BC Cancer Protocol Summary for Therapy for High Risk Gestational Trophoblastic Neoplasia (GTN) using Etoposide, Methotrexate, Leucovorin (Folinic Acid), DACTINomycin, Cyclophosphamide and vinCRIStine

Protocol Code	*GOTDEMACO*
Tumour Group	*Gynecology*
Contact Physician	*Dr. Anna Tinker*

ELIGIBILITY:

- **High risk Gestational Trophoblastic Neoplasm (GTN)** as determined using the modified World Health Organization (WHO) Prognostic Scoring System as adapted by the International Federation of Gynecology and Obstetrics (FIGO).
    - Patients with a Risk Score of ≥7 are considered high risk
    - The risk score is calculated as follows:

Risk Factor	**SCORE**			
	0	**1**	**2**	**4**
Age (years)	<40	>40		
Antecedent pregnancy	Mole	Abortion	Term	
Interval (months)*	<4	4-6	7-12	>12
Pre-treatment serum beta hCG (mIU/mL)**	$<10^3$	10^3-10^4	10^4-10^5	$>10^5$
Sites of metastases	Lung	Spleen and kidney	GI tract	Brain and liver
Number of metastases	-	1-4	5-8	>8
Largest tumour size (including uterus) (cm)		3-4	5	
Prior failed chemotherapy	-	-	Single drug	≥2 drugs

** interval (in months) between end of antecedent pregnancy and start of chemotherapy*
*** use the immediate pre-treatment beta hCG - not the peak hCG during pregnancy or prior to uterine evacuation*

- **<u>Contact BC Cancer for recommendations if more than 1 year post normal pregnancy and not currently pregnant</u>**

EXCLUSIONS:

- Low to moderate risk GTN (prognostic score less than seven). These patients should be treated on the BC Cancer low risk protocol GOTDLRA (risk score of 0 to 4) and moderate risk protocol GOTDMR (risk score of 5 or 6), respectively.

TESTS:

- If the GTN was not confirmed histopathologically (e.g. only products of conception were identified at the time of the dilation and curettage) then a pelvic ultrasound within 5-7 days of treatment initiation is required to rule out a previously undetected viable intra-uterine pregnancy.
- **Baseline:** CBC & diff, beta hCG tumour marker, sodium, potassium, creatinine, Alk Phos, ALT, GGT, LDH, Bilirubin, chest X-ray, CT of brain, CT abdomen and pelvis
- If the beta hCG tumour marker is > 100,000 mIU/mL check TSH
- **Before each treatment (Day 1):** CBC & diff, beta hCG tumour marker, electrolytes panel, creatinine, Alk Phos, ALT, GGT, LDH, Bilirubin
- **Before each treatment (Day 8):** CBC & diff, creatinine (results not required to proceed with treatment)

PREMEDICATIONS:

Antiemetic protocol for high-moderate emetogenic chemotherapy (see protocol SCNAUSEA).

If history of etoposide hypersensitivity:

- hydrocortisone 100 mg IV prior to etoposide
- diphenhydrAMINE 50 mg IV prior to etoposide

PREHYDRATION:

Not routinely necessary.

TREATMENT:

Day	Drug	Dose	BC Cancer Administration Guideline
1	etoposide	100 mg/m^2	IV in NS 250 to 1000 mL over 45 minutes to 1 hour 30 minutes (Use non-DEHP bag and tubing with 0.2 micron in-line filter)
	DACTINomycin	0.5 mg	IV push
	methotrexate	300 mg/m^2	IV in NS 250 to 500 mL over 12 hours
2	etoposide	100 mg/m^2	IV in NS 250 to 1000 mL over 45 minutes to 1 hour 30 minutes (Use non-DEHP bag and tubing with 0.2 micron in-line filter)
	DACTINomycin	0.5 mg	IV push
	leucovorin (folinic acid)	15 mg q12h for 4 doses	**PO** **Start 24 hours after start of Day 1 methotrexate infusion**
8	vinCRIStine	0.8 mg/m^2	IV in NS 50 mL over 10 minutes
	cyclophosphamide	600 mg/m^2	IV in NS 100 to 250 mL over 30 minutes

Repeat every 14 days ***until 3 cycles post fall of beta hCG tumour marker to below 5 mIU/mL***

POST-HYDRATION:

- 1000 mL D5W-1/2NS with 20 mEq Potassium Chloride and 100 mEq Sodium Bicarbonate/L at 200 mL/h IV for 20 hours after the end of the methotrexate infusion. Hydration infusion may be interrupted for administration of Day 2 chemotherapy.

DOSE MODIFICATIONS:

1. **Hematological**
   On treatment day:

ANC ($x10^9$/L)	Platelets ($x10^9$/L)	etoposide dose	DACTINomycin dose	methotrexate dose	cyclophosphamide dose
greater than or equal to 1.0	greater than or equal to 100	100%	100%	100%	100%
0.7 to less than 1.0	75 to less than100	100%	66%	100%	100%
less than 0.7*	less than 75	50 mg PO x 7 days only	Hold until next cycle, then 66%	100%	100%

*unless monocytes greater than 10% of total WBC, then give 66% of DACTINomycin dose

2. **Renal dysfunction:** Dose modification of methotrexate may be required. Refer to BC Cancer Drug Manual.
3. **Neurotoxicity:** vinCRIStine only:

Toxicity	Dose Modification
Dysesthesias, areflexia only	100%
Abnormal buttoning, writing	67%
Motor neuropathy, moderate	50%
Motor neuropathy, severe	omit

4. **Hepatic dysfunction**: Dose modification of all drugs may be required. Refer to BC Cancer Drug Manual.
5. **Third space fluids** (ascites, pleural effusions): See Precaution statement, below.
6. **Stomatitis:** decrease DACTINomycin to 0.4 mg

PRECAUTIONS:

1. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively. Filgrastim (G-CSF) may be needed to maintain white count. Increased frequency and duration of leucovorin rescue may be considered.
2. **Extravasation**: DACTINomycin and vinCRIStine causes pain and tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.
3. **Renal Toxicity**: Nephrotoxicity is possible with high (greater than 1 g/m^2) doses of methotrexate. The risk of renal failure can be minimised by brisk diuresis and alkalinization of the urine with sodium bicarbonate. Encourage oral hydration.
4. **Third Space Fluids**: Evacuation of third space fluids e.g., ascites, pleural effusions, prior to treatment is recommended. Consider methotrexate drug level monitoring and dose reduction if drainage cannot be achieved.

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. Alazzam M1, Tidy J, Osborne R, et al. Chemotherapy for resistant or recurrent gestational trophoblastic neoplasia. Cochrane Database Syst Rev 2016 Jan 13;1:CD008891. 10.1002/14651858.CD008891.pub3.
2. Alifrangis C, Agarwal R, Short D, et al. EMA/CO for high-risk gestational trophoblastic neoplasia: good outcomes with induction low-dose etoposide-cisplatin and genetic analysis. J Clin Oncol 2013;31(2):280-6.
3. Turan T, Karacay O, Tulunay G, et al. Results with EMA/CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine) chemotherapy in gestational trophoblastic neoplasia. Int J Gynecol Cancer 2006;16(3):1432-8.