



Provincial Gestational Trophoblastic Neoplasia Cancer Treatment Guidelines

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Clinical practice guidelines have been developed after multi-disciplinary consensus based on best available literature. As the name suggests, these are to be used as a guide only. These guidelines do not replace physician judgment which is based on multiple factors including, but not limited to, the clinical and social scenario, comorbidities, performance status, age, available resources and funding considerations. The Saskatchewan Cancer Agency disclaims all liability for the use of guidelines except as expressly permitted by the Agency. No portion of these guidelines may be copied, displayed for redistribution to third parties for commercial purposes or any non-permitted use without the prior written permission from the Agency.

Recommendations for drug treatment presented in the Agency's guidelines for a cancer site may not reflect provincial cancer drug funding. Please refer to the current Saskatchewan Cancer Agency drug formulary at www.saskcancer.ca for information on cancer drug listing and funding.

Benefits and risk of the proposed treatment should be discussed with patient.

Participating in clinical trials is encouraged when available. Involvement of a multidisciplinary team is strongly recommended.

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1) **Background and Epidemiology:**

Gestational trophoblastic disease (GTD) is spectrum of clinical and histologic entities arising from the human placenta (an aberrant fertilization) and it encompasses non-invasive (complete and partial Hydatidiform Mole), and invasive (Persistent Invasive Mole, Gestational Choriocarcinoma, Placental Site Tumor, and a rare type Epithelioid trophoblastic tumor).^{1, 2} The incidence of molar pregnancy is North America 0.6 to 1.1 /10000, and in USA 1 in1500, Asia and Latin America 1-12/500, and1 in 500 in India. The choriocarcinoma is quite rare and its incidence is 1 in 20,000 to 40,000.^{1, 3}

Malignant gestational trophoblastic disease (GTN) denotes ability for local invasion and / or metastasis and it includes (invasive mole, gestational choriocarcinoma, placental site trophoblastic tumors and epithelioid trophoblastic tumor.

Approximately 20% (19%) of complete moles develop invasive mole and require chemotherapy, and 5% of invasive mole metastasize. About 2 to 4% (<5%) of partial moles develop invasive mole and require treatment.^{1, 4, 5} Metastasis occurs in GTN most common site being lung (80%) followed by vagina.⁶ When detected and treated early cure rate of GTN can approach 90%.^{7, 8}

Placenta site trophoblastic tumors (PSTT) are derived from the intermediate trophoblast and produce HPL and is usually characterized by low levels of β -hCG and tumor burden does not correlate with serum beta-hCG level. PSTT usually presents as vaginal bleeding following delivery and are relatively unresponsive to chemotherapy. Treatment of choice for disease limited to the uterus is hysterectomy.

Guideline Questions

- When patients should be referred to a gynecologic oncologist after evacuation of a hydatidiform mole?
- What investigations are indicated for the work-up of gestational trophoblastic neoplasia (GTN)?
- How should GTN be managed?
- How patients with GTN should be followed-up?

2) Guideline Development

Existing guidelines considered for this review include the following: Society of Obstetricians and Gynaecologists of Canada guidelines (2002)¹, National Cancer Institute guidelines (2011)⁹, the American College of Obstetrics and Gynaecology (ACOG) guidelines (2008)¹⁰, the BC Cancer Agency (BCCA) guidelines, (2000)¹¹, and Alberta health Services Guideline, (2012)¹², and Best Clinical Practice Gynaecological Cancer Guidelines, Australia, (2009).¹³

3) Target population:

The recommendations outlined in this guideline will apply to adults over the age of 18 years with gestational trophoblastic neoplasia including Invasive mole, gestational choriocarcinoma, and placental site trophoblastic tumors.

4) Referral:

When to refer to a gynaecologic oncologist following evacuation of H mole (indicates development of GTN):

Any patient post evacuation hydatidiform mole if presents with any of the following should be referred to a gynecologic oncologist:

- An abnormal β -hCG regression pattern (a 10% or greater rise in β -hCG levels over three weeks or a plateauing β -hCG of three stable values over four weeks)
 - A rise in β -hCG following a normal regression pattern
 - A histologic diagnosis of choriocarcinoma, placental site trophoblastic tumor, or epithelioid trophoblastic tumor
 - High hCG levels (greater than 20,000 mIU/mL more than four weeks post-evacuation)
 - Persistently elevated β -hCG levels six months post-evacuation
 - The presence of metastases in addition to abnormal β -hCG levels
- A pathologist with experience in gynecologic pathology should review pathology and for discussion at multi-disciplinary tumor board rounds, which will triage patients for further management.

5) Diagnosis and Work-Up:

Detailed history and physical examination should be done. Physical exam must include speculum and bimanual examination.

The lab investigation should include quantitative serum β -hCG, complete blood count (CBC) with differential, platelet determinations, clotting function tests, liver function tests, and renal function tests

Imaging should be performed to rule out metastases. Chest X ray (A positive chest x-ray is sufficient for the detection of lung metastases), CT scan of the chest only if the chest x-ray is negative, CT scans of the abdomen and pelvis, CT head and MRI of the brain for brain stem and cerebellum is indicated which are often the sites of occult metastasis.

An ultrasound of the liver may detect metastatic disease suspected on CT scan abdomen. In selective cases PET scan may be indicated.

6) Staging and Prognostic Scoring:

Staging of GTN is based on the Federation Internationale de Gynecologie et d'Obstetrique (FIGO) system (2009):

Table 1. FIGO staging

Stage	Extent of disease
Stage I	Disease confined to the uterus
Stage II	GTN extends outside of the uterus, but is limited to the genital structures (i.e., adnexa, vagina, broad ligament)
Stage III	GTN extends to the lungs, with or without known genital tract involvement
Stage IV	All other metastatic sites

Table 2. Modified WHO prognostic scoring for gestational trophoblastic neoplasia (FIGO, 2009)

	0	1	2	4
Age	<40	≥ 40	-	-
Antecedent pregnancy	Mole	Abortion	Term	-
Interval months from index pregnancy	<4	4–6	7-12	>12
Pretreatment serum β -hCG (iu/1)	10^3	$10^3 - 10^4$	$10^4 - 10^5$	$>10^5$
Largest tumor size in cm (including uterus)	<3	3–4	≥ 5 cm	-
Site of metastases	Lung	Spleen, kidney	Gastro-intestinal	Liver, brain
Number of metastases	-	1–4	5-8	>8
Previous failed chemotherapy	-	-	One drug	≥ 2 drugs

WHO Prognostic Scoring Index: Total score for a patient is obtained by adding the individual scores for each prognostic factor. The identification of an individual patient's stage and risk score is expressed by allotting a Roman numeral to the stage and an Arabic numeral to the risk score separated by a colon (e.g. I:1, IV:15, or II:10)¹³

Low-risk: individuals with a score ≤ 6

High-risk: individuals with a score ≥ 7

MANAGEMENT:

Options for the management of GTN are dependent on prognostic scoring (WHO).

GTN is classified in to two categories for treatment and prognosis purposes, as chemotherapy is the mainstay of treatment.

Low Risk:

- β -hCG < 40,000U/L
- Duration from antecedent pregnancy to diagnosis < 4 months
- Metastasis to sites to the lung and the vagina
- No previous chemotherapy

High Risk:

- β -hCG > 40,000U/L
- Duration from antecedent pregnancy to diagnosis > 4 months
- Metastasis to sites other than the lung and the vagina
- An antecedent term gestation
- Previous failed therapy

7) Management of Low risk GTN (Non-metastatic (Stage I) and Low-risk Metastatic (Stages II and III, FIGO score ≤ 6) 12, 13

Preferred regimens include:

Table 3: Actinomycin-D regimen for low-risk gestational trophoblastic neoplasia

Days of cycle	Drug	Dose and route	Frequency
1	Actinomycin-D	1.25 mg/m ² IV	Q 2 weekly

Table 4: Alternate drug regimens for low-risk gestational trophoblastic neoplasia

Days of cycle	Drug	Dose and route	Frequency
1, 3, 5, and 7	Methotrexate	1mg/kg (50 mg/m ²) IM	
2, 4, 6, and 8	Folinic Acid (Leucovorin)	7.5 mg oral 24 hours after methotrexate	Q 2 weekly

Table 5: Alternate drug regimens for low-risk gestational trophoblastic neoplasia

Days of cycle	Drug	Dose and route	Frequency
1	Methotrexate	100 mg/m ² IV	
2	Folinic Acid (Leucovorin)	15 mg oral q 6 hour for four doses 24 hours after methotrexate	Q 2 weekly

It is important treatment to proceed on an accurate schedule and in full dose without delay. Dose reductions/delays promote emergence of drug resistance and will affect prognosis. All treatment should be continued 1-2 cycles beyond negative BhCG.

8) Management of High-risk Metastatic (includes Stages II and III, FIGO score ≥ 7 & Stage IV)^{12, 13}

Principles of Treatment

- Combination multi-agent chemotherapy
- Start chemotherapy ASAP
- Proceed on accurate schedule without delay even if counts are low, G-CSF should be used in combination

Preferred Regimens Include:

EMA/CO multi agent chemotherapy, every 2 weeks for 3 cycles beyond negative β -hCG

Table 6: EMA-CO

Day	Drug	Schedule
1	Etoposide Actinomycin-D Methotrexate	100 mg/m ² IV 0.5 mg IV push 300 mg/m ² IV
2	Etoposide Actinomycin-D Folinic acid (Leucovorin)	100 mg/m ² IV 0.5 mg IV push 15 mg PO, q 12 h for 4 doses
8	Vincristine Cyclophosphamide	0.8–1.0 mg/m ² IV 600 mg/m ² IV

EMA/CE multi agent chemo every 2 weeks for 3 cycles beyond negative β -hCG

Table 7: EMA-CE

Day	Drug	Schedule
1	Etoposide Actinomycin-D Methotrexate	100 mg/m ² IV 0.5 mg IV push 300 mg/m ² IV
2	Etoposide Actinomycin-D Folinic acid (Leucovorin)	100 mg/m ² IV 0.5 mg IV push 15 mg PO, q 12 h for 4 doses
8	Etoposide Cisplatin	100 mg/m ² IV 80 mg/m ² IV

MACE multi agent chemotherapy

- Cisplatin (30 mg/m² IV, days 1-3)
- Etoposide (50 mg PO, days 1-10)
- Actinomycin-D (0.5 mg/m² IV, days 8 & 9)
- Methotrexate (100 mg/m² bolus + 300 mg/m² IV, day 8)
- Folinic acid (Leucovorin) (15 mg PO, q 6 h x 9 doses starting 24 hours after methotrexate bolus)

Other regimens include:

BEP multi agent chemotherapy

- Bleomycin: 30 units per week
- Etoposide: 100 mg/m², days 1-5
- Cisplatin: 20 mg/m², days 1-5

5-FU/actinomycin-D multi agent CTX (as second-line therapy), given every 2 weeks for 4-7 cycles beyond negative β -hCG

5-FU: 1500 mg/m² IV, days 1-5
Actinomycin-D: 0.5 mg/m² IV push

Extra-uterine metastases:

Hysterectomy and surgery in conjunction with chemotherapy and or radiation may be of use in selected patients for removing foci of persistent or recurrent high-risk gestational trophoblastic tumors.^{5, 14}

Management of brain metastases:

Brain metastases in gestational trophoblastic disease present a significant risk of cerebral hemorrhage.

- Craniotomy may be required for acute decompression and / or surgical resection.¹⁵
- Whole brain irradiation with or without chemotherapy
- Chemotherapy systemic and or combined with intrathecal methotrexate 12.5 mg.¹⁶ and high dose IV methotrexate as part of EMA-CO may be given.¹⁷

Management of lung metastasis

- Surgery: thoracotomy with pulmonary wedge resection in conjunction with chemotherapy in selected patients. It can be performed to excise persistent viable tumor despite intensive chemotherapy^{4, 15}
- Radiation

Management of liver metastasis

The best treatment for liver metastasis has not been established, there is serious risk of hepatic bleeding and hepatic resection may be required to manage hepatic rupture.

- Extensive disease at multiple sites
 - Chemotherapy \pm Radiotherapy
 - Selective hepatic artery occlusion
 - Selective chemo-embolization

Intensive multi-modality therapy with appropriate chemotherapy EMA-CO or some variation of it

Management of placental site trophoblastic tumor includes:

- Non-metastatic disease: hysterectomy is the treatment of choice
- Metastatic disease at presentation and for patients with poor prognostic factors: (EMA-CO) is indicated.¹³
- Isolated metastatic masses: Surgical resection may be considered

9) Follow up and Surveillance for Gestational Trophoblastic Neoplasia

All patients with GTN are followed with weekly serum quantitative serum β -hCG levels until undetectable for 4 weeks, and then every two weeks for two months. Once it is normalized monthly for a total follow-up of one year. 8-12 Patients with metastatic poor prognosis GTN are followed monthly for 24 months because they are at greater risk for late relapse.

History and physical including pelvic should be done at monthly visit.

10) Discussion:

About 15 to 20% of all molar pregnancies develop into gestational trophoblastic All neoplasia (GTN).^{3,4} Referral to a gynecologic oncologist should be initiated when, following evacuation of a hydatidiform mole, β -hCG levels show an abnormal regression pattern (a 10% or greater rise in β -hCG levels over three weeks or a plateauing β -hCG of three stable values over four weeks), a rise in β -hCG following a normal regression pattern, a histologic diagnosis of choriocarcinoma, placental site trophoblastic tumour, or epithelioid trophoblastic tumour, persistently elevated β -hCG levels six months post-evacuation and /or presence of metastases in addition to abnormal β -hCG levels.^{1,8,12} After the referral a baseline β -hCG, complete blood count, and liver, renal function test and Imaging to rule out metastases should also be performed.⁹⁻¹² Common sites of metastases include the lungs, vagina and CNS and vagina.^{1,5, 12} If chest x-ray reports lung metastasis CT chest is not required. If chest x-ray is normal then chest CT is needed because CXR has 30 to 40% chance of being false negative.^{7,12,13,18,19} Depending on a number of risk factors, including age, antecedent pregnancy, interval months from index pregnancy, pretreatment serum β -hCG, largest tumor size, site of metastases, number of metastases, and previous failed chemotherapy (Table 2), patients are grouped into either low risk (score of ≤ 6) or high risk (score of ≥ 7).^{12,13}

Low risk patients are usually treated with single agent chemotherapy. Single agent actinomycin-D or methotrexate with or without folinic acid is the primary therapy.⁸⁻¹³ With appropriate initial classification and proper treatment, cure rate approaches 100%. Careful monitoring for evidence of drug resistance (plateau or \uparrow β -hCG and/ or development of new metastasis) as 30-50% develop resistance to the first line chemotherapy agent and 5-15% may require multi-agent chemotherapy and / or other modalities. DuBeshter et al, treated 48 patient between 1965 -1990 with low risk metastatic GTN with single agent MTX or actinomycin D and noted all patients achieved sustained remission, although 51% required 2nd single-agent regimen and 14% need multi-agent chemotherapy, and 12% underwent resection of resistant tumor foci.

1 to 2 cycles of maintenance chemotherapy should be given after the first normal β -hCG. Single agent methotrexate typically achieves complete response rates ranging from 48 to 74% after four to five cycles and single agent actinomycin-D has better complete response rates (70 to 100%).²¹⁻²⁶

Actinomycin D in methotrexate resistant patient could increase the cure rate **> 95%**. Despite resistance to first –line chemotherapy, cure rate of almost **100%** is achieved with combination chemotherapy. In GOG 174, Patients with GTN and a WHO score of 6 or less are randomized to 30 mg/M sq methotrexate IM q week vs. 1.25 mg/M sq Actinomycin D IV push every 2 weeks. The biweekly actinomycin D had higher CR rate by 17% ($p=.01$), than the weekly IM methotrexate regimen, while both regimens were well tolerated.^{12, 27, 28} In another retrospective study combination chemotherapy with actinomycin-D and methotrexate for a median three cycles achieved 98% response rate, with limited grade 3 and 4 hematologic toxicities (12% & 8%, respectively).^{12, 29}

High risk metastatic GTN is treated with multi agent chemotherapy. Etoposide, actinomycin-D, methotrexate, vincristine, and cyclophosphamide (EMA/CO) or with cisplatin (EMA/CE) is usually first line therapy (Table 7 and 8). With EMA/CO the complete response rate is up to 71%, and overall survival can be as high as 91% in women with poor prognosis metastatic disease (table 4).³⁰ EMA/CE is associated with greater hematologic and ototoxicity and peripheral neuropathy.³¹⁻³³ The complete response rate varies between 67 to 73% when it is used as second line therapy.^{32, 33} Another regimen that has been used as salvage therapy following resistance to primary therapy with etoposide, methotrexate, and actinomycin-D (MEA)

is 5-FU with actinomycin-D (FA); the author reported overall survival of 82% in 11 women after a mean follow up of 11 years.^{34, 35}

Mutch et al. reported 4/9 (44%), who underwent thoracotomy with pulmonary wedge resection of resistant choriocarcinoma survived. Brain metastasis is significant threat to the survival of patient with GTN (especially if it appears while on chemotherapy. Postmortem examination demonstrates CNS involvement up-to in 40% of cases. Brain metastasis may require multimodality therapy (chemotherapy, stereotactic radiotherapy, and surgery). Brain irradiation serves dual purpose of being both tumoricidal & haemostatic effect. Brain irradiation combined with systemic chemotherapy is successful in controlling brain metastasis, with cure rate up to 75%. A similar primary remission rate was reported among patient treated with combination regimens with high dose systemic and intrathecal MTX without brain irradiation with cure rate 50-80 %. In 1987, Yordon et al reported a retrospective analysis of 70 cases of GTT involving CNS. Half died before therapy was initiated. Patients given chemotherapy alone; 24% survived. Patients who given concurrent chemotherapy plus whole brain irradiation; 50% achieved long-term remission. Craniotomy is reserved for women who require acute decompression of CNS hemorrhagic lesions to allow stabilization and institution of therapy. The level of β -hCG is roughly proportional to the tumor burden and inversely proportional to therapeutic outcome. CSF to serum β -hCG ratios of greater than 1: 60 considered positive predictor for brain metastasis. The best treatment for liver metastasis has not been established as serious risk of hepatic bleeding. Nearly all patients with non-metastatic and metastatic, good prognosis disease are cured by chemotherapy. Approximately 70% of patients with metastatic, poor prognosis disease are cured by chemotherapy.

Advise about future pregnancy:

The risk of abnormal pregnancy (i.e., spontaneous abortion, still birth, repeat mole) is greater during the first six months following treatment (for low risk or high risk GTN) than after a year following treatment;³⁴ therefore, patients are normally advised to avoid pregnancy for the first year following treatment.^{7 8,10,12} Blagden et al, reported outcome of 230 pregnancies from Charing Cross Hospital in London, where majority (71%) resulted in full term delivery. Importantly, the frequency of later major and minor congenital malformations is not increased.³⁷

All patients must be encouraged to use effective contraception during the entire interval of monitoring, oral contraceptives are safe⁸⁻¹² Importantly, and the frequency of later major and minor congenital malformations is not increased.

First trimester ultrasound and serum β -hCG testing is indicated for women who become pregnant for the first time after treatment for GTN. β -hCG testing at 6-8 weeks after delivery to assure it has normalized and placenta should be sent for histopathology .

Summary:

- Low-risk patients with both non-metastatic and metastatic disease should be treated with single-agent or (methotrexate and Actinomycin-D) combination chemotherapy.
- High-risk patients should be treated with multi-agent chemotherapy EMA/CO or EMA/CE as a first line therapy with selective use of surgery and radiotherapy. Salvage chemotherapy with MACE and FA, and surgery should be employed in resistant and refractory disease.

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