BC Cancer Protocol for Primary Treatment of Advanced/Recurrent Non-Small Cell Cancer of the Cervix with CARBOplatin and PACLitaxel in Ambulatory Care Settings

Protocol Code	*GOCXCAT*
Tumour Group	*Gynecology*
Contact Physician	*Dr. Aalok Kumar*

ELIGIBILITY:
- non-small cell cancer of the cervix, vulva, or vagina (squamous, adenocarcinoma or mixed)
- recurrent or IIIb, IVa or IVb
- ineligible for GOCXCRT
- Note: The GOCXCAT and GOCXCAD regimens are alternatives. The clinician's selection should be based upon the patient's circumstances. The docetaxel-containing combination produces more neutropenic complications, diarrhea, edema and hypersensitivity; the PACLitaxel-containing combination produces more peripheral neurotoxicity, arthralgia, myalgia, and alopecia. Physician may choose between PACLitaxel (GOCXCAT) and docetaxel (GOCXCAD). A maximum of 6 cycles* of taxane treatment will be reimbursed for each line of therapy. However, a patient who had previously responded to 6 cycles* of say, a PACLitaxel-based regimen may be retreated with another 6 cycles* of a taxane-based regimen.

  * may extend to 9 cycles if the patient has not achieved a complete response but is continuing to improve

EXCLUSIONS:
- any small cell component
- creatinine greater than 150 micromol/L
- neutrophils less than 1 x 10^9/L
- performance status greater than ECOG2

RELATIVE CONTRAINDICATIONS:
- pre-existing motor or sensory neuropathy greater than grade 2

TESTS:
- Baseline: CBC & diff, platelets, creatinine, tumor marker (CA 125, CA 15-3, CA 19-9), ALT, Alk Phos, bilirubin, chest X-ray, abdominopelvic imaging, camera nuclear renogram for GFR (if available). If clinically indicated: GGT.
- Day 14 (and Day 21 if using 28-day interval) after first cycle (and in subsequent cycle if dose modification made): CBC & diff; once nadir pattern established, check CBC & diff at that point only
- Before each treatment: CBC & diff, creatinine, any initially elevated tumor marker
  - If clinically indicated: bilirubin, ALT, Alk Phos, LDH, GGT, 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)
- Antiemetic protocol for highly emetogenic chemotherapy protocols (see SCNAUSEA)

TREATMENT (give PACLitaxel first):

Drug	Starting Dose	BC Cancer Administration Guideline
PACLitaxel	175 mg/m^2 (or conservative dosing of 155 mg/ m^2 or 135 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

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

** Conservative dosing may be considered in the following cases: 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.

Measured GFR (e.g. nuclear renogram) is preferred whenever feasible, *particularly* in circumstances of co-morbidity that could affect renal function (third-space fluid accumulations, hypoproteinemia, potentially inadequate fluid intake, 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

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

Note: The *same* method of estimation should be used throughout the treatment course (i.e. if lab reported GFR was used initially, this should be used for dosing in all subsequent cycles and not the Cockcroft-Gault estimate).

Repeat every 21 or 28 days up to a maximum of 6 cycles. May extend to 9 cycles if the patient has not achieved a complete response but is continuing to respond.

DOSE MODIFICATIONS:

1. **Hematological**:

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
less than 1.0	or	less than 100	delay until recovery

b) at nadir:

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 or equal to 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 or equal to 75	100%	80%
Febrile neutropenia at any time			80%	80%

2. **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 135 mg/m^2.
3. **Neuropathy**: Dose modification or discontinuation may be required (see BC Cancer Drug Manual).
4. **Renal dysfunction**: If significant increase (greater than 20%) in creatinine, repeat nuclear renogram (if available) and recalculate CARBOplatin dose using new GFR.
5. **Hepatic dysfunction**: Dose reduction may be required for PACLitaxel (see BC Cancer Drug Manual)

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 IV 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
severe symptoms (i.e. *one* or more of respiratory distress requiring treatment, generalized 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.

Call Dr. Aalok Kumar or tumour group delegate at (604) 930-2098 or 1-800-523-2885 with any problems or questions regarding this treatment program.

Reference[1,2]:

1. Vasey PA. Role of docetaxel in the treatment of newly diagnosed advanced ovarian cancer. J Clin Oncol 2003;21(90100):136s-44s.
2. Moore DH, McQuellon RP, Blessing JA, et al. A randomized phase III study of cisplatin versus cisplatin plus paclitaxel in stage IVB, recurrent or persistent squamous cell carcinoma of the cervix: a Gynecologic Oncology Group Study. Proc Am Soc Clin Oncol 2001;20:(abstract 801).
3. Benedetti Panici P, Bellati F, Plotti F, et al. Neoadjuvant chemotherapy followed by radical surgery in patients affected by vaginal carcinoma. Gynecol Oncol. 2008;111(2):307-311.
4. Raspagliesi F, Zanaboni F, Martinelli F, Scasso S, Laufer J, Ditto A. Role of paclitaxel and cisplatin as the neoadjuvant treatment for locally advanced squamous cell carcinoma of the vulva. J Gynecol Oncol. 2014;25(1):22-29.