BC Cancer Protocol Summary for First Line Treatment of Epithelial Ovarian Cancer Using DOXOrubicin Pegylated Liposomal (CAELYX) and CARBOplatin

Protocol Code: GOOVFPLDC
Tumour Group: Gynecologic Oncology
Contact Physician: Dr. Jenny Ko

ELIGIBILITY:
- First line treatment of invasive epithelial ovarian, fallopian tube, or primary peritoneal cancer
- Treatment with paclitaxel-carboplatin combination is not appropriate due to anaphylaxis to paclitaxel, neuropathy, other intolerable side effects related to paclitaxel, or intolerance/relative contraindication to high dose steroids

EXCLUSIONS:
- Performance status ECOG 3 or worse
- Pre-existing cardiomyopathy or congestive heart failure (relative contraindication)
- Hepatic dysfunction (see DOSE MODIFICATIONS, below)

TESTS:
- Baseline: CBC & diff, platelets, creatinine, tumour marker (CA 125, CA 15-3, CA 19-9), liver function tests (LFTs) (ALT, bilirubin, alkaline phosphatase). If clinically indicated: cardiac function tests (echocardiogram or MUGA scan).
- Day 14 and 21 after first cycle (and in subsequent cycle if dose modification made): CBC & diff, platelets.
- Before each treatment: CBC & diff, creatinine, platelets, any initially elevated tumour marker, LFTs (if clinically indicated).

PREMEDICATIONS:
- Antiemetic protocol for chemotherapy with moderate emetogenicity (see SCNAUSEA)

TREATMENT:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BC Cancer Administration Guideline</th>
</tr>
</thead>
</table>
| DOXOrubicin pegylated liposomal (CAELYX) | 30 mg/m² | IV in 250 mL D5W  
Initial dose: at rate of 1 mg/min  
Subsequent doses, if no prior infusion reaction: infuse over 1 hour |
| CARBOplatin                        | AUC* x (GFR +25)  | IV in 250 mL NS  
30 minute infusion duration          |

* use AUC of 5; if extensive prior radiation therapy, use AUC of 4
Measured GFR (e.g., nuclear renogram) is preferred in circumstances of co-morbidity that could affect renal function (third-space fluid accumulations, hypoproteinemia, potentially inadequate fluid intake, etc.).

The lab reported GFR (MDRD formula) may be used as an alternative to the Cockcroft-Gault estimate of GFR.

Cockcroft-Gault Formula

\[
GFR = \frac{1.04 \times (140 - \text{age in years}) \times \text{wt (kg)}}{\text{serum creatinine (micromol/L)}}
\]

The estimated GFR reported by the lab or calculated using the Cockcroft-Gault equation should be capped at 125 mL/min when it is used to calculate the initial CARBOplatin dose. When a nuclear renogram is available, this clearance would take precedence.

Recalculate GFR if creatinine increases by greater than 20% or rises above the upper limit of normal.

Repeat every 28 days up to a maximum of 6 cycles of first line platinum-based chemotherapy total. May extend to 9 cycles if the patient has not achieved a complete response but is continuing to respond.

1. Hematology

   a) Cycle 1:

<table>
<thead>
<tr>
<th>ANC (x 10^9/L)</th>
<th>Platelets (x 10^9/L)</th>
<th>Doses (both drugs)</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>less than 1.0 or less than 100</td>
<td>consider a non-myelosuppressive, single-agent protocol</td>
<td></td>
</tr>
</tbody>
</table>

   b) Cycles 2-6:

<table>
<thead>
<tr>
<th>ANC (x 10^9/L)</th>
<th>Platelets (x 10^9/L)</th>
<th>Doses (both drugs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>greater than or equal to 1.0 and greater than or equal to 100</td>
<td>Cycle 2: treat as per nadir</td>
<td></td>
</tr>
<tr>
<td>Cycle 3-6: use Cycle 2 dose unless additional non-hematologic toxicity in prior cycle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>less than 1.0 or less than 100</td>
<td>delay until recovery</td>
<td></td>
</tr>
</tbody>
</table>

   c) At nadir:

<table>
<thead>
<tr>
<th>ANC (x 10^9/L)</th>
<th>Platelets (x 10^9/L)</th>
<th>DOXOrubicin pegylated liposomal</th>
<th>CARBOplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>greater than or equal to 0.5 and greater than or equal to 75</td>
<td>100%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>less than 0.5 and less than 75</td>
<td>25 mg/m^2</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>less than 0.5 and greater than or equal to 75</td>
<td>25 mg/m^2</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>greater than or equal to 0.5 and less than 75</td>
<td>100%</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>febrile neutropenia at any time</td>
<td>25 mg/m^2</td>
<td>80%</td>
<td></td>
</tr>
</tbody>
</table>
2. **Hepatic dysfunction**

<table>
<thead>
<tr>
<th>Total bilirubin (micromol/L)</th>
<th>DOXOrubicin pegylated liposomal Dose (mg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>less than 50</td>
<td>30</td>
</tr>
<tr>
<td>greater than 50</td>
<td>20</td>
</tr>
</tbody>
</table>

3. **Stomatitis**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Symptoms</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>painless ulcers, erythema, or mild soreness</td>
<td>30 mg/m²</td>
</tr>
<tr>
<td>2</td>
<td>painful erythema, edema or ulcers, but can eat</td>
<td>delay until recovered to Grade 1, then continue at 20 mg/m²</td>
</tr>
<tr>
<td>3</td>
<td>painful erythema, edema or ulcers, and cannot eat</td>
<td>delay until recovered to Grade 1, then continue at 20 mg/m²; or discontinue DOXOrubicin pegylated liposomal</td>
</tr>
<tr>
<td>4</td>
<td>requires parenteral or enteral support</td>
<td>discontinue DOXOrubicin pegylated liposomal</td>
</tr>
</tbody>
</table>

Note: If delay has been necessary due to stomatitis, change of interval to five weeks is recommended.

4. **Palmar-Plantar Erythrodysesthesia (PPE) (Hand-Foot Skin Reaction)**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Symptoms</th>
<th>Dose</th>
</tr>
</thead>
</table>
| 1     | mild erythema, swelling or desquamation not interfering with normal daily activities | if no prior Grade 2 or 3 occurrence, proceed at full dose.  
if prior Grade 2 or 3 occurrence, delay one week; once recovery evident, continue treatment at 20 mg/m² |
| 2     | erythema, swelling or desquamation interfering with but not precluding normal daily activities; small blisters or ulcerations less than 2 cm in diameter | delay one week; once recovery evident, continue treatment at 20 mg/m² |
| 3     | blistering, ulceration or swelling preventing normal daily activities; cannot wear regular clothing | delay one week, and re-assess; consider dexamethasone 2 mg TID until symptoms resolve; if still Grade 3 after a one week delay, discontinue treatment; if resuming, dose at 20 mg/m² |

Note: If delay has been necessary due to PPE, change of interval to five weeks is recommended.
5. **Renal dysfunction:** If significant increase (greater than 20%) in creatinine, recalculate CARBOplatin dose using new GFR, determined using the same method as in the original calculation.

6. **Other Grade 3 or 4 Toxicities**
Reduce DOXOrubicin pegylated liposomal dose by 10 mg/m².

**PRECAUTIONS:**

1. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BC Cancer Febrile Neutropenia Guidelines.

2. **Cardiac Toxicity:** DOXOrubicin is cardiotoxic and must be used with caution, if at all, in patients with severe hypertension or cardiac dysfunction.

3. **Extravasation:** Pegylated liposomal DOXOrubicin is considered an irritant. Refer to BC Cancer Extravasation Guidelines.

4. **Acute Infusion Reaction:** may occur with first infusion, usually within minutes of starting. Refer to BC Cancer Hypersensitivity Guidelines. *Note: the first step is to stop the infusion.* In subsequent cycles, reactions are rare, but prophylaxis with dexamethasone, diphenhydramine, and ranitidine may be used.

5. **Palmar-Plantar Erythrodysesthesia (PPE) (Hand-Foot Skin Reaction):** See BC Cancer Cancer Drug Manual pegylated liposomal DOXOrubicin monograph for suggested strategies for preventing or minimizing PPE. Corticosteroids may reduce the incidence of PPE during treatment.¹

Call Dr. Jenny Ko or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

**REFERENCES:**
