific data base.

Conclusions. Our experience favourably compares to ASCO-ONS standards for safety of chemotherapy administration. Indeed to date there is the need for equivalent and well recognized Italian specific guidelines. Therefore, every Medical Oncology Unit should assess its own compliance with the standards prescribed offering to the patients the best standard of care thus reducing errors of treatment and improper toxicity.

N22 STABILITY OF ANTIBLASTIC PREPARATIONS AFTER DILUTION: A TECHNICAL SUPPORT TO OPERATORS

Micallo G., Palazzo I., Acunzo G., Maiolino P.


Introduction. The proper storage of drugs is important to maintain their characteristics in order to ensure stability: this is essential so that the drugs could explicate the expected pharmacological activity. The active ingredients of medicinal product should not be considered stable indefinitely, but subjected to significant variations of their properties in the time. The period defined as ‘stability period’ is practically the time that elapses between the time of the drugs preparation and the time when it meets no longer the requirements of the F.U., because it has lost more than 10 percent of its activity or because the drugs have changed their general characteristics.

Materials and methods. Data sheets of drugs, Compendium SIFO, Microdex, Medicina oncologica 8a ed., Pubmed. The study started an intensive review of the scientific literature emphasizing the most recent studies and analysis of construction materials of the containers (PE rather than PVC or glass).

Results. The results consist of a summary table which lists the drugs and their active ingredients, the pharmaceutical formulation (powder or solution), the stability after dilution and references that the study has identified.

Conclusions. This list is an excellent support for operators in the preparation and infusion of chemotherapeutic drugs whose activity is crucial for treatment success.
AUTHOR INDEX

Aapro M.S., C3*, C5*
Abbadessa G., A1*
Accettura C., B52, F23
Acunzo G., N22
Adami F., F32
Adamo B., E51
Adamo V., B36, D23, E51
Addati T., E67
Addis M.F., G10
Addoniti M.I., E46
Adua D., B24, B25, B53
Affatato A., A4*, B9
Agati R., G18
Agazzi M.T., C50
Aglietta M., A3*, A9, A17, B18, E12, F13, G3*, N7
Agostaria B., C16, C57
Agostini F., C2*
Agostini S., N6
Agustini F., C3*
Aiello D., N9
Aiello R.A., C51, E52, G23, N2*, N4*, N14
Alfieri R., G17, G19, G24
Agostari G., C16, C57
Aglietta M., A9, A17, B18, E12, F13, G3*, N7
Aleotti M., E29
Alberona B., C56
Alberti P., C32
Albano A., G13
Albani A., E51
Albani A., E10, E61
Albertelli P., C23, D51, F28
Aliemi M., A44
Aliotta G., A25
Alvani F., D52
Altomonte M., G1*, H10
Altavilla G., C29, D17, E52
Aloj L., A36, F6*
Al et al., B24
Aloni M., E64
Allesi S., C38*
Alessandro G., C56
Amore P., A36, F6*
Albani A., E10, E61
Albani A., E44
Amorosa A., A18
Amoroso V., B30, C52, E72
Amoroso A., A18
Amorosi L., G14*
Ammunziata M.A., C34
Amsoloni L., G4*
Anselmi E., A38, B50
Andersen P., E63
Antonellini A., E44
Antonelli G., C23, D51, F28
Antoni G., C10, C15, E20, E61
Antoniotti C., B1*, B5*, B6*, B11, B23, E46
Antonuzzi A., A34, F20
Antonuzzi L., B1*
Anzà M., E21
Apicella M., C17
Aprile G., B4*, B5*, B6*, B10, B33, B34, B35, B45
Aragonà M., C29, E52, N19
Arcangeli G., B24, E52
Arcangeli V., A4*, B9
Archangels C., C46
Ardini E., B61
Arcito R., F6*
Arizzi A., A4*
Arizzi A., E4*
Arizzi C., C5*
Arizzoni A., B37, B50, C8, D1*, D2*, D19, D21,
D30, D41, D44, E31
Aretini P., E56
Armento G., N18
Armstrong A.J., F1*
Argandade J., F7
Arpinio G., L5
Ar ra C., E36
Arrighi G., E5*, E10, E17, E40, E56
Arrigo G., D17
Aste A., B18
Artioli P., E15
Arzase M., C35
Ascierto P.A., G1*, G3*, G15
Assensio Sierra N.M., A40
Assenti M., E68
Astarà G., E61
Astolfi A., A25
Aston A., B21, E52
Astori A., N10
Attard G., F7
Atzeni F., F4*, F6*
Aurilio A., D60
Avalone A., B22, B33, B34, B35
Azzara M., F21
Azzarello G., D50
Baccini G., B37
Bacchi G.P., C8
Bacci A., G5*
Badalamenti G., G19, N5*, N8
Bagalà C., A9, B21, E29
Bagnoli P., H10
Baiano G., B25
Bajetto A., E*
Baldanti F., B35
Baldari S., D30
Baldassarri P., B53
Baldazzi V., F4*, F10
Baldelli A.M., A8*, E53
Baldoni G., G19
Baldoni G., A34
Baldoni E., C61, E16, E54
Baldino G., B26
Baldin A., D40
Ballari A., N7
Ballarini M., E65
Ballatore V., F13
Ballatore Z., A23, D42, D43, D63
Balliezo A., H1*
Ballestrera A., F5*, E78
Balzano G., A15
Balzarotti M., G20
Bani M., C5*
Banna G.L., H2*
Banni S., C18
Banzi M., B1*
Barabino A., A1*
Barana D., C45
Baratelli C., F4*
Barbaro R., E38, E28
Barbaro R., E38
Barbieri A., E36
Barbieri F., D19
Baraldi G.O., C30, C40
Bareghi C., E4*
Baretta Z., E22
Baretta M., A20, A22, A24, A26, A27, A32, A33, A37
Barré C., A5*
Barrisone A., C42
Barletta G., D14, D27, D35, D36
Barin S., A36, B7, B8, B38, C16, C57, D1*, D3*, E2*,
E11, E16, E25, E32, F15, L4, N10, N12
Barone C., A9, A18, B21, D33, G29
Bartoli C., D46
Bartolani I., E5*, E17, E56
Bartoloni S., G5*
Bartolotti M., G18
Barucca V., B24, B25
Barutti C., E65
Barzelloni M.L., C53, F34
Bascianna L., C28
Basso E., C4, E59, E74, G22
Basso M., B21
Basso U., C20, F25
Battelli N., E26, E57
Battistella E., E60
Bazzola L., E24, E35, E44
Bearz A., A2*
Becarza I., A7, A11, A16, A23, B27, B39, D42
Bedognetti D., B31
Beghelli S., A10
Belfiore G., C13
Bella M.A., E31
Bellazzi R., E48
Bellevicere C., B28
Belizzi R., C28
Bellezza G., D20
Bellini C., A6*, A15, A28,
Bellini R., D18, D62
Bellingeri P., C42
Bellini G., C13
Bellizzi L., C56
Bellomo G., E14
Belloni B., D67
Belloumi L., A22, A24, A33
Beneci C., D17
Benedetti B., E15
Benedetti G., E53
Benfante A., L7
Bennati C., D1*, D8, D20, D22, D55
Berrardi R., A12, A23, A36, D42, D43, D63, E26, E57,
G3*, G4*, G5*, G17, G19, G24
Berrardinelli N., C62
Berrichia P., E12
Berenato R., D23
See you at the

15th National Congress of Medical Oncology
Milan (Italy), 12-14 October, 2013

President of the Congress
Stefano Cascinu

Scientific Secretariat
Aiom
Via Enrico Nöe, 23
20133 Milan, Italy
Phone: +39.02.70630279
Fax: +39.02.2360018
aiom@aiom.it
www.aiom.it

Organizing Secretariat
Aiom Servizi s.r.l.
Milan Office
Via Enrico Nöe, 23
20133 Milan, Italy
Phone: +39.02.26683129
Fax: +39.02.59610555
info@aiomservizi.it

Rome Office
Via Domenico Cimarosa, 18
00198 Rome, Italy
Phone: +39.06.8553259
Fax: +39.06.8553221
info@aiomservizi.it
Finito di stampare nel mese di ottobre 2012
dalle Arti Grafiche Tris s.r.l.
Via delle Case Rosse 23, 00131 Roma
per conto de Il Pensiero Scientifico Editore, Roma