Highlights ASCO GU 2016

Neoplasie del testicolo

Ugo De Giorgi
IRST-IRCCS Meldola
Keynote Lectures

Tom Powles, Rare and Testicular Cancers: Year in Review

Torgrim Tandstad, Long-term Toxicity: What to Expect and How to Prevent It?

Darren R. Feldman, Dose Intensification for First-line Therapy of Metastatic Disease: Which Patients and What Type of Intensification?

Katherine L. Nathanson, What Does the Clinician Need to Know about the Molecular Genetics of Testicular Cancer?

Oral presentations

ABSTRACT 472: Conditional survival of patients with metastatic testicular germ-cell tumors treated with first-line curative therapy. Author: Jenny J. Ko

ABSTRACT 473: Actionable targets in patients with cisplatin-resistant advanced germ cell tumors. Author: Aditya Bagrodia
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**ABSTRACT 473**: Actionable targets in patients with cisplatin-resistant advanced germ cell tumors. Author: Aditya Bagrodia
Keynote Lecture Testicular Cancer
Long-term Toxicity: What to Expect and How to Prevent It?

Torgrim Tandstad MD, PhD
St. Olavs University Hospital,
Trondheim, Norway
Why is long-term toxicity important in testicular cancer survivors (TCS)?

Very high cure rate
- CS I
  - 5 years OS: >98%\(^1,2\)
- Metastatic
  - Nonseminoma: 5 years OS: >90%\(^3\)
  - Seminoma: 5 years OS: >96%\(^2\)

Long life-expectancy following treatment (40-70 years)

\(^1\)Tandstad et al. JCO 2009; \(^2\)Tandstad et al. JCO 2011; \(^3\)Olofsson et al. JCO 2011

Cancer in Norway 2013, Cancer Registry of Norway, 2015

Presented by Torgrim Tandstad at Genitourinary Cancers Symposium 2016
The Future – Scope

- Increasing incidence in all western countries
- Prevalence will continue to increase drastically
Second cancers II

- Treatment:\textsuperscript{1,2}
  - RR at 2.0-2.6 after RT
  - RR at 1.8-2.1 after chemo
  - RR at 2.9-3.0 after RT/chemo

- Fung et al.\textsuperscript{3}
  - Metastatic nonseminoma, modern treatment chemotherapy (55% treated after 2000)
  - No increased risk after surgery
  - SIR 1.43 after chemotherapy
  - Median time 12.5 y (short follow-up)

\textsuperscript{1}Travis et al J Natl Cancer Inst 2005; \textsuperscript{2}Van den Belt-Dusebout et al JCO 2007; \textsuperscript{3}Fung et al JCO 2013
Cardiovascular disease (CVD)

- Coronary artery disease (stroke and peripheral artery disease)
- Typically develops several years after treatment
- Increased risk after RT or chemotherapy
- Combination of RT and chemotherapy yields the highest risk

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<th>Treatment</th>
<th>Relative R</th>
<th>Absolute R³</th>
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<td>Surgery</td>
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<tr>
<td>RT</td>
<td>2.1-2.4¹,³</td>
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<tr>
<td>Chemotherapy</td>
<td>1.9-2.6¹,²,³</td>
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<tr>
<td>RT/chemo</td>
<td>2.3-4.8¹,²,³</td>
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¹Huddart et al JCO 2003; ²Van den Belt-Dusebout et al JCO 2006; ³Haugnes et al JCO 2010
Pulmonary disease

- The risk of death due to respiratory disease is nearly 3-fold after chemotherapy compared to the normal population\(^1\)
- Decreased pulmonary function in patients receiving high doses of cisplatin or pulmonary surgery yields the highest risk\(^2\)

\(^1\)Fossa et al. JNCI 2007; \(^2\)Haugnes et al. JCO 2009
Other toxicities

- Neurotoxicity
- Ototoxicity
- Nephrotoxicity
- Fertility

Long-Term Complications After Testicular Cancer Treatment

JANUARY 8, 2016

By Jan Oldenburg, MD, PhD; Hege S. Haugnes, MD, PhD; Silke Gilissen, MD; and Torgrim Tandstad, MD, PhD

Article Highlights

- Survivorship research and long-term side effects are areas of particular importance for testicular cancer survivors because of the high cure rate and the young median age at diagnosis.
- Long-term side effects in this population include secondary malignant neoplasms, pulmonary complications, cardiovascular toxicity, and fertility issues.
- Preventive measures, such as smoking cessation, a healthy diet, and an active lifestyle, may play an important role in reducing the risk of several treatment-related toxicities.
Prevention of late effects – Clinical implications

• Long-term toxicity is related to the burden of treatment

• Minimize burden of treatment
  • Avoid dual therapy (chemotherapy/radiotherapy)
  • Always know what you treat
  • Reduce risk for relapse

Do not compromise cure!

Lege Artis 1st century BC. Staatliche Museen zu Berlin, Antikensammlung
Risk-adapted treatment CS I

- Nonseminoma\textsuperscript{1-4}
  - LVI+: 50%
  - LVI-: 15%

- Seminoma\textsuperscript{5}
  - Stromal invasion rete testis
  - Tumor diameter $>4$cm
  - 0 risk factor: 5%
  - 1-2 risk factors: 20%

\textsuperscript{1}Daugaard et al; AMPIS 2003, \textsuperscript{2}Tandstad et al; JCO 2009, \textsuperscript{3}Kollmannsberger et al; Ann Onc 2009, \textsuperscript{4}Sturgeon et al; Eur Uro 2010, \textsuperscript{5}Tandstad et al; In press 2016

Presented By Torgrim Tandstad at Genitourinary Cancers Symposium 2016
CS I nonseminoma LVI+

- BEP x 1
  - All receive chemotherapy
  - only 2% are in need of salvage chemotherapy

- Surveillance
  - Only patients relapsing receive chemotherapy
  - ~50% need salvage chemotherapy

- Overtreat 50% with one course of BEP, or overtreat 50% with three courses of BEP

Burden of Treatment
Experience or cooperation

Impact of the Treating Institution on Survival of Patients With “Poor-Prognosis” Metastatic Nonseminoma

Lawrence Collette, Richard J. Sylvester, Sally P. Stenning, Sophie D. Fossa, Graham M. Mead, Ronald de Wit, Pieter H. M. de Mulder, Niels Neymark, Eric Løken, and Sten B. Kaye

High annual hospital volume is associated with improved overall survival in clinical stage III non-seminoma testicular cancer: Results from the National Cancer Data Base (1998–2011)

Claudio Jeldres1,2,3, Khanh Pham1,2,4, Sia Daneshmand1,4, Christian Kollmannsberger3,5,6, Brandon Hayes-Lattin3,7, Erika Wolff1, Katherine Odem-Davis3, Christopher R. Porter1,2,3, and Craig R. Nichols1,3,7

1Department of Urology and Renal Transplantation and Multidisciplinary Testis Cancer Program, Virginia Commonwealth University Medical Center, Richmond, VA; 2Multiple Sclerosis and Andrology and Young Adult Oncology Committee, Department of Urology, University of Southern California, Norris Comprehensive Cancer Center, Los Angeles, CA; 3Department of Urology, Boston University School of Medicine, Boston, MA; 4Testicular Cancer Committee, Division of Nephrology and Clinical Urology, Children’s Hospital of Philadelphia, Philadelphia, PA; 5Division of Medical Oncology, UCLA Health, Los Angeles, CA; 6Testicular Cancer Program, Division of Medical Oncology, University of Washington, Seattle, WA; 7Multidisciplinary Testis Cancer Program, Department of Urology, Memorial Sloan-Kettering Cancer Center, New York, NY.
Standards in First-Line Chemotherapy for High-Risk GCT: Does this Include Dose Intensification?

Darren R. Feldman, MD
Memorial Sloan Kettering Cancer Center
Do STM Decline Rates Predict PFS & OS?

Presented By Darren Feldman at Genitourinary Cancers Symposium 2016

<table>
<thead>
<tr>
<th>Graph</th>
<th>Description</th>
<th>Data 1</th>
<th>Data 2</th>
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<tr>
<td>OS¹</td>
<td>Satisfactory Decline</td>
<td>2yr OS: 83% vs. 68% (p=0.01)</td>
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<tr>
<td></td>
<td>Unsatisfactory Decline</td>
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<tr>
<td>PFS²</td>
<td>Favorable Decline</td>
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<td>4yr PFS: 64% vs. 38% (p=0.007)</td>
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<tr>
<td></td>
<td>Unfavorable Decline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OS²</td>
<td>Favorable Decline</td>
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<tr>
<td></td>
<td>Unfavorable Decline</td>
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<td>4yr OS: 83% vs. 58% (p=0.009)</td>
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</table>

¹Motzer JCO 2007; ²Fizazi JCO 2004
Could Treatment Change Benefit the Slow STM Decline Group?

**PFS**
- BEP + HDCT
- BEP Alone

1yr durable CR: 61% vs. 34%
\[ p = 0.04 \]

**OS**
- BEP + HDCT
- BEP Alone

2yr OS 78% vs. 55%
\[ p = 0.10 \]
GETUG 13: Phase III Schema

Presented By Darren Feldman at Genitourinary Cancers Symposium 2016

Poor-risk pts n=254

BEPx1

Evaluate STM Decline

n=51 Favorable

BEPx3 (total 4 cycles) n=51
(70% PFS, 84% OS at 3y)

BEPx3 (total 4 cycles) n=98

R 1:1

Unfavorable n=203

Dose-intense regimen (total 5 cycles) n=105
GETUG 13: PFS and OS in Randomized Pts

3-year PFS: 59% vs. 48%
HR: 0.66 [0.44 – 1.00]  
\( p = 0.05 \)

3-year OS: 73% vs. 65%
HR: 0.78 [0.46 – 1.31]  
\( p = 0.34 \)
GETUG 13: Conclusions & Questions

- It's confirmed! Slow STM decline = worse prognosis
- Chemo switch improved PFS but not OS in pts with slow STM decline
- Dose dense tx more toxic and complicated, uses up salvage drugs
- ? Less salvage HDCT or less salvage options??

Questions:

- Should poor-risk (and other) pts with slow STM decline be switched to the GETUG 13 regimen? Not adapted globally
- If not GETUG 13, another regimen? No data
- Should GETUG 13 make us rethink clinical trials in poor-risk? Yes
Other Standards of Care and Common Questions / Pitfalls in Advanced GCT
Pitfalls in Advanced GCT (Don’ts)

- DON’T Treat based on pre-orchietomy markers
  - Can lead to over or under-treatment
  - Treat based on STM closest to start of chemo (post-orch)
- DON’T Use PET scan in post-chemo nonseminoma
  - No surgery for residual mass b/c “the PET scan was negative”
- DON’T give more chemo beyond 3-4 cycles BEP/EP for residual masses with negative markers
  - “The mass didn’t shrink” (think teratoma)
Pitfalls in Advanced GCT (Don’ts)

- DON’T delay, reduce, or omit drugs in BEP
  - Lowering etoposide (↓ PFS/OS)
  - Using carboplatin instead of cisplatin (↓ PFS/OS)
  - Omitting bleomycin on day 15 due to neutropenia

- DON’T start salvage chemotherapy for slow declining HCG
  - Slow terminal half-life (Zon et al. JCO 1998)
  - Wait for rise in HCG or other sign of POD
  - Consider brain MRI
## Risk of Substituting Carboplatin

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<th>$E_{500}^C$ (n=131)</th>
<th>$E_{500}^P$ (n=131)</th>
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<th>$BE_{360}^P$ (n=299)</th>
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<td>0.05$^1$</td>
<td>56</td>
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<td>Deaths</td>
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<td>-----</td>
<td>14</td>
<td>4</td>
<td>0.02$^2$</td>
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</table>

Cisplatin is superior to Carboplatin
## Risk of Decreasing Etoposide Dose

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<th>$B_{90}E_{500}P \times 3$ (n=83)</th>
<th>$B_{30}E_{360}P \times 4$ (n=83)</th>
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<tr>
<td>CR</td>
<td>88%</td>
<td>87%</td>
<td>NS</td>
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<tr>
<td>8-year PFS</td>
<td>86%</td>
<td>79%</td>
<td>0.15</td>
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<tr>
<td>8-year OS</td>
<td>92%</td>
<td>83%</td>
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<tr>
<td>Deaths from Progression</td>
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</table>

Etoposide 500mg/m2 per cycle is superior to 360mg/m2 per cycle
How to Handle Neutropenia in GCT?

Neutropenia on Day 1 of Cycles 2-4

- **MSKCC approach:** If WBC < 2,500/mm³ **AND** ANC < 500/mm³, delay x 1 week. Otherwise treat on time. *Don’t reduce doses; rarely delay, never > 1 week*
  - ≤ 7-day delay due to ↓ANC did not lead to worse CR rate or EFS¹

- **Indiana approach:** Start on time regardless of WBC/ANC. If patient remains neutropenic on day 4, hold day 5 of etoposide (20% ↓). *Don’t delay treatment; rarely ↓ VP-16*

- Can use G-CSF with future cycles
Conclusions (Int/Poor Risk GCT)

- Slow STM decline predicts worse prognosis but switch to dose intense therapy not globally adopted
- No data for switch to alternative regimens but trials coming
- BEPx4 remains standard of care
- DON’T dose reduce or delay treatment in GCT
- Stay tuned for integration of biology into management
Actionable targets in advanced germ cell tumors

Aditya Bagrodia, Samuel Kaffengerer, Byron Lee, William Lee, Eugene Cha, John Sfakianos, Sizhi Paul Gao, Emily Zabor, Irina Ostrovnaya, Jana Eng, Michael Berger, Dean Bajorin, Nikolaus Schultz, Joel Sheinfeld, George Bosl, Hikmat Al-Ahmadie, David Solit, Darren Feldman
MSK IMPACT

Prepare DNA from tumor & normal cells

Prepare 12-24 Libraries Capture DNA for cancer genes

“Next Gen” Sequencing (HiSeq 2500)

Align to Genome and Analyze

Probes for Exons from 341 Cancer Genes

Presented By Aditya Bagrodia at Genitourinary Cancers Symposium 2016
Methods

- Whole Exome and MSK-IMPACT Sequencing on 19 samples from patients with advanced GCT \textit{(discovery)}
  - 10 platinum-resistant
  - 9 platinum-sensitive

- MSK-IMPACT only on 101 additional GCT patients \textit{(validation)}

- **Platinum-sensitive: 44 patients**
  - CR to chemotherapy including pts with teratoma or necrosis on post-chemo pathology
  - >1yr PR-negative markers
  - No relapse at last f/u

- **Platinum-resistant: 76 patients**
  - Incomplete radiographic or serologic response
  - Viable GCT on post-chemo pathology
Extreme non-responders: TP53/MDM2 alterations are found only in TGCT patients with platinum resistance

Presented By Aditya Bagrodia at Genitourinary Cancers Symposium 2016
Pathway analysis: Receptor Tyrosine Kinase

KIT

- KIT: trans-membrane receptor that activates PI3K/AKT, RAS/MAPK and JAK/STAT

Potential Clinical Applications

Phase II Study of Imatinib Mesylate in Chemotherapy Refractory Germ Cell Tumors Expressing KIT

Lawrence H. Einhorn, MD,* Mary J. Brames, RN,* Michael C. Heinrich, MD,† Christopher L. Corless, MD, PhD,‡ and Ali Madani, MD, PhD.§

Results: There were no complete or partial remissions. Five of 6 patients had progressive disease and 1 patient had stable disease with a >50% decline in serum alpha-fetoprotein for 3 months before developing further progression.

**Actionable targets in resistant patients**

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<th>Pathway</th>
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<th>Alteration</th>
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IN CORSO: Studio fase 2 Olaparib nei GCT platino resistenti:
IRST Meldola e Istituto Tumori Pascale Napoli

Presented By Aditya Bagrodia at Genitourinary Cancers Symposium 2016
Conclusions:

- We have identified actionable mutations in a significant proportion of patients with platinum-resistant advanced germ cell tumors.
- These mutations may lead to individualized novel therapeutic options in resistant patients.
- Further preclinical and early phase investigation is required.
- A significant proportion of patients with platinum-resistance do not have identifiable driver mutations.
TAKE HOME MESSAGES

- Ridurre il “treatment burden”, nei casi iniziali

- Nei casi avanzati a cattiva prognosi, mantenere alta la dose intensity

- Possibili nuovi target, considerare studi clinici anche in Italia per forme platino-resistenti
Grazie per l’attenzione

Italian Germ cell cancer Group (IGG)

Fondato nel 2005 per migliorare lo studio e la cura dei tumori germinali in Italia

Il gruppo conta oltre 100 iscritti, da circa 50 centri, principalmente oncologi, urologi e radioterapisti

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