

BC Cancer Protocol Summary for Primary Treatment of Stage III less than or equal to 1 cm Visible Residual Invasive Epithelial Ovarian Cancer or Stage I Grade 3 or Stage II Grade 3 Papillary Serous Ovarian Cancer Using Intravenous and Intraperitoneal PACLitaxel and Intraperitoneal CARBOplatin

Protocol Code
Tumour Group
Contact Physician

GOOVIPPC
Gynecology
Paul Hoskins

ELIGIBILITY:

- First-line treatment of stage III invasive epithelial ovarian cancer, (epithelial ovarian, primary peritoneal, or fallopian tube carcinoma) residual less than or equal to 1 cm
- First-line treatment of Stage I Grade 3 and Stage II Grade 3 papillary serous ovarian cancer, residual less than or equal to 1 cm, including no visible residual disease
- First-line treatment of low stage clear cell ovarian cancer (i.e., Stage 1c based upon positive washings or surface positivity, or any Stage II): eligible for 3 cycles
- Post-primary debulking surgery
- Placement of intraperitoneal catheter should be performed at the primary laparotomy by individual skilled in its placement*

(*see

www.bccancer.bc.ca/HPI/CancerManagementGuidelines/Gynecology/OvaryEpithelial/Management)

EXCLUSIONS:

- age greater than 80
- ECOG performance status greater than 2
- borderline (low malignant potential) tumours
- gynecologic tumours of origin or histology other than listed above, in Eligibility
- prior chemotherapy or radiotherapy for this malignancy
- bowel obstruction
- brain metastases
- Stage IV disease
- Relapse or recurrence
- Bilirubin greater than or equal to 5xULN or ALT greater than or equal to 10xULN
- Residual greater than 1 cm

RELATIVE CONTRAINDICATIONS:

- pre-existing motor or sensory neuropathy greater than grade 2

TESTS:

- Baseline: CBC & diff, platelets, creatinine, best tumour marker (CA 125, CA 15-3, CA 19-9), **ALT, Alk Phos, bilirubin, LDH, GGT**, camera nuclear renogram for GFR (if available)
- Day 14 after first cycle (and in subsequent cycle if dose modification made): CBC & diff
- Before each treatment (Day 1): CBC & diff, any initially elevated tumour marker
 - **If clinically indicated:** creatinine, **total protein, albumin, bilirubin, GGT, Alk Phos, LDH, ALT, BUN**
- Before each treatment (Day 8): CBC & diff [*NB – results not needed prior to treatment as no dosage adjustment to be made on Day 8*]

PREMEDICATIONS:

On Day 1 (IV PACLitaxel + intraperitoneal CARBOplatin):

- **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 (unless oral dexamethasone 20 mg 12 and 6 hours before PACLitaxel has been given)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

On Day 8 (intraperitoneal PACLitaxel):

- **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 (unless oral dexamethasone 20 mg 12-hours and 6-hours before PACLitaxel has been given)30 minutes prior to PACLitaxel:
 - diphenhydrAMINE 25 mg IV in NS 50 mL over 15 minutes and famotidine 20 mg IV in NS 100 mL over 15 minutes (Y-site compatible)

ANTIEMETIC THERAPY POST-CHEMOTHERAPY:

- dexamethasone 4 mg PO q12h for 4 doses, beginning in the evening of treatment day (following Day 1 only)
- dimenhydrINATE 50-100 mg PO q6h prn nausea/vomiting
- prochlorperazine 10 mg PO q6h prn nausea/vomiting
- if delayed emesis occurs, consider adding ondansetron to regimen

TREATMENT:

q3week cycle (x6 cycles if surgery has occurred; x 3 cycles if clear cell (see Eligibility section); or to complete 6 cycles of chemotherapy treatment if chemotherapy began prior to surgery)

Nurses should use BC Cancer Nursing Practice Reference C-252 for guidance on delivery of IP chemotherapy.

If IP access device fails, patients will complete treatment according to GOOVCA TX protocol, modified to a q3week treatment interval.

If debulking surgery has included bowel resection, IP portion of chemotherapy should be omitted from the treatment cycle that follows the surgery.

DAY ONE (give PACLitaxel first)

Drug	Starting Dose	Route	BC Cancer Administration Standard
PACLitaxel	175 mg/m ² (or conservative dosing of 155 mg/ m ² or 135 mg/ m ²)* [refer to CDM monograph for dose adjustments if bilirubin greater than 1.25xULN]	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	AUC = 6 Dose = 6 x (GFR +25)	IP	in 1000 mL NS, infused as rapidly as possible, by gravity
NS solution for injection	1000 mL	IP	Immediately following infusion of IP CARBOplatin, infused as rapidly as possible, by gravity. Rotate positioning of patient x1 hour, according to Nursing Practice Reference C-252.

* Conservative dosing may be considered in the following cases: existing or potential myelosuppression; reduced bone marrow capacity; elderly i.e. physiologically 75 or greater.

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.

DAY EIGHT

[refer to Premedications section of this protocol for Day 8 recommendations]

Drug	Starting Dose	Route	BC Cancer Administration Standard
PACLitaxel	60 mg/m ²	IP	in 1000 mL NS, infused as rapidly as possible, by gravity (use non-DEHP bag and non-DEHP tubing with 0.2 micron in-line filter)
NS solution for injection	1000 mL	IP	Immediately following infusion of IP PACLitaxel, infused as rapidly as possible, by gravity. Rotate positioning of patient for one hour, according to Nursing Practice Reference C-252

DOSE MODIFICATIONS:

1. Hematology:

a) on Day 1:

ANC (x 10 ⁹ /L)		Platelets (x 10 ⁹ /L)	Doses (all drugs)
greater than or equal to 1.5	and	greater than or equal to 100	treat as per nadir
less than 1.5	or	less than 100	Delay until recovery. Check counts in one week.

b) at nadir:

<ul style="list-style-type: none">If platelet nadir is less than 50, subsequent IP CARBOplatin dose should be reduced to 90% of preceding cycle
<ul style="list-style-type: none">If neutrophil nadir is less than 0.5, subsequent IV PACLitaxel dose should be reduced by 20 mg/m² from dose of preceding cycle (e.g. 175 mg/m² reduce to 155 mg/m²; 155mg/m² reduce to 135 mg/m²)
<ul style="list-style-type: none">No adjustments need be made to IP PACLitaxel dose based on nadir counts

NB – No dosage adjustments to be made for hematologic counts on Day 8.

2. **Febrile neutropenia:** Once resolved, reduce subsequent cycle IP CARBOplatin to 90% and IV PACLitaxel by 20 mg/m². Maintain IP PACLitaxel dose at 100%.

3. **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 5 to 10 days, based on duration of arthromyalgias

If disabling arthralgia and/or myalgia persists, reduce subsequent PACLitaxel doses to 135 mg/m².

4. **Neuropathy:** Dose modification or discontinuation may be required (see BC Cancer Drug Manual)
5. **Renal dysfunction:** If significant increase (greater than 20%) in creatinine, repeat nuclear renogram (if available) and recalculate CARBOplatin dose using new GFR.
6. **Hepatic dysfunction:** Dose reduction may be required for PACLitaxel (see BC Cancer Drug Manual)
7. **Bacterial Peritonitis:** Remove IP access device. After resolution of infection, switch to GOOVCATX protocol, modified to q3week treatment interval, to complete a total of 6 treatment cycles (GOOVIPPC + GOOVCATX combined)
8. **Abdominal Pain:** If Grade 3, i.e. requiring narcotic analgesics or hospital admission, remove IP access device. Switch to GOOVCATX protocol, modified to q3week treatment interval, to complete a total of 6 treatment cycles (GOOVIPPC + GOOVCATX combined)

PRECAUTIONS:

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

<i>Mild</i> symptoms (e.g., mild flushing, rash, pruritus)	<ul style="list-style-type: none"> ▪ complete PACLitaxel infusion. Supervise at bedside ▪ no treatment required
<i>Moderate</i> symptoms (e.g. moderate rash, flushing, mild dyspnea, chest discomfort, mild hypotension)	<ul style="list-style-type: none"> ▪ stop PACLitaxel infusion ▪ give IV diphenhydrAMINEe 25-50 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
<i>Severe</i> symptoms (i.e. <u>one</u> or more of respiratory distress requiring treatment, generalised urticaria, angioedema, hypotension requiring therapy)	<ul style="list-style-type: none"> ▪ stop PACLitaxel infusion ▪ give IV antihistamine and steroid as above. Add epinephrine or bronchodilators if indicated ▪ discontinue PACLitaxel therapy

Refer to BC Cancer Hypersensitivity Guidelines for appropriate premedications in subsequent cycles.

NB: If a patient experiences a hypersensitivity reaction to PACLitaxel or CARBOplatin given intravenously, then that same drug should NOT be given intraperitoneally in that cycle or subsequent cycles. Any rechallenge considered for future treatments should be for the intravenous route only; intraperitoneal treatment with that drug should not be re-instituted.

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.

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