BC Cancer Protocol Summary for Alternative Treatment of Gynecological Malignancies using Bevacizumab, CISplatin and PACLitaxel

Protocol Code:	*GOCISPBEV*
Tumour Group:	*Gynecologic Oncology*
Contact Physician:	*Dr. Aalok Kumar*

ELIGIBILITY:
Patients must have:
- Previous non-life threatening infusion-related reactions to CARBOplatin, and
- Been treated with and eligible for the following protocols:
  - GOOVCATB
  - GOCXCATB, GOCXCATBP

EXCLUSIONS:
Patients must not have:
- Creatinine clearance less than 45 mL/min at baseline
- Major surgery within 4 weeks
- Uncontrolled hypertension
- Bleeding diathesis
- History of bowel obstruction or unresolved bowel obstruction *(see note in Precautions section, below)*

TESTS:
- **Baseline:** CBC & diff, platelets, creatinine, sodium, potassium, magnesium, tumour marker (CA 125, CA 15-3, CA 19-9), alkaline phosphatase, ALT, bilirubin, GGT (if indicated), dipstick or laboratory urinalysis for protein, blood pressure (BP) measurement
- **Before each treatment:** CBC & diff, platelets, creatinine, dipstick or laboratory urinalysis for protein, blood pressure measurement, any initially elevated tumour marker
  - If clinically indicated: bilirubin, ALT, alkaline phosphatase, sodium, potassium, magnesium
- 24 hour urine for protein if occurrence of proteinuria (dipstick urinalysis shows 2+ or 3+ or laboratory urinalysis for protein is greater than or equal to 1 g/L)
- Blood pressure measurement to be taken pre- and post-bevacizumab in first three cycles, and then pre-dose only subsequently
- For patients on warfarin, weekly INR until stable warfarin dose established, then INR at the beginning of each cycle

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	Dose	BC Cancer Administration Guideline
(Administer PACLitaxel first)		
PACLitaxel	175 mg/m^2 * on day 1	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)
CISplatin	75 mg/m^2/day on day 1	Prehydrate with 1000 mL NS over 1 hour, then CISplatin IV in 500 mL NS with potassium chloride 20 mEq, magnesium sulfate 1 g, mannitol 30 g over 1 hour
bevacizumab	For ovarian cancer: 7.5 mg/kg** **OR** For cervical cancer: 15 mg/kg**	IV in 100 mL NS over 15 minutes to 1 hour*** IV in 100 to 250 mL NS over 30 minutes to 1 hour***

Repeat every 21 days to complete total number of cycles in original bevacizumab, CARBOplatin and PACLitaxel protocol. For maintenance bevacizumab in ovarian cancer, continue treatment using GOOVCATB.

* 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.

** bevacizumab dose does not need to be recalculated after cycle 1 even if weight changes

*** first infusion over 60 minutes; subsequent infusions over 15 or 30 minutes depending on the dose, as above. Observe for fever, chills, rash, pruritus, urticaria, or angioedema and stop infusion and contact the physician if any of these occur. Infusion reactions should be treated according to severity. If the bevacizumab infusion is restarted, then it should be given at an initial rate to complete after 60 minutes or longer.

If acute hypertension (increase in BP measurement of greater than 20 mmHg diastolic or greater than 150/100 if previously within normal limits) occurs during bevacizumab infusion – stop treatment. Resume at half the original rate of infusion if blood pressure has returned to pretreatment range within one hour. If blood pressure does not return to pretreatment range within one hour – hold bevacizumab; subsequent infusions of bevacizumab should be given

over 3 hours. Acute hypertension that is symptomatic (e.g., onset of headaches or change in level of consciousness) or BP measurement of greater than 180/110 that does not improve within one hour of stopping bevacizumab is an urgent situation that requires treatment.

DOSE MODIFICATIONS:

1. **Hematological:**

ANC (x 10^9/L)		**Platelets (x 10^9/L)**	**Doses (PACLitaxel and CISplatin)**
greater than or equal to 1.0	and	greater than or equal to 100	100%
less than 1.0	or	less than 100	Delay

2. **Renal Dysfunction:**

Creatinine Clearance (mL/min)	**CISplatin dose**
greater than or equal to 60	75 mg/m^2
45 to 59	35 mg/m^2
less than 45	**Delay**

3. **Proteinuria:**

There are 3 different measures of proteinuria that may be used to assess the need for modification of bevacizumab therapy – urine dipstick analysis (measured in + values), laboratory urinalysis for protein (measured in g/L) and 24-hour urine collections for protein (measured in g/24 hours)

Urine dipstick analysis or laboratory urinalysis for protein should be performed at baseline and then prior to each cycle:

Degree of Proteinuria	
Neg or 1+ dipstick or less than 1 g/L laboratory urinalysis for protein	Administer Bevacizumab dose as scheduled
2+ or 3+ dipstick or greater than or equal to 1 g/L laboratory urinalysis for protein	Administer Bevacizumab dose as scheduled. Collect 24-hour urine for determination of total protein within 3 days before the next scheduled bevacizumab administration. ***Adjust Bevacizumab treatment based on the table below.***
If urine dipstick shows 4+ at baseline or during treatment	Withhold Bevacizumab and proceed with 24 hour urine collection

24-Hour Urine Total Protein (g/24 hours)	Bevacizumab Dose
less than or equal to 2	100%
greater than 2 to 4	Hold dose and recheck 24-hour urine every 2 weeks. When less than or equal to 2 g/24 hour, resume therapy at standard dosing
greater than 4	Withhold/Discontinue bevacizumab

4. **Hypertension:**

Blood Pressure (mmHg)	Bevacizumab Dose
less than or equal to 150/100	100%
greater than 150/100 asymptomatic	100% Notify physician and start or adjust antihypertensive therapy*
hypertensive crisis	discontinue therapy

- Antihypertensive therapy may include hydrochlorthiazide 12.5 to 25 mg PO once daily, ramipril (ALTACE®) 2.5 to 5 mg PO once daily, or amlodipine (NORVASC®) 5 to 10 mg PO once daily.

****Any patients presenting with chest pain, significant leg swelling, shortness of breath, new severe headaches or new neurologic symptoms, must be re-assessed by a physician before receiving further bevacizumab infusions.***

5. **Hepatic dysfunction**: Dose reduction may be required for PACLitaxel.

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

6. **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/m^2 or switching to an alternate taxane may be considered

7. **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 diphenhydrAMINE 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 may, rarely, cause tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.
3. **Bowel-related toxicities**: Use of bevacizumab carries a risk of bowel perforation and other serious bowel problems. In the AURELIA study, the bowel-related exclusion criteria were: history of bowel obstruction (including subocclusive disease) related to underlying disease, a history of abdominal fistula, GI perforation or intra-abdominal abscess, evidence of rectosigmoid involvement by pelvic examination, bowel involvement on CT imaging, or clinical symptoms of bowel obstruction.
4. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
5. **Renal Toxicity:** Nephrotoxicity is common with CISplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics. Use caution with pre-existing renal dysfunction.
6. **Gastrointestinal perforations and wound dehiscence:** Can be fatal. Typical presentation is reported as abdominal pain. Bevacizumab should be discontinued in patients with gastrointestinal perforation or wound dehiscence.

7. **Hemorrhage:** Bevacizumab has been associated with hemorrhage. Cases of CNS hemorrhage, some with fatal outcome, have been observed. Patients should be monitored for signs and symptoms of CNS bleeding. If Grade 3/4 hemorrhage occurs, discontinue bevacizumab. Patients with significant bleeding diatheses should not receive bevacizumab. Platelet inhibitory medications such as NSAIDS (including ASA at doses greater than 325 mg/day) should be discontinued prior to institution of bevacizumab. COX-2 inhibitors are permissible.
8. **Thrombosis:** A history of arterial thromboembolic events or age greater than 65 years is associated with an increased risk of arterial thromboembolic events with bevacizumab. If Grade 3 thromboembolic event or incidentally discovered pulmonary embolus arises, hold bevacizumab for 2 weeks, then consider resumption of bevacizumab if risks of tumour-related hemorrhage are judged low AND the patient is on a stable dose of anticoagulant. If a second Grade 3 thrombosis occurs, or if a Grade 4 thrombosis occurs, discontinue bevacizumab. Patients on warfarin should have INR checked frequently, at least once every 2-3 weeks, while receiving bevacizumab.
9. **Proteinuria:** Has been seen in all clinical trials with bevacizumab to date and is likely dose-dependent. If proteinuria of greater than or equal to 2 g/24 h persists for more than 3 months, consider further investigations - possibly a renal biopsy.
10. **Hypertension:** Has been seen in all clinical trials with bevacizumab to date and is likely dose-dependent. The most commonly used therapies are calcium channel blockers, ACE inhibitors and diuretics. Blood pressure should be monitored through routine vital signs evaluations. If hypertension is poorly controlled with adequate medication, discontinue bevacizumab.
11. **Reversible Posterior Leukoencephalopathy Syndrome (RPLS):** Rarely, patients may develop seizures, headache, altered mental status, visual disturbances, with or without associated hypertension consistent with RPLS. May be reversible if recognized and treated promptly.
12. **Congestive Heart Failure**: Has been reported in up to 3.5% of patients treated with bevacizumab. Most patients showed improvement in symptoms and/or LVEF following appropriate medical therapy.
13. **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. Aalok Kumar or tumour group delegate at 604-930-2098 or 1-800-523-2885 with any problems or questions regarding this treatment program.

References:

Ozols RF, Bundy BN, Greer BE, et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer: a Gynecologic Oncology Group Study. J Clin Oncol 2003;21:3194-200.