BC Cancer Protocol for Treatment of Platinum Resistant Epithelial Ovarian Cancer with Bevacizumab and DOXOrubicin Pegylated Liposomal

Protocol Code	*GOOVBEVLD*
Tumour Group	*Gynecologic Oncology*
Contact Physician	*Dr. Anna Tinker*

ELIGIBILITY:
- Epithelial ovarian cancer, primary peritoneal, or fallopian tube carcinoma
- Platinum resistant disease (progression within six months of completing a platinum-containing protocol
- Any number of prior lines of treatment

EXCLUSIONS:
- Progressed while being treated on prior bevacizumab therapy
- any small cell component
- neutrophils less than 1 x 10^9/L
- performance status greater than ECOG 3
- major surgery within 4 weeks
- uncontrolled hypertension
- pregnancy or breastfeeding
- bleeding diathesis
- history of bowel obstruction or unresolved bowel obstruction (*see note in Precautions section, below)*

RELATIVE CONTRAINDICATIONS:
- pre-existing motor or sensory neuropathy greater than grade 2
- uncontrolled arterial or venous thromboembolism
- MI or CVA within 4 months
- avoid NSAIDS and ASA if possible
- pre-existing cardiomyopathy or congestive heart failure
- premorbid disease affecting ability to tolerate DOXOrubicin pegylated liposomal
- hepatic dysfunction (*see Dose Modification section, below*)
- at risk of bowel obstruction (*see note in Precautions section, below)*

TESTS:
- Baseline: CBC & diff, platelets, creatinine, ALT, Alk Phos, bilirubin, sodium, potassium, dipstick or laboratory urinalysis for protein, blood pressure (BP) measurement, imaging as appropriate, tumor markers as appropriate. If clinically indicated: GGT.
- Before each cycle, on Day 1: CBC & diff, dipstick or laboratory urinalysis for protein, blood pressure measurement, any initially elevated tumor marker
- If clinically indicated: creatinine, ALT, Alk phos, bilirubin, GGT, LDH, protein level, albumin
- No routine labwork required on Day 15.
- 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-dose 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
- Weight at baseline and every scheduled physician's visit

PREMEDICATIONS:

- Antiemetic protocol for chemotherapy with low emetogenicity (see SCNAUSEA)

TREATMENT: (on Day 1, give DOXOrubicin pegylated liposomal first)

DAY 1			
Drug	**Starting Dose**	**BC Cancer Administration Guideline**	
DOXOrubicin pegylated liposomal	40 mg/m^2	IV in 250 mL D5W (doses greater than or equal to 90 mg should be diluted in 500 mL D5W)	*Initial dose*: at rate of 1 mg/min *Subsequent doses, if no prior infusion reaction*: infuse over 1 hour
bevacizumab	10 mg/kg*	IV in 100 mL** NS over 30 minutes to 1 hour**	

DAY 15		
Drug	**Starting Dose**	**BC Cancer Administration Guideline**
bevacizumab	10 mg/kg*	IV in 100 mL** NS over 30 minutes to 1 hour**

Repeat cycle every 28 days for until disease progression (usual treatment 6 cycles); may continue bevacizumab alone if unacceptable toxicity to DOXOrubicin pegylated liposomal occurs.

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

** first infusion over 60 minutes; subsequent infusions over 30 minutes. 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.

Use only normal saline for line priming and flushing.

DOSE MODIFICATIONS:

1. Hematological:

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
Febrile Neutropenia			reduce DOXOrubicin pegylated liposomal by 10 mg/m2 in subsequent cycles

2. 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 **10 mg/kg**
greater than 4	Withhold/Discontinue bevacizumab

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 hydrochlorothiazide 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.***

3. Hepatic dysfunction:

Total bilirubin (micromol/L)	DOXOrubicin pegylated liposomal dose (mg/m2)
less than 21	40
21 to 50	30
greater than 50	20

4. Stomatitis

Grade	Symptoms	DOXOrubicin pegylated liposomal Dose
1	painless ulcers, erythema, or mild soreness	40 mg/m^2
2	painful erythema, edema or ulcers, but can eat	delay until recovered to Grade 1, then continue at 30 mg/m^2
3	painful erythema, edema or ulcers, and cannot eat	delay until recovered to Grade 1, then continue at 30 mg/m^2; or discontinue treatment
4	requires parenteral or enteral support	discontinue treatment

Note: If delay has been necessary due to stomatitis, change of interval to five weeks is recommended.

5. Palmar Plantar Erythrodysesthesia (PPE) (Hand-Foot Skin Reaction)

Grade	Symptoms	DOXOrubicin liposomal Dose
1	mild erythema, swelling or desquamation not interfering with normal daily activities	if no prior Grade 2 or 3 occurrence, proceed at full dose. if prior Grade 2 or 3 occurrence, delay one week; once recovery evident, continue treatment at 30 mg/m^2
2	erythema, swelling or desquamation interfering with but not precluding normal daily activities; small blisters or ulcerations less than 2 cm in diameter	delay one week; once recovery evident, continue treatment at 30 mg/m^2
3	blistering, ulceration or swelling preventing normal daily activities; cannot wear regular clothing	delay one week, and re-assess; consider dexamethasone 2 mg TID until symptoms resolve; if still Grade 3 after a one week delay, discontinue treatment; if resuming, dose at 30 mg/m^2

Note: If delay has been necessary due to PPE, change of interval to five weeks is recommended.

PRECAUTIONS:

1. **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.
2. **Cardiac Toxicity**: DOXOrubicin is cardiotoxic and must be used with caution, if at all, in patients with severe hypertension or cardiac dysfunction.
3. **Extravasation**: DOXOrubicin pegylated liposomal is considered an irritant. Refer to BC Cancer Extravasation Guidelines.
4. **Acute Infusion Reaction**: may occur with first infusion of DOXOrubicin pegylated liposomal, usually within minutes of starting. Refer to BC Cancer Hypersensitivity Guidelines. *Note: the first step is to stop the infusion*. In subsequent cycles, reactions are rare, but prophylaxis with dexamethasone, diphenhydrAMINE, and famotidine may be used.
5. **Palmar-Plantar Erythrodysesthesia (PPE) (Hand-Foot Skin Reaction)**: See BC Cancer Drug Manual DOXOrubicin pegylated liposomal monograph for suggested strategies for preventing or minimizing PPE. Corticosteroids may reduce the incidence of PPE during treatment.
6. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BC Cancer Febrile Neutropenia Guidelines.
7. **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.
8. **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.
9. **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.

10. **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.
11. **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.
12. **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.
13. **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.

Call Dr. Anna Tinker or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References

1. Pujade-Lauraine E, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: the AURELIA open-label randomized phase III trial. *J Clin Oncol 2014;* 32(13):1302-8.