ESMO highlights: Bladder and renal cancer

Tom Powles
Barts Cancer Institute
Disclosures

• Research funding from GSK
Where is research in these tumours?

• Testis cancer is a victim of its own success.
  – Surveillance for stage I disease has an excellent outcome
  – Improving on BEP first line seems hard
  – Not enough patients to perform randomised 2nd line trials.

• Bladder cancer seems stuck in the past
  – The adjuvant and neoadjuvant debate continues
  – No biomarkers
  – No targeted therapies
Multicenter randomized phase 2 trial of Gemcitabine - Platinum +/- Trastuzumab in advanced or metastatic urothelial carcinoma with HER2 overexpression

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Overall Survival (OS)

Stratified Log-Rank: p=0.56

Median Overall Survival (95%CI, months)

- A: 15.7 (12.3-23.7)
- B (+trastuzumab): 14.2 (9.4-28.1)

At risk:

<table>
<thead>
<tr>
<th>Group</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
<th>42</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>29</td>
<td>19</td>
<td>10</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>B (+trastuzumab)</td>
<td>31</td>
<td>20</td>
<td>8</td>
<td>5</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>
## Efficacy Summary

<table>
<thead>
<tr>
<th></th>
<th>Arm A</th>
<th>Arm B (+ T)</th>
<th>p-value (2-sided)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n = 29 Pts</td>
<td>n = 32 Pts</td>
<td></td>
</tr>
<tr>
<td><strong>Median PFS (Months); (95 IC)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cisplatin based-CT</td>
<td>10.2 (5.3 – 13.4)</td>
<td>8.3 (5.9 – 10.6)</td>
<td>0.69</td>
</tr>
<tr>
<td>carboplatin based-CT</td>
<td>6.4 (2.3 – 12.8)</td>
<td>10.6 (5.8 – 22.1)</td>
<td></td>
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<tr>
<td><strong>Median OS (Months); (95 IC)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cisplatin based-CT</td>
<td>15.7 (12.3 – 22.8)</td>
<td>14.2 (9.5 – 28.1)</td>
<td>0.51</td>
</tr>
<tr>
<td>carboplatin based-CT</td>
<td>14.5 (6.7 – 30.9)</td>
<td>33.1 (12.4 – 50.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Objective response rate; n(%)</strong></td>
<td></td>
<td></td>
<td>0.39</td>
</tr>
<tr>
<td>RC</td>
<td>6 (20.7)</td>
<td>7 (21.9)</td>
<td></td>
</tr>
<tr>
<td>RP</td>
<td>13 (44.8)</td>
<td>10 (31.3)</td>
<td></td>
</tr>
<tr>
<td>SD</td>
<td>6 (20.7)</td>
<td>7 (21.9)</td>
<td></td>
</tr>
<tr>
<td>PD</td>
<td>4 (13.8)</td>
<td>4 (12.5)</td>
<td></td>
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</tbody>
</table>

\(T = \text{trastuzumab}\)
Conclusions

• HER2 over-expression is rare (13.3%) in advanced and/or mUCs

• No difference was observed on ORR, PFS, OS and Quality of Live between CG +/- trastuzumab

• CG-trastuzumab was feasible but not more effective

• Trastuzumab could have a synergetic effect with cisplatinum leading to a longer OS
Antagonism between lapatinib and cisplatin in bladder cancer cell lines

Cisplatin + Lapatinib - Algebraic estimate

CI +/- 1.96 s.d.

Fractional Effect

Perry et al MCT 2009
Targeted therapy in bladder cancer

Bevacizumab
Cetuximab
trastruzimab

Gefitinib
Lapatinib
Sorafenib
Sunitinib
Vandatinib

mTOR
HDACi
PI3K
NFkB
Investigating targeted therapy in metastatic bladder cancer.
Trials with targeted therapy in metastatic bladder cancer

Completed trials
- 2\textsuperscript{nd} line vandatinib with chemotherapy
- Cetuximab with chemotherapy
- Maintenance sunitinib post chemotherapy

Ongoing randomised trials
- Maintenance lapatinib post chemotherapy
- Bevacizumab with first line chemotherapy
- Pazopanib v.s. chemotherapy in the 2\textsuperscript{nd} line setting
- OGX 427 with chemotherapy
Neoadjuvant (NACT) and Adjuvant Chemotherapy (ACT) for Muscle-Invasive Bladder Cancer (MIBC):

A Population-Based Outcomes Study in Ontario Canada

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Cancer Care Ontario Chair in Health Services Research
Division of Cancer Care and Epidemiology
Queen’s University, Kingston, Canada
Study Design

Objective: To evaluate utilization of NACT/ACT for MIBC and to explore the survival benefit of ACT at the population-level.

Methods:

• Population-based, retrospective cohort study to describe management and outcome of all cases of resected MIBC in the Canadian province of Ontario 1994-2008.

• Cases identified using the Ontario Cancer Registry (OCR).
Results: NACT/ACT Utilization

- Utilization of NACT was fairly stable over time (4%)
- Utilization of ACT increased over time
  
  16% (94-98), 19% (99-03), 23% (04-08), p=0.001
Results: Outcomes

- Among all MIBC cases
  - 5 yr OS 30% (95%CI 28-31%)
  - 5 yr CSS 34% (95%CI 32-36%)
- Patients treated with ACT had much worse disease characteristics compared to cases without ACT
  - 83% vs 68% T3/T4 tumor
  - 61% vs 17% node positive disease
- Despite having worse prognosis ACT cases had outcomes comparable to cases without ACT
  - 5 yr OS 30% vs 30%
Conclusions

1. Contrary to treatment guidelines use of NACT is low and use of ACT is increasing.

2. In 2004-2008 only 28% of patients with resected MIBC received any form of peri-operative chemotherapy.

3. Poor risk pathology is associated with greater use of ACT.

4. Survival of NACT and ACT cases is substantially lower in the general population than outcomes reported in clinical trials.

5. ACT is associated with a substantial improvement in OS and CSS in the general population.
Gemcitabine, Oxaliplatin, And Paclitaxel (GOT) on a 2-weekly Schedule In Patients With Refractory Germ Cell Carcinoma: A phase II study conducted at the University of Southern California

European Society for Medical Oncology, 30th September 2012
USCNCC 4T-03-1, USC IRB #HS-03B005-AM009. ClinicalTrials.gov Identifier: NCT00183820

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\textsuperscript{b}Levine Cancer Institute, Carolinas HealthCare System, Charlotte, NC, USA
### Phase 2 trials of double- or triple-combination chemotherapy in patients with refractory germ cell tumors

<table>
<thead>
<tr>
<th>Combination regimen</th>
<th>No. of patients</th>
<th>Previous HD-CTX %</th>
<th>ORR (%)</th>
<th>CR/PR (%)</th>
<th>OS (range)</th>
<th>Long-term survival % of patients (months)</th>
<th>Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel/gemcitabine</td>
<td>28</td>
<td>36</td>
<td>21</td>
<td>10/NE</td>
<td>8.3 (≥2-25)</td>
<td>7 (≥15-25)</td>
<td>Hinton et al. [17]</td>
</tr>
<tr>
<td>Gemcitabine/oxaliplatin</td>
<td>28</td>
<td>14</td>
<td>32</td>
<td>14/NE</td>
<td>8.7 (≥2.5-28)</td>
<td>11 (≥14, 19, 28)</td>
<td>Pectasides et al. (2004)</td>
</tr>
<tr>
<td>Oxaliplatin/irinotecan</td>
<td>18</td>
<td>0</td>
<td>40</td>
<td>22/NE</td>
<td>7.5 (≥1.5-19)</td>
<td>9 (≥11, 14, 19)</td>
<td>Pectasides et al. [19]</td>
</tr>
<tr>
<td>Oxaliplatin/gemcitabine</td>
<td>18</td>
<td>22</td>
<td>17</td>
<td>5/5</td>
<td>7 (≥1-44)</td>
<td>16 (≥18, 20, 44)</td>
<td>De Giorgi et al. (2006)</td>
</tr>
<tr>
<td>Gemcitabine/paclitaxel</td>
<td>32</td>
<td>100</td>
<td>31</td>
<td>19/13</td>
<td>8.0 (≥2-63)</td>
<td>13 (≥20, 40, 44, 57)</td>
<td>Einhorn et al. [21]</td>
</tr>
<tr>
<td>Paclitaxel/oxaliplatin</td>
<td>26</td>
<td>NE</td>
<td>30</td>
<td>0/4</td>
<td>8.8 (95% CI: 5-12)</td>
<td>8 (median: 65)</td>
<td>Theodore et al. [22]</td>
</tr>
<tr>
<td>Gemcitabine/oxaliplatin</td>
<td>35</td>
<td>89</td>
<td>46</td>
<td>9/9</td>
<td>6 (1-84)</td>
<td>3 (≥59)</td>
<td>Kollmannsberger et al. (2004); Oechsle et al (2011)</td>
</tr>
<tr>
<td>Gemcitabine/oxaliplatin/paclitaxel</td>
<td>41</td>
<td>78</td>
<td>51</td>
<td>5/34</td>
<td>11 (≥2-48)</td>
<td>17 (≥28, 28, 31, 33, 36, 37, 48)</td>
<td>Bokemeyer et al. (2008); Oechsle et al (2011)</td>
</tr>
<tr>
<td>Gemcitabine/oxaliplatin/paclitaxel</td>
<td>30</td>
<td>20</td>
<td>31</td>
<td>7/23</td>
<td>16.7 (11.0-32.7)</td>
<td>42% at 2 years</td>
<td>Dorff et al USC ESMO (2012)</td>
</tr>
</tbody>
</table>

**NE = Not evaluated, Oechsle K et al. Eur Urol 60: 850 - 855, 2011**
The TAXIF II protocol final results:
A Phase II Trial of High-Dose Chemotherapy (HDCT) supported by Haematopoietic Stem Cell Transplantation (HSCT) in Patients with Disseminated Germ-Cell Tumors (GCTs) Failing Chemotherapy (CT) and with Adverse Prognostic Factors.

F. Selle¹, K. Fizazi², P. Biron³, G. Gravis-Mescam⁴, B. Bui⁵, J.-O. Bay⁶, A. Flechon³, C. Dubot¹, A. Caty⁷ and J.-P. Lotz¹

¹APREC (Alliance Pour La Recherche En Cancerologie), Tenon Hospital, Department of Oncology, Assistance publique des hôpitaux de Paris (AP-HP), France
²Institut Gustave Roussy, Medical Oncology, Villejuif, France.
³Centre Léon Bérard, Medical Oncology, Lyon, France.
⁴Institut Paoli-Calmette, Medical Oncology, Marseille, France
⁵Institut Bergonié, Medical Oncology, Bordeaux, France
⁶Centre Jean Perrin, Medical Oncology, Clermont-Ferrand, France
⁷Centre Oscar Lambret, Medical Oncology, Lille, France
TAXIF II: A novel high dose chemotherapy in selected patients with relapsed GCT

22 months (95%CI, 2-NA)
TIP v.s. TICE in relapsed germ cell tumors: The TIGER trial.

- An investigator led global collaboration
  - USA, Germany, UK, France, Italy.
  - Ireland, Canada, Denmark & Holland
- Funding from multiple sources.
- The Alliance (CALGB) and EBMT will co-sponsor
Summary

• Breakthroughs in bladder cancer remain elusive
• The debate about adjuvant therapy continues
• Clinical trials in testis cancer require collaboration to change clinical practice.