Gestational Trophoblastic Disease Treatment (PDQ®)–Health Professional Version

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General Information About Gestational Trophoblastic Disease

Gestational trophoblastic disease (GTD) is a broad term encompassing both benign and malignant growths arising from products of conception in the uterus.[1]

Incidence and Mortality

The reported incidence of GTD varies widely worldwide, from a low of 23 per 100,000 pregnancies (Paraguay) to a high of 1,299 per 100,000 pregnancies (Indonesia).[2] However, at least part of this variability is caused by differences in diagnostic criteria and reporting. The reported incidence in the United States is about 110 to 120 per 100,000 pregnancies. In the United States, the reported incidence of choriocarcinoma, the most aggressive form of GTD, is about 2 to 7 per 100,000 pregnancies. The U.S. age-standardized (1960 World Population Standard) incidence rate of choriocarcinoma is about 0.18 per 100,000 women between the ages of 15 years and 49 years.[2]

Risk Factors

Two factors have consistently been associated with an increased risk of GTD:[2]

- Maternal age.
- History of hydatidiform mole (HM).

If a woman has been previously diagnosed with an HM, she carries a 1% risk of HM in subsequent pregnancies. This increases to approximately 25% with more than one prior HM. The risk associated with maternal age is bimodal, with increased risk both for mothers younger than 20 years and older than 35 years (and particularly for mothers >45 years). Relative risks are in the range of 1.1 to 11 for both the younger and older age ranges compared with ages 20 to 35 years. However, a population-based HM registry study suggests that the age-related patterns of the two major types of HM—complete and partial HM—are distinct.[3] For more information, see the Cellular Classification of Gestational Trophoblastic Disease section. In that study, the rate of complete HM was highest in women younger than 20 years and then decreased monotonically with age. However, the rates of partial HM increased for the entire age spectrum, suggesting possible differences in etiology. The association with paternal age is inconsistent.[2] A variety of exposures have been examined, with no clear associations found with tobacco smoking, alcohol consumption, diet, and oral contraceptive use.[2]

Clinical Features

GTDs contain paternal chromosomes and are placental, rather than maternal, in origin. The most common presenting symptoms are vaginal bleeding and a rapidly enlarging uterus, and GTD should be considered whenever a premenopausal woman presents with these findings. Because the vast majority of GTD types are associated with elevated human chorionic gonadotropin (hCG) levels, an hCG blood level and pelvic ultrasound are the initial steps in the diagnostic evaluation. In addition to vaginal bleeding and uterine enlargement, other presenting symptoms or signs may include the following:

- Pelvic pain or sensation of pressure.
- Anemia.
- Hyperemesis gravidarum.
- Hyperthyroidism (secondary to the homology between the beta-subunits of hCG and thyroid-stimulating hormone [TSH], which causes hCG to have weak TSH-like activity).
- Preeclampsia early in pregnancy.

The most common antecedent pregnancy in GTD is that of an HM.

Choriocarcinoma most commonly follows a molar pregnancy but can follow a normal pregnancy, ectopic pregnancy, or abortion, and it should always be considered when a patient has continued vaginal bleeding in the postdelivery period. Other possible signs include neurologic symptoms (resulting from brain metastases) in a female within the reproductive age group and asymptomatic lesions on routine chest x-ray.

Prognostic Factors and Survivorship

The prognosis for cure of patients with GTDs is good even when the disease has spread to distant organs, especially when only the lungs are involved. Therefore, the traditional TNM (tumor, node, metastasis) staging system has limited prognostic value.[4] The probability of cure depends on the following:

- Histological type (invasive mole or choriocarcinoma).
- Extent of spread of the disease/largest tumor size.
- Level of serum beta-hCG.
- Duration of disease from the initial pregnancy event to start of treatment.
- Number and specific sites of metastases.
- Nature of antecedent pregnancy.
- Extent of prior treatment.

Selection of treatment depends on these factors plus the patient's desire for future pregnancies. Beta-hCG is a sensitive marker to indicate the presence or absence of disease before, during, and after treatment. Given the extremely good therapeutic outcomes of most of these tumors, an important goal is to distinguish patients who need less-intensive therapies from those who require more-intensive regimens to achieve a cure.

References

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Cellular Classification of Gestational Trophoblastic Disease

Gestational trophoblastic disease (GTD) may be classified as follows:[1]

- Hydatidiform mole (HM).
  - Complete HM.
  - Partial HM.
- Gestational trophoblastic neoplasia.
  - Invasive mole.
  - Choriocarcinoma.
  - Placental-site trophoblastic tumor (PSTT) (very rare).
  - Epithelioid trophoblastic tumor (ETT) (extremely rare).

Choriocarcinoma, PSTT, and ETT are often grouped under the heading gestational trophoblastic tumors.

Hydatidiform Mole (HM)

HM is defined as products of conception that show gross cyst-like swellings of the chorionic villi that are caused by an accumulation of fluid. There is disintegration and loss of blood vessels in the villous core.

Complete HM

A complete mole occurs when an ovum that has extruded its maternal nucleus is fertilized by either a single sperm, with subsequent chromosome duplication, or two sperm, resulting in either case in a diploid karyotype. The former case always yields a mole with a karyotype of 46 XX, since at least one X chromosome is required for viability and a karyotype of 46 YY is rapidly lethal to the ovum. The latter case may yield a karyotype of 46 XX or 46 XY. About 90% of complete HMs are 46 XX. On ultrasound examination, complete moles rarely reveal a fetus or amniotic fluid.

Partial HM

A partial mole occurs when the ovum retains its nucleus but is fertilized by a single sperm, with subsequent chromosome duplication, or is fertilized by two sperm; the possible resulting triploid karyotypes are 69 XXY, 69 XXX, or 69 XYY. Therefore, in contrast to a complete mole, the partial mole chromosomes of a partial mole are only two-thirds paternal in origin. In contrast to complete moles, partial moles usually show a fetus, which may even be viable, and amniotic fluid is visible.

Complete HMs have a 15% to 25% risk of developing into an invasive mole, but transformation to malignancy is much more rare (<5%) in the case of partial moles.

Gestational Trophoblastic Neoplasias

Invasive mole

Invasive moles (chorioadenoma destruens) are locally invasive, rarely metastatic lesions characterized microscopically by trophoblastic invasion of the myometrium with identifiable villous structures. These may be preceded by either complete or partial molar pregnancy. They are usually diploid in karyotype, but may be aneuploid. Microscopically, these lesions are characterized by hyperplasia of cytotrophoblastic and syncytial elements and persistence of villous structures. They may histologically resemble choriocarcinoma. Invasive moles have more aggressive behavior than either complete or partial HMs, and they are treated similarly to choriocarcinoma (i.e., with chemotherapy). However, unlike choriocarcinoma, they may regress spontaneously.

Choriocarcinoma

Choriocarcinoma is a malignant tumor of the trophoblastic epithelium. Uterine muscle and blood vessels are invaded with areas of hemorrhage and necrosis. Columns and sheets of trophoblastic tissue invade normal tissues and spread to distant sites, the most common of which are lungs, brain, liver, pelvis, vagina, spleen, intestines, and kidney. Most choriocarcinomas have an aneuploid karyotype, and about three-quarters of them contain a Y chromosome. Most follow an HM pregnancy, spontaneous abortion, or ectopic pregnancy; but, about one-quarter of them are preceded by a full-term pregnancy. Nearly all GTDs that are preceded by nonmolar pregnancies are choriocarcinomas; the rare exceptions generally are PSTTs.

PSTT

PSTT disease is the result of a very rare tumor arising from the placental implantation site and resembles an exaggerated form of syncytial endometritis. Trophoblastic cells infiltrate the myometrium, and there is vascular invasion. Human placental lactogen is present in the tumor cells, whereas immunoperoxidase staining for human chorionic gonadotropin (hCG) is positive in only scattered cells, and elevations in serum hCG are relatively low compared with the marked elevations seen in choriocarcinoma. hCG is not a reliable marker of tumor volume.[2,3] PSTTs have much lower growth rates than choriocarcinoma, and presentation after a full-term pregnancy is often delayed by months or years. They are generally resistant to chemotherapy. Therefore, hysterectomy is the standard primary treatment if the tumor is confined to the uterus. However, about 35% of PSTTs have distant metastases at diagnosis.[3,4] Common sites of metastasis include the lungs, pelvis, and lymph nodes. Central nervous system, renal, and liver metastases have also been observed.

ETT

ETT is an extremely rare gestational trophoblastic tumor.[5,6] Although this tumor was originally called an atypical choriocarcinoma, ETT appears to be less aggressive than choriocarcinoma and is now regarded as a distinct entity. Pathologically, it has a monomorphic cellular pattern of epithelioid cells and may resemble squamous cell cancer of the cervix when arising in the cervical canal. Its clinical behavior appears to be closer to that of PSTT than to choriocarcinoma. It has a spectrum of clinical behavior from benign to malignant. About one-third of patients present with metastases, usually in the lungs.

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Stage Information for Gestational Trophoblastic Disease

Hydatidiform Mole (HM)

HM (molar pregnancy) is disease limited to the uterine cavity.

Gestational Trophoblastic Neoplasia

Definitions: FIGO

The Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) and the American Joint Committee on Cancer (AJCC) have designated staging to define gestational trophoblastic neoplasia; the FIGO system is most commonly used.[1,2] Some tumor registrars encourage the recording of staging in both systems.

FIGO staging system (and modified World Health Organization [WHO] prognostic scoring system)

The FIGO staging system is as follows:[1]

Table 1. Gestational Trophoblastic Neoplasia[a,b]

FIGO Anatomical Staging	
Stage	
I	Gestational trophoblastic tumors strictly confined to the uterine corpus.
II	Gestational trophoblastic tumors extending to the adnexa or to the vagina, but limited to the genital structures.
III	Gestational trophoblastic tumors extending to the lungs, with or without genital tract involvement.
IV	All other metastatic sites.

Modified WHO Prognostic Scoring System as Adapted by FIGO[b]				
Scores	0	1	2	4
Age	<40	≥40	–	–
Antecedent pregnancy	mole	abortion	term	–
Interval months from index pregnancy	<4	4–6	7–12	>12
Pretreatment serum hCG (IU/L)	$<10^3$	10^3–10^4	10^4–10^5	$>10^5$

FIGO = Fédération Internationale de Gynécologie et d'Obstétrique; hCG = human chorionic gonadotropin; WHO = World Health Organization.

[a]Adapted from FIGO Committee on Gynecologic Oncology.[1]

[b]To stage and allot a risk factor score, a patient's diagnosis is allocated to a stage as represented by a Roman numeral I, II, III, and IV. This is then separated by a colon from the sum of all the actual risk factor scores expressed in Arabic numerals, i.e., stage II:4, stage IV:9. This stage and score will be allotted for each patient.

[c]Size of the tumor in the uterus.

FIGO Anatomical Staging				
Largest tumor size (including uterus[c])	<3	3–4 cm	≥5 cm	–
Site of metastases, including uterus	lung	spleen, kidney	gastrointestinal tract	liver, brain
Number of metastases	–	1–4	5–8	>8
Previous failed chemotherapy	–	–	single drug	≥2 drugs

FIGO = Fédération Internationale de Gynécologie et d'Obstétrique; hCG = human chorionic gonadotropin; WHO = World Health Organization.

[a]Adapted from FIGO Committee on Gynecologic Oncology.[1]

[b]To stage and allot a risk factor score, a patient's diagnosis is allocated to a stage as represented by a Roman numeral I, II, III, and IV. This is then separated by a colon from the sum of all the actual risk factor scores expressed in Arabic numerals, i.e., stage II:4, stage IV:9. This stage and score will be allotted for each patient.

[c]Size of the tumor in the uterus.

In addition, the FIGO staging system incorporates a modified WHO prognostic scoring system. The scores from the eight risk factors are summed and incorporated into the FIGO stage, separated by a colon (e.g., stage II:4, stage IV:9, etc.). Unfortunately, a variety of risk scoring systems have been published, making comparisons of results difficult.

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Treatment Option Overview for Gestational Trophoblastic Disease

Most hydatidiform moles (HMs) are benign and are treated conservatively by dilation, suction evacuation, and curettage. However, since they carry a risk of persistence or progression to malignant

gestational trophoblastic disease (GTD), they must be followed carefully with weekly serum human chorionic gonadotropin (hCG) levels to normalization. Monthly follow-up for 6 months is generally recommended, although the duration of this phase of follow-up is not based on empiric study.[1]

Prompt institution of therapy for GTD and continuing follow-up at very close intervals until normal beta-hCG titers are obtained is the cornerstone of management. When chemotherapy is instituted, the interval between courses should rarely exceed 14 to 21 days, depending on the regimen used. It is recommended that patients receive one to three courses of chemotherapy after the first normal beta-hCG titer, depending on the extent of disease. The modified World Health Organization (WHO) Prognostic Scoring System (see Table 1) should be used, and combination chemotherapy should be initiated when warranted by the patient's score. If a diagnosis of GTD is made, routine work-up includes the following:

- Serum beta-hCG.
- Blood work of liver, renal, and marrow function.
- Chest x-ray.
- Pelvic ultrasound.
- Head computed tomography or magnetic resonance imaging (in the case of choriocarcinoma or central nervous system signs).

Treatment of GTD depends on the risk category determined by the modified WHO Prognostic Scoring System as adapted by the Fédération Internationale de Gynécologie et d'Obstétrique (see Table 1). Since the very rare placental-site trophoblastic tumors and the even more rare epithelioid trophoblastic tumors are biologically distinct entities, their management is discussed separately.

Low Levels of hCG

Accurate monitoring of hCG is critical to successfully diagnose and monitor the treatment course of gestational trophoblastic disease. False-positive results may lead to inappropriate diagnoses and treatment, and must be minimized. The following are possible alternate diagnoses to be considered in cases of low-level hCG.

False-positive hCG

Serum hCG testing relies on detecting two antibodies on the hCG molecule. The antibodies are polyclonal or monoclonal antibodies derived from various animals: mouse, rabbit, goat or sheep. Humans with heterophilic (or cross-species) antibodies bind the antibodies in the assay, leading to a false-positive result. This was a common problem with one of the commercially available assays until it was re-engineered in 2003. Heterophilic antibodies cannot cross the glomerular filtration barrier, so the performance of a urinary hCG can eliminate this source for a positive test result. The urine sample should be run using the same system generally reserved for serum, as opposed to over-the-counter urine-pregnancy tests, to avoid decreased sensitivity in the latter.

Pituitary hCG

The anterior stalk of the pituitary secretes luteinizing hormone (LH), which shares an alpha subunit with hCG. In normal menstrual cycles, pituitary-generated hCG may be detectable at the time of the LH surge. Estrogen provides negative feedback for this LH secretion and acts as a suppressing agent.

In patients in low-estrogen states (perimenopause, menopause, and status postoophorectomy), pituitary hCG may be secreted in increasing amounts, although only levels between 1 to 32 IU/L have been recorded.[2] To confirm a pituitary source for the hCG, patients are started on high-dose oral contraceptive pills to produce an exogenous source of estrogen. In general, patients with pituitary hCG will have their hCG levels suppressed after 3 weeks on this regimen.[2]

References

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Management of Hydatidiform Mole

Treatment of hydatidiform mole (HM) is within the purview of the obstetrician/gynecologist and is not discussed separately here. However, following the diagnosis and treatment of HM, patients should be monitored to rule out the possibility of metastatic gestational trophoblastic neoplasia. In almost all cases, this can be performed with routine monitoring of serum beta human chorionic gonadotropin (beta-hCG) to document its return to normal. An effective form of contraception is important during the follow-up period to avoid the confusion that can occur with a rising beta-hCG as a result of pregnancy.

Chemotherapy is necessary when there is the following:

1. A rising beta-hCG titer for 2 weeks (3 titers).
2. A tissue diagnosis of choriocarcinoma.
3. A plateau of the beta-hCG for 3 weeks.
4. Persistence of detectable beta-hCG 6 months after mole evacuation.
5. Metastatic disease.
6. An elevation in beta-hCG after a normal value.
7. Postevacuation hemorrhage not caused by retained tissues.

Chemotherapy is ultimately required for persistence or neoplastic transformation in about 15% to 20% of patients after evacuation of a complete HM but for fewer than 5% of patients with partial HM. Chemotherapy is determined by the patient's modified World Health Organization score.

In women with complete HM, risk of persistence or neoplastic transformation is approximately doubled in the setting of certain characteristics, which include the following:

- Age older than 35 years or younger than 20 years.
- Pre-evacuation serum beta-hCG greater than 100,000 IU/L.
- Large-for-date uterus.

- Large uterine molar mass.
- Large (>6 cm) ovarian cysts.
- Preeclampsia.
- Hyperthyroidism.
- Hyperemesis of pregnancy.
- Trophoblastic embolization.
- Disseminated intravascular coagulation.

Studies have shown that a single course of prophylactic dactinomycin or methotrexate can decrease the risk of a postmolar gestational trophoblastic disease (GTD).[1-3] However, there is concern that chemoprophylaxis increases tumor resistance to standard therapy in the women who subsequently develop GTD.[1] Therefore, this practice is generally limited to countries in which a large number of women do not return for follow-up.

Current Clinical Trials

Use our advanced clinical trial search to find NCI-supported cancer clinical trials that are now enrolling patients. The search can be narrowed by location of the trial, type of treatment, name of the drug, and other criteria. General information about clinical trials is also available.

References

1. Kim DS, Moon H, Kim KT, et al.: Effects of prophylactic chemotherapy for persistent trophoblastic disease in patients with complete hydatidiform mole. Obstet Gynecol 67 (5): 690-4, 1986. [PUBMED Abstract]
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Treatment of Low-Risk Gestational Trophoblastic Neoplasia (FIGO Score 0–6)

There is no consensus on the best chemotherapy regimen for initial management of low-risk gestational trophoblastic neoplasia (GTN), and first-line regimens vary by geography and institutional preference. Most regimens have not been compared head-to-head, and the level of evidence for efficacy is often limited to C2 except as noted below. Even if there are differences in initial remission rate among the regimens, salvage with alternate regimens is very effective, and the ultimate cure rates are generally 99% or more. The initial regimen is generally given until a normal beta human chorionic gonadotropin (beta-hCG) (for the institution) is achieved and sustained for 3 consecutive weeks (or at least for one treatment cycle beyond normalization of the beta-hCG). A salvage regimen is instituted if any of the following occur:

- A plateau of the beta-hCG for 3 weeks (defined as a beta-hCG decrease of 10% or less for 3 consecutive weeks).
- A rise in beta-hCG of greater than 20% for 2 consecutive weeks.
- Appearance of metastases.

The use of chemotherapy in the first-line management of low-risk GTN has been assessed in a Cochrane Collaboration systematic review.[1] In that systematic review, four randomized controlled trials were identified.[2-5]

Three of the randomized trials [3-5] compared the same two commonly used regimens:

- Biweekly (pulsed) dactinomycin (1.25 mg/m^2 intravenously [IV]).
- Weekly intramuscular (IM) methotrexate (30 mg/m^2).

These three trials included a total of 392 patients. In all three trials, patients who received pulsed dactinomycin had better primary complete response rates without the need for additional salvage therapy (relative risk [RR] of cure, 3.00; 95% confidence interval [CI], 1.10–8.17), even though the magnitude of benefit showed substantial heterogeneity (I^2 statistic = 79%).[3-5][Level of evidence B1] Fewer courses of dactinomycin therapy were needed to achieve complete response and cure. As expected, salvage chemotherapy was nearly uniformly successful, because almost all low-risk GTN patients are ultimately cured, irrespective of the initial chemotherapeutic regimen. There were no statistically significant differences in most toxicities, including the following:

- Nausea and vomiting.
- Diarrhea.
- Hematologic toxicity.
- Hepatic toxicity.

There was a statistically significant increase in dermatologic toxicity, including alopecia, associated with dactinomycin. However, in the largest study,[5] there was more low-grade gastrointestinal toxicity, grade 2 nausea, grade 1 to 2 vomiting, and grades 1 to 3 neutropenia in the dactinomycin group. These values were statistically significant. In this study, patients with choriocarcinoma and risk scores of 5 to 6 had worse complete response rates to initial treatment with single-agent therapy. Methotrexate was virtually ineffective.[5]

The fourth randomized trial was very small and included 45 patients. The study compared a 5-day regimen of dactinomycin (10 µg/kg) with an 8-day regimen of methotrexate (1 mg/kg) and leucovorin (0.1 mg/kg) on alternate days. There was a statistically significant decrease in risk of failure to achieve primary cure without the need for salvage therapy in the dactinomycin arm (RR, 0.57; 95% CI, 0.40–0.81).[2][Level of evidence B1] There was less alopecia associated with methotrexate but more hepatic toxicity.

The Cochrane systematic review also summarized the evidence from four nonrandomized trials, but comparisons across studies are difficult. The regimens evaluated in those studies are included in the lists below.[1][Level of evidence C2]

Commonly used treatment regimens include the following:

1. The 8-day Charing Cross regimen. Methotrexate (50 mg IM on days 1, 3, 5, and 7) and leucovorin (7.5 mg orally on days 2, 4, 6, and 8). This may be the most common regimen worldwide,[1,6] but it has not been directly compared with other regimens.
2. Biweekly pulsed dactinomycin (1.25 mg/m^2 IV).
3. Weekly methotrexate (30 mg/m^2 IM). Efficacy of this regimen appears to be low for choriocarcinoma and for patients with Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) risk scores of 5 to 6.

Other regimens in less-common use include the following:[1]

- An 8-day regimen of methotrexate (1 mg/kg IM on days 1, 3, 5, and 7) and leucovorin (0.1 mg/kg IM on days 2, 4, 6, and 8).
- Methotrexate 20 mg/m^2 IM on days 1 to 5, repeated every 14 days.
- Dactinomycin 12 µg/kg/day IV on days 1 to 5, repeated every 2 to 3 weeks. This regimen is used less often because of substantial alopecia and nausea.
- Methotrexate 20 mg IM daily on days 1 to 5; and dactinomycin 500 µg IV daily on days 1 to 5, repeated every 14 days.
- Dactinomycin 10 µg/kg/day on days 1 to 5, repeated every 2 weeks.
- Methotrexate 0.4 mg/kg/day IM daily on days 1 to 5, repeated after 7 days.
- Etoposide 100 mg/m^2/day IV on days 1 to 5, or 250 mg/m^2 IV on days 1 and 3, at 10-day intervals. [7]

The unusual patient with a tumor that becomes refractory to single-agent chemotherapy is treated with one of the combination regimens described below for high-risk GTN. For more information, see the Treatment of High-Risk Gestational Trophoblastic Neoplasia (FIGO Score ≥7) section.

Current Clinical Trials

Use our advanced clinical trial search to find NCI-supported cancer clinical trials that are now enrolling patients. The search can be narrowed by location of the trial, type of treatment, name of the drug, and other criteria. General information about clinical trials is also available.

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Treatment of High-Risk Gestational Trophoblastic Neoplasia (FIGO Score ≥7)

Multiagent chemotherapy is standard for the initial management of high-risk gestational trophoblastic neoplasia (GTN). A systematic literature review revealed only one randomized controlled trial (and no high-quality trials)—conducted in the 1980s—comparing multiagent chemotherapy regimens for high-risk GTN.[1] In the trial, only 42 women were randomly assigned to either a CHAMOMA regimen (i.e., methotrexate, leucovorin, hydroxyurea, dactinomycin, vincristine, melphalan, and doxorubicin) or MAC (i.e., methotrexate, dactinomycin, and chlorambucil).[2] There was substantially more life-threatening toxicity in the CHAMOMA arm and no evidence of higher efficacy. However, there were serious methodological problems with this trial. It was reportedly designed as an equivalency trial, but owing to the small sample size, the trial was inadequately powered to assess equivalence. In addition, the characteristics of the patients randomly assigned to the two study arms were not reported (although the authors stated that there were no major differences in the patient populations assigned to each arm), nor was the method of randomization or allocation concealment described.

There are no randomized trials comparing regimens in common use to establish the superiority of one over another. Therefore, the literature does not permit firm conclusions about the best chemotherapeutic regimen.[1][Level of evidence C2] However, since EMA/CO (i.e., etoposide, methotrexate, and dactinomycin/cyclophosphamide and vincristine) is the most commonly used regimen, the specifics are provided in Table 2 below.[3-5]

Table 2. Specifics of the EMA/CO Regimen[a,b,c]

Day	Drug	Dose
1	Etoposide	100 mg/m^2 IV for 30 min
	Dactinomycin	0.5 mg IV push
	Methotrexate	300 mg/m^2 IV for 12 h
2	Etoposide	100 mg/m^2 IV for 30 min
	Dactinomycin	0.5 mg IV push
	Leucovorin	15 mg or PO every 12 h × 4 doses, beginning 24 h after the start of methotrexate
8	Cyclophosphamide	600 mg/m^2 IV infusion
	Vincristine	0.8–1.0 mg/m^2 IV push (maximum dose 2 mg)

IV = intravenously; PO = orally.

[a]Adapted from Bower et al.[3]

[b]Adapted from Escobar et al.[4]

[c]Adapted from Lurain et al.[5]

Cycles are repeated every 2 weeks (on days 15, 16, and 22) until any metastases present at diagnosis disappear and serum beta-human chorionic gonadotropin (beta-hCG) has normalized, then the treatment is usually continued for an additional three to four cycles.

Results of a large, consecutive case series of 272 patients with up to 16 years of follow-up showed a complete remission rate of 78% using this regimen, and these results are consistent with other case series in the literature that employed EMA/CO.[3] More than two-thirds of the women who did not have a complete response or subsequently had disease recurrence could be salvaged with cisplatin-containing regimens (with or without resection of metastases), yielding a long-term cure rate of 86.2% (95% confidence interval, 81.9%–90.5%).[3][Level of evidence C1] Moreover, routinely when the addition of cisplatin plus etoposide was added to EMA/CO, a 9% improvement was reported in the survival results of these high-risk patients.[6] Among the women who had an intact uterus, about 50% retained their fertility. Patients with documented brain metastases received higher doses of systemic methotrexate as part of the EMA component of EMA/CO (1 g/m^2 intravenously [IV] for 24 hours, followed by leucovorin rescue, 15 mg orally every 6 hours for 12 doses starting 32 hours after methotrexate). Patients with brain metastases received an increased dose of systemic methotrexate of 1 g/m^2 for 24 hours followed by leucovorin (15 mg orally every 6 hours for 12 doses starting 32

hours after methotrexate). Patients with lung metastases received cranial prophylaxis with irradiation and intrathecal methotrexate 12.5 mg every 2 weeks with the CO (i.e., cyclophosphamide and vincristine) cycles.

Examples of other regimens that have been used include the following:[1]

- MAC: Methotrexate, leucovorin, dactinomycin, and cyclophosphamide.
- Another MAC: Methotrexate, dactinomycin, and chlorambucil.
- EMA: Etoposide, methotrexate, leucovorin, and dactinomycin (EMA/CO without the CO).
- CHAMOCA: Methotrexate, dactinomycin, cyclophosphamide, doxorubicin, melphalan, hydroxyurea, and vincristine.
- CHAMOMA: Methotrexate, leucovorin, hydroxyurea, dactinomycin, vincristine, melphalan, and doxorubicin.

Brain metastases are associated with poor prognosis, particularly when liver metastases are also present.[7-9] However, even patients with brain metastases may achieve long-term remission in 50% to 80% of cases.[3,4,9] Patients with central nervous system (CNS) metastases receive additional therapy simultaneously with the initiation of systemic chemotherapy. Some centers use whole-brain irradiation (30 Gy in 2 Gy fractions) with or without intrathecal methotrexate.[7] However, some investigators omit the cranial radiation, relying on replacement of the standard dose of methotrexate in the EMA/CO regimen with the higher dose of 1,000 mg/m^2 IV for 24 hours on the first day, as noted above, to achieve therapeutic CNS levels.[9]

Current Clinical Trials

Use our advanced clinical trial search to find NCI-supported cancer clinical trials that are now enrolling patients. The search can be narrowed by location of the trial, type of treatment, name of the drug, and other criteria. General information about clinical trials is also available.

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Treatment of Placental-Site Trophoblastic Tumor

Because placental-site trophoblastic tumors (PSTTs) are rare, reports of therapeutic results are confined to relatively small case series with accrual extending for very long time periods. Therefore, few reliable comparisons among surgical approaches or chemotherapeutic regimens can be made. Nevertheless, there are distinctions in underlying biology between PSTTs and the other gestational trophoblastic tumors—particularly resistance to chemotherapy—that justify specific treatment strategies, such as the following:

1. Tumors confined to the uterus (Fédération Internationale de Gynécologie et d'Obstétrique [FIGO] Stage I).

   Hysterectomy is the treatment of choice.[1,2] In a relatively large, retrospective, population-based, consecutive case series of 62 women with PSTT, 33 had disease confined to the uterus and were treated with hysterectomy (n = 17) or with hysterectomy plus chemotherapy (n = 16). Overall survival rates at 10 years were virtually identical between the two groups (90% and 91%, respectively). There was only one recurrence in the surgery group and two in the combination therapy group.[2][Level of evidence C2] There is little evidence to guide the optimal extent of surgery (e.g., lymph node resection or oophorectomy).

2. Tumors with extrauterine spread to genital structures (FIGO stage II).

   Complete resection with or without adjuvant chemotherapy. Because the relapse rate is high after surgery and overall mortality in patients is high, adjuvant multiple-agent chemotherapy should be considered.[1,2][Level of evidence C2] However, the impact of adjuvant therapy on overall mortality is uncertain.

3. Metastatic tumors (FIGO stages III and IV).

   Polyagent chemotherapy. A variety of regimens have been used with no direct comparisons to determine whether one is superior. Some of the regimens include the following:[1,2]

   - EMA/CO: Etoposide, methotrexate with leucovorin rescue, dactinomycin, cyclophosphamide, and vincristine. This appears to be the most commonly used regimen.

- EP/EMA: Etoposide and cisplatin with etoposide, methotrexate, and dactinomycin.
- MAE: Methotrexate with leucovorin rescue, dactinomycin, and etoposide.

In part because of the inherent chemoresistance of PSTTs, resection of tumors is often considered in addition to chemotherapy regimens used for high-risk gestational trophoblastic neoplasias. In retrospective series, adjuvant surgery, such as hysterectomy, excision of lung metastases, or removal of obstructing abdominal lesions, has been associated with favorable disease control. However, it is not clear which component of the favorable outcomes is attributable to the surgery or to patient selection factors.[2,3][Level of evidence C2]

Current Clinical Trials

Use our advanced clinical trial search to find NCI-supported cancer clinical trials that are now enrolling patients. The search can be narrowed by location of the trial, type of treatment, name of the drug, and other criteria. General information about clinical trials is also available.

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Treatment of Epithelioid Trophoblastic Tumor

Epithelioid trophoblastic tumors (ETTs) are exceedingly rare, and there is little information to guide therapy. However, these tumors are similar in behavior and prognosis to placental-site trophoblastic tumors, so it is reasonable to manage them similarly. For more information, see the Treatment of Placental-Site Trophoblastic Tumor section. Few ETTs are malignant in nature, but they are not very responsive to systemic therapy. A variety of chemotherapy regimens have been used.[1]

Current Clinical Trials

Use our advanced clinical trial search to find NCI-supported cancer clinical trials that are now enrolling patients. The search can be narrowed by location of the trial, type of treatment, name of the drug, and other criteria. General information about clinical trials is also available.

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Treatment of Recurrent or Chemoresistant Gestational Trophoblastic Neoplasia

Recurrent disease indicates failure of prior chemotherapy unless initial therapy was surgery alone. One study found recurrence of disease in 2.5% of patients with nonmetastatic disease, 3.7% of patients with good-prognosis metastatic disease, and 13% of patients with poor-prognosis metastatic disease.[1] Nearly all recurrences occur within 3 years of remission (85% before 18 months). A patient whose disease progresses after primary surgical therapy is generally treated with single-agent chemotherapy unless one of the poor-prognosis factors that requires combination chemotherapy supervenes. Relapse after failure of prior chemotherapy automatically places the patient in the high-risk category. These patients should be treated with aggressive chemotherapy.

Reports of combination chemotherapy come from small retrospective case series. Long-term disease-free survival, in excess of 50%, is achievable with combination drug regimens.[2][Level of evidence C2] A variety of regimens have been reported that include combinations of the following:[3-7]

- Cisplatin.
- Etoposide.
- Bleomycin.
- Ifosfamide.
- Paclitaxel.
- Fluorouracil.
- Floxuridine.

A select group of patients with chemotherapy-resistant and clinically detectable gestational trophoblastic neoplasia may benefit from salvage surgery.[8][Level of evidence C2]

Fluorouracil Dosing

The *DPYD* gene encodes an enzyme that catabolizes pyrimidines and fluoropyrimidines, like capecitabine and fluorouracil. An estimated 1% to 2% of the population has germline pathogenic variants in *DPYD*, which lead to reduced DPD protein function and an accumulation of pyrimidines and fluoropyrimidines in the body.[9,10] Patients with the *DPYD*2A* variant who receive fluoropyrimidines may experience severe, life-threatening toxicities that are sometimes fatal. Many other *DPYD* variants have been identified, with a range of clinical effects.[9-11] Fluoropyrimidine avoidance or a dose reduction of 50% may be recommended based on the patient's *DPYD* genotype and number of functioning *DPYD* alleles.[12-14] *DPYD* genetic testing costs less than $200, but insurance coverage varies due to a lack of national guidelines.[15] In addition, testing may delay therapy by 2 weeks, which would not be advisable in urgent situations. This controversial issue requires further evaluation.[16]

Current Clinical Trials

Use our advanced clinical trial search to find NCI-supported cancer clinical trials that are now enrolling patients. The search can be narrowed by location of the trial, type of treatment, name of the drug, and other criteria. General information about clinical trials is also available.

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Latest Updates to This Summary (07/19/2024)

The PDQ cancer information summaries are reviewed regularly and updated as new information becomes available. This section describes the latest changes made to this summary as of the date above.

Treatment of Recurrent or Chemoresistant Gestational Trophoblastic Neoplasia

Added Fluorouracil Dosing as a new subsection.

This summary is written and maintained by the PDQ Adult Treatment Editorial Board, which is editorially independent of NCI. The summary reflects an independent review of the literature and does not represent a policy statement of NCI or NIH. More information about summary policies and the role of the PDQ Editorial Boards in maintaining the PDQ summaries can be found on the About This PDQ Summary and PDQ® Cancer Information for Health Professionals pages.

About This PDQ Summary

Purpose of This Summary

This PDQ cancer information summary for health professionals provides comprehensive, peer-reviewed, evidence-based information about the treatment of gestational trophoblastic disease. It is intended as a resource to inform and assist clinicians in the care of their patients. It does not provide formal guidelines or recommendations for making health care decisions.

Reviewers and Updates

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- be discussed at a meeting,
- be cited with text, or
- replace or update an existing article that is already cited.

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