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Trophoblastic disease

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1. Introduction

Before 1969, metastatic choriocarcinoma was almost invariably fatal, whereas most patients are now cured and usually retain reproductive function. The basis for this dramatic change is earlier diagnosis, the ability to precisely measure human chorionic gonadotropin (hCG), and the availability of effective chemotherapy. Trophoblastic disease needs to be treated by, or at least in consultation with, physicians experienced in the management of this disease spectrum, where the cure rate is greater than 90% even in the presence of widespread metastasis [1].

Precise follow-up of patients and precise monitoring using a reliable assay of hCG are essential to good results. The protocol presented here will help outline these principles.

1.1. Definitions

The term gestational trophoblastic neoplasia (GTN) replaces the terms chorioadenoma destruens, metastasizing mole, and choriocarcinoma. These were pathologic diagnoses. While histologic verification is desirable, it is not essential for the clinical classification now used.

Hydatidiform mole is gestational trophoblastic disease (GTD). Nine to twenty percent of patients with complete hydatidiform mole go on to have GTN. This may be chemical only, or associated with evidence of invasive mole. If the process is confined to the uterus, it is termed nonmetastatic trophoblastic neoplasia. If metastases are demonstrated in the lungs or vagina and/or in the brain, liver, kidney, or elsewhere, the diagnosis is that of metastatic GTN. Besides postmolar trophoblastic neoplasia, trophoblastic tumor may also follow abortion (30%) or normal pregnancy (20%).

Placental site trophoblastic tumor (PSTT) is a variant of GTD but should be classified separately as it has a distinct clinical presentation and its course and management differ from GTD.

Nongestational trophoblastic disease is choriocarcinoma of the ovary or testis.

1.2. Etiology of hydatidiform mole

Perspectives of the pathophysiology of hydatidiform mole and trophoblastic neoplasia have also become significantly focused. The distinction between complete mole and partial mole has been validated by genetic analysis and DNA fingerprinting.

The reported incidence of hydatidiform mole is 1 in 125 live births in Taiwan, 2 in 1000 pregnancies in South East Asia and Japan, 1 in 1000 in Europe, and 1 in 1500 in the USA [2,3]. With complete mole, the chromosomal material from the ovum is lost and the genetic material in the conceptus is paternally derived. Fertilization of this “empty” ovum by 1 sperm results in a 46,XX androgenic conceptus. Fertilization may be by 2 sperms giving an XX or XY androgenic conceptus. A YY fertilization will not develop beyond an embryo of a few cells. With complete mole, no fetus develops from this androgenic fertilization. The placenta develops hydatidiform changes and trophoblastic hyperplasia, resulting in a mole with a 9%–20% chance of subsequent neoplasia.

Partial mole is being increasingly recognized as a cause of fetal loss. Many first trimester abortions are associated with triploidy and are in fact partial moles when examined histologically and confirmed by flow cytometry. Clinically, there is a high hCG titer, a variable amount of abnormal fetus present, and hydatidiform changes in the placenta. Early pregnancy pre-eclampsia may occur, and there is usually less trophoblastic hyperplasia than with a complete androgenic mole. The incidence of trophoblastic sequelae is around 1%.

Hydatidiform degeneration is a sign of a poorly functioning early placenta, and may occur with spontaneous abortion without trophoblastic hyperplasia.

The diagnosis of metastatic GTN in a patient who has not had a hydatidiform mole may be difficult. All physicians need to be aware that any female patient of reproductive years who has an obscure disease may have choriocarcinoma. This applies particularly to women presenting with cerebrovascular accidents or persistent pneumonia. All such patients need to have an hCG titer.

2. Diagnosis, evacuation, and follow-up after evacuation of hydatidiform mole

Ultrasonic examination of the first trimester uterus, and particularly vaginal color Doppler flow ultrasound, has made possible the detection of abnormalities of early pregnancy. The potential diagnosis of hydatidiform mole is often made by ultrasound, but histological examination of the evacuated material is essential to confirm the diagnosis. After mole evacuation, patients are followed closely with hCG monitoring at least every 2 weeks. The diagnosis of GTN is made on the basis of an elevated hCG plateau or rising hCG titers over a period of several weeks. Histologic choriocarcinoma and/or the appearance of metastases with a persistently raised serum hCG level is an absolute indication for chemotherapy.

Physical examination and investigations such as chest X-ray, ultrasound, CT scanning, or MRI of the brain, chest, abdomen, and pelvis particularize the extent of disease present. GTN is very sensitive to chemotherapy, and even with extensive high-risk metastatic disease, a mortality of 90% has been converted to a cure rate of 92% or better.

Hydatidiform mole should be treated by evacuating the uterus. The patient must then be followed by serial hCG titers at least every 2 weeks until undetectable titers occur, and then monthly for a maximum of 6 months of normal values. In the 10%–20% of patients in whom the levels of hCG remain elevated, several courses of chemotherapy may be required. In general, patients are no longer treated for moles with prophylactic chemotherapy, as this exposes 80% to unnecessary chemotherapy. Prophylactic or rather adjuvant chemotherapy (i.e. not 1 course, but several courses to nondetectable hCG) should only be offered to patients who cannot be followed.

2.1. hCG assays, nicked hCG, phantom hCG

A reliable assay for total hCG is central to the management of patients with trophoblastic disease. The assay must measure all portions of the hCG molecule, particularly the free beta subunit, hyperglycosylated hCG (hCG-H), nicked hCG, and hCG missing the terminal carboxyl segment. These products are more common in neoplasia than is total hCG. Several commercial assay kits do not measure the free beta subunit or nicked hCG, or differentially recognize hCG-H. Physicians treating patients with trophoblastic disease must ensure that the laboratory used provides accurate assay results, otherwise falsely low values may result in inappropriate management.

In the last few years there have been instances of patients who have positive serum pregnancy tests but no trophoblastic disease and in fact no pregnancy-associated events. The serum of these patients contains heterophilic antibody that reacts with the antibody of certain assay kits to give (false) positive hCG results. This is called phantom hCG. It is important that physicians are aware of this problem because such patients do not require any therapy. Recent work has demonstrated that false-negative results can occur with a number of commercial hCG assays.

The presence of real hCG may be easily confirmed and phantom hCG ruled out by performing hCG assays in dilution that should provide proportionate results or by demonstrating the similar presence of hCG in serum and in urine. However, hCG of less than 50 mIU/mL in urine is inaccurate.

2.2. Quiescent gestational trophoblastic disease

In the last 5 years, clinicians have encountered patients with elevated hCG titers – usually in the range 50–100 mIU/mL – following a molar pregnancy. Occasionally, such titers are discovered incidentally. This is real hCG and not false-positive hCG. The patients have no abnormal clinical findings and imaging is negative. The hCG persists despite treatment with chemotherapy or surgery. In about 20% of these patients, the hCG becomes re-elevated after a period of several weeks to several years, and overt tumor becomes detectable. During the quiescent period, the patient has no detectable hCG-H, but as soon as the hCG rises, a significant proportion is hCG-H, and this is found frequently prior to the appearance of clinically detectable neoplasia. At this time, therapy is effective.

2.3. Pathology

The histologic diagnosis of both complete and partial hydatidiform mole is well recognized. If there is doubt in distinguishing between partial mole and complete mole, flow cytometry may be helpful and is now a well-established technique. The major current difficulty is the recognition of tissue obtained from the uterus at 4–8 weeks of gestation as hydatidiform mole. The criteria for making the diagnosis of these early moles – made possible by the earlier ultrasonic diagnosis – have been described by Sebire et al. [4]. The classical features may not yet be present, and fetal membrane and even fetal erythrocytes may still be present.

The histologic diagnosis of placental site tumor may also be difficult from curettage material and may require the expertise of a gynecologic pathologist with extensive experience in this refined area of gynecologic pathology. This becomes particularly important when hysterectomy is indicated in young nulliparous women in whom this diagnosis is believed to be present.

3. Detailed discussion of trophoblastic disease management

3.1. Hydatidiform mole

3.1.1. Diagnosis of hydatidiform mole

1. History.
2. Clinical examination.
3. Ultrasonic examination, preferably with vaginal color Doppler flow ultrasound.
4. Radiologic examination by MRI or CT scan is indicated only when ultrasonic examination is inconclusive.
5. Serum hCG levels are helpful.

Bleeding or excessive vomiting in the first trimester merits ultrasound examination to allow a positive diagnosis of mole, multiple pregnancy, or fetal abnormality. No fetal heart or high hCG above 80 000 mIU/mL equals mole.

3.1.2. Required studies for patients with hydatidiform mole

1. Clinical examination including neurological examination, eye fundus examination, and blood pressure.
2. Chest X-ray.
3. Blood count with platelet count, blood urea nitrogen (BUN) test, creatinine, and liver function tests on admission. Blood group and hold clot. Thyroid function tests may be indicated. Clinical thyrotoxicosis is very rare. Prothrombin time (PT), partial thromboplastin time (PTT), prothrombin, fibrinogen, if clinically indicated.
4. Serum hCG immunoassay. A specimen of serum for hCG should be obtained: (1) prior to; and (2) 1 day after the evacuation of the mole before the patient leaves the hospital.
5. Digital oximetry, blood gases, and lung scan are mandatory if there is suspicion of pulmonary embolization or pulmonary metastases that are not demonstrable by chest X-ray.

3.1.3. Management of hydatidiform mole

The hydatidiform mole is surgically evacuated as soon as possible after diagnosis. If necessary, the patient is stabilized after the

diagnosis is established. If hematologic, thyroid, or pulmonary problems are present, these are treated: the essential principle is mole evacuation. Evacuation should be done by suction curettage with accompanying synthetic oxytocin infusion plus ergonovine if necessary [1] (**Level of Evidence D**). The cervix may be dilated gently and slowly. With complete mole, a 9 mm or 10 mm suction curettage usually suffices and greater dilatation of the cervix is usually not necessary. A careful, "light" sharp curettage should be performed following the suction procedure to ensure that the uterus has been completely evacuated. Hydatidiform moles of gestational age greater than 16 weeks should be evacuated at a Trophoblast Center because of the risk of pulmonary embolization of molar tissue.

Hysterectomy may be performed in patients who have finished childbearing.

If the patient wishes to retain her uterus, she should be allowed to do so as hysterectomy does not improve the prognosis. Rho(D) Immuno Globulin (RhoGAM) should be given if indicated.

3.1.4. Management post evacuation

1. The patient should be followed by weekly hCG measurements until hCG becomes undetectable (**Level of Evidence D**). Anemia or infection should be treated if present. When the hCG becomes undetectable, 2 further specimens should be obtained at weekly intervals. Subsequently, the patient should be tested monthly for 6 months and then every 2 months for a further 6 months to insure that the hCG levels remain undetectable.
2. An assay for hCG sensitive to 2 mIU/mL or less is essential for follow-up. The assay must be able to detect all portions of the hCG molecule equally well.
3. The patient should be given reliable contraception, preferably in the form of the oral contraceptive pill. If the decrease in hCG is logarithmic, the patient can become pregnant after 6 months of follow-up (**Level of Evidence C**). If there is a very slow decrease in hCG post mole, a longer delay is indicated. It is useful to obtain an ultrasound scan early during the subsequent pregnancy, and to follow hCG titers early in that next pregnancy to document its normalcy. hCG should also be followed to negative levels after delivery of that baby.
4. Patients with a uterus 4 weeks larger in size than the conception dates and with theca lutein cysts have a 50% chance of trophoblastic sequelae.

3.2. Gestational trophoblastic neoplasia

Gestational trophoblastic neoplasia follows hydatidiform mole (60%), previous spontaneous abortion/abortion (30%), and normal pregnancy or ectopic gestation (10%). GTN most commonly follows hydatidiform mole as a persistently elevated hCG titer. There may also be continuing and recurring bleeding after a mole. Metastatic GTN will frequently manifest itself by symptoms from the metastases, such as intracranial neoplasia or "pneumonia."

3.2.1. Diagnosis of postmolar GTN

The diagnosis of GTN is made on the basis of elevated hCG levels supported, if possible, by histologic or radiologic evidence. The agreed criteria to diagnose GTN include:

1. At least 4 values of persistently elevated hCG plateau (days 1, 7, 14, and 21) or longer, or sequential rise of hCG for 2 weeks (days 1, 7, 14) or longer. The actual values of hCG are left to the discretion of individual physicians.
2. Lung metastases are diagnosed by chest X-ray.

Management should only be undertaken by an experienced team: mortality outside a trophoblastic center is much greater than morbidity in a center.

3.2.2. Management of GTN

Required studies

1. Clinical examination (watch for vaginal metastasis).
2. Serial weekly hCG measurements on serum.
3. Complete blood count and platelets. PT, PTT, fibrinogen, BUN, creatinine, liver function tests.
4. Chest X-ray.
5. Brain, MR (or CT) scan when there is any suspicion of cerebral metastases.
6. Liver CT scans when indicated. A whole body CT scan is normally performed in patients who have lung metastases.
7. Curettage should be performed if there is uterine bleeding (**Level of Evidence D**). Biopsies may be obtained from accessible sites. There is severe risk of hemorrhage at the biopsy site.
8. MRI when indicated.
9. T4, thyroid studies when indicated.
10. Selective scanning using anti-hCG antibody linked to radioactive iodine or indium may be done if there is persistent disease resistant to chemotherapy.

3.2.3. Staging

3.2.3.1. FIGO staging of GTN

In 2000, FIGO recommended a clinical staging of gestational trophoblastic tumors and requested that such cases be reported in the Annual Report on the Results of Treatment of Gynecological Cancers. The definitions of the clinical stages of gestational trophoblastic tumors are shown in Table 1.

Table 1
FIGO staging of trophoblastic tumors.

FIGO Stage	Description
I	Gestational trophoblastic tumors strictly confined to the uterine corpus
II	Gestational trophoblastic tumors extending to the adnexae 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

According to FIGO, hydatidiform mole should be registered but should not be staged as Stage 0 because if hCG persists and the patient requires chemotherapy, restaging would be required.

Cases that do not fulfill the criteria for any given stage should be listed separately as unstaged. Most cases of low-risk metastatic disease are encompassed by Stage III, while the high-risk group of metastatic tumors first described by Hammond et al. [5] is the group that comes under Stage IV.

3.2.3.2. A modified WHO scoring system has been combined with the FIGO staging

In 2000, FIGO accepted the WHO scoring system based on prognostic factors that were first devised by Bagshawe [6] (Table 2). The score values for the risk factors are 1, 2, and 4. Blood groups are not used in the scoring system. Liver metastases are given a score of 4. The cut-off scores for low-risk and high-risk neoplasia were ratified by the FIGO Committee on Gynecologic Oncology in June 2002. A score of 6 or less is low-risk disease treatable by single agent chemotherapy. A score of 7 or greater is high-risk disease that requires combination chemotherapy. Medium-risk disease has been eliminated.

This combining of the modified WHO risk factor scoring system with the FIGO staging was accepted by the FIGO Committee on Gynecologic Oncology in September 2000 and ratified in June 2002 with the FIGO announcement [7]. It is now part of the FIGO staging and scoring system for GTN.

Table 2
FIGO/WHO scoring system based on prognostic factors.

FIGO/WHO risk factor scoring with FIGO staging	0	1	2	4
Age	<40	>40	–	–
Antecedent pregnancy	Mole	Abortion	Term	
Interval from index pregnancy, months	<4	4–6	7–12	>12
Pretreatment hCG mIU/mL	$<10^3$	$>10^3$–10^4	$>10^4$–10^5	$>10^5$
Largest tumor size including uterus, cm	–	3–4	≥5	–
Site of metastases including uterus	Lung	Spleen, kidney	Gastrointestinal tract	Brain, liver
Number of metastases identified	–	1–4	5–8	>8
Previous failed chemotherapy	–	–	Single drug	Two or more drugs

3.2.4. Treatment of GTN (trophoblastic tumor)

3.2.4.1. Low-risk GTN

Low-risk GTN includes nonmetastatic neoplasia (except lung metastasis) where the WHO score is 6 or less in FIGO Stage I–III.

1. Drug schedules: single agent chemotherapy:
   a. Methotrexate 0.4 mg/kg intramuscularly for 5 days, repeated every 2 weeks. This is one of the original protocols used in GTD and is still used at Yale University. It is the standard protocol at the Brewer Trophoblast Center in Chicago, where it is used intravenously. The primary failure rate is 11%–15% for nonmetastatic disease and 27%–33% for metastatic disease [8]. **Level of Evidence C**
   b. Methotrexate with leucovorin rescue (see Appendix A). Methotrexate 50 mg intramuscularly or 1 mg/kg every other day for 4 doses with leucovorin 15 mg or 0.1 mg/kg 24–30 hours after each dose of methotrexate. This is a widely used protocol in the UK and the USA, but has a 20%–25% primary failure rate [9]. **Level of Evidence C**
   c. Methotrexate 50 mg/m^2 intramuscularly given weekly. This regimen is associated with a 30% primary failure rate. If this occurs, methotrexate 0.4 mg/kg intramuscularly for 5 days may be administered or the medication may be changed to actinomycin D 12 μg/kg for 5 days [10]. **Level of Evidence C**
   d. Actinomycin D 1.25 mg/m^2 intravenously given every 2 weeks. This protocol carries a 20% primary failure rate. It is an alternative to the pulsed weekly methotrexate protocol [11, 12].
   e. Actinomycin D 12 μg/kg intravenously or 0.5 mg intravenously daily for 5 days, repeated every 2 weeks. This protocol is an alternative to the 5-day methotrexate protocol. It may be used with patients who have hepatic dysfunction. It carries an 8% primary failure rate [13].
   f. Methotrexate 250-mg infusion over 12 hours. This is the methotrexate portion of the EMA-CO protocol (EMA-CO is etoposide, methotrexate with leucovorin rescue and actinomycin D, given on day 1 and 2 and cyclophosphamide and vincristine (Oncovin) given on day 8). It is associated with a 30% primary failure rate [14]. **Level of Evidence C**

Note: Actinomycin D causes severe sloughing of the skin if infiltrated, and must be injected via a new free-running intravenous infusion. If any extravasation does occur, the area should be infiltrated with 100 mg hydrocortisone and 2 mL of lidocaine.

The Cochrane review, which was published in 2009 and included 4 randomized controlled trials and 4 cohort/case-control studies, showed that pulsed actinomycin D appeared to be superior to methotrexate [15] (**Level of Evidence A**). However, the review included 6 different regimens and it was difficult to draw a clear conclusion. A recent randomized controlled trial comparing weekly intramuscular methotrexate and biweekly intravenous actinomycin D showed a better response in the latter group, with modest toxicity [16] (**Level of Evidence A**). A large multicenter randomized controlled trial is warranted to compare the actinomycin D regimen with other more commonly used methotrexate regimens to better define the use of actinomycin D as the first-line treatment.

2. Repeat complete blood count, platelets, creatinine, BUN, and SGOT (serum glutamic oxaloacetic transaminase) are obtained on the first day of each course.
3. At least 1 course, and usually 2–3 courses of chemotherapy should be given beyond the first negative hCG titer, particularly if the decrease in hCG is slow or there has been extensive disease.

3.2.4.2. High-risk GTN

High-risk GTN (tumor) is defined as FIGO Stages I, II, and III with a WHO score of 7 or greater or FIGO Stage IV.

Experience in high-risk patients has shown that single-agent chemotherapy leads to poor results. Such patients are now treated with the combination chemotherapy, EMA-CO, as primary therapy [17,18]. This combination has been found to be more acceptable and less toxic than MAC chemotherapy (methotrexate, actinomycin D, and cyclophosphamide [originally "C" was chlorambucil]; Bagshawe II regimen) [17] (**Level of Evidence C**). However, several centers are returning to the use of MAC because of the risk of leukemia when EMA-CO is given for more than 6 courses.

The patient is closely monitored and courses of EMA-CO are repeated sequentially until remission is obtained. Filgrastim is usually given to sustain white cells.

4. Consolidation chemotherapy

Three further courses of chemotherapy, at least the first of which should be combination therapy, are given beyond the first nondetectable hCG value. A negative hCG value implies that the number of malignant cells present in the body is less than 10^5. It does not mean the disease at that time is completely eradicated.

Certain metastatic sites may require special therapy. For example, brain lesions are treated with an increased dose of methotrexate to 1 g/m^2 in the EMA-CO protocol. With this relatively high dose of methotrexate, the urine must be maintained alkaline. Depending on the size and number of brain metastases, patients may be treated with 25–30 Gy whole brain irradiation or excisional surgery. Patients with liver metastases may be treated with 20 Gy liver radiation or hepatic artery infusion [14]. **Level of Evidence C**

Those patients presenting with very advanced disease involving, for example, the lungs, brain, and/or liver, might be commenced on reduced-dose chemotherapy to avoid life-threatening complications such as pulmonary, cerebral, or liver decompensation from tumor edema or hemorrhage. One regimen that appears to be effective at preventing early loss of life is etoposide 100 mg/m^2 and cisplatin 20 mg/m^2 administered on days 1 and 2, and repeated if necessary 1 week later before commencing standard therapy. **Level of Evidence D**

Patients resistant to EMA-CO or recurring after previous multiagent chemotherapy may be treated by the EMA-EP (EP-EMA) protocol: this is EMA alternating with etoposide and platinum [19] (**Level of Evidence C**). On occasion, EMA with cisplatin and doxorubicin may be used.

For EMA-EP resistant cases, paclitaxel with cisplatin alternating with paclitaxel-etoposide [20] or paclitaxel and 5-fluorouracil or ifosfamide, cisplatin, and etoposide (ICE) or bleomycin, etoposide, and cisplatin (BEP) have been used [21]. **Level of Evidence C**

4.1. Surgery for chemotherapy-resistant and persistent metastases

Metastases to lung, liver, brain, or other sites that do not regress with chemotherapy may be amenable to surgical extirpation. **Level of Evidence C**

4.2. Pregnancy after metastatic trophoblastic disease

Patients need to wait for 12 months after ceasing chemotherapy before undertaking pregnancy. **Level of Evidence C**

4.3. Placental site trophoblastic tumor

Placental site trophoblastic tumor should be separated from gestational trophoblastic tumors such as hydatidiform mole and choriocarcinoma. It should be treated by a Trophoblastic Center. Tumor load with placental site trophoblastic tumor is not reflected by hCG, and while human placental lactogen (hPL) may be seen immunohistochemically it is rarely detectable in serum. It has recently been discovered that free beta hCG is a reliable marker for placental site trophoblastic tumor, especially in situations where there is uncertainty about whether the patient has choriocarcinoma (high proportion hCG-H) or placental site trophoblastic tumor (high proportion free beta hCG). Patient management with both chemotherapy and surgery requires individualization. The most commonly used chemotherapy regimen is EMA-EP (etoposide, methotrexate, actinomycin, etoposide, and cisplatin); an alternative is TE/TP (paclitaxel etoposide/paclitaxel cisplatin) [22]. **Level of Evidence C**

4.4. Epithelioid trophoblastic tumor

Epithelioid trophoblastic tumor (ETT) is derived from the chorionic-type intermediate trophoblast. Rarely, ETT can coexist with choriocarcinoma or PSTT. The majority of ETT occurs in the reproductive age group. Patients often have symptoms resembling those in PSTT and about 70% of patients have abnormal vaginal bleeding. The serum hCG level is usually mildly elevated. Similar to PSTT, ETT is not chemosensitive and it is mainly treated by surgery.

5. Trophoblastic patient record

Physicians treating trophoblastic disease are urged to maintain an active record of weekly hCG measurements on semilogarithmic graph paper. Treatment events such as chemotherapy and radiologic investigations should be recorded on the same record.

Conflict of interest

The authors have no conflicts of interest to declare.

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Appendix 1: Chemotherapy protocols

Single-agent chemotherapy protocols for low-risk trophoblastic neoplasia. WHO Score 6 or less.

(1) Methotrexate 0.4 mg/kg daily for 5 days given intramuscularly.
(2) Methotrexate with citrovorum factor rescue protocol.

Day	Therapy
1	CBC, platelet count, SGOT MTX 1 mg/kg IM
2	CF 0.1 mg/kg IM
3	MTX 1 mg/kg IM

4	CF 0.1 mg/kg IM
5	MTX 1 mg/kg IM
6	CF 0.1 mg/kg IM
7	MTX 1 mg/kg IM
8	CF 0.1 mg/kg IM

Abbreviations: CBC, complete blood count; SGOT, serum glutamic oxaloacetic transaminase; MTX, methotrexate; CF, citrovorum factor; IM, intramuscularly.

(3) Methotrexate 50 mg/kg given weekly by intramuscular injection.
(4) Actinomycin D 12 μg/kg daily for 15 days.
(5) Actinomycin D 1.25 mg/m^2 given every 2 weeks (pulsed actinomycin D).
(6) Methotrexate 250 mg infusion over 12 hours.

Suggestions for the management of primary failure of single-agent chemotherapy in low-risk GTN (Risk Factor Score 6)

If pulsed single-agent chemotherapy, either methotrexate 50 mg/m^2 or actinomycin D 1.25 mg/m^2 or methotrexate with leucovorin rescue do not effect response, it may be worthwhile to use the same agent given as a 5-day course; i.e. methotrexate 0.4 mg/kg daily for 5 days or actinomycin D 12 μg/kg daily for 5 days, before switching to the alternate agent. The failure of pulsed single-agent chemotherapy is thought to be associated with insufficient exposure of cells in cycle during the relatively brief time effective drug levels are present in the circulation. This practice may avoid having to give multiagent chemotherapy in such a situation in more than 50% of these patients.

Current multiagent chemotherapy for high-risk GTN, EMA-CO WHO Score 7 or greater

Etoposide, methotrexate, actinomycin D, alternating weekly with cyclophosphamide and vincristine. EMA-CO is administered on a weekly basis with anticipated cycling between each course of 14 days.

Day 1 (A) Actinomycin D 500 μg IV push IV.
Etoposide 100 mg/m^2 over 30–50 minutes.
Methotrexate 100 mg/m^2 IV infusion over 1 hour and then, methotrexate 200 mg/m^2 IV infusion over 12 hours by pump.
Day 2 (A) Actinomycin D 500 μg IV push new IV.
Etoposide 100 mg/m^2 over 30–50 minutes.
Leucovorin 15 mg IV push every 6 hours for 8 doses beginning 24 hours after methotrexate bolus. Some physicians administer the leucovorin orally, 15 mg every 12 hours for 4 doses, starting 24 hours after commencing methotrexate.
Day 8 (B) Vincristine 1 mg/m^2 IV.
Cyclophosphamide 600 mg/m^2 IV.

Notes:
(1) Filgrastim may be administered. Note that this must be started 24 hours after day 2 chemotherapy and then be stopped 24 hours before cyclophosphamide and vincristine.
(2) If the creatinine is greater than 2.0, creatinine clearance should be done prior to therapy and should be 50 or more.
(3) Cycles are repeated on day 15 of cycle.
(4) Chemotherapy is administered when white cell count is greater than 3000 per mL, granulocytes are greater than 1500 per mL, platelets are greater than 100 000 per mL, and a Grade 3 gastrointestinal infection and mucositis morbidity have cleared. If toxicity necessitates a delay in course B for longer than 6 days, course A is recycled.

Combination chemotherapy for trophoblastic neoplasia with brain metastases – EMA-CO with high-dose methotrexate

For GTN with brain metastases, the EMA-CO protocol is modified. The dose of methotrexate is increased to 1000 mg/m^2 (1 g/m^2). The methotrexate infusion is given over 24 hours. The urine must be kept alkaline with a measured pH of greater than 7.5 at all times by administration of bicarbonate IV. Urinary volume and pH must be followed assiduously.

If filgrastim is given, it needs to be given commencing 24 hours after the last chemotherapy and ceasing 24 hours prior to the next planned chemotherapy.

Combination chemotherapy for high-risk trophoblastic neoplasia resistant to EMA-CO or recurring after combination chemotherapy

The majority of Trophoblast Centers use EP-EMA (EMA-CO) under such circumstances. EMA is administered in the standard way and etoposide and platinum are substituted for cyclophosphamide and vincristine. This is a more demanding and more toxic regimen. The following schedule is taken from the Charing Cross protocol as they have had the most experience and the greatest success [1].

Combination chemotherapy for EMA-CO failure in trophoblastic neoplasia: EP-EMA

Cisplatin is given on Day 1 by infusion of 80 mg/kg in 1 liter by infusion pump over 12 hours. Etoposide 100 mg/m^2 is given over 1 hour. On Day 8, EMA is given in standard doses but on the second day, actinomycin D and etoposide are omitted. The cycle is repeated every 15 days.

Filgrastim is commenced 24 hours after first methotrexate infusion and stopped 24 hours before day 8 platinum. It is recommenced 24 hours after stopping platinum and stopped 24 hours before next EMA. The timing of filgrastim has to be carefully planned.

Alternate combination chemotherapy for high-risk GTN: Methotrexate, actinomycin D, cyclophosphamide (MAC) protocol for high-risk GTN

This regimen has been largely superseded by EMA-CO.

Day	Therapy
1	CBC, platelet count, SGOT Compazine 25 mg, IM, PO, or PR Methotrexate 1.0 mg/kg, IM Actinomycin D 12 μg/kg, stat IV Cyclophosphamide 3 mg/kg, stat IV
2	CBC, platelet count Compazine 25 mg, IM, PO, or PR Leucovorin 0.1 mg/kg, IM Actinomycin D 12 μg/kg, stat IV Cyclophosphamide 3 mg/kg, stat IV
3, 4, 5	Repeat day 1 and 2
6	Leucovorin 0.1 mg/kg, IM
7	CBC, platelet count, SGOT Methotrexate 1.0 mg/kg, IM
8	Leucovorin 0.1 mg/kg, IM

Abbreviations: CBC, complete blood count; SGOT, serum glutamic oxaloacetic transaminase; IM, intramuscularly; PO, orally; PR, rectally.

Courses are repeated every 2 weeks or as soon as the white cells and platelets recover.

Bagshawe 9-day multiagent chemotherapy

This protocol has been reported to be more toxic than MAC and will probably be used only in exceptional circumstances. However, several Trophoblast Centers use it for high-risk disease as initial therapy because of the leukemogenic association of EMA-CO.

Bleomycin, etoposide, cisplatin (BEP) for chemotherapy-resistant GTN and for primary ovarian germ cell tumor

Etoposide 100 mg IV in 500 mL normal saline over 1 hour: Days 1, 2, 3, 4.

Cisplatin 100 mg/m^2 day 1 IV continuous infusion $\times$ 24 hours with normal saline $\times$6 at 250 mL per hour; add 20 mEq potassium chloride and 2 mg magnesium sulfate to each of last 2 liters.

Bleomycin 10 units/m^2 per day for 3 days; days 2, 3, and 4; IV continuous infusion for 96 hours.

Give day 1, etoposide prior to cisplatin. Give day 2, etoposide as part of cisplatin post hydration; then complete post hydration (concurrent with first bleomycin infusion) with 5% dextrose or normal saline at 150 mL per hour for 11 hours. Give day 3 and 4, etoposide prior to starting second and third bleomycin infusion. Granisetron, compazine, and diphenhydramine are given with these medications.

Validity of studies on which the protocols are based

In an age of evidence-based medicine, very few of the chemotherapy protocols used to treat trophoblastic disease have undergone the rigors of a prospective randomized study. No study fulfills a Cochrane category I or II for clinical studies. The evidence on which management of GTN is presently based throughout the world fulfills only a Cochrane category III. This applies to all the management protocols in this document.

Consultation

Physicians wishing for consultation concerning case management should contact their nearest Trophoblast Center early rather than late following mole evacuation.

References

1. Bower M, Newlands ES, Holden L, Short D, Brock C, Rustin GJ, et al. EMA/CO for high-risk gestational trophoblastic tumors: results from a cohort of 272 patients. J Clin Oncol 1997;15(7):2636–43. Erratum: 15(9):3168.