Diagnosis and Management of Gestational Trophoblastic Disease

Jocelyn Garcia-Sayre, Antonio V. Castaneda, Lynda D. Roman, and Koji Matsuo

Abstract

Gestational trophoblastic disease (GTD) refers to all tumors that arise from the maternal placenta. Gestational trophoblastic neoplasm (GTN) is a subset of GTD and refers to choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor. Persistent GTD may develop after treatment of a molar pregnancy and is also referred to as GTN. The treatment of GTN is stratified based on whether the patient is low risk or high risk as determined by the World Health Organization (WHO) score and International Federation of Gynecology and Obstetrics (FIGO) staging system. Low-risk GTN is treated with single-agent chemotherapy, whereas high-risk GTN should be treated with combination regimens. GTN that does not respond to first-line treatment is said to be resistant or refractory. Resistance to a particular chemotherapeutic regimen is evidenced by a plateau or rise in beta-hCG levels. The overall prognosis for GTN is excellent, even in the setting of refractory disease. GTN affects women of reproductive age, and comprehensive counseling must be performed prior to initiation of gonadotoxic treatment. This chapter also discusses the management of GTN with special considerations such as brain and vaginal metastasis, role of secondary curettage, and post-molar prophylactic chemotherapy.

Keywords

Gestational trophoblastic neoplasm • Persistent gestational trophoblastic disease • Invasive mole • Choriocarcinoma • Placental site trophoblastic tumor • Epithelioid trophoblastic tumor • High-risk gestational trophoblastic neoplasm • Low-risk gestational trophoblastic neoplasm

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1 Introduction

Gestational trophoblastic disease (GTD) is the general term used to describe growth disturbances of the placental trophoblast. GTD encompasses the complete mole, partial mole, invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT). Gestational trophoblastic neoplasia (GTN) is a subset of GTD and refers to the latter four. The term persistent GTD is often used interchangeably with GTN when referring to the diagnosis of post-hydatidiform mole trophoblastic neoplasia. Typically, GTN will arise after a molar pregnancy but can occur in the setting of a normal pregnancy and in rare cases may not be associated with pregnancy. With the advent of various chemotherapeutic regimens, the prognosis for GTN is excellent.

1.1 Epidemiology

The overall incidence of GTD and GTN is low within the general population. The incidence varies widely based on geographical location and race. Southeast Asia and Japan have the highest incidence of GTD. It is unknown at this time why various ethnicities have a higher incidence of GTD and GTN. Currently, the incidence of GTD is documented at 1–3 per 1000 pregnancies (Froeling and Seckl 2014). Given that GTN typically arises from GTD, the incidence of GTN is much lower. In North America the incidence is quoted to be 1 in 40,000 and at 9 per 40,000 in Southeast Asia and Japan (Lurain 2010).

1.2 Presentation

The presentation of GTN is diverse and dependent on the type of neoplasm. Benign moles such as the complete hydatidiform mole present most often with vaginal bleeding and significantly elevated beta-hCG. The elevation in beta-hCG often correlates to the burden of trophoblastic disease (Froeling and Seckl 2014). A single elevated beta-hCG should not be used to make the diagnosis of GTD or GTN. When an ultrasound is performed, hydropic villi are observed, and this is often referred to as a snowstorm appearance (Froeling and Seckl 2014).

Following evacuation of GTD, beta-hCG levels should steadily decline. The majority of patients will have normal beta-hCG levels around 12–14 weeks after evacuation. A plateauing or increase of the beta-hCG is concerning for the development of GTN or persistent GTD. Regression curves have been developed to help identify patients at risk (Schlaerth et al. 1981). Persistent GTD develops when molar tissue invades into the myometrium. Typically, this is seen with the invasive mole but can also be seen in choriocarcinoma, PSTT, and ETT. Table 1 describes the criteria for the diagnosis of post-hydatidiform mole trophoblastic neoplasia or GTN (Committee 2002). GTN can be diagnosed if any one of the criteria is established.

Histologically, the invasive mole appears as excessive growth of the trophoblastic tissue which invades into the myometrium of the uterus. Invasive

Table 1 Criteria for the diagnosis of post-hydatidiform mole trophoblastic neoplasia

GTN may be diagnosed when the plateau of beta-hCG lasts for four measurements over a period of 3 weeks or longer, that is, days 1, 7, 14, and 21[a]
GTN may be diagnosed when there is a rise of beta-hCG of three weekly consecutive measurements or longer, over at least a period of 2 weeks or more, days 1, 7, and 14[a]
GTN is diagnosed when the beta-hCG level remains elevated for 6 months or more

Adopted and modified from FIGO committee report on FIGO staging for gestational trophoblastic neoplasia 2000 (Committee 2002)

[a]A difference of 10% or less between measurements is considered stable and should not be interpreted as a change

Table 2 Summary of clinical presentation and histopathologic findings

GTN type	Presentation /behavior	Histopathology	Management
Invasive mole	• Presents with irregular bleeding after dilation and curettage • Associated with localized invasion; however 15% metastasize to the lung or vagina • High levels of beta-hCG	• Molar tissue which invades the myometrium. • Growth of trophoblastic tissue with the presence of chorionic villi invading myometrium	Chemotherapy
Choriocarcinoma	• Associated with irregular bleeding after dilation and curettage • 50% arise from hydatidiform moles • Increased risk of hemorrhage and vaginal bleeding • Highly malignant tumor with propensity for widespread metastasis via vascular channels- spreading to the lung, liver, and brain • High levels of beta-hCG	• Sheets of anaplastic cytotrophoblasts and syncytiotrophoblasts with absence of chorionic villi	Chemotherapy
Placental Site Trophoblastic Tumor (PSTT)	• Rare • Presents with non-specific vaginal bleeding • Chemoresistant, persistent low levels beta-hCG • Presence of human placental lactogen (hPL) • Metastasizes via lymphatics	• Intermediate trophoblastic tissue without chorionic villi seen invading into the myometrium	Hysterectomy +/− Chemotherapy
Epithelioid Trophoblastic Tumor (ETT)	• Rare • Majority occur after term pregnancy • Presents with non-specific vaginal bleeding • Chemoresistant • Elevated beta-hCG but usually less than 2500	• Mononucleate trophoblastic cells arranged in cords associated with eosinophilic, fibrillary and necrotic debris	Hysterectomy +/− Chemotherapy

Adopted and modified from Lurain (2010)

moles often have local invasion and are less often associated with metastasis. Choriocarcinoma is a highly malignant tumor associated with hemorrhage, widespread metastasis, and sheets of anaplastic cytotrophoblasts and syncytiotrophoblasts. Choriocarcinomas are typically very chemosensitive. Placental site trophoblastic tumor is a rare form of GTN that arises after a term pregnancy and histologically consists of intermediate trophoblasts. PSTT has slow growth within the uterus and only metastasizes late in its course. Patients with PSTT usually present with low levels of beta-hCG and irregular vaginal bleeding. Surgery of the primary tumor and multi-agent chemotherapy are the mainstays of treatment for PSTT (Lurain 1990); (Abrão et al. 2008; Papadopoulos et al. 2002). Epithelioid trophoblastic tumor is an extremely rare type of GTN with little documentation in the literature. ETT can arise from either a previously gestation or without a previously documented gestation. ETT is chemoresistant; therefore, surgery is the mainstay of treatment when confined to the uterus. Histologically, ETT develops from the chorionic-type intermediate trophoblast (Allison et al. 2006; Lurain 1990) (Table 2).

1.3 Treatment Overview

The treatment for GTN is determined by whether the patient is found to be low risk or high risk. There are two classification systems for GTN: International Federation of Gynecology and Obstetrics (FIGO) and the World Health Organization (WHO). The FIGO staging criteria

defines stage based on extent of disease (Table 3). The World Health Organization (WHO) proposed a classification system that divides patients into low-risk and high-risk categories with the purpose of defining the best course of treatment (Table 4). It uses independent prognostic factors to risk stratify patients based on the likelihood of being successfully treated with single-agent versus multi-agent chemotherapy. Low-risk patients are likely to achieve 90% response to single-agent chemotherapy, whereas high-risk patient will need multi-agent chemotherapy (Lurain et al. 1991).

After successful treatment for GTD, it is imperative to follow the patient with serial beta-hCG levels weekly until undetectable levels are noted for 3 weeks. Monthly beta-hCG measurements should then be drawn for 6–12 months. Six months follow-up may be sufficient if the decline in beta-hCG follows the normal regression curve as detailed by Morrow et al. (1977). However, 12 months follow-up is recommended if regression is irregular. During the monitoring for declining serial beta-hCG, it is necessary for the patient to be on effective contraception. A concomitant pregnancy at the time of beta-hCG evaluation will lead to an inability to monitor for disease recurrence. The intrauterine device, however, is not recommended as birth control for patients with GTD given the risk for uterine perforation. Oral contraceptive pills and implantable devices are both safe for use (Berkowitz and Goldstein 2009).

Table 3 FIGO staging system

Stage	Extent of disease
I	Limited to the uterus
II	Extension beyond uterus to adnexa, broad ligament, or the vagina
III	Extension to the lungs with or without extension to genital tract
IV	Other metastatic sites

Adopted and modified from FIGO Committee on Gynecologic Oncology (Oncology 2009)

2 Management of Primary GTN

Primary GTN is highly curable with chemotherapy. Primary treatment is dictated by the WHO and FIGO score as above. A WHO score of 6 or less with FIGO stages I–III is considered to be low-risk disease and can be treated with a single chemotherapeutic agent. A score of 7 or greater with FIGO stages I–III or FIGO stage IV is considered to be high-risk disease and calls for treatment with a combination of agents.

Table 4 WHO prognostic scoring system

Score assigned	0	1	2	4
Age at diagnosis	Less than 40	40 or greater	-	-
Prior pregnancy	Mole	Abortion	Term	-
Interval between index pregnancy (months)	Less than 4	4–6	7–12	More than 1 year
Pretreatment beta-hCG	Less than1000	1000–10,000	10,000–100,000	Greater than 100,000
Tumor size (cm); including uterine mass size	Less than 3	Greater than 3 but less than 5	5 or greater	-
Metastatic location	Lung*	Kidney/spleen	GI	Brain or liver
Number of metastases	0	1–4	5–8	9 or more
Failed chemotherapy	-	-	Single agent	Multi-agent

*Lung metastases should only be included in the WHO score if seen on Chest X-Ray (CXR). Lung CT-Scan may be used but should not influence the score because of the likely presence of lung micro-metastases. If counted, they would increase the score without adding any clinical benefit. While a lung metastasis receives a score of 0, it may be included when counting the total number of metastatic lesions if visualized on CXR

Adopted and modified from FIGO Committee on Gynecologic Oncology (Abrão et al. 2008; Oncology 2009)

Table 5 Response rate for chemotherapy regimens for low-risk GTN

Regimen	Primary Remission Rate (%)
(a) MTX 0.4 mg/kg IM for 5 days, repeated q2 weeks	87–93
(b) MTX 50 mg IM or 1 mg/kg QOD for four doses with leucovorin 15 mg or 0.1 mg/kg administered 24–30 h after each MTX dose	74–90
(c) MTX 30 mg/m^2 or 50 mg/m2 IM given weekly	49–74
(d) Act-D 1.25 mg/m^2 IV q2 weeks (pulsed regimen)	69–90
(e) Act-D 12 μg/kg for 5 days, repeated q2 weeks	77–94
(f) (i) MTX 20 mg IM on D1–D5 with 500ug Act-D IV on D1–D5 q2 weeks (ii) Act-D 0.6 mg/m^2 on D1 and D2 with MTX 100 mg/m^2 IV push and then infusion of 300 mg/m^2 on D1–D2 followed by leucovorin for 2 weeks	100

Adopted and modified from Lurain (2011)
Abbreviations: *MTX*, methotrexate; *Act-D*, actinomycin D; *QOD*, every other day; *q2 week*, every 2 weeks

2.1 Low-risk GTN: Chemotherapy

As mentioned above, low-risk GTN is usually treated with single-agent chemotherapy. Two agents are typically used for treatment of low-risk disease, methotrexate and actinomycin D with cure rates of approximately 100%. Etoposide was historically used for low-risk disease, but this has fallen out of favor due to the slightly increased risk of secondary malignant tumors, especially leukemia (Rustin et al. 1996). Several different dosing regimens have been studied for methotrexate and actinomycin D; these are discussed below. Table 5 summarizes the regimens and includes their primary remission rates.

(a) Methotrexate 0.4 mg/kg intramuscularly (IM) for 5 days, repeated every 2 weeks. The primary failure rate is approximately 11% for non-metastatic disease (Lurain and Elfstrand 1995). The response rate in women with metastatic disease has been quoted to be 60% (Soper et al. 1994).

(b) Methotrexate with folinic acid (leucovorin) rescue: Methotrexate 50 mg IM or 1 mg/kg every other day for four doses with leucovorin 15 mg or 0.1 mg/kg administered 24–30 h after each methotrexate dose. In patients with nonmetastatic disease, only 7.7% of those treated with methotrexate alone developed resistant disease requiring a change in chemotherapy for induction of remission, while 27.5% of patients initially treated with the leucovorin rescue required a change in regimen to achieve remission. Thus, the frequency of drug resistance is significantly higher in those treated with the leucovorin rescue (Matsui et al. 2005). However, the use of methotrexate alone has been shown to be more toxic than the methotrexate-folinic acid combination.

(c) Methotrexate 30 mg/m^2 or 50 mg/m^2 IM given weekly. This regimen was used in GOG-174 to compare response rates to those of actinomycin D 1.25 mg/m^2 IV every 2 weeks (Osborne et al. 2011). Actinomycin D was found to be more effective with a response rate of 70% compared to 53% for weekly methotrexate.

(d) Actinomycin D 1.25 mg/m^2 IV every 2 weeks (pulsed regimen). Actinomycin D is associated with alopecia and is therefore less favored by patients.

(e) Actinomycin D 12 μg/kg for 5 days. This is an alternative to the 5-day methotrexate regimen. This regimen has shown to be effective in patients who failed to respond to the 1.25 mg/m^2 pulse actinomycin D regimen with an 80% response rate (Kohorn 2002).

(f) Combined methotrexate and actinomycin D: The following dosing regimens have been used for this combination regimen:

(i) Methotrexate 20 mg IM on D1–D5 with 500 μg actinomycin D IV on D1–D5 every 14 days (Abrão et al. 2008).

(ii) Actinomycin D 0.6 mg/m^2 on D1 and D2 with methotrexate 100 mg/m^2 IV push and then infusion of 300 mg/m^2 on D1–D2 followed by leucovorin for 14 days (Eiriksson et al. 2012). Higher remission rates have been reported when the combination is used as compared to each drug alone. It is has also proven to lead to a cure faster, requiring a fewer number of cycles (Eiriksson et al. 2012). The combination regimens ultimately yielded a greater number of grades 3 and 4 toxicities as defined by the Common Terminology Criteria of Adverse Events (CTCAE). Therefore, taking into consideration the frequency of toxic effects and a modest increase in remission rate, a combined regimen may be better suited for second-line therapy (Abrão et al. 2008).

GOG-275 is an ongoing multicenter phase III randomized control trial that compares the use of multiday methotrexate versus actinomycin D in treating patients with low-risk GTN. At present, the question of whether methotrexate versus actinomycin D should be used as first-line treatment for GTN remains unanswered (Alazzam et al. 2012a). While GOG-174 attempted to answer this question, it used the weekly methotrexate regimen which has been shown to be inferior to the multiday regimen. A Cochrane review meta-analysis concluded that actinomycin D is much more likely to achieve a primary cure when compared to methotrexate (82% in the actinomycin D group compared to 53% in the methotrexate group); however, the review included data from different dosing regimens making it difficult to draw a clear conclusion. The results from GOG-275 will help determine whether actinomycin D or methotrexate should be first-line choice for treatment of low-risk GTN (Alazzam et al. 2012a).

In general, treatment should be continued beyond the first negative beta-hCG titer; this is known as consolidation therapy (Lybol et al. 2012). Usually 2–3 cycles of chemotherapy are recommended, especially if the decrease in beta-hCG is slow or if there is extensive disease.

2.2 Low-risk GTN: Adjuvant Surgery

2.2.1 Second Curettage

Attempts have been made to curtail chemotherapy in the setting of low-risk GTN. The theory behind a second curettage is that debulking the tumor will lead to a decreased need for chemotherapy. Single institution retrospective studies have reported varying outcomes. The Dutch published a retrospective cohort study evaluating the effect of a second curettage on low-risk GTN (van Trommel et al. 2005). Their primary outcome measures were the need for chemotherapy and the number of chemotherapy courses required. Unfortunately, only 9.4% of patients were cured after curettage and required no further chemotherapy. However, those patients who received a second curettage required a fewer number of chemotherapy cycles, and the authors concluded that the second curettage offers a "debulking" effect. A second curettage is not without complications; 4.8% of patients in this study had a major complication such as uterine perforation and hemorrhage. Another retrospective study from the United Kingdom concluded that 60% of their patients did not require chemotherapy after a second evacuation (Pezeshki et al. 2004).

Until recently there was only one published prospective study from Iran evaluating the clinical response to a second curettage, with a small sample size of 12 (Yarandi et al. 2014): 83% of patients did not require chemotherapy and were cured by a second curettage. Eight percent of patients experienced a complication such as uterine perforation.

A second curettage has not been considered standard practice. Most practitioners believe that a second curettage should be reserved for patients who experience significant vaginal bleeding and anemia after the first curettage. The GOG recently published a multicenter prospective phase II study evaluating the efficacy and safety of a second curettage in lieu of chemotherapy for patients with low-risk GTN (persistent GTD). The study population included women with non-metastatic low-risk GTN. Patients whose first curettage revealed choriocarcinoma, PSTT, or ETT were excluded. Patients with previously treated low-risk GTN were excluded. The method of

Table 6 Efficacy of second curettage for persistent GTD/low-risk GTN

Author	Year	Study type	No.[a]	Response rate (%)	Complication rate
van Trommel et al. 2005	2005	Retrospective, multicenter	85	9.4	4.8 %
Pezeshki et al. 2004	2004	Retrospective, multicenter	282	60	n.a.
Yarandi et al. 2014	2014	Prospective, single institution	12	83	8 %
Osborne et al. 2016	2016	Prospective, multicenter	60	40	10 %

[a]Patients who underwent second curettage for persistent GTD

evacuation was not specified by the study but could include intraoperative ultrasound localization of the residual trophoblast or directed hysteroscopic resection. Forty percent of the patients were cured after the second curettage with only 10% of patients experiencing a complication. 1.6% of patients experienced uterine perforation that was managed by observation, 6.7% grade 1, and 1.6% grade 3 incidents of uterine hemorrhage as defined by the CTCAE 3.0. They concluded that a second curettage as initial treatment for low-risk GTN cures 40% of patients without significant morbidity (Osborne et al. 2016).

Table 6 provides a summary of the above-referenced studies evaluating the use of second curettage in the setting of low-risk GTN. Generally, the decision for second curettage should not be taken lightly, and patients must be counseled regarding the risks including hysterectomy if profuse bleeding and/or uterine perforation are encountered. Whether or not to perform a second curettage should be determined on a case-by-case basis given that methotrexate and actinomycin D are generally well tolerated and have excellent response rates.

2.2.2 Adjuvant Hysterectomy

Historically, the accepted indications for hysterectomy in women with GTN were removal of chemoresistant disease and to control hemorrhage or infection in emergency cases. However, a hysterectomy can be employed to help decrease the amount of chemotherapy required for treatment of low-risk GTN. The Japanese published a prospective trial evaluating the efficacy of adjuvant hysterectomy in women with and without metastatic disease (Suzuka et al. 2001). They treated 115 women with single-agent chemotherapy (the majority treated with etoposide) and then performed interval hysterectomy. Adjuvant hysterectomy decreased the total dose of etoposide given to achieve primary remission in women with nonmetastatic disease. There was no difference in the number of chemotherapy cycles required for remission in patients with metastatic disease. Thus, the authors concluded that adjuvant hysterectomy is a viable option for women who have completed childbearing and whose disease is confined to the uterus. Another study also concluded that adjuvant hysterectomy significantly reduced the amount of chemotherapy used to achieve remission (Hammond et al. 1980).

2.3 High-Risk GTN: Chemotherapy

Unlike treatment of low-risk GTN, high-risk GTN should be treated with combination regimens, as opposed to single-agent therapy. High-risk GTN patients are at risk of developing drug resistance to methotrexate when it is used as a single agent. Below are the most widely studied combination regimens and associated toxicities:

(a) Cyclophosphamide, hydroxyurea, actinomycin D, methotrexate, doxorubicin, melphalan, and vincristine (CHAMOMA). In 1981 the GOG instituted a prospective randomized protocol comparing CHAMOMA and methotrexate, actinomycin D, and chlorambucil (MAC) (Curry et al. 1989). At that time, MAC was the standard of care for patients with high-risk disease, and their goal was to find a less toxic and more effective regimen. The study, however, concluded the opposite; the CHAMOMA regimen was more toxic and

Table 7 EMA-CO regimen

Day	Agents	Dosing
1	Etoposide	100 mg/m^2 IV over 30 min
	Actinomycin D	0.5 mg IV push
	Methotrexate	100 mg/m^2 IV and 200 mg/m^2 IV in 1000 mL of D5W over 12 h
2	Etoposide	100 mg/m^2 IV over 30 min
	Actinomycin D	0.5 mg IV bolus
	Folinic acid	15 mg IM or PO every 12 h for four doses starting 24 h after initiation of methotrexate
8	Cyclophosphamide	600 mg/m^2 IV
	Vincristine	1.0 mg/m^2 IV push

Adopted and modified from Escobar et al. (2003)
Repeat cycle on days 15, 16, and 22 (every 2 weeks)

possibly less effect. It closed prematurely because of a 30% death rate in the CHAMOMA arm, compared to a 4% death rate in the MAC arm.

(b) MAC: This regimen has a response rate of approximately 77% and was routinely used up until the 1990s when the combination regimen of EMA-CO was found to be well tolerated and has a response rate of approximately 83% (Curry et al. 1989) (Bower et al. 1997). EMA-CO has now become the preferred first-line combination regimen in the United States and Europe.

(c) MEA: This regimen, like EMA-CO, uses etoposide, methotrexate, and actinomycin D but omits the use of etoposide and Oncovin (vincristine); it has a 74.4% response rate (Matsui et al. 2000). It has been favored by some European centers because of its tolerability.

(d) 5-Flurouracil, methotrexate, etoposide (5-FUME): This regimen is mostly used in China and has an 80.8% remission rate in high-risk patients, which appears to be comparable to the published results seen with EMA-CO. It also appears that the toxicity profile of this regimen may be slightly better than that of EMA-CO. However, this regimen is far less studied, and further investigation is warranted (Wang et al. 2006).

(e) EMA-CO: In the late 1970s, it was discovered that etoposide was a very effective chemotherapeutic agent for GTD. EMA-CO was subsequently formulated by Newlands et al. (1986). Table 7 outlines the treatment regimen. As mentioned above, complete response rates and long-term survival rates of well over 80% have been reported with this regimen (Newlands et al. 1991). The toxicities of this regimen are manageable with the most common being anemia and neutropenia which may require a treatment delay of about a week (Schink et al. 1992; Escobar et al. 2003). Colony-stimulating factors (G-CSF 300 μg subcutaneous) can be administered on days 9–14 of the cycle if any neutropenia-related treatment delays are experienced. Treatment delays should be minimized as resistance can develop if interruption is experienced. This regimen is now the preferred first-line regimen for high-risk GTN.

3 Management of Refractory/ Persistent Disease

GTN that does not respond to first-line treatment is said to be resistant or refractory. Resistance to a particular chemotherapeutic regimen is evidenced by a plateau or rise in beta-hCG levels. Approximately 5% of low-risk patients and 25% of high-risk patients will have an incomplete response or experience a recurrence following the first-line therapy (Lurain and Nejad 2005). In this setting, salvage chemotherapy and surgical resection, when appropriate, are employed. A new WHO score must be assigned, and treatment is once again determined based on low- versus high-risk WHO score.

3.1 Low-Risk Refractory GTN

In treating low-risk GTN, if resistance to methotrexate is noted, it is common practice to use the sequential 5-day actinomycin D, followed

Table 8 EMA-EP schedule

Day	Agents	Dosing
EP		
1	Etoposide	150 mg/m^2 IV in 250 mL NS over 30 min
	Cisplatin	25 mg/m^2 IV in 1 L NS + 20 mmol KCL 4 h
EMA		
1	Etoposide	100 mg/m^2 IV in 250 mL NS over 30 min
	Methotrexate	300 mg/m^2 IV in 1 L NS over 12 h
	Actinomycin D	0.5 mg IV bolus
2	Folinic acid	15 mg PO or IM[a] BID for four doses 24 h after start of methotrexate

Adopted and modified from Newlands et al. (2000)
EP and EMA are alternated at weekly intervals
[a]The decision as to route of administration depends on development of nausea and ability to tolerate oral intake

by MAC or EMA-CO if further salvage treatment is required (Alazzam et al. 2012b).

3.2 High-Risk Refractory/ Recurrent GTN

Patients with persistent or recurrent high-risk GTN who develop resistance to methotrexate-containing regimens should be treated with platinum-containing combination regimens.

EMA-EP substitutes etoposide and cisplatin for cyclophosphamide and Oncovin in the EMA-CO protocol and is commonly the initial approach employed for patients who responded to EMA-CO and have plateauing beta-hCG levels or experience a recurrence (Table 8) (Lurain and Nejad 2005). Response rates can be as high as 75% in patients who previously failed EMA-CO. This regimen is moderately toxic; in particular it can be nephrotoxic and myelosuppressive, thus renal function must be closely monitored (Newlands et al. 2000).

Other regimens have also been described for use in this setting: BEP (bleomycin, etoposide, and cisplatin), VIP (vinblastine, ifosfamide, and cisplatin), ICE (ifosfamide, cisplatin, and etoposide), and TP/TE (paclitaxel, cisplatin/paclitaxel, etoposide) (Lurain and Nejad 2005); (Wang et al. 2008). At the Brewer Trophoblastic Disease Center, BEP is the first choice for treating high-risk patients who are resistant to EMA-CO/EMA-EP (Lurain and Nejad 2005). Charing Cross Hospital in London has presented TP/TE as an effective, relatively well-tolerated salvage regimen for patients with heavily pretreated high-risk GTN (Wang et al. 2008).

Figure 1 provides a proposed chemotherapy treatment algorithm for both low-risk/high-risk GTN and refractory disease as described above. It is important to note that refractory cases should be referred to a trophoblastic disease center for consultation.

3.3 Non-gestational Trophoblastic Tumors (Non-GTT)

In the setting of high-risk refractory GTN, one must also think of and evaluate for non-gestational trophoblastic tumors (Alifrangis et al. 2013). These are choriocarcinomas that are not associated with pregnancy. Oftentimes, the distinction can be made on histopathology by finding the absence of syncytiotrophoblasts. However, some non-GTTs can exhibit trophoblastic differentiation making the distinction difficult. Genetic testing of the tumor with microsatellite genotyping can be employed to examine the genetic origin of these tumors (Fisher et al. 2007). Non-GTTs do not respond to chemotherapy and have a very poor prognosis; being able to distinguish between GTT and non-GTT helps optimize patient care.

4 Special Considerations

4.1 Vaginal Metastases

The incidence of vaginal metastasis in choriocarcinoma is 8.6% (Yingna et al. 2002). The vagina is the second most common metastatic site in GTN, with the lung being the most common. These patients present with friable, vascular lesions located in the anterior wall of

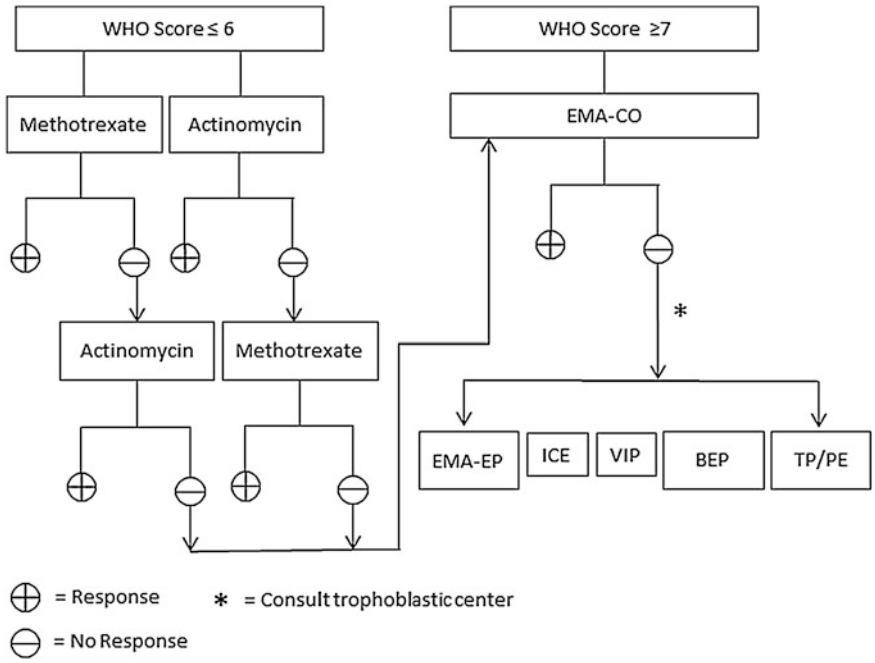

Fig. 1 Proposed chemotherapy treatment algorithm. Abbreviations: *WHO*, World Health Organization; *EMA-CO*, etoposide, methotrexate, actinomycin D, cyclophosphamide, and Oncovin; *EMA-EP*, etoposide, methotrexate, actinomycin D, etoposide, and cisplatin; *BEP*, bleomycin, etoposide, and cisplatin; *ICE*, ifosfamide, cisplatin, and etoposide; and *TP/TE*, paclitaxel, cisplatin/paclitaxel, etoposide

the lower vagina. Though performing a biopsy for diagnostic conformation may be tempting, it puts the patient at great risk for hemorrhage and is therefore discouraged when metastatic GTN is suspected. If patients present with spontaneous hemorrhage, vaginal packing with the use of hemostatic agents should be employed. Selective angiographic embolization by interventional radiology is another viable option in the setting of acute hemorrhage. Treatment for vaginal metastasis includes systemic treatment with chemotherapy as well as local injection with 5-FU (Yingna et al. 2002).

4.2 Brain Metastases

Metastases to the brain and central nervous system (CNS) are observed in up to 10–15% of patients with GTN. CNS involvement is frequent enough that it is one of the criteria used to assign patients to the high-risk category. Treatment of CNS metastasis has evolved to include whole brain radiation (WBRT). It has shown to have significant therapeutic benefit in the treatment of GTN with improved overall survival. The survival of patients with metastatic GTN to the brain is excellent if extracranial disease is controlled (Schechter et al. 1998). It is recommended that WBRT be initiated simultaneously with the start of multi-agent systemic chemotherapy (Yordan et al. 1987). Should chemotherapy be initiated before WBXRT there is increased risk of intracranial hemorrhage. Treatment initiation with WBRT can reduce the incidence of hemorrhage and resultant sequela in the first 2 weeks of chemotherapy administration (Schechter et al. 1998).

When treating patients with brain metastases, the systemic dose of methotrexate administered IV must be increased because the concentrations of methotrexate in the cerebrospinal fluid have been found to be less than 5% of plasma concentrations. The use of high-dose methotrexate regimens without concomitant

WBRT has achieved remission rates as high as 69%; the addition of WBRT can increase remission rates to 78% (Schechter et al. 1998).

Intrathecal chemotherapy in conjunction with systemic chemotherapy has also been evaluated in the setting of CNS metastasis and has yielded excellent survival rates (Small et al. 1996). A direct comparison between intrathecal chemo administration and WBRT has yet to be made. However, it appears that treatment with WBRT is more commonly employed.

WBRT is not without toxicity. It can lead to long-term sequelae including impaired cognitive function, dementia, behavioral changes, and ataxia. For this reason, in the setting of a solitary brain lesion, craniotomy with surgical resection should be employed in efforts to avoid WBRT. More recently, the use of stereotactic radiosurgery has been employed and reported by Charing Cross to treat multiple brain metastases or solitary lesions in locations that are inaccessible with surgery (Soper et al. 2007).

If a CNS recurrence is suspected during surveillance and no lesion is noted on imaging, a plasma to spinal fluid ratio can be obtained. In the absence of brain metastases, the spinal fluid beta-hCG level is proportional to that of plasma. A plasma to spinal fluid ratio less than 60 is confirmatory of CNS recurrence (Bagshawe and Harland 1976). Overall patients with brain metastases have a good prognosis; however, those who develop brain metastases during treatment with systemic therapy or recur to brain after WBRT have the poorest prognosis (Evans et al. 1995).

4.3 Reproductive Outcomes After Treatment for GTN

GTN affects women of reproductive age; thus, fertility and reproductive outcomes following treatment are of utmost importance. Studies evaluating the reproductive outcome of patients treated for both low- and high-risk GTN have concluded that reproductive outcomes do not differ from the general population. In addition the chemotherapy regimen does not affect reproductive performance when comparing single-agent methotrexate to multi-agent therapy (Woolas et al. 1998). However, data regarding the risk of congenital malformation appears to be conflicting; while some studies conclude that the risk is similar to that of the general population in both frequency and type for both single and multi-agent therapy, another concluded that the risk of congenital heart abnormalities (particularly ventricular septal defects) is higher in the group receiving multi-agent treatment (Goto et al. 2004). The overall risk of congenital anomalies is relatively low but should be discussed with patients receiving multi-agent therapy for GTN. The American Society of Clinical Oncology stresses the importance of discussing the potential for infertility with all patients undergoing treatment for cancer. While treatment for GTN appears to have minimal effect on reproductive outcomes, the possibility of infertility should be addressed and documented.

4.4 Post-molar Prophylactic Chemotherapy

To date, the use of chemotherapy for primary prevention of post-molar GTN remains controversial as there is conflicting data regarding efficacy (Ayhan et al. 1990). Patients with high-risk hydatidiform moles, as defined in Table 9, have up to a 50% chance of developing post-molar GTN (Uberti et al. 2009). It has been argued that chemotherapy administered at the time of uterine evacuation in this patient population can prevent the development of GTN; however, studies have shown that prophylactic chemotherapy is not without risk. Those who receive chemoprophylaxis are known to have prolonged hospital stays and chemotherapy-related toxicities and require more courses of chemotherapy to cure subsequent GTN, all of which may seem too risky for a disease with an excellent cure rate. Nevertheless, it does not affect reproductive outcomes and has also been shown to reduce psychological angst, medical visits, and operational costs associated with management of post-molar GTN/persistent GTD (Uberti et al.

Table 9 Risk scoring system for the prediction of developing GTN in women with a molar pregnancy

Score	0	1	2	3
Ultrasound diagnosis of HM in current pregnancy	Partial	Complete	Recurrent	-
Uterine size for gestational age at diagnosis of molar pregnancy	Size = or < dates	Size 4 weeks greater than corresponding gestational age	Size 8 weeks greater than corresponding gestational age	Size 12 weeks greater than corresponding gestational age
Beta-hCG levels (mU/mL)	<50,000	50,000–100,000	100,000–1,000,000	>1,000,000
Diameter of theca lutein cyst (cm)	-	<6	6–10	>10
Patient's age (years)	-	<20	≥40	>
Associated medical complications[a]	-	≥1	-	-

Adopted and modified from Uberti et al. (2006)
Final score of <4 is low risk; ≥4 is high risk
HM, hydatidiform mole
[a]Hyperthyroidism, hyperemesis, preeclampsia, trophoblastic embolization, disseminated intravascular coagulation

2009). Though the use of chemoprophylaxis is not widely accepted, most agree that its use is most appropriate for patients with high-risk moles in settings where serial beta-hCG levels cannot be followed and in those with poor compliance, such as in the adolescent population (Uberti et al. 2006). Table 9 offers a scoring system for the prediction of developing GTN in women with a molar pregnancy. Women with a score of greater than or equal to 4 are deemed to be high-risk of developing GTN and may benefit from post-molar prophylactic chemotherapy. Table 10 provides a summary of the published studies evaluating the efficacy of post-molar chemoprophylaxis. Methotrexate administered at 0.4 mg/kg IM for 5 days did not prove effective for post-molar prophylaxis. However, actinomycin D at 1.25 mg/m^2 IV X 1 dose has shown to reduce the rate of post-molar GTN in high-risk molar pregnancies.

Table 10 Summary of prophylactic chemotherapeutic regimens and response

Chemotherapy	Schedule	Rate of post-molar GTN in high-risk mole Control versus Prophylactic Chemotherapy
Methotrexate (Ayhan et al. 1990)	0.4 mg/kg IM, 5 days	26.2% vs 25%
Actinomycin D (Uberti et al. 2009)	1.25 mg/m^2 IV, one dose	34.3% vs 18.4%
Actinomycin D (Uberti et al. 2006)	1.25 mg/m^2 IV, one dose	29% vs 6.9%

4.5 Phantom Beta-hCG, Quiescent GTD, and Physiologic Beta-hCG

After treatment for GTN is complete, it is recommended that quantitative serum beta-hCG levels be followed monthly for 6–12 months after normalization as the risk of relapse is about 3% during the first year and significantly decreases thereafter (Lurain 2011). Women with persistent mildly elevated beta-hCG levels can exhibit false-positive results caused by non-specific heterophilic antibodies. This can lead to unnecessary workup and treatment intervention for presumed persistent or recurrent disease. Two criteria have been developed to identify false-positive beta-hCG levels: (1) elevated serum beta-hCG levels in the setting of a negative urine pregnancy test and (2) finding of more than a fourfold difference between commercially available immunoassays

employed in the common clinical setting and those used by reference laboratories (Rotmensch and Cole 2000).

False-positive beta-hCG must be differentiated from quiescent GTD. Quiescent GTD is defined by persistent low levels of beta-hCG present for at least 3 months with no changed in beta-hCG trend. It is caused by a small focus of persistent slow-growing syncytiotrophoblasts that produce low levels of beta-hCG but do not typically progress to invasive disease (Cole 2010). Testing for hyperglycosylated hCG (h-hCG) can be employed to discriminate quiescent GTD from active trophoblastic malignancy. Quiescent GTD does not respond to chemotherapy. H-hCG is produced by invasive cytotrophoblasts and therefore a marker of invasive cells. It can be used by clinicians to decide when treatment is not indicated but also help detect active disease at its inception so that appropriate treatment can be initiated (Cole et al. 2006).

Low levels of physiologic beta-hCG are secreted from the pituitary alongside luteinizing hormone (LH) during the LH surge of the ovulatory cycle. Pituitary beta-hCG production increases with age and is frequently detected in perimenopausal or postmenopausal women. Physiologic expression of beta-hCG has led to unnecessary treatment for GTN. Pituitary expression of beta-hCG can be suppressed with a short course of combined oral contraceptives and can help rule out GTN (Cole et al. 2008).

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