ESMO PRECEPTORSHIP ON METASTATIC BLADDERS AND KIDNEY CANCER

Lugano, 29-30 November 2019

Side effects of chemotherapy in metastatic urothelial cancer

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Honoraria, Advisory, Steering Committee, Research Support:
ROCHE, AZ, BMS, MSD, NOVARTIS, PFIZER, JANSSEN
OUTLINE

Side effects of monotherapy
Side effects of combination chemotherapy
Toxicity profiles as tools for therapeutic decisions
OUTLINE

Side effects of monotherapy
Side effects of combination chemotherapy
Toxicity profiles as tools for therapeutic decisions
# SAFETY

## Patients n = 253

### Haematological toxicities (grade 3/4)

- Neutropenia: 50%
- Anaemia: 19.1%
- Thrombopenia: 5.7%
- Febrile neutropenia: 6%
- Leucopenia: NR

## Patients n = 253

### Non-haematological toxicities (grade 3/4)

- Constipation: 16.1%
- Asthenia/fatigue: 19.3%
- Pain: NR
- Nausea: 2.4%
- Vomiting: 2.8%

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## REAL-WORLD DATA METANALYSIS

### Neutropenia (Grade 3/4) vs. Constipation

<table>
<thead>
<tr>
<th>Study</th>
<th>ES (95% CI)</th>
<th>Percent weight (random effects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castellano et al. [18]</td>
<td>0.13 (0.07, 0.21)</td>
<td>11.71</td>
</tr>
<tr>
<td>Hegele et al. [30]</td>
<td>0.10 (0.01, 0.30)</td>
<td>7.81</td>
</tr>
<tr>
<td>Palacka et al. [31]</td>
<td>0.38 (0.15, 0.65)</td>
<td>6.93</td>
</tr>
<tr>
<td>Di Lorenzo et al. [29]</td>
<td>0.50 (0.19, 0.81)</td>
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</tr>
<tr>
<td>Retz et al. [19]</td>
<td>0.01 (0.00, 0.07)</td>
<td>11.23</td>
</tr>
<tr>
<td>Holmsten et al. [26]</td>
<td>0.23 (0.15, 0.32)</td>
<td>11.68</td>
</tr>
<tr>
<td>Médioni et al. [25]</td>
<td>0.17 (0.11, 0.25)</td>
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</tr>
<tr>
<td>Pistamaltzian et al. [20]</td>
<td>0.16 (0.07, 0.30)</td>
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</tr>
<tr>
<td>Hussain et al. [27]</td>
<td>0.02 (0.00, 0.11)</td>
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</tr>
<tr>
<td>Pasalacqua et al. [28]</td>
<td>0.09 (0.05, 0.13)</td>
<td>12.60</td>
</tr>
<tr>
<td>Random overall (I² = 82.28%, p = 0.00)</td>
<td>0.13 (0.07, 0.20)</td>
<td>100.00</td>
</tr>
<tr>
<td>Fixed overall</td>
<td>0.11 (0.09, 0.14)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>ES (95% CI)</th>
<th>Percent weight (random effects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Castellano et al. [18]</td>
<td>0.06 (0.02, 0.12)</td>
<td>12.36</td>
</tr>
<tr>
<td>Hegele et al. [30]</td>
<td>0.00 (0.00, 0.16)</td>
<td>6.76</td>
</tr>
<tr>
<td>Palacka et al. [31]</td>
<td>0.00 (0.00, 0.21)</td>
<td>5.76</td>
</tr>
<tr>
<td>Di Lorenzo et al. [29]</td>
<td>0.30 (0.07, 0.65)</td>
<td>4.23</td>
</tr>
<tr>
<td>Retz et al. [19]</td>
<td>0.05 (0.01, 0.13)</td>
<td>11.54</td>
</tr>
<tr>
<td>Holmsten et al. [26]</td>
<td>0.22 (0.14, 0.31)</td>
<td>12.31</td>
</tr>
<tr>
<td>Médioni et al. [25]</td>
<td>0.08 (0.04, 0.14)</td>
<td>13.04</td>
</tr>
<tr>
<td>Pistamaltzian et al. [20]</td>
<td>0.12 (0.05, 0.25)</td>
<td>10.01</td>
</tr>
<tr>
<td>Hussain et al. [27]</td>
<td>0.08 (0.02, 0.20)</td>
<td>10.01</td>
</tr>
<tr>
<td>Pasalacqua et al. [28]</td>
<td>0.05 (0.02, 0.08)</td>
<td>13.98</td>
</tr>
<tr>
<td>Random overall (I² = 71.60%, p = 0.00)</td>
<td>0.07 (0.04, 0.12)</td>
<td>100.00</td>
</tr>
<tr>
<td>Fixed overall</td>
<td>0.07 (0.05, 0.09)</td>
<td></td>
</tr>
</tbody>
</table>

OUTLINE

Side effects of commonly used agents
Side effects of combination chemotherapy
Toxicity profiles as tools for therapeutic decisions
COMBO VS. MONO
Loehlrer et al. 1992

M-VAC vs. CDDP

- leukopenia
- mucositis
- neutropenic fever
- drug-related mortality
## MVAC

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 3/4 (%)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Von der Maase¹</td>
</tr>
<tr>
<td>neutropenia</td>
<td>82</td>
</tr>
<tr>
<td>thrombocytopenia</td>
<td>20</td>
</tr>
<tr>
<td>mucositis</td>
<td>22</td>
</tr>
<tr>
<td>N+V</td>
<td>21</td>
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<tr>
<td>Renal</td>
<td>3</td>
</tr>
<tr>
<td>Neutropenic fever/sepsis</td>
<td>14</td>
</tr>
<tr>
<td>Treatment-related death</td>
<td>3</td>
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</tbody>
</table>

Reference
OUTLINE

Side effects of commonly used agents
Side effects of combination chemotherapy

Toxicity profiles as tools for therapeutic decisions
GC became a standard due to favorable toxicity profile at visits!

Both regimens showed a similar toxicity profile.


World Health Organization Toxicity Grades

<table>
<thead>
<tr>
<th>Hematologic Toxicity</th>
<th>GC (% of patients)</th>
<th>MVAC (% of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>State of consciousness</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Anemia</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>1.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>2.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Alopecia</td>
<td>2.5</td>
<td>0.5</td>
</tr>
<tr>
<td>Constipation</td>
<td>3.0</td>
<td>1.5</td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>2.0</td>
<td>5.5</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Mucositis</td>
<td>29.9</td>
<td>2.5</td>
</tr>
<tr>
<td>Nephritis</td>
<td>2.9</td>
<td>0.5</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>15.5</td>
<td>2.5</td>
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<tr>
<td>Alopecia</td>
<td>3.1</td>
<td>0.5</td>
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<tr>
<td>Nausea/vomiting</td>
<td>0.5</td>
<td>0.5</td>
</tr>
</tbody>
</table>

...VS GC
the HD-MVAC arm (P < .001). On the HD-MVAC arm, only 20% of patients had grade 3 to 4 WBC toxicity. In terms of thrombocytopenia, more than 70% on the MVAC arm and more than 60% in the HD-MVAC arm did not have grade 2 to 4 toxicity at any time during their courses. Neutropenic fever was significantly less frequent on the HD-MVAC arm (10%) than on the MVAC arm (26%; P < .001). G-CSF was given infrequently to patients on the MVAC arm in this study. Only 19% received G-CSF, as opposed to 94% on the HD-MVAC arm. Mucositis was more frequent with MVAC than with HD-MVAC. The toxic death rate was 3% on the HD-MVAC arm and 4% on the MVAC arm. MVAC chemotherapy may have been the cause of death in six cases (4%). One of these patients had hemorrhage and ischemic colitis, two patients had gastrointestinal bleeding, two patients had pulmonary infection, and one had granulocytopenic fever resulting in candida septicemia 1 month after chemotherapy. On the HD-MVAC arm, there were four deaths (3%) that may have been due to chemotherapy. Two patients had septic shock, one had neutropenia and pneumonia, and one stopped therapy after two cycles because of urosepsis but died 5 months later because of infection. There was no difference in creatinine toxicity between the two arms, despite the schedule of administration every 2 weeks (P = .815). Grade 2 to 3 toxicity occurred in 5% (MVAC) and 6% (HD-MVAC). Chemotherapy was rarely definitively stopped because of toxicity. Patients were more apt to stop taking vinblastine (2% of patients on the MVAC arm vs 2% on the HD-MVAC arm) or cisplatin (6% on the MVAC arm vs 2% on the HD-MVAC arm) because of toxicity. Methotrexate therapy was stopped by only 2% on the MVAC arm and 0% on the HD-MVAC arm. Doxorubicin therapy was stopped because of toxicity by only 1% of patients receiving MVAC and 0% receiving HD-MVAC.

### Table 7. Toxicity (WHO grade)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>MVAC (n = 129)</th>
<th>HD-MVAC (n = 134)</th>
<th>P(trend)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic Toxicity</strong></td>
<td></td>
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<td></td>
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<tr>
<td>WBC</td>
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</tr>
<tr>
<td>0</td>
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<td>4</td>
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</tr>
<tr>
<td>1</td>
<td>8</td>
<td>46</td>
<td>.001</td>
</tr>
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<td>28</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>59</td>
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<tr>
<td><strong>Platelets</strong></td>
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<td>4</td>
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</tr>
<tr>
<td>4</td>
<td>4</td>
<td>3</td>
<td></td>
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<tr>
<td><strong>Nausea and/or vomiting</strong></td>
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<td>.025</td>
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<td>3</td>
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<tr>
<td>1</td>
<td>9</td>
<td>7</td>
<td></td>
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<td>2</td>
<td>27</td>
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<td>52</td>
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<tr>
<td>4</td>
<td>32</td>
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<tr>
<td><strong>Neurotoxicity</strong></td>
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<td>1</td>
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<td>5</td>
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<tr>
<td>2</td>
<td>7</td>
<td>5</td>
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</tr>
<tr>
<td>3</td>
<td>10</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>70</td>
<td>54</td>
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</tbody>
</table>

**DISCUSSION**

In this trial, the dose-intensities of the individual drugs in the MVAC regimen were increased and this new regimen was compared with classic MVAC. A statistically significant difference in terms of CR rate and progression-free survival in favor of HD-MVAC was noted in this patient population.
<table>
<thead>
<tr>
<th>Condition</th>
<th>DD-MVAC ($n = 61$)</th>
<th></th>
<th>DD-GC ($n = 59$)</th>
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</tr>
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<tbody>
<tr>
<td></td>
<td>3 n (%)</td>
<td>4 n (%)</td>
<td>5 n (%)</td>
<td>3 n (%)</td>
</tr>
<tr>
<td>Toxicity</td>
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<td>5 (8)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Anemia</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>7 (11)</td>
<td>5 (8)</td>
<td>5 (8)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>2 (3)</td>
<td>3 (5)</td>
<td>5 (8)</td>
<td>0</td>
</tr>
<tr>
<td>Renal</td>
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<td>1 (2)</td>
<td>0</td>
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<tr>
<td>Nausea</td>
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<td>Vomiting</td>
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<tr>
<td>Neuropathy</td>
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<td>1 (2)</td>
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</tr>
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<td>Stomatitis</td>
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</tr>
<tr>
<td>Hearing</td>
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<td>0</td>
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<td>0</td>
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<tr>
<td>Fatigue</td>
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<td>0</td>
<td>3 (5)</td>
<td>0</td>
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<tr>
<td>Vascular</td>
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<td>1 (2)</td>
<td>0</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>2 (3)</td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Infection [normal absolute neutrophil count (ANC)]</td>
<td>3 (5)</td>
<td>0</td>
<td>2 (3)</td>
<td>3 (5)</td>
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</table>
## TRIPLETS

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Gemcitabine/Cisplatin (n = 305)</th>
<th>Paclitaxel/Cisplatin/Gemcitabine (n = 302)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Grade 3</td>
<td>Grade 4</td>
</tr>
<tr>
<td></td>
<td>No. of Patients</td>
<td>%</td>
</tr>
<tr>
<td>Nonhematologic adverse events</td>
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<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>19</td>
<td>6.2</td>
</tr>
<tr>
<td>Pulmonary toxicity</td>
<td>12</td>
<td>3.9</td>
</tr>
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<td>Cardiovascular events*</td>
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<td>11.8</td>
</tr>
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<td>0</td>
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<td>11.1</td>
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<td>7.0</td>
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<tr>
<td>Infection</td>
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<tr>
<td>Renal toxicity</td>
<td>10</td>
<td>3.3</td>
</tr>
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<td>Neuropathy/sensory</td>
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<td>0.3</td>
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<td>0.7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10</td>
<td>3.3</td>
</tr>
<tr>
<td>Hematologic adverse events</td>
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<tr>
<td>WBC</td>
<td>102</td>
<td>33.4</td>
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<tr>
<td>Neutropenia</td>
<td>93</td>
<td>30.5</td>
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<tr>
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<td>45.9</td>
</tr>
<tr>
<td>Hemoglobin</td>
<td>70</td>
<td>23.0</td>
</tr>
</tbody>
</table>

*Includes edema, hypotension, thrombosis/embolism, and other cardiovascular events.
TABLE 3

Differences in Selected Toxicities by Treatment Arm

<table>
<thead>
<tr>
<th>Toxicity grade</th>
<th>M-VAC (n = 43)</th>
<th>CP arm (n = 41)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Neutropenic fever</td>
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<td>6</td>
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<tr>
<td>Thrombocytopenia</td>
<td>16</td>
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<td>8</td>
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<tr>
<td>Sensory neuropathy</td>
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<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Stomatitis</td>
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<td>13</td>
<td>4</td>
</tr>
<tr>
<td>Creatinine</td>
<td>19</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

M-VAC: methotrexate, vinblastine, doxorubicin, and cisplatin; CP: carboplatin and paclitaxel.
VS CARBO

QoL

![Chart showing QoL comparison between M-VAC and CP treatments over days and the number of patients.](chart.png)
<table>
<thead>
<tr>
<th></th>
<th>GC (n = 118)</th>
<th></th>
<th>M-CAVI (n = 118)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>Severe acute toxicity*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>107</td>
<td>90.7</td>
<td>93</td>
<td>78.8</td>
</tr>
<tr>
<td>Yes</td>
<td>11</td>
<td>9.3</td>
<td>25</td>
<td>21.2</td>
</tr>
<tr>
<td>Leucopenia grade†</td>
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CONCLUSIONS

Modern cisplatin-based chemotherapy is well tolerated with infrequent significant renal toxicity.
Better tolerability has modified practice patterns in spite of lack of evidence for equal efficacy.