BC Cancer Protocol Summary for First Line Treatment of Epithelial Ovarian Cancer using DOXOrubicin Pegylated Liposomal and CARBOplatin

Protocol Code:	*GOOVFPLDC*
Tumour Group:	*Gynecologic Oncology*
Contact Physician:	*Dr. Jenny Ko*

ELIGIBILITY:

- First line treatment of invasive epithelial ovarian, fallopian tube, or primary peritoneal cancer
- Treatment with paclitaxel-carboplatin combination is not appropriate due to anaphylaxis to paclitaxel, neuropathy, other intolerable side effects related to paclitaxel, or intolerance/relative contraindication to high dose steroids

EXCLUSIONS:

- performance status ECOG 3 or worse
- 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: bilirubin, Alk Phos, GGT, ALT, LDH, protein level, albumin

PREMEDICATIONS:

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

TREATMENT:

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

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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

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

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 of first line platinum-based chemotherapy total. May extend to 9 cycles if the patient has not achieved a complete response but is continuing to respond.

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%

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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.

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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 DOXOrubicin pegylated liposomal 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. Jenny Ko 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.

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