BCCA Protocol Summary for Primary Treatment of Advanced Epithelial Ovarian, Primary Peritoneal, or Fallopian Tube Carcinoma Using CARBOplatin and Weekly PACLitaxel

Protocol Code: GOOVDDCAT
Tumour Group: Gynecologic Oncology
Contact Physician: Dr. Anna Tinker

ELIGIBILITY:
- Primary treatment of histologically or cytologically proven Stage III or IV epithelial ovarian, fallopian tube or primary peritoneal carcinoma
- First-line treatment of Stage I or Stage II serous ovarian cancer
- Adequate hematologic, liver, and cardiac function
- In situations where GOOVIPPC would be appropriate but cannot be delivered due to logistics or because an IP access device (“port”) cannot be placed
- PS ECOG 3 or better
- Neoadjuvant treatment is acceptable

EXCLUSIONS:
- AST and/or ALT greater than 10 times the Upper Limit of Normal
- Total bilirubin greater than 128 micromol/L
- Second line treatment; use alternate protocol

RELATIVE CONTRAINDICATIONS:
- Peripheral neuropathy Grade 2 or higher
- Prior severe arthromyalgia unresponsive to treatment

TESTS:
- Baseline: CBC & diff, platelets, creatinine, bilirubin, AST, magnesium, appropriate tumour marker(s), camera nuclear renogram for GFR (optional)
- Prior to Day 1, each cycle: CBC & diff, platelets, appropriate tumour marker(s)
- Prior to Day 8 and 15, each cycle: CBC & diff, platelets
- If clinically indicated: creatinine, bilirubin, AST, magnesium
**PREMEDICATIONS:**

- **PACLitaxel must not be started unless the following drugs have been given:**

  45 minutes prior to PACLitaxel:
  - dexamethasone 10 mg IV in 50 mL NS over 15 minutes
  - diphenhydramINE 25 mg IV and ranitidine 50 mg IV in 50 mL NS over 20 minutes (compatible up to 3 hours when mixed together in bag)

- **NOTE:** If no PACLitaxel hypersensitivity reactions occur, no premedications may be needed for subsequent Day 8 and 15 PACLitaxel doses and may be omitted at physician’s discretion.

- **NOTE:** If no PACLitaxel hypersensitivity reactions occur, dexamethasone 8 mg PO may be given on Day 1 of each cycle (day of CARBOplatin treatment) in place of the regimen in the first bullet point above.

- If hypersensitivity reactions occur, premedications for re-challenge include dexamethasone 20 mg PO given 12 hours and 6 hours prior to treatment, plus IV premedications given 30 minutes prior to PACLitaxel: dexamethasone 10 mg, diphenhydramINE 25 mg, and H₂-antagonist (e.g., ranitidine 50 mg). If no hypersensitivity reactions occur, standard premedications (see above) will be used for subsequent PACLitaxel doses.

- ondansetron 8 mg PO 30 minutes prior to CARBOplatin on Day 1 of each cycle.

**TREATMENT:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BCCA Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>PACLitaxel</td>
<td>70 mg/m² once weekly (Day 1, 8, 15)*</td>
<td>IV in 250* mL NS over 1 hour (use non-DEHP bag and non-DEHP tubing with 0.22 micron or smaller inline filter)</td>
</tr>
<tr>
<td>CARBOplatin</td>
<td>Dose = AUC 6 x (GFR** + 25) once every 3 weeks (Day 1 only)</td>
<td>IV in 250 mL NS over 30 minutes</td>
</tr>
</tbody>
</table>

*Use 100 mL for dose less than 87 mg

*PACLitaxel dose may be increased to 80 mg/m² in Cycle 2 or later at physician’s discretion if good tolerance is demonstrated.
Cycle length = 3 weeks. Repeat every 21 days for 2 to 6 cycles (3 cycles if clear cell histology – see Eligibility section). Six cycles may be exceeded to achieve two post-operative cycles for those undergoing delayed interval debulking.

Discontinue if there is evidence of progression.

**Measured GFR** (e.g. nuclear renogram) is preferred in circumstances of co-morbidity that could affect renal function (third-space fluid accumulations, hypoproteinaemia, 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.
DOSE MODIFICATIONS:

1. **Hematological Toxicity, Day 1**

<table>
<thead>
<tr>
<th>ANC (x 10^9/L)</th>
<th>Platelets (x 10^9/L)</th>
<th>PACLitaxel Dose</th>
<th>CARBOplatin Dose</th>
<th>Subsequent Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater than or equal to 1 and Greater than or equal to 100</td>
<td>100%</td>
<td>100%</td>
<td><strong>If second occurrence of Day 1 low ANC, reduce PACLitaxel to 60 mg/m^2.</strong> <strong>If second occurrence of Day 1 low platelet count, reduce CARBOplatin to AUC 5.</strong></td>
<td></td>
</tr>
<tr>
<td>0.5 to 0.99 and/or 75 to 99</td>
<td>Delay until recovery</td>
<td>Delay until recovery</td>
<td><strong>For Day 1 low ANC, reduce PACLitaxel to 60 mg/m^2.</strong> <strong>If Day 1 low ANC recurs, further reduce PACLitaxel to 50 mg/m^2.</strong> <strong>For Day 1 low platelets, reduce CARBOplatin to AUC 5.</strong> <strong>If Day 1 low platelet count recurs, further reduce CARBOplatin to AUC 4.</strong></td>
<td></td>
</tr>
<tr>
<td>Less than 0.5 and/or Less than 75</td>
<td>Delay until recovery</td>
<td>Delay until recovery</td>
<td><strong>For Day 1 low ANC, reduce PACLitaxel to 60 mg/m^2.</strong> <strong>If Day 1 low ANC recurs, further reduce PACLitaxel to 50 mg/m^2.</strong> <strong>For Day 1 low platelets, reduce CARBOplatin to AUC 5.</strong> <strong>If Day 1 low platelet count recurs, further reduce CARBOplatin to AUC 4.</strong></td>
<td></td>
</tr>
</tbody>
</table>

Note: patients who cannot tolerate treatment after 2 dose reductions or require a treatment delay of greater than 2 weeks, should discontinue the weekly PACLitaxel protocol.
Hematologic Toxicity, Day 8 and 15

<table>
<thead>
<tr>
<th>ANC (x 10^9/L)</th>
<th>Platelets (x 10^9/L)</th>
<th>PACLitaxel Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater than or equal to 0.5 and Greater than or equal to 50</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>
| Less than 0.5 and/or Less than 50 | Omit | AND, reduce subsequent treatments:  
  *if ANC was low, reduce paclitaxel by one dose level*;  
  *if Platelets were low, reduce next cycle’s Day 1 CARBOplatin by one dose level*.  

*Note: “Dose levels” for PACLitaxel 70 → 60 → 50 mg/m²; for CARBOplatin = AUC 6 → 5 → 4.*
2. Non-Hematological Toxicity

<table>
<thead>
<tr>
<th>Grade</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 2 motor or sensory neuropathy</td>
<td>Decrease PACLitaxel dose by 10 mg/m²</td>
</tr>
<tr>
<td>All other Grade 2 non-hematologic toxicities</td>
<td>Hold treatment until toxicity resolved to less than or equal to Grade 1</td>
</tr>
<tr>
<td></td>
<td>Decrease subsequent PACLitaxel doses by 10 mg/m²</td>
</tr>
<tr>
<td>Greater than or equal to Grade 3 non-hematologic toxicities</td>
<td>Hold treatment. Re-evaluate treatment plan. Consider discontinuing treatment with this protocol.</td>
</tr>
</tbody>
</table>

Note: Patients who cannot tolerate treatment after two dose reductions or require a treatment delay of greater than two weeks should discontinue the weekly PACLitaxel protocol.

3. Hepatic Dysfunction

<table>
<thead>
<tr>
<th>Bilirubin (micromol/L)</th>
<th>AST</th>
<th>Dose (mg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than or equal to 25 and less than 2 x ULN</td>
<td>AST</td>
<td>70 mg/m²</td>
</tr>
<tr>
<td>Less than or equal to 25 and Greater than or equal to 2 x ULN with no liver metastases or Greater than or equal to 5 x ULN with liver metastases</td>
<td>65 mg/m²</td>
<td></td>
</tr>
<tr>
<td>25 to 50</td>
<td>40 mg/m²</td>
<td></td>
</tr>
<tr>
<td>Greater than 50</td>
<td>25 mg/m²</td>
<td></td>
</tr>
</tbody>
</table>

ULN = upper limit of normal

4. Arthralgia and/or myalgia
If arthralgia and/or myalgia of Grade 2 (moderate) or higher is not relieved by adequate doses of NSAIDs or acetaminophen with codeine (e.g., TYLENOL #3), 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 7 to 10 days
If arthralgia and/or myalgia persists, reduce subsequent PACLitaxel doses to 65 mg/m².
5. Neuropathy  
Dose modification or discontinuation may be required (see BCCA Cancer Drug Manual).

PRECAUTIONS

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

<table>
<thead>
<tr>
<th>Symptom Level</th>
<th>Action</th>
</tr>
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</table>
| **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 tissue necrosis if extravasated. Refer to BCCA Extravasation Guidelines.

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

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.

Date Activated: 1 May 2012  
Date Revised: 1 May 2017 (Total number of cycles clarified)

**REFERENCES**