Management of «unfit» patients

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Disclosures

Advisory Boards

Bayer
Curevac
Janssen Cilag
Janssen Diagnostics
Millenium
Astellas
Novartis
Sanofi Aventis
Pfizer
ProteoMediX

Pending patent application for a method for biomarker WO 375 2009 138392 A1
Standard Chemotherapy 2014

First-line treatment for "fit" patients:

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

Median survival: 13-15 mo
Long term survival: about 15%

ESMO CPG 2011; EAU Guidelines 2011
Clinical Trial

- Patients with significant comorbidities excluded
- Older patients under-represented
Cancer patients getting older

Cancer occurrence and age distribution (Prediction US)

Cases of cancer (millions)

Year

Age (years)

≥85
75–84
65–74
50–64
<50

2000 2010 2020 2030 2040 2050

2010


Slide courtesy of T. Cerny
More complicated

Identical chronologic, but different functional age
Comprehensive Geriatric Assessment (CGA)

Recommended for routine use in the older cancer patient

• SIOG (International Society of Geriatric Oncology)
• NCCN Practice Guidelines in Oncology

So far, Comprehensive Geriatric Assessment (CGA) is not standard in oncological trials
Cisplatin: Do we really need it?

- No completed Phase III data
- Randomized Phase II data:

<table>
<thead>
<tr>
<th>regimen</th>
<th>n</th>
<th>CR %</th>
<th>OS mos</th>
<th>source</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVAC vs MVECa</td>
<td>57</td>
<td>25</td>
<td>13</td>
<td>Petrioli, 1996</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11</td>
<td>9.5</td>
<td></td>
</tr>
<tr>
<td>MVAC vs Carbo/ MV</td>
<td>47</td>
<td>13</td>
<td>16</td>
<td>Bellmunt, 1997</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>Cis/ Gem vs Carbo/Gem</td>
<td>110</td>
<td>15</td>
<td>12.8</td>
<td>Dogliotti, 2007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>9.8</td>
<td></td>
</tr>
</tbody>
</table>

→ Metaanalysis Cisplatin: CR and OR ↑

- Phase II data with carboplatin/paclitaxel: disappointing

„Unfit“ for cisplatin

• 30-50% of patients

• Definition:
  • Performance Status
    WHO or ECOG ≥ 2
    Karnofsky ≤ 60-70%
  • Creatinine Clearance
    < 1 ml/s
  • Audiometric hearing loss ≥ G2
  • Peripheral neuropathy ≥ G2
  • NYHA class Ill heart failure

Dash Cancer 2006; Galsky J Clin Oncol 2011; Sonpavde Clin Genitourin Cancer 2012; Galsky Lancet Oncology 2011
Reality in patients ≥ 66yrs

Figure 1: Therapeutic Regimens Administered in Patients Presenting With Unresectable Locally Advanced or Metastatic Urothelial Carcinoma in the SEER-Medicare Database (N = 1031)
Renal function assessment in the elderly

Formulas Calculating Creatinine Clearance Are Inadequate for Determining Eligibility for Cisplatin-Based Chemotherapy in Bladder Cancer
Ganesh V. Raj, Alexia Iasonos, Harry Herr, and Sherri Machele Donat

Calculated creatinine clearance underestimates clearance in patients > 65 y
How to make the patient „fit” for cisplatin?

• **Creatinine clearance**
  – Calculation: which formula (Cockroft, MDRD, CKD-EPI)?
  – Measurement?
  – Radionuclide GFR?

• **Consider**
  ▪ i.v. hydration (but no „cosmetics“)
  ▪ Ureter-stenting
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
Randomized phase II/III trial assessing gemcitabine/carboplatin (GC) and methotrexate/carboplatin/vinblastine (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

M. De Santis¹, J. Bellmunt², R. de Wit³, G. Mead⁴, J.M. Kerst⁵, M. Leahy⁶, P. Maroto⁷, I. Skoneczna⁸, S. Marreaud⁹, R. Sylvester¹⁰

¹ Kaiser Franz Josef - Spital and ACR-ITR VIEnna, Vienna; ² Hospital Vall d'Hebrón, Barcelona; ³ Erasmus Univ Med Center, Rotterdam, ⁴ Royal South Hants Hospital, Southampton;⁵ Netherlands Cancer Institute, Amsterdam; ⁶ St James Hospital, Leeds; ⁷ Hospital Santa Creu, Barcelona; ⁸ Warsaw; Maria Sklodowska-Curie Memorial Cancer Centre, ⁹ EORTC Data Center, Brussels

Phase II, JCO 2009
Phase III, JCO 2011

Slide courtesy M De Santis
Treatments

Treatment 1: Methotrexate / Carboplatin / Vinblastine

- Methotrexate: 30 mg/m² i.v. days 1, 15, 22
- Carboplatin: AUC 4.5 i.v. day 1
- Vinblastine: 3 mg/m² i.v. days 1, 15, 22

> Every 4 weeks for at least 2 cycles

Treatment 2: Gemcitabine / Carboplatin

- Gemcitabine: 1000 mg/m² i.v. days 1 and 8
- Carboplatin: AUC 4.5 x i.v. day 1

> Every 3 weeks for at least 2 cycles
## Objectives

**Primary Endpoint:** Overall Survival

**Secondary Endpoints:** PFS, Side effects, QoL

<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) Median</td>
<td>70</td>
<td>72</td>
</tr>
<tr>
<td>Range</td>
<td>36 - 87</td>
<td>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></td>
<td></td>
</tr>
<tr>
<td>0, n (%)</td>
<td>20 (16.8)</td>
<td>19 (16.0)</td>
</tr>
<tr>
<td>1, n (%)</td>
<td>46 (38.7)</td>
<td>46 (38.7)</td>
</tr>
<tr>
<td>2, 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>

238 patients (2001-2008)

*De Santis J Clin Oncol 2011*
## 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>Leukopenia G 3/4 a</td>
<td>53 (44.9)</td>
<td>55 (46.6)</td>
</tr>
<tr>
<td>Neutropenia G 3/4 a</td>
<td>62 (52.5)</td>
<td>75 (63.5)</td>
</tr>
<tr>
<td>Thrombocytopenia G 3/4 a</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 a</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

De Santis J Clin Oncol 2011
# Results: Efficacy

<table>
<thead>
<tr>
<th></th>
<th>GC (n=119)</th>
<th>M-CAVI (n=119)</th>
<th>Significance (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CR+PR n (%)</strong></td>
<td>49 (41.2)</td>
<td>36 (30.3)</td>
<td>0.08</td>
</tr>
<tr>
<td><strong>Confirmed response (%)</strong></td>
<td>43</td>
<td>25</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>PFS (mos)</strong></td>
<td>5.8</td>
<td>4.2</td>
<td>0.78</td>
</tr>
<tr>
<td><strong>OS (mos)</strong></td>
<td>9.3</td>
<td>8.1</td>
<td>0.64</td>
</tr>
</tbody>
</table>

HR: 0.94

*De Santis J Clin Oncol 2011*
### Treatment according to subgroup analyses?

<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 (months)</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 n (%)</td>
<td>9/46 (20)</td>
<td>10/49 (20)</td>
</tr>
</tbody>
</table>

*De Santis J Clin Oncol 2011*

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**Monotherapy, clinical trial with novel agents, BSC ?**
Ongoing trials

• Gemcitabine/Carboplatin +/- Vandetanib

• Gemcitabine/Carboplatin vs Gemcitabine/Oxaliplatin
Metastatic Urothelial Cancer: Treatment - Algorithm

Patient characteristics:
PS 0-1/ 2/ >2
GFR ≥/ < 60ml/min
Comorbidities

Second-line treatment

GFR = Glomeruläre Filtrationsrate; PS = Performance Status; CHT= Chemotherapy; BSC = best supportive care
GC = Gemcitabin, Cisplatin; MVAC = Methotrexat, Vinblastin, Adriblastin, Cisplatin; HD= Hochdosis; Carbo = Carboplatin;
Conclusions I

- Cisplatin based chemotherapy is **THE** standard
- About 50% of patients not eligible for cisplatin
- EORTC definition of “unfit”: PS 2 and/or GFR <60 ml/min
- The first randomized phase II/III - trial in „unfit“ patients showed that M-CAVI and Gem/Carbo are active
- Toxicity profile in favor of gemcitabine/ carboplatin
Conclusions II

• Patients ineligible for cisplatin („unfit“) are not an uniform group
  • GFR < 60ml/min: Benefit from combination chemotherapy
  • PS 2 and GFR <60 ml/min or 2 Bajorin poor prognostic factors:
    little benefit from combination chemotherapy
Thank you!
Advanced Prostate Cancer Consensus Conference
(APCCC) St.Gallen / Switzerland
SAVE THE DATE: 12 -14 March 2015