

BCCA Protocol Summary for Second Line Treatment Using Pegylated Liposomal DOXOrubicin (PLD) and CARBOplatin for Epithelial Ovarian Cancer Relapsing after Primary Treatment

Protocol Code:	GOOVPLDC
Tumour Group:	Gynecologic Oncology
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PREFACE:

- In platinum sensitive disease: patients will ideally receive doublet therapy consisting of CARBOplatin plus either a taxane, gemcitabine, or pegylated liposomal DOXOrubicin (e.g., GOOVCA^{TR}, GOOVCA^{DR}, GOOVCA^G, UGOOVPLDC)
- 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., GOOVCA^{RB})
- 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: GOOVTO^P, GOOVLDO^X, GOOVGE^M, GOOVET^O, GOOVVI^N, GOOVTAX³, GOOVDO^C. If gemcitabine (GOOVGE^M), topotecan (GOOVTO^P) or pegylated liposomal DOXOrubicin (GOOVLDO^X) 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 BCCA 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 relapsing [after remission of at least four months' duration](#) in response to primary treatment with CARBOplatin in combination with paclitaxel, docetaxel, or gemcitabine
- A “Class II Drug Registration Form” must be submitted at the time of initiation of treatment (included in BCCA PPPO; separate submission not needed if PPPO used)

EXCLUSIONS:

- performance status ECOG 3 or better
- 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), liver function tests (LFTs) (AST, bilirubin, alkaline phosphatase). 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, platelets, any initially elevated tumour marker, LFTs (if clinically indicated), creatinine (if clinically indicated)

PREMEDICATIONS:

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

TREATMENT: ¹

Drug	Dose	BCCA Administration Guideline	
DOXOrubicin liposomal (PLD)	30 mg/m ²	IV in 250 mL D5W (doses greater than or equal 90 mg should be diluted in 500 mL D5W)	<i>Initial dose:</i> at rate of 1mg/min <i>Subsequent doses, if no prior infusion reaction:</i> 1 hour infusion duration
CARBOplatin	Dose = AUC* x (GFR +25)	IV in 250 mL D5W	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

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

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	and	greater than or equal to 100	100%
less than 1	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	and	greater than or equal to 100	<u>Cycle 2:</u> treat as per nadir <u>Cycle 3-6:</u> use Cycle 2 dose unless additional non-hematologic toxicity in prior cycle
less than 1	or	less than 100	delay until recovery

c) At nadir:

ANC (x 10 ⁹ /L)		Platelets (x 10 ⁹ /L)	PLD	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)	PLD 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 PLD
4	requires parenteral or enteral support	discontinue PLD

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/m².

PRECAUTIONS:

- 1. Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BCCA 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 BCCA Extravasation Guidelines.
- 4. Acute Infusion Reaction:** may occur with first infusion, usually within minutes of starting. Refer to BCCA Hypersensitivity Guidelines. *Note: the first step is to stop the infusion.* In subsequent cycles, reactions are rare, but prophylaxis with dexamethasone, diphenhydramine, and ranitidine may be used.
- 5. Palmar-Plantar Erythrodysesthesia (PPE) (Hand-Foot Skin Reaction):** See BCCA 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.

Date activated: 01 November 2009

Date revised: 01 Sep 2011 (*Eligibility clarified*)

REFERENCES:

- 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.
- Alberts DS, et al. Efficacy and safety of liposomal anthracyclines in phase I/II clinical trials. *Semin Oncol* 2004;32(Suppl 13):53-90.