BC Cancer Protocol Summary for the Neoadjuvant or Adjuvant Treatment of Endometrial Cancer using CARBOplatin and PACLitaxel

Tumour Group:	*Gynecology*
Protocol Code:	*GOENDAJCAT*
Contact Physician:	*Dr. Yvette Drew*

ELIGIBILITY:

Patients must have endometrial cancer and meet one of the following criteria:

- **Requiring adjuvant chemotherapy for** International Federation of Gynecology and Obstetrics (FIGO):
  - Stage IA (with evidence of myometrial invasion) to stage IVA ***AND*** p53 abnormal sub-type (p53abn)†, ANY histologies*
  - Stage III or IVA any molecular sub-type†, ANY histologies*
  - Stage IA (with evidence of myometrial invasion) to stage IVA molecular sub-type: No specific molecular profile (NSMP) with non-endometrioid histology
  - Stage Ib to II NSMP sub-type with endometrioid histology AND at least one of the following adverse features: grade 3, extensive lymphovascular invasion, deep myometrial invasion.
- **Requiring neoadjuvant chemotherapy for** any molecular sub-type and any histology* that is deemed not suitable for upfront surgery (it is strongly recommended that these patient's management should be discussed at provincial gynecological cancer conference)

** Mixed histologies of any component, other than those listed in Exclusions below*

†The 4 Molecular subtypes for Endometrial Cancer are detailed below and the specific definition of each sub-type is defined in the Cancer Management Manual (please refer to this if needed)
1. POLE mutant (POLEmut)
2. p53 abnormal (p53abn)
3. Mismatch Repair Deficient (MMRd)
4. No specific molecular profile (NSMP)
If the Endometrial cancer is positive for more than one molecular sub-type (multiple classifier):
- *p53abn and POLEmut and/or MMRd: treat as POLEmut*
- *p53abn and MMRd: treat as MMRd*

EXCLUSIONS

Patients must not have:

- Uterine sarcoma or small cell/neuroendocrine carcinoma,
- AST and/or ALT greater than 10 times the Upper Limit of Normal (ULN), or
- Total bilirubin greater than 5 x ULN

CAUTIONS

- Pre-existing motor or sensory neuropathy greater than grade 2
- Performance status greater than ECOG 2

TESTS

- Baseline: CBC & Diff, creatinine, total bilirubin, ALT, alkaline phosphatase
- If clinically indicated at baseline: CA 125, CA 15-3, CA 19-9, CEA
- Before each treatment: CBC & Diff, creatinine, total bilirubin, ALT, alkaline phosphatase
- If clinically indicated before each treatment: CA 125, CA 15-3, CA 19-9, CEA

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:

Drug	Starting Dose	BC Cancer Administration Guideline
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 5 or 6** x (GFR + 25)	IV in 100 to 250 mL NS over 30 minutes

* Conservative dosing (i.e., 155 mg/m^2 or 135 mg/m^2) with escalation up to 175 mg/m^2 if tolerated may be considered in the following cases: ECOG greater than or equal to 2, existing or potential myelosuppression; existing or potential arthralgia and myalgia; prior radiotherapy, particularly to the pelvic region; reduced bone marrow capacity.
** use AUC of 6; if extensive prior radiation therapy, use AUC of 5

Repeat every 21 days for up to 6 cycles. Chemotherapy may be given before and after radiotherapy (sandwich approach).

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**:

   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	proceed at same doses
less than 1.0	or	less than 100	Delay until recovery. If 2nd delay, use filgrastim (G-CSF) or dose reduction.

*Note: If dose has been reduced, dose increase/re-escalation is not recommended.

2. **Arthralgia and/or myalgia**: If arthralgia and/or myalgia from PACLitaxel 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/m^2 or switch PACLitaxel to DOCEtaxel (GOENDCAD).

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

4. **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.

5. **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 Protocol Summary for Management of Infusion-Related Reactions to Chemotherapeutic Agents – SCDRUGRX

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 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, 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 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. Yvette Drew or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. de Boer SM, Powell ME, Mileshkin L, et al. PORTEC Study Group. Adjuvant chemoradiotherapy versus radiotherapy alone in women with high-risk endometrial cancer (PORTEC-3): patterns of recurrence and post-hoc survival analysis of a randomised phase 3 trial. Lancet Oncol. 2019 Sep;20(9):1273-1285
2. León-Castillo A, de Boer SM, Powell ME, et al. TransPORTEC consortium. Molecular Classification of the PORTEC-3 Trial for High-Risk Endometrial Cancer: Impact on Prognosis and Benefit From Adjuvant Therapy. J Clin Oncol. 2020 Oct 10;38(29):3388-3397.
3. BC Cancer. Cancer Management Guidelines: Endometrium. Vancouver, Canada: BC Cancer; 2023