Current Management of Gestational Trophoblastic Neoplasia

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KEYWORDS

• Gestational trophoblastic neoplasia • Invasive mole
• Choriocarcinoma • Human chorionic gonadotropin

Gestational trophoblastic neoplasms (GTN) are malignant lesions that arise from placental villous and extravillous trophoblast. Four clinicopathologic conditions make up this entity: (1) invasive mole, which follows either complete hydatidiform mole (CHM) or partial hydatidiform mole (PHM), (2) choriocarcinoma (CCA), (3) placental-site trophoblastic tumor (PSTT), and (4) epithelioid trophoblastic tumor (ETT). Each of these conditions can perforate the uterine wall, metastasize, and lead to death if left untreated. Approximately 50% of cases of GTN arise from molar pregnancy, 25% from miscarriage or tubal pregnancy, and 25% from term or preterm pregnancy.[1] Invasive mole and CCA, which make up the majority of these tumors, always produce easily detectable amounts of human chorionic gonadotropin (hCG) and are highly responsive to chemotherapy with an overall cure rate exceeding 90%, making it usually possible to achieve cure while preserving reproductive function. This success is attributable to several factors, the most important of which are the unique sensitivity of these two trophoblastic neoplasms to chemotherapeutic agents and the use of hCG as a tumor marker for diagnosis, monitoring treatment, and follow-up. By contrast, PSTT and ETT, which rarely occur, produce scant amounts of hCG and are relatively resistant to chemotherapy, making surgery the primary treatment modality. Chemotherapy is used for PSTT and ETT only when the disease has metastasized.

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EPIDEMIOLOGY

The incidence and etiologic risk factors that contribute to the development of GTN have been difficult to characterize because of problems in accumulating reliable epidemiologic data, bias, and interpretation and differing methods of expressing incidences in terms of hospital-based versus population-based data. Despite these problems, there are sufficient data to indicate that there are wide regional variations in the incidence of CHM.[2,3] Estimates from North America, Australia, New Zealand, and Europe have shown the incidence of CHM to range from 0.57 to 1.1 per 1000 pregnancies, whereas studies from Southeast Asia and Japan report an incidence approaching 2.0 per 1000 pregnancies.[2–6] Similarly there are data that show an increased incidence of CHM among American Indians, Eskimos, Hispanics, and African Americans as well as various Asian populations.[7] There is no conclusive evidence that genetic traits, cultural factors, or differences in reporting account for this increase. The etiologic risk factors that have been linked to the development of CHM are advanced maternal age (>40 years) and prior molar pregnancy.[8,9] Familial clusters of biparental CHM have been associated with NLRP7 gene mutations on chromosome 19q.[10] In addition, well-documented nutritional studies have shown an inverse relationship between β-carotene and animal dietary fat intake and the incidence of CHM.[11,12] In this regard, it is of interest that the documented decrease in the incidence of CHM in South Korea has been associated with a gradual Westernization of the Korean diet.[13]

Determining the incidence rate of CCA is even more problematic because of the rarity of this condition and the difficulty in clinically distinguishing postmolar CCA from metastatic mole. In Europe and North America CCA affects approximately 1 in 40,000 pregnancies, whereas in Southeast Asia and Japan CCA rates are higher at 9.2 and 3.3 per 40,000 pregnancies, respectively. The incidence of both CHM and CCA has gradually declined over the past 30 years.[14,15]

Risk factors for CCA include prior CHM, ethnicity, and advanced maternal age. CCA is 1000 times more likely to occur after CHM than after another type of pregnancy. The risk is also increased in women of Asian, American Indian, and African descent.[15]

PATHOLOGY

Invasive mole develops when molar villi invade the myometrium. Metastases of invading molar villi occur via direct extension through venous channels. Approximately 15% of CHM will result in local invasion, and 5% will develop metastases usually to the lungs or vagina.[16] The development of local invasion after PHM occurs in only 3% to 5% of patients, and metastatic disease is rare.[16] The diagnosis of postmolar GTN is based on a plateau or elevation of hCG levels after molar evacuation rather than on pathology. Therefore, treatment with chemotherapy is frequently initiated without a histopathologic diagnosis other than the antecedent pregnancy.[17]

CCA is a highly malignant disease characterized by hyperplastic and anaplastic syncytioblasts and cytotrophoblasts, absence of chorionic villi, hemorrhage, and tissue necrosis. CCA spreads by directly invading the myometrium and vascular channels, resulting in involvement at distant sites, most commonly the lungs, adnexa, vagina, brain, liver, kidney, intestines, and spleen. In contrast to invasive mole, the vast majority of cases of CCA arise following a nonmolar pregnancy.

PSTT is an extremely rare tumor that arises from the placental implantation site and consists of mononuclear intermediate trophoblasts without chorionic villi that infiltrates between myometrial fibers in sheets or chords. PSTT is associated with less vascular invasion, necrosis, and hemorrhage than CCA. Unlike CCA, PSTT has

a propensity for lymphatic metastases. Immunohistochemical staining reveals the diffuse presence of cytokeratin and human placental lactogen (hPL), whereas hCG is only present focally. Because of its slow growth, paucity of symptoms, and low hCG production, early detection is the exception rather than the rule. Most PSTTs follow nonmolar gestations.[18] Because of their relative insensitivity to chemotherapy, the mortality rate of PSTT exceeds that of CCA.

ETT is a rare variant of PSTT that develops from neoplastic transformation of chorionic-type extravillous trophoblast. Like PSTTs, ETTs can present many years after a term delivery. When diagnosed these tumors appear grossly as nodular infiltrates in the myometrium.[19,20]

CLINICAL PRESENTATION

GTN has a varied presentation depending on the antecedent pregnancy, extent of disease, and histopathology. Postmolar GTN (usually invasive mole, occasionally CCA) most commonly presents following evacuation of CHM whose preevacuation uterine size is larger than dates and/or whose hCG level is greater than 100,000 mIU/mL.[21] Bilateral ovarian enlargement is frequently present when the hCG level is markedly elevated. Signs suggestive of persistent disease are an enlarged uterus, irregular bleeding, and persistent bilateral enlarged ovaries. Rarely a metastatic nodule will be present in the vagina, which can bleed vigorously, particularly if biopsied. The Cancer Committee of the International Federation of Gynecologists and Obstetricians (FIGO) has established the following guidelines for the diagnosis of postmolar GTN[22]:

1. Four values or more of hCG plateaued over at least 3 weeks
2. An increase in hCG of 10% or greater for 3 or more values over at least 2 weeks
3. The histologic diagnosis of CCA
4. Persistence of hCG 6 months after molar evacuation.

CCA, the most common histopathologic type of GTN that develops following term pregnancies or miscarriages, may present with nonspecific signs and symptoms, making the diagnosis difficult; this frequently accounts for a delay in diagnosis that often adversely affects prognosis. Therefore, GTN should be considered and an hCG test performed in any woman in the reproductive age group who presents with abnormal uterine bleeding or unexplained metastatic disease. GTN following a term or preterm gestation usually presents with uterine bleeding due to invasion of tumor, or bleeding from a metastatic site. Bleeding from uterine perforation or metastatic lesions may result in abdominal pain, hemoptysis, or melena. Patients with central nervous system metastases often exhibit evidence of increased intracranial pressure from intracerebral hemorrhage, leading to headaches, dizziness, seizures, or hemiplegia. Patients who develop extensive pulmonary metastases may present with dyspnea, cough, or chest pain. PSTTs and ETTs almost always cause irregular bleeding or amenorrhea, frequently long after the antecedent pregnancy. There are rare reported cases of nephrotic syndrome and virilizing syndrome associated with these conditions.[18–20]

WORKUP

Once the diagnosis of GTN is suspected or established, a metastatic workup should be undertaken to determine the extent of disease. Selection of appropriate therapy for patients with GTN is based on both the anatomic staging system adopted by FIGO and the Prognostic Scoring System adopted by the World Health Organization (WHO).[23]

The workup needed to adequately stage and score GTN should include:

1. History and physical examination, baseline (pretreatment) serum quantitative hCG level, complete blood and platelet count, and tests of hepatic and renal function
2. Review of all available pathologic specimens.
3. Pelvic ultrasonography to detect the extent and nature of uterine involvement to help identify patients with deep uterine wall involvement who are at risk of uterine perforation, or who would benefit from a tumor-debulking hysterectomy.
4. Chest radiograph to determine the presence of lung metastases. If the chest radiograph is negative a computed tomography (CT) scan of the chest may be obtained because approximately 40% of patients with negative chest radiographs have metastatic lesions on CT scan. Controversy exists as to the significance of these micrometastases with regard to the patient's response to chemotherapy.[24] In the absence of chest metastases, imaging of other organs may not be necessary because distant metastases are then rarely encountered.
5. Magnetic resonance imaging (MRI) of the brain and abdominopelvic CT scan or MRI are indicated to identify lesions in the brain, liver, and other abdominal organs if the chest radiograph or chest CT indicates the presence of lung metastases.
6. Repeat curettage after molar evacuation is not indicated unless there is excessive uterine bleeding associated with retained molar tissue. Controversy exists as to whether repeat dilation and curettage reduces the incidence of persistent postmolar GTN.[25,26]
7. Cerebrospinal fluid/plasma hCG ratio is sometimes used to confirm cerebral involvement.[27,28]
8. Additional imaging such as ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) may be useful to accurately identify sites of metabolically active disease or viable metastases and to help determine the potential for tumor resectability.[29]

STAGING AND RISK ASSESSMENT

In 2002, the FIGO adopted a combined anatomic staging (**Box 1**) and modified WHO risk-factor scoring system (**Table 1**) for GTN. The FIGO stage is designated by a Roman numeral followed by the modified WHO score designated by the Arabic number separated by a colon.[22] PSTTs and ETTs are classified separately. Treatment is based on the total score, which signifies the risk of the patient developing drug resistance. Patients whose WHO scores are less than 7 are considered to be at low risk,

Box 1
FIGO staging of gestational trophoblastic neoplasia

Stage I

Disease confined to the uterus

Stage II

Disease extends to the outside of the uterus, but is limited to the genital structures

Stage III

Disease extends to the lungs, with or without genital tract involvement

Stage IV

All other metastatic sites

Table 1
World Health Organization risk scoring system based on prognostic factors

	Score			
Prognostic Factors	**0**	**1**	**2**	**4**
Age (y)	<40	>39	—	—
Antecedent pregnancy	Mole	Abortion	Term	—
Interval (mo)[a]	<4	>3, <7	>6, <13	>12
Pretreatment serum hCG (mIU/mL)	$<10^3$	10^3 to $<10^4$	10^4 to $<10^5$	$>10^5$
Largest tumor, including uterine (cm)	—	3 to <5	>4	—
Site of metastases	Lung	Spleen, kidney	Gastrointestinal tract	Brain, liver
Number of metastases	—	1–4	5–8	>8
Prior failed chemotherapy	—	—	Single drug	Two drugs

[a] Interval (in months) between end of antecedent pregnancy (where known) or onset of symptoms.

and patients with scores greater than 6 are considered to be at high risk of developing drug resistance. Patients with nonmetastatic disease (Stage I) and low-risk metastatic GTN (Stages II and III, score <7) can be treated initially with single-agent chemotherapy with cure rates approaching 80% to 90%. On the other hand, patients classified as having high-risk metastatic disease (Stage IV and Stages II–III with scores >6) require multiagent chemotherapy, possibly with adjuvant radiation and/or surgery, as indicated, to achieve similar cure rates.[1] There is growing evidence that patients with low-risk GTN who have a large tumor burden reflected in hCG levels of greater than 100,000 mIU/mL and/or prognostic scores of 5 to 6 are associated with an increased risk of initial drug resistance and, therefore, should be treated initially with multiagent chemotherapy.[30] The use of the FIGO staging/scoring system has become the accepted basis for determining the optimal initial therapy that affords the patient the best outcome with the least morbidity.

TREATMENT OF LOW-RISK GTN

Patients with nonmetastatic (Stage 1) and low-risk metastatic GTN (Stages II–III, score <7) should be treated initially with single-agent methotrexate (Mtx) or actinomycin D (actD).[31] Several different outpatient protocols have been used and have yielded fairly comparable results (**Box 2**). The variability in primary remission rates reflect differences in drug dosages, schedules, and routes of administration, as well as patient selection criteria. In general, the weekly intramuscular (IM)[32–34] and intermittent intravenous (IV) infusion of Mtx[35–37] and the biweekly single-dose actD[38–42] protocols are less effective than the 5-day Mtx or actD protocols and the 8-day Mtx/folinic acid (FA) regimen.[43–47] Despite these differences in primary remission rates, all patients with low-risk GTN are eventually cured, with preservation of fertility when desired.

At the New England Trophoblastic Disease Center (NETDC), the initial regimen consists of the sequential use of 8-day Mtx/FA and 5-day actD regimens. A recent study from NETDC found the 8-day Mtx/FA protocol to be not only a highly effective regimen but the most cost-effective as well. Most patients are treated initially with Mtx because it has fewer side effects than actD.[47–49] actD should be used as first-line therapy in patients with evidence of preexisting or chemotherapy-related hepatic

Box 2
Single-agent regimens for low-risk gestational trophoblastic neoplasms

Mtx Regimens

1. Mtx: 0.4–0.5 mg/kg IV or IM daily for 5 days
2. Mtx: 30–50 mg/m^2 IM weekly
3. Mtx/FA:
   a. Mtx 1 mg/kg IM or IV on days 1, 3, 5, 7
   b. FA 10 mg PO days 2, 4, 6, 8
4. High-dose Mtx/FA
   a. Mtx 100 mg/m^2 IV bolus
   b. Mtx 200 mg/m^2 12 h infusion
   c. FA 15 mg every 12 h in 4 doses IM or PO beginning 24 h after starting Mtx

Actinomycin D Regimens

1. actD 10–12 μg/kg IV push daily for 5 days
2. actD 1.25 mg/m^2 IV push every 2 weeks

Abbreviations: actD, actinomycin D (Cosmegan); FA, folinic acid (calcium leucovorin); IM, intramuscular; IV, intravenous; Mtx, methotrexate; PO, by mouth.

dysfunction, or who have had a known adverse reaction to Mtx, and as sequential therapy if the patient exhibits Mtx resistance. Unlike Mtx, which can be given IM or IV, actD must be administered through an adequate vein to reduce the risk of local tissue injury due to extravasation. The most bothersome side effects of actD are severe nausea and vomiting (which is rarely encountered with Mtx), hair loss, and a pruritic acneiform rash. Treatment is usually continued at 2- to 3-week intervals until the hCG level becomes undetectable. One or two courses of consolidation therapy are administered after gonadotropin remission (3 consecutive weekly undetectable hCG titers) is achieved in patients with Stage I GTN who require sequential or multiagent therapy, and in all patients with low-risk Stage II and III metastatic GTN. The authors usually do not administer consolidation therapy to patients with FIGO Stage I GTN (nonmetastatic disease) who respond completely to the initial single-agent regimen. In select patients with Stage I GTN and low FIGO scores (<3), it is their practice to closely monitor the hCG level after the first course of therapy and administer additional courses only if the hCG level fails to decline by 1 log within 18 days, if the hCG level plateaus or rises.

If the hCG level declines by less than 1 log, the patient is considered to be relatively resistant to that drug, and either an alternative agent is considered or the dose of the original drug is escalated, toxicity permitting. In general, patients with low-risk GTN should be treated with the least toxic effective therapy. When resistance to single-agent therapy is encountered for both Mtx and actD, combination chemotherapy with either MAC (Mtx, actD, and cyclophosphamide) or EMA/CO (etoposide, Mtx, actD, cyclophosphamide, and vincristine) is initiated. Factors found to be associated with resistance to initial Mtx chemotherapy were high pretreatment hCG levels, nonmolar antecedent pregnancy, and clinicopathologic diagnosis of CCA.[50] The use of etoposide as in EMA/CO in GTN patients has been associated with an increased risk of secondary tumors including leukemia, breast and colon carcinoma, and

melanoma.[51] For that reason it is the authors' policy to use MAC as the combination chemotherapy in patients with low-risk GTN who become resistant to single-agent therapy.

Regardless of the treatment protocol used, chemotherapy should be continued until the hCG level becomes undetectable. At that point consolidation therapy may be indicated, as discussed earlier. Chemotherapy is changed to an alternative singe-agent regimen if the hCG level plateaus above normal during treatment, or if toxicity precludes adequate dose or frequency of treatment. Multiagent therapy should be initiated promptly if resistance to sequential single-agent chemotherapy develops as reflected by inadequate hCG response or disease progression.

Table 2 summarizes the authors' experience with the treatment of low-risk GTN patients at the NETDC. A total of 745 women with low-risk GTN were treated between 1965 and 2010. Complete remission was achieved with single-agent chemotherapy in 501 of 588 patients (85.2%) with Stage I GTN, 17 of 21 patients (81%) with low-risk Stage II disease, and 108 of 136 patients (79.4%) with low-risk Stage III GTN. All 118 patients (15.8%) with low-risk GTN who developed resistance to initial single-agent therapy achieved remission with combination chemotherapy with or without surgery.

Hysterectomy was used as initial therapy in 33 patients with Stage I GTN who no longer wished to preserve fertility. Because of the risk of occult metastatic disease, it is the authors' practice to administer adjunctive chemotherapy with either high-dose

Table 2
Results for patients with low-risk gestational trophoblastic neoplasia treated at the NETDC, 1995–2010

Stage	No. of Patients	No. of Remissions
I	588	588 (100%)
Initial Therapy		502 (85.4%)
Sequential Mtx/actD		459
Combination chemotherapy[a]		1
Hysterectomy[b] (with adjunctive chemotherapy)		33
Local resection[b] (with adjunctive chemotherapy)		9
Resistant Therapy		86 (14.6%)
Combination chemotherapy[a]		71
Hysterectomy/local resection[b]		14
Pelvic infusion		1
II	21	21 (100%)
Initial Therapy		17 (81%)
Sequential Mtx/actD		17
Resistant Therapy		4 (19%)
Combination chemotherapy[a]		4
III	136	136 (100%)
Initial Therapy		108 (79.4%)
Sequential Mtx/actD		108
Resistant Therapy		28 (20.6%)
Combination chemotherapy[a]		28

[a] Includes MAC (methotrexate, actinomycin D, cyclophosphamide), EMA (etoposide, methotrexate, actinomycin D), EMA/CO (EMA, cyclophosphamide, vincristine), EMA/EP (EMA, cisplatin).
[b] With adjunctive chemotherapy.

IV Mtx/FA or bolus actD at the time of surgery. Hysterectomy should also be considered when the uterus is extensively involved with tumor to prevent or treat hemorrhage, perforation, and/or infection. Under these circumstances, hysterectomy may shorten the duration of treatment with multiagent chemotherapy in patients with resistance to single-agent therapy.

In summary, cure rates for both nonmetastatic and low-risk metastatic GTN should approach 100% with the use of single-agent Mtx and actD administered sequentially and the use of multiagent protocols when resistance to single agents develops. Approximately 10% to 30% of low-risk patients will develop resistance to the initial agent used and thus require a second drug, and 15% to 20% will require multiagent chemotherapy with or without hysterectomy to achieve remission. The patients most likely to prove resistant to single-agent therapy are those with higher risk scores.

TREATMENT OF HIGH-RISK GTN

Patients with high-risk metastatic GTN (FIGO Stage IV and Stages II–III, score >6) should be treated initially with multiagent chemotherapy with or without adjuvant radiation therapy and/or surgery. During the 1970s and 1980s the preferred first-line multiagent regimen consisted of Mtx, actD, and cyclophosphamide or chlorambucil (MAC), which achieved cure rates in this group of patients of 50% to 71%.[52–54] In the 1980s etoposide was found to be a highly effective agent for GTN when used as a single agent in patients with low-risk disease[55] and in combination with Mtx, actD, cyclophosphamide, and vincristine (EMA/CO). EMA/CO is now the preferred primary combination chemotherapy regimen in high-risk metastatic GTN with an 80% to 90% remission rate.[56–58] **Tables 3** and **4** summarize the most commonly used multiagent protocols for patients with high-risk GTN and low-risk GTN who are resistant to single agents.

Table 5 summarizes the experience at the NETDC of 115 patients with high-risk GTN. Six of 8 patients (75%) with high-risk Stage II disease, and 55 of 64 patients (85.9%) with high-risk Stage III GTN achieved remission with their initial therapy. All but one of the 11 remaining patients with high-risk Stage II and III GTN who were resistant to their initial regimen ultimately achieved remission. Of the 23 patients with Stage IV disease treated after 1975 when initial multiagent chemotherapy became standard procedure, 18 (78.3%) were cured. The only patients who died in this series were 14 Stage IV patients treated before 1975 initially with single-agent regimens, and 5 Stage IV patients treated after 1975 with initial multiagent regimens. Most reports concur that mortality occurs almost exclusively in those patients with high-risk scores characterized by a histopathologic diagnosis of CCA who present with brain and/or liver metastases.[59]

In patients with high-risk GTN, optimal cure rates are achieved by the intermittent intensive administration of chemotherapy at 2- to 3-week intervals, toxicity permitting. Medications to support blood cell production should be used as necessary. However, the regimens are generally well tolerated. No treatment-related deaths or life-threatening toxicity should occur if marrow, renal, and hepatic function are monitored carefully. Neutropenia necessitating a 1-week delay of treatment, anemia requiring blood transfusions, and grades 3 to 4 neutropenia without thrombocytopenia are reported to occur in only 14%, 5.8%, and 1.9% of treatment cycles, respectively.[60–64] Patients who develop resistance to EMA/CO can be treated with EMA/EP, a regimen that substitutes cyclophosphamide and vincristine on day 8 with cisplatin or carboplatin and etoposide.[65–67] In patients with EMA/CO resistance, EMA/EP induced

Table 3
Protocols for EMA/CO and EMA/EP regimens

Day	Drug	Dose
Protocol for EMA/CO		
1	Etoposide	100 mg/m^2 by infusion in 200 mL saline over 30 min
	actD	0.5 mg IVP
	Mtx	100 mg/m^2 IVP
		200 mg/m^2 by infusion over 12 h
2	Etoposide	100 mg/m^2 by infusion in 200 mL saline over 30 min
	actD	0.5 mg IVP
	Folinic acid	15 mg every 12 h $\times$ 4 doses IM or PO beginning 24 h after starting Mtx
8	Cyclophosphamide	600 mg/m^2 by infusion in saline over 30 min
	Vincristine	1 mg/m^2 IVP
Protocol of EMA/EP		
1	Etoposide	100 mg/m^2 by infusion in 200 mL saline over 30 min
	actD	0.5 mg IVP
	Mtx	100 mg/m^2 IVP
		200 mg/m^2 by infusion over 12 h
2	Etoposide	100 mg/m^2 by infusion in 200 mL saline over 30 min
	actD	0.5 mg IVP
	Folinic acid	15 mg every 12 h $\times$ 4 doses IM or PO
8	Cisplatin	60 mg/m^2 IV with prehydration
	Etoposide	100 mg/m^2 by infusion in 200 mL saline over 30 min

Abbreviations: actD, actinomycin (Cosmegan); EMA/CO, etoposide, actinomycin D, methotrexate, cyclophosphamide, vincristine; EMA/EP, etoposide, methotrexate, actinomycin D, cisplatin; FA, folinic acid; IM, intramuscular; IVP, intravenous push; Mtx, methotrexate; PO, by mouth.

remission, sometimes with surgical intervention, in 9 of 12 (75%) patients.[67] In contrast to the management of patients with low-risk GTN, it is mandatory to continue chemotherapy for high-risk disease for at least 2 to 3 courses after the first normal hCG in order to reduce the likelihood of relapse.

MANAGEMENT OF CENTRAL NERVOUS SYSTEM METASTASES

When central nervous system metastases are present, either whole brain irradiation (3000 cGy in 200 cGy fractions) or surgical excision with stereotactic irradiation in selected patients is usually given simultaneously with the initiation of systemic chemotherapy.[68–71] During radiotherapy, it is advisable to increase the Mtx infusion dose to 1 g/m^2 with 30 mg of FA every 12 hours for 3 days starting 32 hours after the start of the infusion, to facilitate passage of the drug through the blood-brain barrier.[72] An alternative to brain irradiation is surgical excision, particularly in those patients whose lesion is solitary and located peripherally.[72]

MANAGEMENT OF PULMONARY METASTASES

Surgery is also an important adjunct to chemotherapy in the management of solitary pulmonary nodules, particularly if they prove resistant to chemotherapy.[73–78] Tomoda and colleagues[73] reported on 19 patients with chemoresistant GTN who were treated with adjuvant thoracotomy. Based on their experience they proposed the following criteria to predict successful outcome: (1) patient is a good surgical candidate; (2)

Table 4
Protocol for MAC regimen

Day	Drug	Dose
1	Mtx	1 mg/kg IM
	actD	0.5 mg IVP
	Cyclophosphamide	3 mg/kg IVB over 45–60 min
2	FA	0.1 mg/kg PO[a]
	actD	0.5 mg IVP
	Cyclophosphamide	3 mg/kg IVB over 45–60 min
3	Mtx	1 mg/kg IM
	actD	0.5 mg IVP
	Cyclophosphamide	3 mg/kg IVB over 45–60 min
4	FA	0.1 mg/kg PO[a]
	actD	0.5 mg IVP
	Cyclophosphamide	3 mg/kg IVB over 45–60 min
5	Mtx	1 mg/kg IM
	actD	0.5 mg IVP
	Cyclophosphamide	3 mg/kg IVB over 45–60 min
6	FA	0.1 mg/kg PO[a]
7	Mtx	1 mg/kg IM
8	FA	0.1 mg/kg PO[a]

Abbreviations: actD, actinomycin D; FA, folinic acid (calcium leucovorin); IM, intramuscular; IVB, intravenous bolus; IVP, intravenous push; Mtx, methotrexate; PO, by mouth.
[a] Administer as either 5-mg or 10-mg tablets.

primary malignancy is controlled; (3) no evidence of other metastatic sites; (4) pulmonary metastasis is limited to one lung; (5) hCG level is less than 1000 mIU/mL. Complete remission was achieved in 14 of 15 (93%) patients who met all 5 criteria, but in none of 4 patients who met only 4 or fewer. Similar findings were reported from the NETDC by Fleming and colleagues,[74] who noted that 10 of 11 (90.9%) carefully selected patients with drug- resistant pulmonary metastases achieved remission following resection of the solitary pulmonary tumor. An undetectable hCG level within 2 weeks of resection of a solitary nodule is highly predictive of a favorable outcome. Pulmonary resection can also establish the diagnosis of GTN in cases where a histopathologic diagnosis is desired. An example of this would be a patient with an elevated hCG level and no history of a recent antecedent pregnancy. Although pulmonary resection can be useful, it must be noted that thoracotomy is seldom necessary and should be undertaken in carefully selected cases, because most lung lesions are successfully treated with chemotherapy.

MANAGEMENT OF HEPATIC METASTASES

Although hepatic involvement poses perhaps the most serious problem, successful treatment with chemotherapy alone has been reported by both Wong and colleagues[79] and Bakri and colleagues,[80] who reported 90% and 62.4% complete remission, respectively, with primary intensive chemotherapy. Surgical intervention is limited to patients with acute bleeding, or for peripheral lesions that are drug resistant. Embolization has also been reported to be effective in controlling hemorrhage, although its use in the management of resistant disease has not been reported.[81,82]

Table 5
Results for patients with high-risk gestational trophoblastic neoplasia treated at the NETDC, 1995–2010

Stage	No. of Patients	No. of Remissions
II	8	8 (100%)
Initial Therapy		6 (75%)
Sequential Mtx/actD		2
Combination chemotherapy[a]		4
Resistant Therapy		2 (25%)
Combination chemotherapy[a]		2
III	64	63 (98.4%)
Initial Therapy		55 (85.9%)
Sequential Mtx/actD		14
Combination chemotherapy[a]		41
Resistant Therapy		8 (12.5%)
Combination chemotherapy[a]		8
IV		
Before 1975	20	6 (30%)
Initial Therapy		5 (25%)
Sequential Mtx/actD		5
Resistant Therapy		1 (5%)
Combination chemotherapy[a]		1
After 1975	23	18 (78.3%)
Initial Therapy		4 (17.4%)
Sequential Mtx/actD		2
Combination chemotherapy[a]		2
Resistant Therapy		14 (60.9%)
High-dose Mtx/actD		4
Combination chemotherapy[a]		10

[a] Includes MAC, EMA, EMA/CO, EMA/EP.

MANAGEMENT OF RECURRENT AND CHEMORESISTANT GTN

Chemoresistant disease poses a significant treatment challenge, which is most likely to occur in patients with Stage IV or high-risk Stage III GTN. Despite the use of multimodal primary therapy, up to 40% of patients will have an incomplete response to first-line chemotherapy or relapse after remission.[83–85] Most of these patients will have multiple metastatic sites to organs other than the lungs, pelvis, and vagina, and many will have had inadequate prior chemotherapy. Patients who relapse or develop resistance to multiagent chemotherapy should be restaged to determine the site of metastases and the feasibility of surgical resection or radiation. The use of FDG-PET imaging may be useful in detecting otherwise occult metastases. Mutch and colleagues[86] reported recurrence rates of 13% in patients with high-risk disease. At the NETDC recurrence rates range from 2.9% in Stage I, 8.3% in Stage II, 4.2% in Stage III, to 9.1% in Stage IV.[23] Several salvage regimens in addition to EMA/EP have been shown to be capable of inducing remission in selected patients. Osborne and colleagues[87] described a novel, 3-drug doublet regimen consisting of paclitaxel, etoposide, and cisplatin (TP/TE) that induced complete remission in 2 patients. Wang and colleagues[88] further studied this regimen in 16 patients with chemoresistant disease, including 6 patients previously treated with a platinum-based regimen. Of the 16 patients, 3 (19%) achieved a complete and 5 (31%) a partial response. Wan

and colleagues[89] reported 100% efficacy of a floxuridine-containing regimen when given to 21 patients with drug resistance. Matsui and colleagues[90] found that 5-fluorouracil in combination with actD induced complete remission in 9 of 11 cases (82%). Gordon and colleagues,[91] DuBeshter and colleagues,[92] and Azab and colleagues[93] reported on the efficacy of cisplatin, vinblastine, and bleomycin (PVB), which achieved remission in 2 of 11 patients (18%), 4 of 7 patients (57%) and 5 of 8 patients (62%), respectively. Regimens containing ifosfamide and paclitaxel have also been shown to have some success anecdotally in patient reports.[94,95] Autologous bone marrow transplantation or stem cell support concurrent with high-dose chemotherapy have also been used, with mixed success.[96,97] Because the number of truly resistant patients is small, it is difficult to study any of these regimens with any degree of statistical accuracy.

In summary, cure rates for high-risk GTN of 80% to 90% are now achievable with intensive multimodal therapy, with EMA/CO in conjunction with adjuvant radiotherapy and/or surgery when indicated. Recently, Alifrangis and colleagues from Charing Cross noted that survival for GTN patients who relapsed following EMA/CO improved significantly from 87% to 98%, when they were treated with 2 cycles of low-dose EP-induction chemotherapy (etoposide 100 mg/m^2 and cisplatin 20 mg/m^2) on days 1 and 2, repeated weekly $\times$ 2 before commencing EMA/CO.[98] This regimen is highly successful because its relatively low toxicity allows for adherence to the treatment schedule, high complete response rates, and overall high survival. Approximately 20% of high-risk patients will fail therapy or relapse from remission. Salvage therapy with platinum-containing drug combinations such as EMA/EP, often in conjunction with surgical resection of resistant sites, will result in cure of most high-risk patients with resistant disease. Even those patients with brain, liver, and gastrointestinal involvement now have a 75%, 73%, and 50% survival rate, respectively.[99]

MANAGEMENT OF COMPLICATIONS

Women with GTN may present with complications related to their disease, which may necessitate urgent management, including surgical or radiologic intervention. Bleeding from the uterus or metastatic sites is by far the most common complication. Hysterectomy may be necessary to control profuse bleeding or, occasionally, sepsis.[100–102] Cagayan and Suyen Magallanes[100] reported that of 134 women with GTN, 13 (9%) underwent hysterectomy for profuse bleeding, whereas 31 (24%) underwent hysterectomy for uterine rupture. Patients in whom preservation of fertility is a goal and who are hemodynamically stable may be candidates for angiographic uterine artery embolization.[81]

Vaginal metastases should not be biopsied because they are highly vascular and can bleed profusely. When bleeding cannot be controlled by a simple measure such as packing, embolization of pelvic vessels or wide local excision can be performed.[103] Bleeding from hepatic metastases are more problematic, sometimes requiring either local resection or selective hepatic arterial occlusion.[82]

MANAGEMENT OF PSTT AND ETT

Patients diagnosed with PSTT and ETT are managed similarly. Hysterectomy rather than chemotherapy is the first-line treatment in nonmetastatic disease because these neoplasms are relatively chemoresistant. At the time of surgery pelvic lymph nodes should be sampled because, in contrast to CCA, these tumors may spread via lymphatics. The survival rate for patients with nonmetastatic disease treated with hysterectomy alone is approximately 100%. Patients with metastatic disease may still

achieve remission with intensive multiagent chemotherapy, particularly when they are diagnosed within 4 years of the antecedent pregnancy.[104–106] The risk factors for metastatic disease in patients with PSTT include interval from previous pregnancy of longer than 2 years, deep myometrial invasion, tumor necrosis, and mitotic count of more than 6 of 10 high-power fields. At present a platinum-containing regimen, such as EMA/EP, is the treatment of choice, with survival rates approaching 50% to 60%.[106–108]

FOLLOW-UP AFTER TREATMENT OF GTN

After achieving 3 consecutive weekly undetectable hCG levels and completion of chemotherapy, serum quantitative hCG levels should be obtained at monthly intervals for 12 months for patients with Stage I to III GTN, and 24 months for patients with Stage IV GTN, before allowing pregnancy. In general, the overall risk of relapse is about 3% to 9% in the first year after completing therapy, but is uncommon after 12 months of normal hCG levels. Physician examinations should be performed at intervals of 3 months during the period of hCG testing. Other tests such as radiographs or scans are indicated for special circumstances only. Contraception is mandatory during treatment and for the 12 (or 24) months of follow-up after completing chemotherapy, preferably by the use of oral contraceptives. Intrauterine devices should not be inserted until the hCG level becomes undetectable. Because of the 1% to 2% risk of another gestational trophoblastic event in a subsequent pregnancy, a pelvic ultrasound scan is recommended in later conceptions at 10 weeks to assure normal fetal development. The products of conception from future miscarriages should be reviewed by pathologists, and the placentas of future pregnancies should be examined grossly for abnormal areas which, if noted, should be reviewed pathologically. Finally, a serum hCG level should be obtained 6 weeks after completion of all future pregnancies, at which point it should be undetectable. Postterm or postabortal CCA should be considered if a patient with a history of molar pregnancy or GTN presents with unusual bleeding or signs of metastatic disease after a term pregnancy or miscarriage.

The introduction of etoposide-containing drug combinations for treatment of GTN in the 1980s has been reported to increase the risk of secondary malignances including acute myelogenous leukemia (1%), colon cancer, melanoma, and breast cancer.[51] This increased susceptibility appears to be dose-related, affecting primarily those patients whose total dose of etoposide exceeds 2 g. Heightened awareness of these conditions should be part of the health care surveillance in susceptible patients.

PERSISTENT LOW LEVELS OF HCG (QUIESCENT GTN)

There is a subset of patients with a history of GTN or molar pregnancy in whom the hCG level plateaus at very low levels for several weeks or months. Metastatic workup in these patients is usually negative. Real hCG is present but is predominantly the nonhyperglycosylated form.[109–112] These patients are characterized as having “quiescent GTN.” The source of the hCG is presumably dormant though viable trophoblastic tissue that is resistant to chemotherapy. In most of these patients, the hCG level ultimately becomes undetectable spontaneously. Close follow-up is required, however, because 6% to 19% of women with quiescent GTN will eventually develop active progressing chemosensitive disease as reflected by rising hCG levels, which is now characterized by a high percentage of the hyperglycosylated form of hCG.[113,114]

In addition to persistent low levels of real hCG, patients occasionally present with an elevated hCG level without a clear antecedent pregnancy. False-positive hCG levels are caused by several conditions, including the presence of circulating heterophilic

antibodies or elevated cross-reacting luteinizing (LH) hormone levels in perimenopausal/menopausal women. Most of the currently available hCG platforms correct for heterophilic antibodies and false-positive hCG levels due to LH cross-reaction in the perimenopause or menopause can be suppressed with oral contraceptives.[110] Furthermore, low levels of real hCG are produced in the menopause by the pituitary gland.[110] Of importance is that if the patient has false-positive hCG due to heterophile antibodies (phantom hCG), the hCG will not be detectable in the urine.

SUBSEQUENT PREGNANCY EXPERIENCE

The most common concern patients express when diagnosed with molar pregnancy or GTN has to do with the effect of this disease on future reproductive function. Patients with a history of molar pregnancy have an increased risk of developing a second molar pregnancy of from approximately 1 in 1000 to 1 in 100 in subsequent pregnancies.[115] This increased risk can even occur with a different partner, suggesting that the ovum holds the key to this disease. Despite an increased risk for developing a second molar pregnancy, patients with a history of a mole or GTN can generally anticipate normal future reproductive outcomes. Summarizing the experience from the NETDC (**Table 6**) and 9 other centers, data have been reported concerning the outcomes of 2657 later pregnancies in women treated with chemotherapy for GTN.[115–123] These subsequent pregnancies resulted in 76.7% live births at or near term, 5.3% premature births, 1.3% stillbirths, 14.2% miscarriages, and congenital malformations in 1.8%. These rates are comparable with those in the general population except for the increased risk of stillbirths. The secondary infertility rate among women receiving chemotherapy was only 7%. Woolas and colleagues[122] reported no difference in conception rates or pregnancy outcomes between women treated with single-agent chemotherapy and those on multiagent chemotherapy.

Patients occasionally become pregnant before the recommended 12-month follow-up period has elapsed. When a patient's hCG level reelevates after completing chemotherapy, an ultrasound examination enables the clinician to distinguish between a concurrent new pregnancy and disease recurrence. Matsui and colleagues[123] has shown that pregnancies that occur within 6 months following remission are at increased risk of abnormalities including spontaneous miscarriages, stillbirths, and repeat moles.

Table 6
Subsequent pregnancy outcomes following chemotherapy at the NETDC, 1965–2010

Outcome	*N*	%
Total pregnancies	759	100
Total deliveries	593	
Term live	441	58.1
Preterm live	44	5.8
Stillbirth	10	1.3
Congenital anomalies	11	1.4
Cesarean section	87	17.6
Spontaneous miscarriage	122	16.1
Induced abortion	28	3.7
Ectopic	7	0.9
Repeat molar pregnancy	9	1.2

PSYCHOSOCIAL CONSEQUENCES OF GTN

Women who develop GTN may experience significant mood disturbance and marital and sexual problems, in addition to their concerns over future fertility.[124,125] Because GTN is a result of pregnancy, patients and their partners must confront the loss of a pregnancy at the same time they face the threat of malignancy. Significant levels of anxiety, fatigue, anger, confusion, sexual problems, and concern for future pregnancy may last for protracted periods of time. Patients with metastatic disease and active disease who are particularly at risk for severe psychosocial reactions should be provided with psychosocial assessments and interventions. At the time of clinic visits, patients and their partners should be reassured that many patients experience psychosocial distress requiring support and counseling services. The psychological and social stresses related to persistent GTN may last for many years beyond remission. A study conducted at the NETDC and in England revealed that even 5 to 20 years after attaining remission, 51% of patients indicated that they would be "somewhat likely" to "very likely" to participate in a counseling program to discuss issues raised by having GTN.[124]

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