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
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 250 to 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>
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* 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 continue to treat 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>PACLitaxel</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-PACLitaxel
   - 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 PACLitaxel doses to 135 mg/m² or switch taxane to DOCEtaxel (GOOVCADX)

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</th>
<th>Bilirubin</th>
<th>Dose</th>
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<tbody>
<tr>
<td>less than 10 x ULN</td>
<td>and less than or equal to 1.25 x ULN</td>
<td>175 mg/m²</td>
</tr>
<tr>
<td>less than 10 x ULN</td>
<td>and 1.26 to 2 x ULN</td>
<td>135 mg/m²</td>
</tr>
<tr>
<td>less than 10 x ULN</td>
<td>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>
<td></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.**