BC Cancer Protocol Summary for Treatment of Epithelial Ovarian Cancer Relapsing after Primary Treatment using DOXOrubicin Pegylated Liposomal and CARBOplatin

Protocol Code:	*GOOVPLDC*
Tumour Group:	*Gynecologic Oncology*
Contact Physician:	*Dr. Paul Hoskins*

PREFACE:

- In platinum sensitive disease: patients should be considered for doublet therapy consisting of CARBOplatin plus either a taxane, gemcitabine, or DOXOrubicin pegylated liposomal (e.g., GOOVCATR, GOOVCAD, GOOVCAG, GOOVPLDC)
- In platinum resistant disease (i.e., cancer progresses within four months of completing a platinum-containing treatment protocol): patients will ideally receive single agent CARBOplatin, as it is the least toxic and most convenient choice of the equally efficacious agents available (i.e., GOOVCARB)
- In platinum refractory disease (i.e., cancer progresses while being treated with a platinum) choose between available agents based upon toxicity profile and convenience of dosing regimen. Options include: GOOVTOP, GOOVLDOX, GOOVGEM, GOOVETO, GOOVVIN, GOOVTAX3, GOOVDOC. If gemcitabine (GOOVGEM), topotecan (GOOVTOP) or DOXOrubicin pegylated liposomal (GOOVLDOX) is used, only one of these options will be reimbursed in any one patient. Subsequently, if a patient is thought likely to benefit from one of the other two, a request should be submitted to the BC Cancer Compassionate Access Program (CAP).
- Patients who will not benefit from further therapy after second or subsequent rounds of chemotherapy can be identified by the following formula: "day 1 of treatment N to day of progression on treatment N+1 is less than or equal to 6 months." They should be offered symptomatic management or investigational protocols.

ELIGIBILITY:

- epithelial ovarian cancer, primary peritoneal, or fallopian tube carcinoma relapsing after remission of at least four months' duration in response to primary treatment with CARBOplatin in combination with paclitaxel, docetaxel, or gemcitabine

EXCLUSIONS:

- performance status ECOG 3 or worse
- gynecologic tumours of other origin or histology
- brain metastases as sole site of relapse
- pre-existing cardiomyopathy or congestive heart failure (relative contraindication)
- hepatic dysfunction (see DOSE MODIFICATIONS, below)

TESTS:

- Baseline: CBC & diff, platelets, creatinine, tumour marker (CA 125, CA 15-3, CA 19-9), bilirubin, ALT, Alk Phos. If clinically indicated: cardiac function tests (echocardiogram or MUGA scan).
- Day 14 and 21 after first cycle (and in subsequent cycle if dose modification made): CBC & diff, platelets.
- Before each treatment: CBC & diff, creatinine, platelets, any initially elevated tumour marker
- If clinically indicated: CEA, ALT, Alk Phos, bilirubin, LDH, albumin, protein level, GGT

PREMEDICATIONS:

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

TREATMENT: [1]

Drug	Dose	BC Cancer Administration Guideline	
DOXOrubicin pegylated liposomal	30 mg/m^2	IV in 250 mL D5W	*Initial dose*: at rate of 1 mg/min *Subsequent doses, if no prior infusion reaction*: infuse over 1 hour
CARBOplatin	AUC* x (GFR +25)	IV in 100 to 250 mL NS	30 minute infusion duration

* use AUC of 5; if extensive prior radiation therapy, use AUC of 4

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, etc.).

The lab reported GFR (MDRD formula) may be used as an alternative to the Cockcroft-Gault estimate of GFR.

Cockcroft-Gault Formula

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

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.

Recalculate GFR if creatinine increases by greater than 20% or rises above the upper limit of normal.

Repeat every 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. Hematology

a) Cycle 1:

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	100%
less than 1.0	or	less than 100	consider a non-myelosuppressive, single-agent protocol

b) Cycles 2-6:

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	Cycle 2: treat as per nadir Cycle 3-6: use Cycle 2 dose unless additional non-hematologic toxicity in prior cycle
less than 1.0	or	less than 100	delay until recovery

c) At nadir:

ANC (x 10^9/L)		Platelets (x 10^9/L)	DOXOrubicin pegylated liposomal	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	25 mg/m^2	80%
less than 0.5	and	greater than or equal to 75	25 mg/m^2	100%
greater than or equal to 0.5	and	less than 75	100%	80%
febrile neutropenia at any time			25 mg/m^2	80%

2. Hepatic dysfunction

Total bilirubin (micromol/L)	DOXOrubicin pegylated liposomal Dose (mg/m^2)
less than 50	30
greater than 50	20

3. Stomatitis

Grade	Symptoms	Dose
1	painless ulcers, erythema, or mild soreness	30 mg/m^2
2	painful erythema, edema or ulcers, but can eat	delay until recovered to Grade 1, then continue at 20 mg/m^2
3	painful erythema, edema or ulcers, and cannot eat	delay until recovered to Grade 1, then continue at 20 mg/m^2; or discontinue DOXOrubicin pegylated liposomal
4	requires parenteral or enteral support	discontinue DOXOrubicin pegylated liposomal

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

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

Grade	Symptoms	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 20 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 20 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 20 mg/m^2

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

5. **Renal dysfunction:** If significant increase (greater than 20%) in creatinine, recalculate CARBOplatin dose using new GFR, determined using the same method as in the original calculation.
6. **Other Grade 3 or 4 Toxicities**
   Reduce PLD dose by 10 mg/m^2.

PRECAUTIONS:

1. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BC Cancer Febrile Neutropenia Guidelines.
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**: Pegylated liposomal DOXOrubicin is considered an irritant. Refer to BC Cancer Extravasation Guidelines.
4. **Acute Infusion Reaction**: may occur with first infusion, 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 pegylated liposomal DOXOrubicin monograph for suggested strategies for preventing or minimizing PPE. Corticosteroids may reduce the incidence of PPE during treatment.[2]

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.

REFERENCES:

1. Pujade-Lauraine E, et al. A randomized, phase III study of carboplatin and pegylated liposomal doxorubicin versus carboplatin and paclitaxel in relapsed platinum-sensitive ovarian cancer (OC): CALYPSO study of the Gynecologic Cancer Intergroup (GCIG). J Clin Oncol 2009;27:18s: abstr LBA5509.
2. Alberts DS, et al. Efficacy and safety of liposomal anthracyclines in phase I/II clinical trials. Semin Oncol 2004;32(Suppl 13):53-90.