

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:

GO Systemic Therapy

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, creatinine, total bilirubin, ALT
- Baseline, if clinically indicated: sodium, potassium, magnesium, calcium, alkaline phosphatase, LDH, GGT, CA 125, CA 19-9, CA 15-3, CEA, SCC
- Prior to Day 1 of each cycle: CBC & Diff, creatinine, total bilirubin, ALT
- Prior to Day 8 and 15 of each cycle: CBC & Diff
- If clinically indicated: alkaline phosphatase, GGT, LDH, magnesium, sodium, potassium, calcium, CA 125, CA 19-9, CA 15-3, CEA, SCC

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 H₂-antagonist (e.g., famotidine 20 mg). If no hypersensitivity reactions occur, standard premedications (see above) will be used for subsequent PACLitaxel doses.
- For CARBOplatin on Day 1 of each cycle: Antiemetic protocol for highly emetogenic chemotherapy protocols (see [SCNAUSEA](#))

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/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. 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	<i>If second occurrence of Day 1 low ANC, reduce PACLitaxel to 60 mg/m².</i> <i>If second occurrence of Day 1 low platelet count, reduce CARBOplatin to AUC 5.</i>
Less than 0.5	and/ or	Less than 75	Delay until recovery	Delay until recovery	<i>For Day 1 low ANC, reduce PACLitaxel to 60 mg/m².</i> <i>If Day 1 low ANC recurs, further reduce PACLitaxel to 50 mg/m².</i> <i>For Day 1 low platelets, reduce CARBOplatin to AUC 5.</i> <i>If Day 1 low platelet count recurs, further reduce CARBOplatin to AUC 4.</i>

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	<p>AND, reduce subsequent treatments:</p> <p><i>if ANC was low</i>, reduce paclitaxel by one dose level*;</p> <p><i>if Platelets were low</i>, reduce next cycle's Day 1 CARBOplatin by one dose level*.</p>

*Note: "Dose levels" for PACLitaxel 70 → 60 → 50 mg/m²; 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

Total 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/m².

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.

<u>Mild</u> symptoms (e.g. mild flushing, rash, pruritus)	<ul style="list-style-type: none">▪ complete PACLitaxel infusion. Supervise at bedside▪ no treatment required
<u>moderate</u> symptoms (e.g. moderate rash, flushing, mild dyspnea, chest discomfort, mild hypotension)	<ul style="list-style-type: none">▪ 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
<u>severe</u> 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

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.

Contact the GO Systemic Therapy physician at your regional cancer centre or GO Systemic Therapy Chair 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.