BC Cancer Protocol Summary for Neo-Adjuvant Therapy for Urothelial Carcinoma using CISplatin and Gemcitabine

**Protocol Code**
GUNAJPG

**Tumour Group**
Genitourinary

**Contact Physicians**
Dr. Christian Kollmannsberger  
Dr. Bernie Eigl  
Dr. Jean-Michel Lavoie

**ELIGIBILITY:**
Patients must have:
- Muscle invasive urothelial cancer (cT2-4, N0-1), and
- Be planned for curative intent local therapy (cystectomy or trimodality therapy with surgery, radiation, chemotherapy)

Patients should have:
- ECOG performance status 0 or 1

Note: GUBDDMVAC protocol is the preferred treatment for the majority of patients. GUNAJPG is for use in patients ineligible for GUBDDMVAC (e.g., specific contraindications to methotrexate or DOXOrubicin) per physician discretion

**EXCLUSIONS:**
Patients must not have:
- Pure adenocarcinoma,
- Pure small-cell carcinoma (platinum and etoposide should be used, see protocol GUSCPERT),
- Poor renal function (initial creatinine clearance less than 45 mL/min by GFR measurement or Cockcroft-Gault formula)
- Contraindication for curative intent local therapy, such as major co-morbid illness

**TESTS:**
- Baseline: CBC & Diff, platelets, creatinine, total bilirubin, ALT, alkaline phosphatase
- Before each treatment:
  - Day 1: CBC & Diff, platelets, creatinine, total bilirubin, ALT, alkaline phosphatase
  - Day 8: CBC & Diff, platelets, creatinine
- Baseline imaging of bladder and pelvis

**PREMEDICATIONS:**
- Antiemetic protocol for highly emetogenic chemotherapy protocols (see protocol SCNAUSEA).
TREATMENT:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BC Cancer Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>gemcitabine</td>
<td>1250 mg/m²/day on Days 1 and 8 (total dose per cycle = 2500 mg/m²)</td>
<td>IV in 250 mL NS over 30 min</td>
</tr>
<tr>
<td>CISplatin</td>
<td>70 mg/m²/day on Day 1</td>
<td>Prehydrate with 1000 mL NS over 1 hour, then CISplatin IV in 500 mL NS with 20 mEq potassium chloride, 1 g magnesium sulfate, 30 g mannitol over 1 hour</td>
</tr>
</tbody>
</table>

- Repeat every 21 days for total of two cycles prior to restaging.
- Plan for 4 cycles maximum prior to surgery or radiation, if tolerated and if no disease progression.

DOSE MODIFICATIONS:

1. Hematology

For gemcitabine **Day 1 of each cycle**

<table>
<thead>
<tr>
<th>ANC (x 10⁹/L)</th>
<th>Platelets (x 10⁹/L)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>greater than or equal to 1.0 and greater than or equal to 100</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>0.5 to less than 1.0 or 75 to less than 100</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>less than 0.5 or less than 75</td>
<td><strong>Delay</strong></td>
<td></td>
</tr>
</tbody>
</table>

*CISplatin also delayed*

For gemcitabine **Day 8 of each cycle**

<table>
<thead>
<tr>
<th>ANC (x 10⁹/L)</th>
<th>Platelets (x 10⁹/L)</th>
<th>Dose**</th>
</tr>
</thead>
<tbody>
<tr>
<td>greater than or equal to 1.0 and greater than or equal to 100</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>0.5 to less than 1.0 or 75 to less than 100</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>less than 0.5 or less than 75</td>
<td><strong>Omit</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Dose adjustment only for the day of treatment the CBC is drawn**
2. Renal Dysfunction

<table>
<thead>
<tr>
<th>Creatinine Clearance (mL/min)</th>
<th>CISplatin dose</th>
<th>gemcitabine dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>greater than or equal to 60</td>
<td>70 mg/m² on Day 1</td>
<td>100%</td>
</tr>
<tr>
<td>45 to less than 60</td>
<td>35 mg/m² on Days 1 and 8 (same prehydration as 70 mg/m² dose)</td>
<td>100%</td>
</tr>
<tr>
<td>less than 45</td>
<td><strong>Delay</strong></td>
<td>**Delay/omit ***</td>
</tr>
</tbody>
</table>

*Delay if Day 1; if Day 8, omit if serum creatinine greater than 3 x ULN where ULN = local upper limit of normal range.

PRECAUTIONS:

1. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
2. **Renal Toxicity**: Nephrotoxicity is common with CISplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics. Irreversible renal failure associated with hemolytic uremic syndrome may occur (rare) with gemcitabine. Use caution with pre-existing renal dysfunction.
3. **Pulmonary Toxicity**: Acute shortness of breath may occur. Discontinue treatment if drug-induced pneumonitis is suspected.
4. **Ototoxicity**: CISplatin is ototoxic and its use must be cautioned in individuals with existing hearing loss.

Contact Dr. Bernie Eigl, Dr. Christian Kollmannsberger, Dr. Jean-Michel Lavoie or tumour group delegate at (604) 877-2730 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:
5. Pfister C, Gravis G, Flechon A, et al. Multicenter randomized phase III trial of dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (dd-MVAC) or gemcitabine and cisplatin (GC) as perioperative chemotherapy for muscle-invasive bladder cancer (MIBC): Overall survival (OS) data at 5 years in the GETUG/AFU V05 VESPER trial. JCO ; 2023;41(17):LBA4507_suppl.LBA4507