Chemotherapy in Urothelial Cancer

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Urothelial Cancer and Chemo

• Localised disease: Neoadjuvant or adjuvant?

• Metastatic disease: first line

• Metastatic disease: second line
Adjuvant Chemotherapy: Overview

Prospektive randomised trials

<table>
<thead>
<tr>
<th>Investigator</th>
<th>Year</th>
<th>Regimen</th>
<th>Chemo</th>
<th>No chemo</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Logothitis et al [42]</td>
<td>1988</td>
<td>CISCA</td>
<td>62</td>
<td>71</td>
<td>Benefit but not randomized</td>
</tr>
<tr>
<td>Skinner et al [41]</td>
<td>1991</td>
<td>CAP</td>
<td>47</td>
<td>44</td>
<td>Benefit few patients received therapy</td>
</tr>
<tr>
<td>Stockle et al [45,46]</td>
<td>1992</td>
<td>M-VAC/M-VEC</td>
<td>23</td>
<td>26</td>
<td>Benefit no treatment at relapse</td>
</tr>
<tr>
<td>Studer et al [47]</td>
<td>1994</td>
<td>DDP</td>
<td>40</td>
<td>37</td>
<td>No benefit</td>
</tr>
<tr>
<td>Bono et al [43]</td>
<td>1995</td>
<td>CM</td>
<td>48</td>
<td>35</td>
<td>No benefit for N0</td>
</tr>
<tr>
<td>Otto et al [44]</td>
<td>2001</td>
<td>M-VEC</td>
<td>55</td>
<td>53</td>
<td>No benefit</td>
</tr>
<tr>
<td>Cognetti et al [49]</td>
<td>2008</td>
<td>GC</td>
<td>97</td>
<td>86</td>
<td>No benefit for N0 or N+</td>
</tr>
</tbody>
</table>

Guidelines EAU, ESMO: **not enough evidence for routine use of adjuvant chemo in urothelial cancer**

Calabro, Eur Urol 2009
Neoadjuvant Chemotherapy

- Two randomised phase III trials:
  - 3 cycles MVAC: Grossman et al NEJM 2003 (307 pts)
  - 3 cycles CMV: Griffith et al JCO 2011 (976 pts)

- Three metaanalyses
  - Lancet 2003
  - J Urol 2004
  - ABC metaanalysis Eur Urol 2005
**CMV trial:**
5-YS 49% vs 43%
10-YS 36% vs 30%
p = 0.037 HR 0.84

**MVAC trial:**
5-YS 57% vs 43%
p = 0.06 two sided

Griffith et al. J Clin Oncol 2011

Grossman et al. NEJM 2003
Neoadjuvant Chemo Metaanalysis 2005

3005 individual patient data
all received cisplatin-based combination chemo
independent of definitive local treatment (OP or RT)

- 14% ↓ risk of death
- 5% absolute OS benefit after 5 years
  (95% CI 1 to 7%)
- OS ↑ (45% → 50%)

Guidelines: strongly consider cisplatin-based neoadjuvant chemo if good performance status and adequate renal function
Metastatic disease: Historical background

Loehrer et al. JCO 1992
- M-VAC vs Cisplatin
- RR: 39% vs 12%
- OS: 12.5 vs 8.2 mts
- But Tox: 10% FN, 4% toxic deaths, 17% G3/4 mucositis

Logothetis et al. JCO 1990
- M-VAC vs CISCA
- RR: 65% vs 46%
- OS: 62.6 vs 48.3 weeks
- Tox: 5% FN, no toxic death with MVAC

269 pts vs 110 pts
Cisplatin/Gemcitabine vs M-VAC

- Randomized phase III trial; 405 patients

- Regimens:
  - **GC**: Cis 70mg/m2, Gem 1000mg/m2 d1,8,15 q28d
  - **MVAC**: MTX 30mg/m2 d1,15,22, Vinblastine 3mg/m2 d2,15,22, Doxo 30mg/m2 d2, Cis 70mg/m2 d1 q28d

- GC less toxic:
  - Neutropene Sepsis: 14% vs 1%
  - Mucositis Grad 3/4: 22% vs 1%
  - Toxic death: 3% vs 1%

Von der Maase H et al. JCO 2000;17:3068-3077
Time to Progression M-VAC vs GC

**GC** 7.4 months (6.6-8.1)

**M-VAC** 7.4 months (6.7-9.1)

**HR:** 1.05 (0.85-1.30)

**Response rate:** GC 49% vs 46%

Von der Maase H et al. JCO 2000;17:3068-3077
Overall survival for M-VAC vs GC

**GC** 13.8 months (12.3-15.8)

**M-VAC** 14.8 months (13.2-16.8)

HR: 1.04 (0.82-1.32)

Von der Maase H et al. JCO 2000;17:3068-3077

Cisplatin + Gemcitabine new standard
Dose dense M-VAC better than M-VAC?

• Randomized phase III trial; 263 pts
• HD MVAC:
  – MTX 30mg/m2 d1, Vinblastine 3mg/m2 d2, Doxo 30mg/m2 d2, Cis 70mg/m2 d2 q14 days; GCSF

• HD MVAC less toxic:
  – Hematological toxicity ↓
  – Mucositis ↓
  – Toxic deaths 3-4% in both groups

Sternberg CN et al. JCO 2001;19:2638-46
DD M-VAC: PFS and RR

Response rate: 62% vs 50%
Complete remission: 21% vs 9%
DD M-VAC: overall survival

Not accepted as a new standard

Fig 2. Overall survival. HR, hazards ratio; N, number of patients treated; O, number of observed events.

Logrank test: p=0.1218
HR: 0.80 (95% CI: 0.60 - 1.05)
P = 0.121
Can we improve Cis/Gem? – EORTC 30987

626 patients

Presented at ASCO 2007

Bellmunt J et al JCO 2012;30:1107-1113
Cis/Gem + Paclitaxel: Results

- RR: 55% vs 44%
- PFS: 8.8 vs 7.7 months p=0.109
- OS: 15.8 vs 12.7 months p=0.1
- Toxicity:
  - 60% dose reduction; 15% terminated early
  - FN 13% vs 4%
  - Toxic deaths: 6 vs 3

→ not a new standard
Interim Conclusions 1\textsuperscript{st} line

- Urothelial carcinoma is chemosensitive disease
- Cis/Gem is standard chemotherapy for urothelial Ca if:
  - Good performance status
  - Normal renal function: GFR >60mg/m2

- More chemo not necessarily better

- 2 questions:
  - What about the "unfit for cisplatin" patients?
  - Possibilities of "targeted" treatments?
1st line "unfit for cisplatin": EORTC 30986

- "Unfit for cisplatin":
  - Performance Status ≥ 2
  - Renal function ↓: GFR <60 but >30ml/min

- Carbo/Gem vs M-CAVI
  - Carbo AUC 4.5 d1; Gem 1000mg/m² d1,8 q21d
  - MTX 30mg/m² d1,15,22; Vinblastin 3mg/m² d1,15,22; Carbo AUC 4.5 q28d

- Randomized phase III trial; 238 pts

1st line "unfit for cisplatin": Results

- RR: Carbo/Gem 41% vs 30%
- OS: Carbo/Gem 9.3 vs 8.1 months

- Toxicity:
  - Severe acute toxicity: 9% vs 21%

- Problem: heterogenous population

1st line "unfit for cisplatin": Results

Combination of several risk factors lead to dismal outcome

Bajorin risk factors:
- Karnofsky <80%
- Visceral mets
Her1/2 or VEGF as targets?

**HER 1 and 2**
- Preclinical rationale
- Overexpression in TCC
  - HER1 (60-75%)  
  - HER2 (10-80%)
- Associated with poor prognosis
  - Trastuzumab, Cetuximab
  - Lapatinib, Gefitinib

**VEGF**
- Preclinical rationale
- Associated with metastases and poor prognosis
  - Sunitinib, Sorafenib, Pazopanib
  - Bevacizumab
Targeted therapy – lost hope?

- Phase II Sunitinib, Sorafenib, Pazopanib: negative
- Phase II Lapatinib: negative
- Phase II Trastuzumab: negative
- Phase II Gem/Cis + Bevacizumab: signal?
  - But toxicity↑
  - Phase III ongoing

sobering!
Patient characteristics:
PS 0-1/ 2/ >2
GFR ≥/≤ 60ml/min
Comorbidities?

YES
PS 0 -1 AND
GFR ≥ 60ml/min
STANDARD:
Gem/Cis
MVAC
HD MVAC

C I S P L A T I N ?

NO
PS 2 OR
GFR <60ml/min
Combination Chemo:
Carbo-based

Second line treatment?

PS ≥2 AND
GFR <60ml/min
No combi chemo:
Trials, monotherapy, BSC
## 2nd line: monotherapies

<table>
<thead>
<tr>
<th>Autoren</th>
<th>Substanz</th>
<th>N</th>
<th>ORR</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorusso, 1998, Albers, 2002</td>
<td>Gemcitabin</td>
<td>35</td>
<td>23%</td>
<td>6,0 Mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>30</td>
<td>11%</td>
<td>10,2 Mo</td>
<td></td>
</tr>
<tr>
<td>Pronzato, 1997, Witte, 1997</td>
<td>Ifosfamide</td>
<td>20</td>
<td>5%</td>
<td>kA</td>
<td>8 Mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>20%</td>
<td>5.1 Mo</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>45</td>
<td>10%</td>
<td>kA</td>
<td>kA</td>
</tr>
<tr>
<td></td>
<td>Docetaxel</td>
<td>30</td>
<td>13%</td>
<td>5,5 Mo</td>
<td>9,0 Mo</td>
</tr>
<tr>
<td>McCaffrey, 1997</td>
<td>Docetaxel</td>
<td>45</td>
<td>12%</td>
<td>kA</td>
<td>8,0 Mo</td>
</tr>
<tr>
<td>Dreicer, 2006, Sweeney, 2006, Galsky, 2007</td>
<td>Epothilone B</td>
<td>47</td>
<td>28%</td>
<td>2,6 Mo</td>
<td>9,6 Mo</td>
</tr>
<tr>
<td></td>
<td>Pemetrexed</td>
<td>13</td>
<td>8%</td>
<td>kA</td>
<td>kA</td>
</tr>
</tbody>
</table>

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Small phase II trials: RR ↓, PFS ↓, OS ↓
# 2nd line combination chemotherapy

<table>
<thead>
<tr>
<th>Phase II</th>
<th>N</th>
<th>ORR</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweeney, 1999 Paclitaxel Ifosfamid</td>
<td>13</td>
<td>15%</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Sternberg, 2001 Paclitaxel Gemcitabin</td>
<td>41</td>
<td>60%</td>
<td>14,4 Mo</td>
<td>9 Mo 13 Mo</td>
</tr>
<tr>
<td>Fechner, 2006 Paclitaxel Gemcitabin</td>
<td>15</td>
<td></td>
<td>kA</td>
<td>9 Mo</td>
</tr>
<tr>
<td>Soga, 2007 Paclitaxel Carboplatin</td>
<td>18</td>
<td>33%</td>
<td>5 Mo</td>
<td>12 Mo</td>
</tr>
<tr>
<td>Lin, 2007 Paclitaxel Carboplatin</td>
<td>10</td>
<td>20%</td>
<td>3,5 Mo</td>
<td>4,8 Mo</td>
</tr>
<tr>
<td>Krege, 2006 Ifosfamid Docetaxel</td>
<td>22</td>
<td>25%</td>
<td>-</td>
<td>4 Mo</td>
</tr>
</tbody>
</table>

**Small phase II trials: RR ↑ BUT PFS ↓, OS ↓**

<table>
<thead>
<tr>
<th>Phase III: 6 cycles vs „maintenance“</th>
<th>N</th>
<th>ORR</th>
<th>PFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albers, 2011 Gemcitabin Paclitaxel</td>
<td>48</td>
<td>37%</td>
<td>3,7 Mo</td>
<td>7.8</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>41%</td>
<td>3,5 Mo</td>
<td>8.0</td>
</tr>
</tbody>
</table>
**2nd line phase III trial: Vinflunine vs BSC**

- Randomized phase III trial; 2:1; N= 370
- 320mg/m2 PS 0; 280mg/m2 if PS1 or RT

RR: 8.6% vs 0%; DCR 41% vs 25%
PFS: 3.0 vs 1.5 months

**OS: ITT population 6.9 vs 4.6 months (p=0.28)**
significant if only eligible population analysed

EAU/ESMO: Vinflunine can be offered, Evidence level 1B

Bellmunt et al. J Clin Oncol 2009
Prognostic factors 2nd line chemo

Risk factors:
- Hb < 10gr/dl
- PS ≥1
- Liver mets

Conclusions

2nd line chemotherapy

• PS $\geq$ 2: best supportive care, clinical trial

• PS 0-1:
  – $>$ 6 months since 1st line: repeat same chemo
  – $<$ 6 months since 1st line: trial, Vinflunine, (other chemo?)

Maria de Santis, adapted from EAU guidelines 2012
Take home messages

• Urothelial cancer is a chemosensitive disease

• Treatment decisions should be based on PS and renal function

• First line: good response if cisplatin can be used
• Second line: still unsatisfaying

...room for improvement...