

# GESTATIONAL TROPHOBLASTIC NEOPLASIA

Effective Date: June 2012

The recommendations contained in this guideline are a consensus of the Alberta Provincial Gynecologic Oncology Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

## BACKGROUND

Gestational trophoblastic disease refers to a group of pregnancy-related tumours that develop from trophoblastic cells in the placenta. The four types of gestational trophoblastic disease include complete or partial hydatidiform mole, which is non-invasive, and invasive mole, choriocarcinoma, placental site trophoblastic tumour, and epithelioid trophoblastic tumour, each of which are invasive<sup>1</sup> and will be herein collectively referred to as gestational trophoblastic neoplasia (GTN). The incidence of hydatidiform mole is less than 10 per 1000 pregnancies<sup>2</sup>. As many as 20% of complete hydatidiform moles will develop into GTN, whereas the rate in partial hydatidiform moles is about five percent.<sup>3,4</sup>

Metastases can occur in patients with GTN, the most common site being the lungs (81%); other sites include the vagina (5%), the central nervous system concurrent with the lungs (7%), the gastrointestinal tract concurrent with the lungs (4%), and the liver concurrent with the lungs (1.5%).<sup>5</sup> When detected and managed early, cure rates for GTN are greater than 90%.<sup>6,7</sup> The purpose of this guideline is to recommend options for the management of GTN, based on the best evidence available.

## GUIDELINE QUESTIONS

- Which patients should be referred to a gynecologic oncologist after evacuation of a hydatidiform mole?
- What investigations are appropriate for the work-up of gestational trophoblastic neoplasia (GTN)?
- How should GTN be staged and scored prognostically?
- How should GTN be managed?
- What investigations are recommended for the follow-up of patients with GTN?

## DEVELOPMENT

This guideline was reviewed and endorsed by the Alberta Provincial Gynecologic Oncology Tumour Team. Members of the Alberta Provincial Gynecologic Oncology Tumour Team include gynecologic oncologists, radiation oncologists, medical oncologists, pathologists, and nurses. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Gynecologic Oncology Tumour Team and a Knowledge Management Specialist from the Guideline Utilization Resource Unit. A detailed description of the methodology followed during the guideline development process can be found in the [Guideline Utilization Resource Unit Handbook](#).

This guideline was originally developed in June 2012

## SEARCH STRATEGY

The Ovid Medline, PubMed, EMBASE, and Cochrane databases were searched for relevant articles published between 1965 and 2011 October. Clinical practice guideline databases (e.g. National Guidelines Clearinghouse, CancerView, etc.) were also searched for evidence relevant to this topic, published between 2006 and 2011 October.

For the evidence on work-up, search terms included: gestational trophoblastic neoplasia AND workup or chest x-ray or magnetic resonance imaging or computed tomography or pelvic ultrasound or complete blood count or beta hCG or liver function tests or renal function tests or marrow function tests. A total of 1086 citations were returned; only studies that looked at blood work or imaging tests in a cohort of patients

(i.e., ten or more) with diagnosed gestational trophoblastic neoplasia (no case studies) and were published in English from 2000 to 2011 October were included. The terms, gestational trophoblastic neoplasia AND metastases, were also searched, with the results limited to clinical trials only. In total, nine articles and four guidelines were included as evidence. For the evidence on staging and prognostic scoring, as well as evidence on follow-up, the term gestational trophoblastic neoplasia was searched using the National Guidelines Clearinghouse database as well as individually searching Canadian cancer guidelines developers' websites. For the evidence on management, the terms *gestational trophoblastic neoplasia* and *chemotherapy* were searched in the EMBASE, Ovid Medline and PubMed databases, with results limited to clinical trials published from 2000 to 2011 October that looked at a single agent or multi-agent regimen in a cohort of patients (i.e., ten or more) with diagnosed gestational trophoblastic neoplasia.

Existing guidelines considered for this review included those published by the following groups: Society of Obstetricians and Gynaecologists of Canada (2002),<sup>8</sup> National Cancer Institute (2011),<sup>9</sup> American College of Obstetricians and Gynecologists (2008),<sup>10</sup> and BC Cancer Agency (2000).<sup>11</sup> An effort was made to either adapt or adopt the most appropriate guidelines from other sources so that work wasn't duplicated. An evidence based perspective was used to draft proposals. Where evidence was weak, recommendations were based on group consensus.

## TARGET POPULATION

The recommendations outlined in this guideline apply to women with gestational trophoblastic neoplasia, including invasive mole, choriocarcinoma, and placental site trophoblastic tumour.

## RECOMMENDATIONS

Follow-up after evacuation of a molar pregnancy (complete or partial hydatidiform mole) should include:<sup>8</sup>

1. Weekly quantitative hCG until negative x 3, then monthly x 6 months
2. Regular pelvic examination, at 1, 3, and 6 months post-evacuation
3. Contraception x 6 months (preferably OCP)
4. Chest x-ray

### I. Indications for Referral to a Gynecologic Oncologist Following Evacuation of a Hydatidiform Mole

Patients who have undergone evacuation of a hydatidiform mole *and* who present with any of the following should be referred to a gynecologic oncologist:<sup>1,3</sup>

- an abnormal  $\beta$ -hCG regression pattern (a 10% or greater rise in  $\beta$ -hCG levels over three weeks or a plateauing  $\beta$ -hCG of three stable values over four weeks)
- a rise in  $\beta$ -hCG following a normal regression pattern
- a histologic diagnosis of choriocarcinoma, placental site trophoblastic tumour, or epithelioid trophoblastic tumour
- high  $\beta$ -hCG levels (greater than 20,000 mIU/mL more than four weeks post-evacuation)
- persistently elevated  $\beta$ -hCG levels six months post-evacuation
- the presence of metastases in addition to abnormal  $\beta$ -hCG levels

### II. Work-up for Gestational Trophoblastic Neoplasia

History and physical exam should be performed, along with the following investigations:

- Blood work: serum  $\beta$ -hCG, complete blood count (CBC) with differential, platelet determinations, clotting function tests, liver function tests, and renal function tests.
- Imaging to check for metastases: chest x-ray with computed tomography (CT) scan of the chest if the chest x-ray is negative, CT scans of the abdomen and pelvis, and CT scan or magnetic resonance imaging (MRI) of the brain.

### III. Staging and Prognostic Scoring for Gestational Trophoblastic Neoplasia

Staging of GTN is based on the Federation Internationale de Gynecologie et d'Obstetrique (FIGO) system (2009):<sup>12</sup>

- 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

Risk assessment is based on several indicators, including age, antecedent pregnancy, interval months from index pregnancy, pretreatment serum  $\beta$ -hCG, largest tumor size (including uterus), site of metastases, number of metastases, and previous failed chemotherapy (see Table 1).<sup>12</sup>

Table 1. Prognostic scoring for gestational trophoblastic neoplasia (FIGO, 2009; modified from WHO)

Scores	0	1	2	4
age	<40	$\geq$ 40	–	–
antecedent pregnancy	mole	abortion	term	–
interval months from index pregnancy	<4	4–6	7–12	>12
pretreatment serum $\beta$ -hCG (iu/1)	<103	103–104	104–105	>105
largest tumor size (including uterus)	<3	3–4 cm	$\geq$ 5 cm	–
site of metastases	lung	spleen, kidney	gastrointestinal	liver, brain
number of metastases	–	1–4	5–8	>8
previous failed chemotherapy	–	–	single drug	$\geq$ 2 drugs

- Low-risk: individuals with a score  $\leq$ 6.<sup>9,10,12</sup>
- High-risk: individuals with a score  $\geq$ 7.<sup>9,10,12</sup>

### IV. Treatment of Gestational Trophoblastic Neoplasia

Options for the management of GTN are dependent on prognostic scoring and include the following:

#### **Non-metastatic (Stage I) and Low-risk Metastatic (Stages II and III, FIGO score $\leq$ 6)**

- Preferred regimens include:
  - Actinomycin-D and methotrexate with folinic acid, given every 2 weeks for 1 to 3 cycles beyond negative  $\beta$ -hCG
    - Actinomycin-D (0.5 mg/m<sup>2</sup> IV) given days 1-2
    - Methotrexate (100 mg/m<sup>2</sup> IV push + 300 mg/m<sup>2</sup> IV) on day 1
    - Folinic acid (15 mg PO, q 6 h x 9 doses starting 24 hours after methotrexate bolus)

- Actinomycin-D (1.25 mg/m<sup>2</sup> IV), given every 2 weeks for 1 to 3 cycles beyond negative β-hCG
- Methotrexate (30 mg/m<sup>2</sup> or 50 mg/m<sup>2</sup> IM), given weekly for 1 to 3 cycles beyond negative β-hCG
- Other regimens include:
  - Methotrexate (50 mg/m<sup>2</sup> IM, days 1, 3, 5, 7) and folinic acid (7.5 mg oral, days 2, 4, 6, 8), given every 2 weeks for 1 to 3 cycles beyond negative β-hCG
  - Methotrexate (100 mg/m<sup>2</sup> IV) and folinic acid (15 mg oral, q 6 h x 4 doses starting 24 h after methotrexate), given weekly for 1 to 3 cycles beyond negative β-hCG
- In select patients, consider performing adjuvant surgery (i.e., hysterectomy).

**High-risk Metastatic (Stages II and III, FIGO score ≥7 and Stage IV)**

- Preferred regimens include:
  - EMA/CO multi agent chemotherapy, given every 2 weeks for 3 cycles beyond negative β-hCG
    - Etoposide (100 mg/m<sup>2</sup> IV, days 1, 2)
    - Actinomycin-D (0.5 mg IV push days 1, 2)
    - Methotrexate (300 mg/m<sup>2</sup> IV, day 1)
    - Folinic acid (15 mg PO, q 12 h, days 2, 3)
    - Vincristine (0.8–1.0 mg/m<sup>2</sup> IV, day 8)
    - Cyclophosphamide (600 mg/m<sup>2</sup> IV, day 8)
  - EMA/CE multi agent chemotherapy, given every 2 weeks for 3 cycles beyond negative β-hCG
    - Course 1: same as EMA/CO
    - Course 2: etoposide (100 mg/m<sup>2</sup> IV, day 8), cisplatin (80 mg/m<sup>2</sup> IV, day 8), plus magnesium supplementation (30 ml PO, q 12 h, day 1)
  - MACE multi agent chemotherapy
    - Cisplatin (30 mg/m<sup>2</sup> IV, days 1-3)
    - Etoposide (50 mg PO, days 1-10)
    - Actinomycin-D (0.5 mg/m<sup>2</sup> IV, days 8 and 9)
    - Methotrexate (100 mg/m<sup>2</sup> bolus + 300 mg/m<sup>2</sup> IV, day 8)
    - Folinic acid (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/m<sup>2</sup>, days 1-5
    - Cisplatin: 20 mg/m<sup>2</sup>, days 1-5
  - 5-FU/actinomycin-D multi agent chemotherapy (as second-line therapy), given every 2 weeks for 4-7 cycles beyond negative β-hCG
    - 5-FU: 1500 mg/m<sup>2</sup> IV, days 1-5
    - Actinomycin-D: 0.5 mg/m<sup>2</sup> IV push
- Adjuvant surgery for resection of metastases in selected patients
- Radiotherapy in selected patients

**V. Follow Up for Gestational Trophoblastic Neoplasia**

Serial serum β-hCG measurements should be determined as follows:

- q 1-2 weeks for the first three months or while elevated;
- then q 1-2 months for a total follow-up of one year.

Patients should be advised about future pregnancy:

- Pregnancy should be avoided until  $\beta$ -hCG levels have been normal for a minimum of six months up to one year (depending on risk score) following chemotherapy for gestational trophoblastic neoplasia; however, among patients who do conceive within 6-12 months of treatment, a favorable outcome is likely.
- The combined oral contraceptive pill is safe for use by women with GTN.
- First trimester ultrasound and serum  $\beta$ -hCG testing is recommended for women who become pregnant for the first time after treatment for GTN. In addition,  $\beta$ -hCG testing at 6-8 weeks after delivery may be performed.

In patients for whom hormone replacement therapy (HRT) is indicated, HRT may be used safely once  $\beta$ -hCG levels have returned to normal.

## DISCUSSION

About 15% of all molar pregnancies will develop into gestational trophoblastic neoplasia (GTN).<sup>3,4</sup> Referral to a gynecologic oncologist should be initiated when, following evacuation of a hydatidiform mole,  $\beta$ -hCG levels show an abnormal regression pattern (i.e., a 10% or greater rise or a plateauing for three stable values over two weeks), rebound, are high (>20,000 mIU/mL) more than four weeks post-evacuation, or are persistently elevated six months post-evacuation.<sup>1,3</sup> Other reasons for referral include a histologic diagnosis of choriocarcinoma or placental site trophoblastic tumour, or metastasis to one or more sites.<sup>1,3</sup> Once a referral has been made, blood work should include at minimum a baseline  $\beta$ -hCG, complete blood count, and liver, renal, and marrow function tests.<sup>9-11</sup> Imaging to rule out metastases should also be performed.<sup>8-11</sup> Common sites of metastases include the lungs, the central nervous system, the vagina, and the liver concurrent with the lungs.<sup>5</sup> A positive chest x-ray is sufficient for the detection of lung metastases and CT doesn't offer any advantage in terms time to remission;<sup>13,14</sup> however, metastases are seen on chest CT scan in 30-40% of patients with normal chest x-rays, necessitating the need for chest CT.<sup>7</sup>

Depending on a number of risk factors, including age, antecedent pregnancy, interval months from index pregnancy, pretreatment serum  $\beta$ -hCG, largest tumor size (including uterus), site of metastases, number of metastases, and previous failed chemotherapy (Table 1), patients will be grouped into one of two risk categories: low risk (score of  $\leq 6$ ) or high risk (score of  $\geq 7$ ).<sup>12</sup> Treatment of non-metastatic (stage I) and low risk metastatic (stage II and III, risk score  $\leq 6$ ) GTN typically requires a less aggressive approach than treatment of high risk metastatic GTN (stage II and III, risk score  $\geq 7$  and stage IV).

Most groups recommend single agent actinomycin-D or methotrexate with or without folinic acid as primary therapy for non-metastatic or low risk metastatic GTN.<sup>8-10</sup> Single agent methotrexate typically achieves complete response rates ranging from 48 to 74%<sup>15-20</sup> after four to five cycles.<sup>19</sup> Single agent actinomycin-D has produced better complete response rates, which range from 70 to 100%.<sup>15,16,19-21</sup> A phase III clinical trial comparing methotrexate with actinomycin-D found that actinomycin-D significantly improved the complete response rate by 17% ( $p=.01$ ), while both regimens were well tolerated.<sup>15</sup> A recent retrospective study by Eiriksson L, et al. at the Alberta Cross Cancer Institute and the BC Cancer Agency demonstrated a response rate of 98% using combination chemotherapy with actinomycin-D and methotrexate for a median three cycles, with limited grade 3 and 4 hematologic toxicities (12% and 8%, respectively).<sup>22</sup>

High risk metastatic GTN is treated with multi agent chemotherapy. Etoposide, actinomycin-D, methotrexate, vincristine, and cyclophosphamide is commonly used, alone (EMA/CO) or with cisplatin (EMA/CE), as first line therapy.<sup>8-10</sup> Among patients receiving EMA/CO as first or second line therapy for high-risk metastatic GTN, the complete response rate was 71%, with overall survival reaching 91%.<sup>23</sup> A retrospective study reported a cure rate of 86% for EMA/CO.<sup>24</sup> The addition of cisplatin (EMA/CE) may produce a slightly better remission rate (88%) when used as first line therapy; however, EMA/CE is associated with greater hematologic toxicity.<sup>25-27</sup> As second line therapy, EMA/CE has achieved complete response rates, ranging from 67 to 73%.<sup>26,27</sup> 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); among 11 patients who relapsed after MEA, the overall survival rate with FA was 82% after a mean follow-up of over 11 years.<sup>28</sup> More recently, floxuridine has been used in combination with etoposide, vincristine, and actinomycin-D (FAEV) and yielded a complete response rate of 64% among drug resistant patients with high risk metastatic GTN, but was associated with myelosuppression and required support with granulocyte colony stimulating factor.<sup>29,30</sup>

Patients with gestational trophoblastic neoplasia are typically followed up monthly for one year after treatment, with a higher frequency (i.e., q 1 week for one month, then q 2 weeks for two months) for the first three months; serum  $\beta$ -hCG levels are monitored.<sup>8,10,11</sup> During follow up, patients report anxiety around fear of recurrence, of infertility, and of conceiving again; however compliance with recommended follow up is good.<sup>31</sup> 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;<sup>32,33</sup> therefore, patients are normally advised to avoid pregnancy for the first year following treatment.<sup>7,8,10,34</sup> Patients should be reassured, though, that if they do conceive early (within 12 months of treatment), outcomes will likely be favorable. Among 230 early pregnancies at the Charing Cross Hospital in London, 71% were delivered at full term, while 11% were spontaneously aborted, 1.3% developed into new hydatidiform moles, and 1% were still born (the remaining 15% were terminated); spontaneous miscarriages were more likely to occur in the multi-agent group ( $p=.04$ ).<sup>35</sup> Regarding the use of hormones, the combined oral contraceptive pill is considered safe for use by women who have been treated for GTN; further, patients taking hormone replacement therapy may do so safely once  $\beta$ -hCG levels have returned to normal.<sup>8,34</sup>

## GLOSSARY OF ABBREVIATIONS

Acronym	Description
CBC	complete blood count
CT	computed tomography
FIGO	Fédération Internationale de Gynecologie et d'Obstetrique
FU	fluorouracil
GTN	gestational trophoblastic neoplasia
HRT	hormone replacement therapy
IM	intramuscular
IT	intrathecally
IV	intravenous
MRI	magnetic resonance imaging
PET-CT	positron emission tomography, computed tomography
PO	orally
serum $\beta$ -hCG	serum beta-human chorionic gonadotropin
U/S	ultrasound

## DISSEMINATION

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services website.
- Send an electronic notification of the new guideline to all members of CancerControl Alberta.

## MAINTENANCE

A formal review of the guideline will be conducted at the Annual Provincial Meeting in 2014. If critical new evidence is brought forward before that time, however, the guideline working group members will revise and update the document accordingly.

## CONFLICT OF INTEREST

Participation of members of the Alberta Provincial Gynecologic Oncology Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Gynecologic Oncology Team are involved in research funded by industry or have other such potential conflicts of interest. However the developers of this guideline are satisfied it was developed in an unbiased manner.

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