

BC Cancer Protocol Summary for Treatment of Primary Advanced or Recurrent Endometrial Cancer using CARBOplatin and PACLitaxel

Tumour Group:	Gynecology
Protocol Code:	GOENDCAT
Contact Physician:	Dr. Paul Hoskins

ELIGIBILITY:

- advanced endometrial cancer, including malignant mixed Mullarian tumour (MMMT) or carcinosarcoma
 - Stage I papillary serous or MMTT or clear cell, with myometrial invasion
 - Stage 1a, Grade 3 endometrioid with myometrial invasion or other risk feature
 - Stage 1b, Grade 3 endometrioid
 - Stage II, Grade 3
 - Stage III, Grade 2 or Grade 3
 - Stage IIIb or IIIc, Grade 1
 - Stage IV (any grade**)
- recurrent disease

* any component if mixed histology

** though if Grade 1, consider hormonal therapy

EXCLUSIONS:

- uterine sarcomas, small cell histology
- AST and/or ALT greater than 10 times the Upper Limit of Normal (ULN)
- 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

TESTS:

- Baseline: CBC & diff, platelets, creatinine, tumour marker (CA 125, CA 15-3, CA 19-9, CEA), [ALT](#), [Alk Phos](#), [bilirubin](#) (if abnormal liver function is a potential concern), camera nuclear renogram for GFR (optional)
- Day 14 (and Day 21 if using 4 week 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).
- [If clinically indicated: bilirubin, Alk Phos, GGT, ALT, LDH, protein level, 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 50-100 mg 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/m² or 135 mg/m²) 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/m² is recommended in patients greater than 75 years of age, with escalation to 155 mg/m² and then 175 mg/m² if tolerated.

** use AUC of 6; if extensive prior radiation therapy, use AUC of 5

Repeat every 21-28 days for:

- 3 cycles if to be followed by radical radiation therapy (i.e. patients with disease that is radio-encompassable)
- up to 6 cycles (may extend to 9 cycles if the patient has not achieved a complete response but is continuing to respond). BC Cancer CAP application must be made to continue beyond 9 cycles.

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. 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 2 nd delay, use G-CSF or dose reduction.

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.

- 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/m² or switch PACLitaxel to DOCEtaxel (GOENDCAD).
- Neuropathy:** Dose modification or discontinuation may be required (see BC Cancer Drug Manual).
- 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.

4. **Hepatic dysfunction:** reduce PACLitaxel dose:

ALT		Total bilirubin	Dose (mg/m ²)
less than 10 x ULN	and	less than or equal to 1.25 x ULN	175
less than 10 x ULN	and	1.26-2 x ULN	135
less than 10 x ULN	and	2.01-5 x ULN	90
greater than or equal to 10 x ULN	and/or	greater than 5 x ULN	not recommended

ULN = upper limit of normal

PRECAUTIONS:

1. **Hypersensitivity:** Reactions 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 diphenhydrAMINE 25 to 50 mg and hydrocortisone IV 100 mg after recovery of symptoms resume PACLitaxel infusion at 20 mL/hr for 5 minutes, 30 mL/hr for 5 minutes, 40 mL/hr for 5 minutes, then 60 mL/hr 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 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. Paul Hoskins or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.