Systemische medikamentöse Therapie des Harnblasenkarzinoms

Welche Therapie für welchen Patienten?

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Disclosure of Potential Conflicts of Interest

1. Employment or Leadership Position
   none

2. Advisory Role
   Novartis, GSK, Pierre-Fabre, Roche, Amgen,

3. Stock Ownership
   none

4. Honoraria
   Pfizer, Sanofi Aventis, Eli Lilly

5. Financing of Scientific Research
   none

6. Expert Testimony
   none

7. Other Financial Relationships
   none
First-line treatment for "fit" patients:

- Gemcitabine / Cisplatin
- MVAC (+ GCSF)
- HD-MVAC + GCSF

↓

Level 1 evidence
Grade of recommendation: A

ESMO CPG 2010
EAU Guidelines, © European Association of Urology 2010
Long term follow-up of cisplatin combination-chemotherapy of the post-MVAC-era (randomized phase III-trials)

<table>
<thead>
<tr>
<th>Author</th>
<th>Treatment arm</th>
<th>N (ITT)</th>
<th>median f-up (yrs)</th>
<th>Median survival (mos)</th>
<th>5-year (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sternberg, 2006</td>
<td>MVAC</td>
<td>263</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>HD-MVAC</td>
<td>129</td>
<td>7.3</td>
<td>14.9</td>
<td>13.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>134</td>
<td></td>
<td>15.1</td>
<td>21.8</td>
</tr>
<tr>
<td>von der Maase, 2005</td>
<td>MVAC</td>
<td>405</td>
<td>&gt;5</td>
<td>14.0</td>
<td>15.3</td>
</tr>
<tr>
<td></td>
<td>Gem/Cis</td>
<td>203</td>
<td></td>
<td>15.2</td>
<td>13.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>202</td>
<td></td>
<td></td>
<td>21.9</td>
</tr>
</tbody>
</table>

There is long term survival (only) with cisplatin combination-chemotherapy!
Survival for all patients grouped according to number of risk factors present at baseline

Risk factors:
0 = KPS > 80, no visceral mets
1 = KPS < 80 or visceral mets
2 = KPS < 80 and visceral mets

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"Unfit" for cisplatin

- More than 50% of patients with urothelial cancer are not eligible for cisplatin based chemotherapy.¹⁻⁴

- So far no standard chemotherapy has been established for this patient group.

⁴ De Santis et al, Curr Opin Urol 17:363–368, 2007
Who are the „unfit“?

Ineligibility for cisplatin:

- **Comorbidities:**
  - renal function impairment
  - congestive heart failure
  - cardiovascular risk factors
  - neuropathy

- **Performance status**
Comorbidity, age and trials

• Incidence and prevalence of comorbidity increase with age. .....Comorbidity is the rule, not the exception.


• Patients with a history of cancer have an average of three comorbid conditions.


• “Despite the importance of comorbidity in clinical practice, it has not gained a considerable role in clinical trials, medical statistics and clinical practice“.

Projected change in frequency of invasive cancers in the United States by age and sex.
Inconvenience of cisplatin

- Time consuming (need for overnight hospitalization, prolonged outpatient i.v. hydration)
- Quality of life-reduction
- Nausea
- Fatigue
- Fluid overload
- Cardiovascular risk
- Renal toxicity
- Neurotoxicity
Do we need cisplatin?

• A matter of debate....


2. REPLY TO G. SONPAVDE ET AL
   JCO SEP 1, 2010:E443E444; PUBLISHED ONLINE ON JULY 19, 2010; 10.1200/JCO.2010.29.3779
Cisplatin vs Carboplatin in cisplatin-eligible patients

- No data from randomised phase III studies
  - Dreicer, 2004

- Randomized phase II studies

<table>
<thead>
<tr>
<th>regimens</th>
<th>CR %</th>
<th>OS mos</th>
<th>source</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVAC vs MVECa</td>
<td>25</td>
<td>13</td>
<td>Petrioli, 1996</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>9.5</td>
<td></td>
</tr>
<tr>
<td>MVAC vs Carbo/MV</td>
<td>13</td>
<td>16</td>
<td>Bellmunt, 1997</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>9</td>
<td>(DSS)</td>
</tr>
<tr>
<td>Cis/Gem vs Carbo/Gem</td>
<td>14.5</td>
<td>12.8</td>
<td>Dogliotti, 2007</td>
</tr>
<tr>
<td></td>
<td>1.8</td>
<td>9.8</td>
<td></td>
</tr>
</tbody>
</table>

- MVAC vs Carbo/Ptx: Early termination due to slow accrual

- Carbo: CR ↓ Survival ↓

- RR 21 - 50%
  - CR 0 - 20%
  - OS 8.5 - 9.5 mos

- Phase II studies with Carboplatin/Paclitaxel
  - Redman, 1998
  - Vaughn, 1998
  - Small, 2000
EORTC definition of „fit“ and „unfit“ for cisplatin

„fit“
GFR ≥ 60 ml/min
and
PS 0-1

„unfit“
GFR < 60 ml/min
and /or
PS 2

Purpose of study strategy - development
Randomized phase II/III trial assessing gemcitabine/carboplatin (GC) and methotrexate/carboplatin/vinblastinine (M-CAVI) in patients (pts) with advanced urothelial cancer (UC) “unfit” for cisplatin based chemotherapy: updated phase II results and risk group analysis of EORTC study 30986

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EORTC:
First randomized phase II/III trial for „unfit“ TCC patients

phase II, JCO 2009
phase III, ASCO 2010
## Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>GC (n=119)</th>
<th>M-CAVI (n=119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>90 (75.6)</td>
<td>96 (80.7)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>29 (24.4)</td>
<td>23 (19.3)</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>Median 70</td>
<td>Median 72</td>
</tr>
<tr>
<td></td>
<td>Range 36 - 87</td>
<td>Range 34 - 86</td>
</tr>
<tr>
<td>≥71 yrs, n (%)</td>
<td>57 (47.9)</td>
<td>67 (56.3)</td>
</tr>
<tr>
<td>WHO – PS</td>
<td>20 (16.8)</td>
<td>19 (16.0)</td>
</tr>
<tr>
<td>0, n (%)</td>
<td>46 (38.7)</td>
<td>46 (38.7)</td>
</tr>
<tr>
<td>1, n (%)</td>
<td>53 (44.5)</td>
<td>54 (45.4)</td>
</tr>
<tr>
<td>Associated chronic disease, n (%)</td>
<td>60 (50.4)</td>
<td>55 (46.2)</td>
</tr>
</tbody>
</table>
## Phase III results of EORTC study 30986

### Disease characteristics

<table>
<thead>
<tr>
<th></th>
<th>GC (n=119) n (%)</th>
<th>M-CAVI (n=119) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver mets</td>
<td>20 (16.8)</td>
<td>29 (24.4)</td>
</tr>
<tr>
<td>Visceral mets</td>
<td>55 (46.2)</td>
<td>66 (55.5)</td>
</tr>
<tr>
<td>Bladder primary</td>
<td>90 (75.6)</td>
<td>87 (73.1)</td>
</tr>
<tr>
<td>- Bladder primary target</td>
<td>24 (26.7)</td>
<td>33 (37.9)</td>
</tr>
<tr>
<td>- Bladder primary only target</td>
<td>14 (15.6)</td>
<td>12 (13.8)</td>
</tr>
<tr>
<td>Cystectomy / Cytoprostatectomy</td>
<td>25 (21.0)</td>
<td>23 (19.3)</td>
</tr>
</tbody>
</table>
### Phase III results of EORTC study 30986

#### Results: Toxicity

<table>
<thead>
<tr>
<th></th>
<th>GC (n=118) n (%)</th>
<th>M-CAVI (n=118) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leucopenia G 3/4</td>
<td>53 (44.9)</td>
<td>55 (46.6)</td>
</tr>
<tr>
<td>Neutropenia G 3/4</td>
<td>62 (52.5)</td>
<td>75 (63.5)</td>
</tr>
<tr>
<td>Thrombocytopenia G 3/4</td>
<td>57 (48.3)</td>
<td>23 (19.4)</td>
</tr>
<tr>
<td>Febrile Neutropenia G 3/4</td>
<td>5 (4.2)</td>
<td>17 (14.4)</td>
</tr>
<tr>
<td>Infection G 3/4</td>
<td>14 (11.8)</td>
<td>15 (12.7)</td>
</tr>
<tr>
<td>Severe Acute Toxicity (SAT)*</td>
<td>11 (9.3)</td>
<td>25 (21.2)</td>
</tr>
</tbody>
</table>

*a not a SAT ; *patients with at least 1 SAT

SAT= severe acute toxicity (death due to toxicity, G4 thrombocytopenia with bleeding, G 3/4 renal toxicity, neutropenic fever G 3/4 or mucositis G 3/4 at least possibly related to study drug)
Phase III results of EORTC study 30986
Results: Best Overall Response

<table>
<thead>
<tr>
<th></th>
<th>GC (n=119) n (%)</th>
<th>M-CAVI (n=119) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Confirmed response</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR+PR</td>
<td>49 (41.2)</td>
<td>36 (30.3)</td>
</tr>
<tr>
<td>No change</td>
<td>39 (32.8)</td>
<td>41 (34.5)</td>
</tr>
<tr>
<td>Progression</td>
<td>18 (15.1)</td>
<td>17 (14.3)</td>
</tr>
<tr>
<td>Early death</td>
<td>4 (3.4)</td>
<td>10 (8.4)</td>
</tr>
<tr>
<td>Not assessable</td>
<td>9 (7.6)</td>
<td>15 (12.6)</td>
</tr>
</tbody>
</table>

The difference in response rate between the two treatment arms is not significant (p=0.08)
The difference in confirmed response rate between the two treatment arms is significant (p=0.01)
Phase III results of EORTC study 30986

Progression-Free Survival

HR = 1.04 (95% CI: 0.80, 1.35)

p = 0.78

4.2 months (95% CI: 3.7, 5.9)

5.8 months (95% CI: 4.8, 6.9)
## Phase III results of EORTC study 30986

### Results: Survival Status

<table>
<thead>
<tr>
<th></th>
<th>GC (n=119)</th>
<th>M-CAVI (n=119)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive</td>
<td>9 (7.6%)</td>
<td>11 (9.2%)</td>
</tr>
<tr>
<td>Death, cause:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Progression</td>
<td>110 (92.4%)</td>
<td>108 (90.8%)</td>
</tr>
<tr>
<td>- Toxicity</td>
<td>82</td>
<td>75</td>
</tr>
<tr>
<td>- Chronic disease</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>- Other</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>- Unknown</td>
<td>11</td>
<td>10</td>
</tr>
</tbody>
</table>

M. De Santis  phase III 30986  ASCO 2010
Phase III results of EORTC study 30986

Overall Survival

HR = 0.94 (95% CI: 0.72, 1.22)
p = 0.64

8.1 months (95% CI: 6.1, 10.3)
9.3 months (95% CI: 7.6, 11.3)

Number of patients at risk:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>M-CAVI</td>
<td>108</td>
<td>119</td>
<td>37</td>
<td>13</td>
<td>7</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>GC</td>
<td>110</td>
<td>119</td>
<td>44</td>
<td>15</td>
<td>5</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
Phase III results of EORTC study 30986
Overall Survival

**Stratification factors**

<table>
<thead>
<tr>
<th>O</th>
<th>N</th>
<th>Number of patients at risk:</th>
</tr>
</thead>
<tbody>
<tr>
<td>39</td>
<td>42</td>
<td>11 2 0 0 0 0 WHO - PS = 2</td>
</tr>
<tr>
<td>120</td>
<td>131</td>
<td>56 19 9 3 2 GFR &lt; 60</td>
</tr>
<tr>
<td>59</td>
<td>65</td>
<td>14 7 3 2 1 Both</td>
</tr>
</tbody>
</table>

**Bajorin risk group**

<table>
<thead>
<tr>
<th>O</th>
<th>N</th>
<th>Number of patients at risk:</th>
</tr>
</thead>
<tbody>
<tr>
<td>39</td>
<td>15</td>
<td>7 3 2 1</td>
</tr>
<tr>
<td>28</td>
<td>8</td>
<td>4 2 1</td>
</tr>
<tr>
<td>14</td>
<td>5</td>
<td>1 0 0</td>
</tr>
</tbody>
</table>

- **10.6 months (95% CI: 8.7, 14.2)**
- **9.2 months (95% CI: 5.8, 11.3)**
- **5.5 months (95% CI: 4.1, 8.3)**

- **12.0 months (95% CI: 9.6, 16.1)**
- **9.3 months (95% CI: 7.6, 10.7)**
- **5.5 months (95% CI: 4.2, 7.3)**

M. De Santis

phase III 30986

ASCO 2010
Options for patients with PS 2 and GFR < 60 ml/min or Bajorin risk group 2?

<table>
<thead>
<tr>
<th></th>
<th>PS 2 and GFR &lt; 60ml/min*</th>
<th>Bajorin risk group 2*</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS (mos)</td>
<td>5.5</td>
<td>5.5</td>
</tr>
<tr>
<td>RR (%)</td>
<td>26</td>
<td>21</td>
</tr>
<tr>
<td>SAT (%)</td>
<td>26</td>
<td>24</td>
</tr>
<tr>
<td>Only one chemo-cycle*</td>
<td>9/46 (20)</td>
<td>10/49 (20)</td>
</tr>
<tr>
<td>N (%)</td>
<td>9/46 (20)</td>
<td>10/49 (20)</td>
</tr>
</tbody>
</table>

*phase II data

* EORTC 30986 phase II/III results, JCO 2009; LBA, ASCO 2010

- Monochemotherapy (gemcitabine, oxaliplatin, taxanes,.....)
- Clinical trial setting (novel agents, monochemotherapy..........)
- Best supportive care (therapeutic goal in unfit and elderly?)
How to better select patients for chemotherapy?

- Performance status
  - Valuable, not accurate enough for elderly (>75y)

- Rating of comorbidity?
  - Charlson score, no standard

- Renal function assessment
  - GFR calculation or measurement?

- Comprehensive geriatric assessment, functional status
  - Most probably helpful, but no standard, not validated
Pending results or ongoing trials in unfit or elderly urothelial cancer patients, first-line

- **M-CAVI vs. Gem/Carbo, EORTC 30986-study** in unfit TCC patients (phase III results LBA, **ASCO 2010**)

- **Gemcitabine/ vinflunine**
  - [closed prematurely due to strategic reasons by company]
  - front-line placebo controlled phase II/III in cisplatin ineligible pts
    - [BMS, NCT00389155]

- **Paclitaxel/ gemcitabine (old vs. younger, but NOT unfit)**
  - Pts **aged 70 years or older** (and pts younger than 60 years)
    - [SWOG, NCT00022633] → **ASCO 2010**

- **Gemcitabine/ oxaliplatin**
  - Pts unable to receive cisplatin-based chemotherapy due to crcl 30-60 ml/min or PS 2
    - [France; NCT00627432]

- **Carboplatin/ gemcitabine/ bevacizumab (ineligible for cisplatin)**
  - KPS>60%, creat <2,0 or GFR>30ml/min
    - [MSKCC; NCT00588666]
“Ready to go“ trial in unfit urothelial cancer patients (Pierre-Fabre)

Randomized phase II trial

vinflunine / gemcitabine vs vinflunine / carboplatin

→ Phase III will compare the „winner“ with gem/ carbo
Komorbidität ist die Regel und nicht die Ausnahme beim Harnblasenkarzinompatienten.

Cisplatin basierte Kombinationschemotherapie ist der Standard, ABER: > 50% der Patienten sind nicht “fit” für Cisplatin.

EORTC Definition von “unfit”: PS 2 und/oder GFR <60 ml/min

In der ersten randomisierten Phase II/III – Studie für „nicht fitte“ Patienten waren M-CAVI und Gem/Carbo wirksam.

Schwere akute Toxizitäten waren etwas häufiger unter M-CAVI.
Nicht „fitte“ Patienten sind keine einheitliche Gruppe
Metastatische Urothelialkarzinom – Therapie - Algorithmen

Patientenmerkmale:
PS 0-1/ 2/ >2
GFR ≥/≤ 60ml/min
Komorbiditäten

CISPLATIN?

YES

PS 0 -1 and
GFR ≥ 60ml/min
STANDARD¹: GC
MVAC
HD MVAC

NO

PS 2 or
GFR <60ml/min
Comb. Chemo: Carbo-based
(EORTC 30986-phase III?)²

NO

PS ≥2 and
GFR <60ml/min
NO comb. Chemo³:
studies, monotherapy, BSC

Second-Line Treatment

GFR = Glomeruläre Filtrationsrate; PS = Performance Status; CHT = Chemotherapie; BSC = best supportive care
GC = Gemcitabin, Cisplatin; MVAC = Methotrexat, Vinblastin, Adriblastin, Cisplatin; HD = Hochdosis; Carbo = Carboplatin;
¹ Stenzl, Eur Urol 2009; ² EORTC 30986 study, De Santis, ASCO 2010; ³ De Santis, JCO 2009
Urothelkarzinom: welche Therapie für welchen Patienten?

Zusammenfassung (3)

- Dringend erforderlich:
  - bessere Selektionskriterien
  - bessere Therapieoptionen für Patienten mit Komorbiditäten
  - klinische Studien für Subgruppen („unfit“)!
DANKE !!!