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
- Stage III or IV disease (patients may have upfront or interval debulking surgery – see below)

EXCLUSIONS:
- no visible residual disease (use protocol GOOVCATM or GOOVCADM)
- borderline (low malignant potential) tumours with non-invasive implant – contact BC Cancer
- 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 markers as indicated (CA 125, CA 15-3, CA 19-9, CEA), bilirubin, ALT, alkaline phosphatase, 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
  - If clinically indicated: bilirubin, alkaline phosphatase, GGT, ALT, LDH, total protein, albumin

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 in NS 50 mL over 15 minutes and famotidine 20 mg IV in NS 100 mL over 15 minutes (Y-site compatible)
- 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):

Drug	Starting Dose	BC Cancer Administration Standard
PACLitaxel	175 mg/m^2 *	IV in 250 to 500 mL NS over 3 hours (use non-DEHP bag and non-DEHP tubing with 0.2 micron in-line filter)
CARBOplatin	Dose = AUC** x (GFR +25)	IV in 100 to 250 mL NS over 30 minutes

* Conservative dosing (i.e., 155 mg/m^2 or 135 mg/m^2) 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/m^2 is recommended in patients greater than 75 years of age, with escalation to 155 mg/m^2 and then 175 mg/m^2 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

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

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:

ANC (x 10^9/L)		Platelets (x 10^9/L)	Doses (both drugs)
greater than or equal to 1.0	and	greater than or equal to 100	treat as per nadir (if applicable); otherwise, proceed at same doses
less than 1.0*	or	less than 100	Delay until recovery. If using 21-day interval, switch to 28-day interval. If 2nd delay, use filgrastim (G-CSF) or dose reduction.

* 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):

ANC (x 10^9/L)		Platelets (x 10^9/L)	PACLitaxel	CARBOplatin*
greater than or equal to 0.5	and	greater than or equal to 75	100%	100%**
less than 0.5	and	less than 75	80%	80%
less than 0.5	and	greater than or equal to 75	80%	100%
greater than or equal to 0.5	and	less than 75	100%	80%
febrile neutropenia at any time			80%	80%

* % 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#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 5 to 15 days (based on duration of arthromyalgia)

   If arthralgia and/or myalgia persists, reduce subsequent PACLitaxel doses to 135 mg/m^2 or switch taxane to DOCEtaxel (GOOVCADX)

3. **Neuropathy**: Dose modification or discontinuation may be required (see BC 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

ALT		Bilirubin	Dose
less than 10 x ULN	and	less than or equal to 1.25 x ULN	175 mg/m^2
less than 10 x ULN	and	1.26 to 2 x ULN	135 mg/m^2
less than 10 x ULN	and	2.01 to 5 x ULN	90 mg/m^2
greater than or equal to 10 x ULN	and/or	greater than 5 x ULN	not recommended

PRECAUTIONS:

1. **Hypersensitivity**: Reactions are common. See BC Cancer 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 BC Cancer 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.