

ONCOLOGY

Gestational trophoblastic disease II: classification and management of gestational trophoblastic neoplasia

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Gestational trophoblastic neoplasia (GTN) includes invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT). The epidemiology, pathology, clinical presentation, and diagnosis of these tumors were discussed in part I of this review. The overall cure rate in treating these tumors is currently >90%. This success is the result of the inherent sensitivity of trophoblastic neoplasms to chemotherapy, the effective use of the tumor marker human chorionic gonadotropin (hCG) for diagnosing disease and monitoring therapy, the referral of patients to or consultation with clinicians who have special expertise in management of these diseases, the identification of prognostic factors that predicts treatment response and enhances individualization of therapy, and the use of combined modality treatment with chemotherapy, radiation, and surgery in the highest risk patients. PSTT and its related ETT remain therapeutic challenges, since they are more frequently chemotherapy resistant and do not have the same hCG marker relationship as invasive mole and choriocarcinoma.

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Gestational trophoblastic neoplasia (GTN) includes invasive mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor. The overall cure rate in treating these tumors is currently >90%. Thorough evaluation and staging allow selection of appropriate therapy that maximizes chances for cure while minimizing toxicity. Nonmetastatic (stage I) and low-risk metastatic (stages II and III, score <7) GTN can be treated with single-agent chemotherapy resulting in a survival rate approaching 100%. High-risk GTN (stages II-IV, score ≥7) requires initial multiagent chemotherapy with or without adjuvant radiation and surgery to achieve a survival rate of 80-90%.

Key words: chemotherapy, choriocarcinoma, gestational trophoblastic disease, gestational trophoblastic neoplasia

★ EDITORS' CHOICE ★

Classification/staging

When the diagnosis of GTN is suspected or established, a metastatic workup and an evaluation for risk factors is undertaken.¹⁻⁴ Along with a complete history and physical examination, the following laboratory tests should be obtained: complete blood cell count including platelets, coagulation studies, serum chemistries including renal and liver function panels, blood type and antibody screen, and quantitative serum hCG level. Recommended radiologic studies include 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 of the brain (Figure). If the physical examination and chest x-ray are normal in the absence of symptoms, other sites of metastasis are uncommon. Measurement of hCG in cerebrospinal fluid may be helpful in detecting brain involvement. Pelvic ultrasound or magnetic resonance imaging may also be useful in detecting extensive uterine disease for which hysterectomy may be of benefit. Repeat curettage after hydatidiform mole evacuation is generally not recommended unless there is excessive uterine bleeding and evidence of intracavitary molar tissue exists on scan,

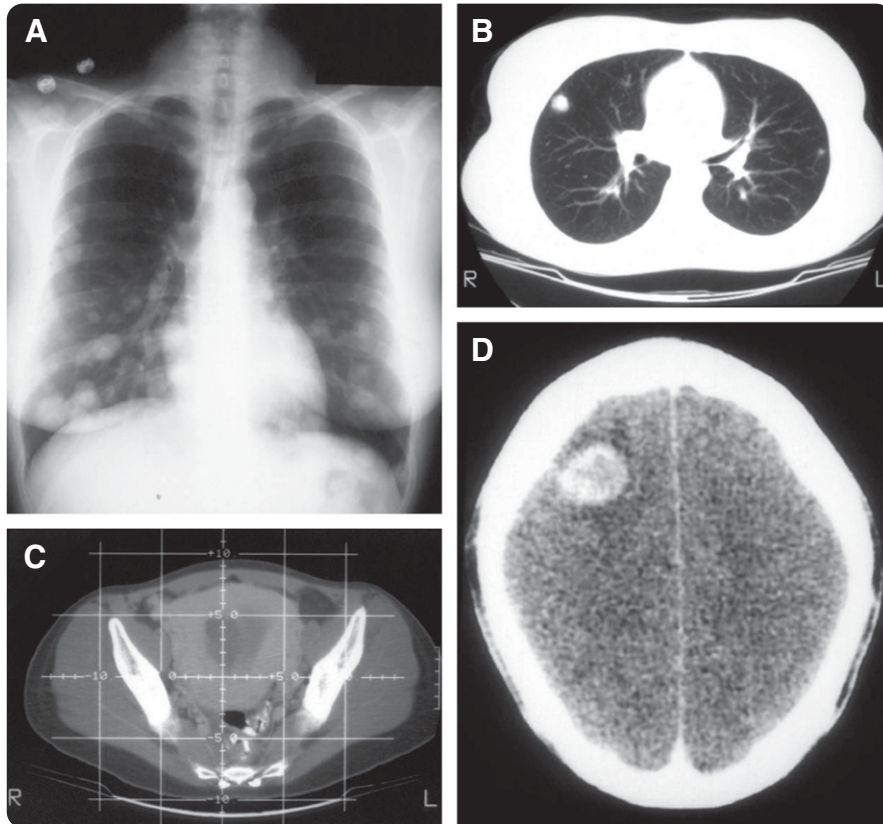
because it does not often induce remission or influence treatment and it may result in uterine perforation and hemorrhage.⁵⁻⁸

In 2002, the International Federation of Gynecology and Obstetrics (FIGO) defined criteria for the diagnosis of postmolar disease and adopted a combined anatomic staging and modified World Health Organization (WHO) risk-factor scoring system for GTN.⁹ The components needed to diagnose postmolar GTN include at least 1 of the following: (1) hCG plateau for 4 consecutive values over 3 weeks; (2) hCG rise of ≥10% for 3 values over 2 weeks; (3) hCG persistence 6 months after molar evacuation; (4) histopathologic diagnosis of choriocarcinoma; or (5) presence of metastatic disease. The FIGO stage (Table 1) is designated by a Roman numeral followed by the modified WHO score (Table 2) designated by an Arabic numeral, separated by a colon. PSTTs and ETTs are classified separately.

Treatment is based on classification into risk groups defined by the stage and scoring system.¹⁰ Patients with non-metastatic (stage I) and low-risk metastatic (stages II and III, score <7) GTN can be treated with single-agent chemotherapy, with resulting survival rates approaching 100%. Patients classified as having high-risk metastatic disease (stage IV and stages II-III, score ≥7)

FIGURE

Radiologic studies of gestational trophoblastic neoplasia



A, Chest x-ray of classic appearance of pulmonary metastases from gestational trophoblastic neoplasia (GTN). **B**, Lung computed tomography (CT) showing micropulmonary metastases in GTN. Metastases are seen on chest CT scan in 30-40% of patients with normal chest x-rays. **C**, Pelvic CT scan of 21-year-old woman with uterine hemorrhage and human chorionic gonadotropin of 140,000 mIU/mL 8 weeks postpartum. Enlarged uterus contains necrotic tumor; curettage showed choriocarcinoma. **D**, Brain CT scan showing left frontal lobe tumor of 35-year-old woman with gestational choriocarcinoma.

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Treatment

Low-risk disease

Patients with nonmetastatic (stage I) and low-risk metastatic (stages II and III, score <7) GTN should be treated with single-agent methotrexate or actinomycin D chemotherapy.^{11,12} Several different outpatient chemotherapy protocols have been used, which in mostly nonrandomized, retrospective studies have yielded fairly comparable overall results (Table 3). The variability in primary remission rates reflects differences in drug dosages, schedules, and routes of administration, as well as patient selection criteria. In general, the weekly intramuscular (IM) or intermittent intravenous (IV) infusion methotrexate and the biweekly single-dose actinomycin D protocols are less effective than one of the 5-day methotrexate or actinomycin D protocols and the 8-day methotrexate-folinic acid regimen. Also, older patient age, higher hCG levels, nonmolar antecedent pregnancy, histopathologic diagnosis of choriocarcinoma, presence of metastatic disease, and higher FIGO score are each associated with an increased risk of initial chemotherapy resistance. Despite these differences in primary remission rates with initial chemotherapy, almost all patients are eventually cured with most being able to preserve fertility.

Methotrexate 0.4 mg/kg (maximum 25 mg) IM or IV push daily for 5 days every other week seems to be the most effective treatment protocol.¹³⁻¹⁵ In 1995, we reviewed nearly 30 years' experience in treating nonmetastatic GTN at the Brewer Trophoblastic Disease Center to determine effectiveness of therapy, evaluate toxicity, and assess factors associated with chemotherapy resistance. Of the 253 patients initially treated with single-agent methotrexate 0.4 mg/kg (maximum 25 mg) IV push daily for 5 days every 2 weeks, 226 (89.3%) achieved primary remission, 22 (8.7%) were placed into remission with subsequent single-agent actinomycin D, and only 5 (2.0%) required multiagent chemotherapy or hysterectomy for cure, with all 253 patients achieving permanent remission. Significant toxicity to methotrexate necessitating a change to another chemo-

should be treated in a more aggressive manner with multiagent chemotherapy \pm adjuvant radiation or surgery to achieve cure rates of 80-90%. Use of the

FIGO staging system is essential for determining initial therapy for patients with GTN to assure the best possible outcomes with the least morbidity.

TABLE 1

Staging for gestational trophoblastic neoplasia

Stage	Description
I	Disease confined to uterus
II	Disease extends outside uterus but is limited to genital structures (adnexa, vagina, broad ligament)
III	Disease extends to lungs with or without genital tract involvement
IV	Disease involves other metastatic sites

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therapeutic agent occurred in only 12 patients (4.7%); no life-threatening toxicity occurred. The most common toxicity was stomatitis; there was no alopecia and nausea was not a common side effect. Factors found to be associated with resistance to initial methotrexate chemotherapy were: high pretreatment hCG level, nonmolar antecedent pregnancy, and clinicopathologic diagnosis of choriocarcinoma. Our results of about 90% complete response and 100% survival confirmed earlier reports from our center and others that single-agent methotrexate in a 5-day outpatient course every 2 weeks is a highly effective and well-tolerated treatment.¹⁵

An alternative methotrexate regimen consists of slightly higher doses of methotrexate (1.0-1.5 mg/kg) IM every other day alternating with folinic acid (0.1-0.15 mg/kg) IM over 8 days with at least a 1-week interval between courses. This methotrexate-folinic acid protocol is reported to have decreased toxicity (especially stomatitis), but is more expensive and inconvenient, and is associated with a more frequent need for a change in chemotherapy to achieve remission.¹⁶⁻²² High-dose methotrexate infusion (100 mg/m² IV push followed by 200 mg/m² IV 12-hour infusion with folinic acid rescue), with the interval between doses reliant on posttreatment hCG trends, is another modified methotrexate dosage schedule used for treatment of low-risk GTN. This treatment protocol also results in more frequent need for second-line therapy and is expensive.²²⁻²⁵ Methotrexate administered in single weekly IM doses of 30-50 mg/m², although having the advantages of convenience, decreased cost, and lower toxicity, has the lowest complete response rate of any regimen and is not appropriate therapy for metastatic disease or choriocarcinoma.²⁶⁻²⁸

Actinomycin D (10-12 mg/kg IV daily for 5 days every other week or as a single 1.25 mg/m² IV dose every 2 weeks) is an acceptable alternative to methotrexate. Actinomycin D has a more toxic side effect profile (nausea, alopecia) than methotrexate and produces local tissue injury if IV extravasation occurs. Therefore, actinomycin D has most often been

TABLE 2

Scoring system for gestational trophoblastic neoplasia

Risk factor	Score			
	0	1	2	4
Age, y	≤39	>39	—	—
Antecedent pregnancy	Mole	Abortion	Term	
Pregnancy event to treatment interval, mo	<4	4-6	7-12	>12
Pretreatment hCG, mIU/mL	<10 ³	10 ³ -10 ⁴	10 ⁴ -10 ⁵	>10 ⁵
Largest tumor mass, including uterus, cm	<3	3-4	≥5	—
Site of metastases	—	Spleen, kidney	GI tract	Brain, liver
No. of metastases	—	1-4	5-8	>8
Previous failed chemotherapy	—	—	Single drug	≥2 drugs

GI, gastrointestinal; hCG, human chorionic gonadotropin.

Total score for patient is obtained by adding individual scores for each prognostic factor: low risk <7; high risk ≥7.

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used as secondary therapy in the presence of methotrexate resistance or as primary therapy for patients with hepatic or renal compromise or effusions contraindicating the use of methotrexate.²⁹⁻³⁴

Several studies have compared different methotrexate and actinomycin D regimens for treatment of low-risk, mostly nonmetastatic GTN. Three randomized clinical trials compared weekly IM methotrexate to biweekly actinomycin D.³⁵⁻³⁷ In each trial, the primary complete response rates were significantly lower for weekly IM methotrexate

(49-53%) than for pulsed actinomycin D (69-90%). Two retrospective case studies compared 5-day IM methotrexate with the 8-day methotrexate-folinic acid protocol for treatment of low-risk or nonmetastatic postmolar GTN.^{19,38} There was no difference in remission rates in the study by Wong et al¹⁹ (76%) whereas in the study by Smith et al³⁸ the remission rates were 92% for patients with methotrexate alone vs 72% for patients treated with methotrexate-folinic acid. Gleeson et al³⁹ reported primary remission rates of 69% and 75% in patients

TABLE 3

Chemotherapy for low-risk gestational trophoblastic neoplasia

Chemotherapy regimen	Primary remission rate, %
1. MTX 0.4 mg/kg (maximum 25 mg)/d IV or IM for 5 d; repeat every 14 d	87-93
2. MTX 30-50 mg/m ² IM weekly	49-74
3. MTX 1 mg/kg IM d 1, 3, 5, 7; folinic acid 0.1 mg/kg IM d 2, 4, 6, 8; repeat every 15-18 d, or as needed	74-90
4. MTX 100 mg/m ² IVP, then 200 mg/m ² in 500 mL D5W over 12 h; folinic acid 15 mg IM or PO q 12 h for 4 doses beginning 24 h after start of MTX; repeat every 18 d, or as needed	69-90
5. Act-D 10-13 μg/kg IV qd for 5 d; repeat every 14 d	77-94
6. Act-D 1.25 mg/m ² IV every 2 wk	69-90
7. Alternating MTX/Act-D regimens 1 and 5	100

ACT-D, actinomycin D; D5W, dextrose 5% in water; IM, intramuscular; IV, intravenous; IVP, intravenous push; MTX, methotrexate; PO, by mouth; qd, daily.

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with nonmetastatic postmolar GTN treated with weekly IM methotrexate or methotrexate-folinic acid, respectively. Lertkhachonsuk et al⁴⁰ randomly assigned patients with nonmetastatic GTN to treatment with either methotrexate-folinic acid or 5-day actinomycin. Complete remission was achieved in 74% of the women in the methotrexate-folinic acid arm vs 100% of the women in the actinomycin D arm. Kohorn⁴¹ compared 5-day actinomycin to pulse actinomycin for treatment of patients with nonmetastatic postmolar GTN. The primary remission rate was 88% for the 5-day course vs 78% for the pulsed regimen. Abrao et al⁴² retrospectively analyzed patients with low-risk, mostly nonmetastatic GTN treated with 5-day regimens of methotrexate and actinomycin D or a combination of methotrexate and actinomycin D. Complete remission rates were not significantly different at 69%, 61%, and 79%, respectively; however, the adverse side effect rate was much greater with combination therapy (62%) than with single-agent methotrexate (29%) or actinomycin D (19%).

Patients categorized as having low-risk metastatic GTN (FIGO stages II and III, score <7) can usually be treated successfully with initial single-agent chemotherapy using one of the 5-day dosage schedules of methotrexate or actinomycin D, as for nonmetastatic disease (Table 3). The weekly methotrexate or biweekly actinomycin D single-dose protocols currently in use for nonmetastatic postmolar disease should not be used for treatment of metastatic disease. The combined experience of 3 specialized trophoblastic disease centers in the United States with single-agent methotrexate or actinomycin D treatment of low-risk metastatic GTN yielded excellent outcomes. Primary remission was achieved in 48-67% of patients with the first single-agent chemotherapy regimen. From 1-14% of patients needed multiagent chemotherapy after failed sequential single-agent chemotherapy with or without surgery to achieve remission, but eventually all patients were cured. Risk factors for drug resistance to initial single-agent chemotherapy in this group of patients with low-risk meta-

static GTN were pretherapy hCG level >100,000 mIU/mL, age >35 years, FIGO score >4, and large vaginal metastases.⁴³⁻⁴⁵

Regardless of the treatment protocol used, chemotherapy is continued until hCG values have returned to normal and at least 1 course has been administered after the first normal hCG level. Chemotherapy is changed to an alternative single-agent if the hCG level plateaus above normal during treatment or if toxicity precludes an adequate dose or frequency of treatment. If there is a significant elevation in hCG level, development of metastases, or resistance to sequential single-agent chemotherapy, multiagent chemotherapy should be initiated. Hysterectomy for low-risk GTN may be performed as adjuvant treatment coincident with the initiation of chemotherapy to shorten the duration of treatment if fertility preservation is not desired. Hysterectomy may also become necessary to eradicate persistent, chemotherapy-resistant disease in the uterus or to remedy uterine hemorrhage from tumor. Hysterectomy is the treatment of choice for PSTT and ETT.

This past year, we updated our results of treatment of low-risk GTN (FIGO stage I and stages II-III; score <7) at the Brewer Trophoblastic Disease Center over the past 28 years. From 1979 through 2006, we treated 359 patients with low-risk GTN. The complete response rate to the initial single-agent chemotherapeutic drug was 79%: 78% (276/352) for methotrexate and 86% (6/7) for actinomycin D, with 92% of patients having a complete response to sequential single-agent chemotherapy. The remaining 8% of patients were all placed into remission with the use of multiagent chemotherapy and/or surgery. Resistance to the initial chemotherapeutic agent was associated with presence of metastatic disease, clinicopathologic diagnosis of choriocarcinoma, and increasing FIGO score.⁴⁶

In summary, cure rates for both nonmetastatic and low-risk metastatic GTN should approach 100% with the use of initial single-agent methotrexate or actinomycin D chemotherapy. Approximately 20% of low-risk patients will

develop resistance to the initial chemotherapeutic agent, but >90% will be cured by the use of sequential single-agent chemotherapy. Eventually, approximately 10% of patients will require multiagent chemotherapy with or without surgery to achieve remission.

High-risk metastatic disease

Patients with high-risk metastatic GTN (FIGO stage IV and stages II-III score ≥ 7) should be treated initially with multiagent chemotherapy with or without adjuvant surgery or radiation therapy.¹² Over time, the multiagent chemotherapy regimen of choice for high-risk disease has changed. Throughout the 1970s and 1980s, methotrexate, actinomycin D, and cyclophosphamide or chlorambucil (MAC) was the preferred first-line therapy, yielding cure rates of 63-71%.⁴⁷ In the early 1980s, the combination regimen of cyclophosphamide, hydroxyurea, actinomycin D, methotrexate with folinic acid, vincristine, and doxorubicin (CHAMOCA) was reported to have an improved primary remission rate of 82%⁴⁸; however, in a randomized trial of CHAMOCA vs MAC, both the primary remission rate (65% vs 73%) and the ultimate cure rate (70% vs 95%) were inferior for CHAMOCA compared with MAC, and CHAMOCA was more toxic.⁴⁹ In the 1980s, etoposide was discovered to be a very effective agent for treatment of GTN, and the addition of etoposide to multiagent chemotherapy in the regimen of etoposide, high-dose methotrexate with folinic acid, actinomycin D, cyclophosphamide, and vincristine (EMA-CO) resulted in improved remission and survival rates (Table 4).⁵⁰

Over the last 15 years, several groups have confirmed the efficacy of the EMA-CO regimen as primary therapy for high-risk GTN, reporting complete response rates of 71-78% and long-term survival rates of 85-94%.⁵¹⁻⁵⁸ In our 2 reported series, the complete response rates were 71% and 67%, and the overall survival rates were 91% and 93%, respectively.^{55,56} The only patients who died had FIGO stage IV disease with scores >12. No treatment-related deaths or life-threatening toxicity occurred. Neu-

tropenia necessitating a 1-week delay of treatment, anemia requiring blood transfusion, and grades 3-4 neutropenia without thrombocytopenia were associated with only 14%, 5.8%, and 1.9% of treatment cycles, respectively. The EMA-CO protocol, or some variation of it, is currently the initial treatment of choice for high-risk metastatic GTN because of low toxicity allowing adherence to treatment schedules, high complete response rates, and overall high resultant survival. Chemotherapy for high-risk disease is continued for at least 2-3 courses after the first normal hCG.¹²

When central nervous system metastases are present, 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. During radiotherapy, the methotrexate infusion dose in the EMA-CO protocol is increased to 1 g/m² and 30 mg of folinic acid is given every 12 hours for 3 days starting 32 hours after the infusion begins. An alternative to brain irradiation is the use of intrathecal as well as high-dose IV methotrexate. Reported cure rates with brain metastases are 50-80%, depending on patient symptoms as well as number, size, and location of the brain lesions.⁵⁹⁻⁶³

Adjuvant surgical procedures, especially hysterectomy and pulmonary resection for chemotherapy-resistant disease as well as procedures to control hemorrhage, are important components in the management of high-risk GTN. Approximately half of high-risk patients will require some form of surgical procedure during the course of treatment to effect cure.⁶⁴⁻⁷⁵ In a series of 50 patients with high-risk GTN treated with EMA-CO as primary or secondary therapy at the Brewer Center from 1986 through 2005, 24 (48%) underwent 28 adjuvant surgical procedures, and 21 (87.5%) were cured. Fifteen (88%) of 17 patients who underwent hysterectomy; 4 (80%) of 5 patients who had resistant foci of choriocarcinoma in the lung resected; all 4 patients who had suturing of the uterus, uterine artery embolization, small bowel resection, and salpingectomy for bleeding; and the 1 patient who

TABLE 4

Chemotherapy for high-risk gestational trophoblastic neoplasia

Day	Drug	Dosing
1	Etoposide	100 mg/m ² IV over 30 min
	Actinomycin D	0.5 mg IVP
	MTX	100 mg/m ² IVP, then 200 mg/m ² in 500 mL D5W over 12 h
2	Etoposide	100 mg/m ² IV over 30 min
	Actinomycin D	0.5 mg IVP
	Folinic acid	15 mg IM or PO every 12 h for 4 doses starting 24 h after start of MTX
8	Cyclophosphamide	600 mg/m ² IV
	Vincristine	1.0 mg/m ² IVP

IM, intramuscular; IV, intravenous; IVP, intravenous push; MTX, methotrexate. Repeat cycle on days 15, 16, and 22 (every 2 wk).

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had uterine wedge resection for resistant choriocarcinoma survived.⁷⁰

Despite the use of multimodel primary therapy in high-risk GTN, approximately 30% of patients will have an incomplete response to first-line chemotherapy or relapse from remission.⁷⁶⁻⁷⁹ Most of these patients will have multiple metastases to sites other than the lung and vagina, and many will have had inadequate chemotherapy. Salvage chemotherapy with drug regimens employing etoposide and a platinum agent often combined with surgical excision of persistent tumor will result in cure of most of these high-risk patients. The EMA-EP regimen, substituting etoposide and cisplatin for cyclophosphamide and vincristine in the EMA-CO protocol, is considered the most appropriate therapy for patients who have responded to EMA-CO but have plateauing low hCG levels or who have developed re-elevation of hCG levels after a complete response to EMA-CO.^{80,81} In patients who have clearly developed resistance to methotrexate-containing protocols, drug combinations containing etoposide and platinum with bleomycin, ifosfamide, or paclitaxel have been found to be effective.^{12,76,82}

In 2005, we reported on 26 patients with persistent or relapsed high-risk GTN who received secondary platinum-based salvage chemotherapy at the Brewer Center. The overall survival was 61.5% (16/26). Of the 16 patients who failed primary therapy with methotrexate/actinomycin D-based chemotherapy without etoposide, 10 (63%) had com-

plete clinical responses to bleomycin, etoposide, and cisplatin; etoposide, ifosfamide, and cisplatin; and ifosfamide, carboplatin, and etoposide, and 10 (63%) were cured. Of the 10 patients who failed primary therapy with EMA-CO, 9 (90%) had complete clinical responses to EMA-EP or bleomycin, etoposide, cisplatin, but only 6 (60%) subsequently achieved a lasting remission.⁷⁶

In summary, cure rates for high-risk GTN of 80-90% are now achievable with intensive multimodality therapy with EMA-CO chemotherapy, along with adjuvant radiotherapy or surgery when indicated. Approximately 30% of high-risk patients will fail first-line therapy or relapse from remission. Salvage therapy with platinum-containing drug combinations, often in conjunction with surgical resection of sites of persistent tumor, will result in cure of most of these high-risk patients with resistant disease. Even those patients with metastatic disease to the brain, liver, and gastrointestinal tract now have a 75%, 73%, and 50% survival rate, respectively.⁴⁶

PSTTs and ETTs

Hysterectomy with lymph node dissection is the recommended treatment for PSTT and ETT, because of the relative resistance of these tumors to chemotherapy and their propensity for lymphatic spread. Chemotherapy should be used in patients with metastatic disease and in patients with nonmetastatic disease who have adverse prognostic factors, such as interval from last known pregnancy to

diagnosis >2 years, deep myometrial invasion, tumor necrosis, and mitotic count >6/10 high power fields. Although the optimal chemotherapy regimen for PSTT and ETT remains to be defined, the current clinical impression is that a platinum-containing regimen, such as EMA-EP or a paclitaxel/cisplatin–paclitaxel/etoposide doublet, is the treatment of choice. The survival rate is approximately 100% for nonmetastatic disease and 50–60% for metastatic disease.^{83–85}

Reasons for treatment failure

We recently reviewed our experience in treating patients with GTN whose care was transferred to the Brewer Center after failing treatment elsewhere to determine causes of treatment failure and to compare our results of treating these patients from 1979 through 2006 with those previously reported from 1962 through 1978. The most common reasons for unsuccessful GTN treatment before transfer to the Brewer Center were: (1) use of single-agent chemotherapy for patients with high-risk disease; and (2) inappropriate use of weekly IM methotrexate chemotherapy for treatment of patients with metastatic disease, FIGO scores ≥ 7 , and/or nonpostmolar chorionicarcoma. Successful secondary GTN treatment in this patient group improved from 59% during 1962 through 1978 to 93% during 1979 through 2006, seemingly as a result of more experienced clinicians administering more effective chemotherapy treatment protocols.⁸⁶ Request for advice from or referral for treatment to clinicians with expertise in management of gestational trophoblastic disease is recommended for a patient who fails single-agent therapy for low-risk disease and for any patient with high-risk disease.⁸⁷

Follow-up after treatment for GTN

After hCG regression to normal and completion of chemotherapy, serum quantitative hCG levels should be obtained at 1-month intervals for 12 months. The risk of relapse is about 3% in the first year after completing therapy, but is exceedingly low after that. Physical examinations are performed at intervals

of 6–12 months; other testing such as x-rays or scans are rarely indicated. Contraception should be maintained during treatment and for 1 year after completion of chemotherapy, preferably using oral contraceptives. Because of the 1–2% risk of a second gestational trophoblastic disease event in subsequent pregnancies, pelvic ultrasound is recommended in the first trimester of a subsequent pregnancy to confirm a normal gestation, the products of conception or placentas from future pregnancies should be carefully examined histopathologically, and a serum quantitative hCG level should be determined 6 weeks after any pregnancy.

Successful treatment of GTN with chemotherapy has resulted in a large number of women who maintain their reproductive potential despite exposure to drugs that have ovarian toxicity and teratogenic potential. Most women resume normal ovarian function after chemotherapy and exhibit no increase in infertility. Many successful pregnancies have been reported, without an increase in abortions, stillbirths, congenital anomalies, prematurity, or major obstetric complications. There is no evidence for reactivation of disease because of subsequent pregnancies, although patients who have had 1 trophoblastic disease episode are at greater risk for the development of a second episode in a subsequent pregnancy, unrelated to whether they had previously received chemotherapy. Patients are advised to delay conception for 1 year after cessation of chemotherapy to allow for uninterrupted hCG follow-up and to permit the elimination of mature ova that may have been damaged by exposure to cytotoxic drugs.^{88–90}

Because many anticancer drugs are known carcinogens, there is concern that the chemotherapy used to induce long-term remissions or cures of one cancer may induce second malignancies. Until recently, there were no reports of increased susceptibility to the development of other malignancies after successful chemotherapy for GTN, probably because of the relatively short exposure of these patients to intermittent schedules of methotrexate and actinomycin D and the infrequent use of alkylating agents. After the introduction

of etoposide-containing drug combinations for treatment of GTN in the 1980s, an increased risk of secondary malignancies, including acute myelogenous leukemia, colon cancer, melanoma, and breast cancer, was identified.⁹¹ ■

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