BC Cancer 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, ALT, 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: bilirubin, alk phos, GGT, ALT, LDH, protein, albumin, creatinine, 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

  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)

- **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 H_2-antagonist (e.g., famotidine 20 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:

Drug	Dose	BC Cancer Administration Guideline
PACLitaxel	70 mg/m^2 once weekly (Day 1, 8, 15)*	IV in 100 to 250 mL NS over 1 hour (use non-DEHP bag and non-DEHP tubing with 0.2 micron in-line filter)
CARBOplatin	Dose = AUC 6 x (GFR** + 25) once every 3 weeks (Day 1 only)	IV in 100 to 250 mL NS over 30 minutes

*PACLitaxel dose may be increased to 80 mg/m^2 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. 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, 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.

DOSE MODIFICATIONS:

1. Hematological Toxicity, Day 1

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

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

ANC (x 10^9/L)		**Platelets** (x 10^9/L)	**PACLitaxel Dose**	
Greater than or equal to 0.5	and	Greater than or equal to 50	100%	
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/m^2; for CARBOplatin = AUC 6 → 5 → 4.

2. Non-Hematological Toxicity

Grade	Dose
Grade 2 motor or sensory neuropathy	Decrease PACLitaxel dose by 10 mg/m^2
All other Grade 2 non-hematologic toxicities	Hold treatment until toxicity resolved to less than or equal to Grade 1 Decrease subsequent PACLitaxel doses by 10 mg/m^2
Greater than or equal to Grade 3 non-hematologic toxicities	Hold treatment. Re-evaluate treatment plan. Consider discontinuing treatment with this protocol.

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

Bilirubin (micromol/L)		ALT and/or AST	Dose (mg/m^2)
Less than or equal to 25	and	less than 2 x ULN	70 mg/m^2
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	65 mg/m^2
25 to 50			40 mg/m^2
Greater than 50			25 mg/m^2

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/m^2.

5. Neuropathy
Dose modification or discontinuation may be required (see BC Cancer Drug Manual).

PRECAUTIONS

1. **Hypersensitivity**: Reactions to PACLitaxel 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 diphehydrAMINE 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 BC Cancer 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.

REFERENCES

Katsumata N, et al., Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomized controlled trial, Lancet 2009;374:1331-38.