BC Cancer Protocol Summary for Primary Treatment of Visible Residual (Extreme Risk) Invasive Epithelial Ovarian, Fallopian Tube or Peritoneal Cancer Using CARBOplatin and PACLitaxel

Protocol Code: GOOVCATX

Tumour Group: Gynecologic Oncology

Contact Physicians: Dr. Anna Tinker

ELIGIBILITY:
• visible residual, invasive epithelial ovarian, fallopian tube or peritoneal cancer, or borderline with invasive implants

EXCLUSIONS:
• no visible residual disease (use protocol GOOVCATM or GOOVCADM)
• borderline (low malignant potential) tumours with non-invasive implant – contact BCCA
• prior chemotherapy or radiotherapy for this malignancy (use relapse protocols)
• uncontrolled brain metastases
• AST and/or ALT greater than 10 times the Upper Limit of Normal
• total bilirubin greater than 128 micromol/L

RELATIVE CONTRAINDICATIONS:
• pre-existing motor or sensory neuropathy greater than grade 2
• performance status greater than ECOG 3

INCOMPLETE PRIMARY SURGERY:
Responders with "incomplete" primary surgery i.e., debulking to less than 2 cm not carried out, should be discussed for consideration of re-laparotomy after 3-4 cycles. Survival benefits may be realised with "interval debulking" after several cycles of chemotherapy.

NO PRIMARY SURGERY:
If no primary surgery was carried out, these patients are candidates for interval debulking after three or four cycles.

TESTS:
• Baseline: CBC & diff, platelets, creatinine, tumour marker (CA 125, CA 15-3, CA 19-9, CEA), LFT’s (if abnormal liver function is a potential concern), camera nuclear renogram for GFR (optional)
• Day 14 (and Day 21 if using a 4 week cycle interval) of first cycle (and in subsequent cycle(s) if a dose modification has been made): CBC & diff, platelets. No need for interim count check once safe nadir pattern has been established.
• Before each treatment: CBC & diff, creatinine, any initially elevated tumour marker, LFT’s (if clinically indicated).

PREMEDICATIONS:
• PACLitaxel must not be started unless the following drugs have been given:
  45 minutes prior to PACLitaxel:
  • dexamethasone 20 mg IV in 50 mL NS over 15 minutes
  30 minutes prior to PACLitaxel:
  • diphenhydRAMINE 50 mg IV and ranitidine 50 mg IV in 50 mL NS over 20 minutes (compatible up to 3 hours when mixed in bag)
  • ondansetron 8 mg po 30 minutes pre-CARBOplatin

Warning: The information contained in these documents are a statement of consensus of BC Cancer professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is at your own risk and is subject to BC Cancer's terms of use available at www.bccancer.bc.ca/legal.htm
ANTIEMETIC THERAPY POST-CHEMOTHERAPY:
- Antiemetic protocol for moderate emetogenic chemotherapy protocols (see SCNAUSEA)
- Dexamethasone 4 mg PO bid for 2 days and dimenhydrinate 50 to 100 mg PO prn after treatment is usually adequate

TREATMENT (give PACLitaxel first):

<table>
<thead>
<tr>
<th>Drug</th>
<th>Starting Dose</th>
<th>BCCA Administration Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>PACLitaxel</td>
<td>175 mg/m²*</td>
<td>IV in 500 mL NS over 3 hours (use non-DEHP bag and non-DEHP tubing with 0.22 micron or smaller in-line filter)</td>
</tr>
<tr>
<td>CARBOplatin</td>
<td>Dose = AUC** x (GFR +25)</td>
<td>IV in 250 mL NS over 30 minutes</td>
</tr>
</tbody>
</table>

* Conservative dosing (i.e., 155 mg/m² or 135 mg/m²) may be considered in the following cases: ECOG greater than 2, existing or potential myelosuppression; existing or potential arthralgia and myalgia; prior radiotherapy, particularly to the pelvic region; reduced bone marrow capacity. An initial dose of 135 mg/m² is recommended in patients greater than 75 years of age, with escalation to 155 mg/m² and then 175 mg/m² if tolerated.

** use AUC of 6; if extensive prior radiation therapy, use AUC of 5

Repeat every 21-28 days for 6 cycles. May extend to 9 cycles or until disease progression if the patient has not achieved a complete response but is continuing to respond.

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, age greater than 70, etc.). The lab reported GFR (MDRD formula) may be used as an alternative to the Cockcroft-Gault estimate of GFR; 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.

Cockcroft-Gault Formula

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

Recalculate GFR if, at a point of (optional) checking, creatinine increases by greater than 20% or rises above the upper limit of normal.

If PACLitaxel toxicity is a concern or becomes problematic, consider use of single agent CARBOplatin (GOOVCARB at AUC = 5) or protocols GOOVCAD or GOOVCAG.
DOSE MODIFICATIONS:
1. Hematology:
a) on treatment day:

<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>treat as per nadir (if applicable); otherwise, proceed at same doses</td>
<td></td>
</tr>
<tr>
<td>less than 1.0* or less than 100</td>
<td>Delay until recovery. If using 21-day interval, switch to 28-day interval. If 2nd delay, use filgrastim (G-CSF) or dose reduction.</td>
<td></td>
</tr>
</tbody>
</table>

* If ANC greater than 0.8 and monocytes greater than or equal to 20%, neutrophil count recovery is likely imminent. Continuation without delay may occur at physician’s discretion.

b) at nadir (until nadir pattern established):

<table>
<thead>
<tr>
<th>ANC (x 10^9/L)</th>
<th>Platelets (x 10^9/L)</th>
<th>PACLtaxel</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>80%</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>less than 0.5 and greater than or equal to 75</td>
<td>80%</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>80%</td>
<td>80%</td>
<td></td>
</tr>
</tbody>
</table>

* % of previous cycle’s dose, at physician’s discretion. If dose is changed, subsequent nadir counts must be checked.
** If dose has been reduced, dose increase/re-escalation for good nadir counts is not recommended.

2. Arthralgia and/or myalgia: If arthralgia and/or myalgia of grade 2 (moderate) or higher was not adequately relieved by NSAIDs or acetaminophen with codeine (e.g., TYLENOL®), a limited number of studies report a possible therapeutic benefit using:
   - predniSONE 10 mg PO bid x 5 days starting 24 hours post-PACLtaxel
   - gabapentin 300 mg PO on day before chemotherapy, 300 mg bid on treatment day, then 300 mg tid x 5 to 15 days (based on duration of arthromyalgia)
If arthralgia and/or myalgia persists, reduce subsequent PACLtaxel doses to 135 mg/m² or switch taxane to DOCEtaxel (GOOVCAADX)

3. Neuropathy: Dose modification or discontinuation may be required (see BCCA Cancer Drug Manual).

4. Renal dysfunction: If significant increase (greater than 20% or rises above the upper limit of normal) in creatinine, recheck/recalculate GFR and recalculate CARBOplatin dose using new GFR.
5. **Hepatic dysfunction**: Dose reduction may be required for PACLitaxel

<table>
<thead>
<tr>
<th>ALT less than 10 x ULN and bilirubin</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>less than 10 x ULN and less than or equal to 1.25 x ULN</td>
<td>175 mg/m²</td>
</tr>
<tr>
<td>less than 10 x ULN and 1.26 to 2 x ULN</td>
<td>135 mg/m²</td>
</tr>
<tr>
<td>less than 10 x ULN and 2.01 to 5 x ULN</td>
<td>90 mg/m²</td>
</tr>
<tr>
<td>greater than or equal to 10 x ULN and/or greater than 5 x ULN</td>
<td>not recommended</td>
</tr>
</tbody>
</table>

**PRECAUTIONS:**

1. **Hypersensitivity**: Reactions are common. See BCCA Hypersensitivity Guidelines

   - **Mild** symptoms (e.g., mild flushing, rash, pruritus)
     - complete PACLitaxel infusion. Supervise at bedside
     - no treatment required

   - **Moderate** symptoms (e.g. moderate rash, flushing, mild dyspnea, chest discomfort, mild hypotension)
     - stop PACLitaxel infusion
     - give IV diphenhydrAMINE 25 to 50 mg and hydrocortisone IV 100 mg
     - after recovery of symptoms resume PACLitaxel infusion at 20 mL/h for 5 minutes, 30 mL/h for 5 minutes, 40 mL/h for 5 minutes, then 60 mL/h for 5 minutes. If no reaction, increase to full rate.
     - if reaction recurs, discontinue PACLitaxel therapy

   - **Severe** symptoms (i.e. one or more of respiratory distress requiring treatment, generalised urticaria, angioedema, hypotension requiring therapy)
     - stop PACLitaxel infusion
     - give IV antihistamine and steroid as above. Add epinephrine or bronchodilators if indicated
     - discontinue PACLitaxel therapy

2. **Extravasation**: PACLitaxel causes pain and may, rarely, cause tissue necrosis if extravasated. Refer to BCCA Extravasation Guidelines.

3. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.

4. **Drug Interactions**: PACLitaxel is a CYP 2C8/9 and CYP 3A4 substrate. Drug levels may be increased by inhibitors of these enzymes and decreased by inducers of these enzymes.

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