Neoplasie del pene, dell’uretra e tumori rari
Revisione Posters

Paolo Grassi
2016 ASCO GU: penile cancer and rare tumors

Poster session: 7 posters

• 3 ecological (observational)
• 1 observational retrospective
• 1 prospective study with TTs
• 2 translational (genomic)
Prognostic factors of adjuvant chemotherapy with taxane, cisplatin, and 5FU combination (TPF) in patients (pts) with nodal metastases of penile squamous cell carcinoma (PSCC).

A. Necchi, S. Lo Vullo, N. Nicolai, D. Raggi, P. Giannatempo, M. Colecchia, M. Catanzaro, T. Torelli, L. Piva, D. Biasoni, S. Stagni, L. Mariani, R. Salvioni; Fondazione IRCCS Istituto Nazionale Tumori, Milan, Italy; Unit of Clinical Epidemiology and Trial Organization, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

Patients and Methods

• Retrospective data on 21 pts who received 2-4 courses of adjuvant TPF following N+ surgery

• Evaluation of potential prognostic factors of DFS and OS

• p53 IHC evaluated in N+ using 10 random hotspots/specimen:

<table>
<thead>
<tr>
<th>p53</th>
<th>% of positive nuclei</th>
<th>&lt;90%: negative</th>
<th>≥90%: positive</th>
</tr>
</thead>
</table>
## Results

Table 3. Results of Cox analyses of overall survival.

<table>
<thead>
<tr>
<th>Factor</th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>p53 IHC:</strong> Positive vs Negative</td>
<td>4.54</td>
<td>0.96-21.56</td>
</tr>
<tr>
<td><strong>No. prior LAD:</strong> 2-3 vs 1</td>
<td>1.54</td>
<td>0.43-5.48</td>
</tr>
<tr>
<td>Time from diagnosis of cN+ to TPF:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weeks, continuous</td>
<td>0.95</td>
<td>0.85-1.07</td>
</tr>
<tr>
<td>Time from LAD to start TPF:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weeks, continuous</td>
<td>0.89</td>
<td>0.71-1.12</td>
</tr>
<tr>
<td>Pelvic pN+: Yes vs No</td>
<td>1.81</td>
<td>0.47-7.04</td>
</tr>
<tr>
<td>pN3:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes vs No</td>
<td>2.93</td>
<td>0.62-13.87</td>
</tr>
<tr>
<td>Bilateral pathologic N+: Yes vs No</td>
<td>1.17</td>
<td>0.30-4.52</td>
</tr>
</tbody>
</table>

**Abbreviations:** CI: confidence interval; HR: hazard ratio; IHC: immunohistochemistry; LAD: lymphadenectomy; TPF: taxane (paclitaxel: N=3; docetaxel: N=18), cisplatin, 5FU.  

*P: two-sided Wald test p value.
Results

Median DFS (median FUp 52 mo):
- p53 +ve (11 pts) 8.9 mo
- p53 - ve (8 pts) not reached (p=.051)

Median OS (median FUp 52 mo):
- p53 +ve (11 pts) 17.2 mo
- p53 - ve (8 pts) not reached (p=.037)
Conclusions and future directions

• p53 IHC +ve pts who received TPF for N+ PSCC seem associated to poorer outcome

• Findings support the prognostic role of p53 in N+ PSCC

• Information might be useful to patients selection

• Further studies warranted in larger datasets

Background

- PSCC is an orphan malignancy
- Biology and molecular drivers remain unclear
- TCGA is not studying PSCC and the COSMIC has analysed specific genes only
- Here reported the first integrated analyses of comprehensive WES from PSCC patients
Whole-exome sequencing (WES) of penile squamous cell carcinoma (PSCC) to identify multiple recurrent mutations

Methods

• Fresh PSCC tumor tissue (n=11) and adjacent normal tissue (n=3) samples from CHTN

• DNA isolated and WES done on Illumina HiSeq2500

• Data analysed for SNPs and CNV focusing on missense mutation and amplifications ≥2 samples
Whole-exome sequencing (WES) of penile squamous cell carcinoma (PSCC) to identify multiple recurrent mutations


Results

Top 10 genes with >4 missense mutations in ≥ 2 samples:
- AR
- EGFR/HER2
- BRCA1/BRCA2/ATM
- JAK2/JAK3
- ALK
- PTEN

→ potentially actionable targets

Abstr #484
Conclusions and future directions

• First reported WES of PSCC samples
• Identified multiple potential therapeutic targets including AR, EGFR/HER2, BRCA1/BRCA2, JAK2/JAK3, ALK and PTEN
• Data require validation in larger cohort of patients
• Immunotherapy may warrant development given the relatively large mutation burden
Background

- PSCC is a rare cancer with poor prognosis and limited response to conventional chemotherapy
- Targeting HER pathway is promising in PSCC. Dacomitinib is a potent, irreversible TKI of EGFR, HER2 and HER4
- Two trials are enrolling in the 1st-line/neoadjuvant setting (dacomitinib, NCT01728233) and salvage setting (afatinib, NCT02541903)
- Here presented the preliminary results of the ongoing NCT02541903 study
Pan-HER tyrosine-kinase inhibitors (TKI) Dacomitinib and Afatinib in penile squamous cell carcinoma (PSCC): results from an ongoing open-label, single-group, phase 2 trial of Dacomitinib in chemonaive patients (pts)

D. Raggi,¹ A. Necchi,¹ P. Giannatempo,¹ N. Nicolai,¹ M. Colecchia,¹ G. Calareso,¹ E. Togliardi,¹ F. Crippa,¹ L. Mariani,¹ F. Perrone,¹ G. Pelosi,¹ R. Salvioni,¹ G. Sonpavde²

¹Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy; ²UAB Comprehensive Cancer Center, Birmingham, AL, USA

Study design

Primary endpoint: ORR (%) by RECIST v 1.1
Secondary endpoint: incidence of AEs, pCR rate, PFS, OS, QoL, translational (i.e. EGFR/KRAS/NRAS mut)
Pan-HER tyrosine-kinase inhibitors (TKI) Dacomitinib and Afatinib in penile squamous cell carcinoma (PSCC): results from an ongoing open-label, single-group, phase 2 trial of Dacomitinib in chemonaive patients (pts)


1Fondazione IRCCS Istituto Nazionale dei Tumori, Milano, Italy; 2UAB Comprehensive Cancer Center, Birmingham, AL, USA

Results

Response and Survival of the first 15 patients enrolled and evaluable.

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. (%)</th>
</tr>
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<tbody>
<tr>
<td>Best Response to Dacomitinib 45 mg/day (RECIST v1.1)</td>
<td></td>
</tr>
<tr>
<td>Partial Response: N (% , 95%CI)</td>
<td>5 (33.3, 95CI15.2-58.3)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>8 (53.3)</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td>Densitometric response (necrosis)</td>
<td>3 (20.0)</td>
</tr>
<tr>
<td>Metabolic Response according to 18FDG-PET</td>
<td>9 (60.0)</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td></td>
</tr>
<tr>
<td>6-month Progression-free survival (% , 95%CI)</td>
<td>43.1 (17.8-66.3)</td>
</tr>
<tr>
<td>Overall Survival</td>
<td></td>
</tr>
<tr>
<td>Alive patients at last follow up (median 14.2 months)</td>
<td>9 (60)</td>
</tr>
<tr>
<td>Median overall survival (months)</td>
<td>13.7</td>
</tr>
</tbody>
</table>

Toxicity

<table>
<thead>
<tr>
<th>Variable</th>
<th>G1</th>
<th>G2</th>
<th>G3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin rash (n)</td>
<td>7</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhoea (n)</td>
<td>-</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Bleeding skin mets (n)</td>
<td>-</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>

Abstr #483
Early Conclusions and future directions

- Dacomitinib showed antitumor activity in PSCC with favorable safety profile
- Results are pending for the whole sample size.
- TKIs trials will provide insights into the targeting HER pathway in PSCC
- Preliminary data on molecular alterations awaited
Background

• Collecting duct carcinoma (CDC) of the kidney is a rare tumor with poor prognosis.

• This study aimed to identify the most deregulated pathways in CDC to gain insights into new possible molecular targets.
Methods

- RNA from FFPE samples of primary CDC (n=9), ccRCC (n=7) and healthy (n=7) adjacent renal tissues
- Gene expression profile performed by GeneChip® Human Transcriptome Array 2.0
- Analysis validated on the same population by qRT-PCR
- Functional enrichment analysis identified the most deregulated pathways in CDC
Results

- 1079 genes significantly deregulated ($p<.05$)
- In CDC vs normal tissue 484 genes up-regulated (339 coding) and 49 down-regulated ($p<.05$)
- 4 most highly expressed transcripts in CDC are unknown
- FN1, miR-21, KNG1 and AQP2 associated with advanced disease and poor prognosis in RCC
- Strong deregulation in DNA damage response pathway in CDC
Conclusions and future directions

- Several coding and non-coding transcripts differentially expressed in CDC vs ccRCC and normal tissue identified
- Association of deregulated transcripts with cancer pathogenesis, progression and prognosis
- Deregulation in DNA damage response pathway supports the possible role of platinum compounds
- Further studies are ongoing to identify possible druggable targets
Grazie dell’attenzione