Gestational trophoblastic disease


Gestational trophoblastic disease encompasses a range of pregnancy-related disorders, consisting of the premalignant disorders of complete and partial hydatidiform mole, and the malignant disorders of invasive mole, choriocarcinoma, and the rare placental-site trophoblastic tumour. These malignant forms are termed gestational trophoblastic tumours or neoplasia. Improvements in management and follow-up protocols mean that overall cure rates can exceed 98% with fertility retention, whereas most women would have died from malignant disease 60 years ago. This success can be explained by the development of effective treatments, the use of human chorionic gonadotropin as a biomarker, and centralisation of care. We summarise strategies for management of gestational trophoblastic disease and address some of the controversies and future research directions.

Introduction

Hippocrates was probably the first to describe gestational trophoblastic disease around 400 BC in his description of dropsy of the uterus. Although other observations have been made since, Marchand first associated hydatidiform mole with pregnancy in 1889. Healthy trophoblastic tissue aggressively invades the endometrium and develops a rich uterine vasculature, generating an intimate connection between the fetus and the mother known as the placenta. Invasion is one of the distinct features of malignant disease, and healthy trophoblast can be detected by PCR in the maternal circulation. Fortunately, malignant-like behaviour is tightly controlled in healthy trophoblast. However, in gestational trophoblastic disease the regulatory mechanisms fail, resulting in tumours that are highly invasive, metastatic, and very vascular. In this Seminar we discuss the epidemiology, origins, pathological changes, and clinical behaviour of the various forms of gestational trophoblastic disease.

Epidemiology

Gestational trophoblastic disease arises more frequently in Asia than in North America or Europe, which could be due to differences in prevalence, discrepancies between hospital-based and population-based data, or disparity in availability of central pathology review. In the UK, all patients are included on a national register, with central pathology review; and the incidence of complete hydatidiform mole is around one per 1000 pregnancies and three per 1000 for partial hydatidiform mole. Other developed countries report similar data. The incidence of molar pregnancy has decreased in South Korea from 4-4 cases per 1000 births in the 1960s to 1-6 cases per 1000 births in the 1990s, possibly because of improved socioeconomic conditions and dietary changes—especially since findings from studies in animals show that diet can reset the genetic imprint. Additionally, an increased risk of molar pregnancy is associated with reduced consumption of dietary carotene and animal fat, and advanced maternal age. Ova from older women are more susceptible to abnormal fertilisations than are those from younger women.

After a molar pregnancy, the risk of further complete and partial mole rises to 1–2%. After two molar gestations, the risk of a third mole is 15–20%, and the risk is not decreased by change of partner. Some repeat molar pregnancies are due to familial or sporadic biparental molar disease (figure 1).

The frequency of choriocarcinoma or placental-site trophoblastic tumour is less well known, since these diseases can arise after any type of pregnancy. Choriocarcinoma develops in around one in 50 000 deliveries, and placental-site trophoblastic tumour accounts for about 0–2% of cases of gestational trophoblastic disease in the UK. The risk of gestational trophoblastic neoplasia might also be linked to hormonal factors, since women with menarche after 12 years of age, light menstrual flow, and previous use of oral contraceptives are at increased risk. Additionally, risk of malignant disease after hydatidiform mole has been associated with oral contraceptive use (if started when human chorionic gonadotropin [hCG] concentrations are raised) in some but not all studies.

Causes and genetics

In most cases, complete hydatidiform mole usually arises when an ovm without maternal chromosomes

Search strategy and selection criteria

is fertilised by one sperm that then duplicates its DNA, resulting in a 46XX androgenetic karyotype, in which all chromosomes are paternally derived.25–27 About 10% of complete moles are 46XY,28 arising from fertilisation by two sperm (figure 1). Although nuclear DNA is entirely paternal, mitochondrial DNA remains maternal in origin.29 Findings from some studies30 show that patients with recurrent disease can have biparental molar rather than typical androgenetic disease, which might be familial or sporadic. Genetic studies in such families showed that the related genes are at chromosome 19q13.3–13.4,31 and subsequent analysis noted NLRP7 mutations in this region.32 The function of the normal protein and the mechanism by which mutations are associated with imprinting abnormalities and gestational trophoblastic disease are unknown.33 Data show clustering of mutations in the leucine-rich region of NLRP7 (figure 2), suggesting that this region is crucial for normal function.3 Some androgenetic diploid complete moles and possibly even triploid partial hydatidiform moles might also carry NLRP7 mutations,35 but confirmation from large studies is needed.

Partial hydatidiform moles are almost always triploid (figure 1), and they result from fertilisation of a seemingly healthy ovum by two sperm;36–38 diploid partial moles probably do not exist, with most reported cases being misdiagnosed complete moles.39

**Pathology**

All gestational trophoblastic disease is derived from the placenta. Hydatidiform moles and choriocarcinoma arise from villous trophoblast and placental-site trophoblastic tumours from interstitial trophoblast. Most complete and partial hydatidiform moles have distinctive morphological characteristics, although diagnostic criteria have changed because evacuation is done earlier in gestation (median 8–9 weeks in the UK). First-trimester complete moles show a characteristic abnormal budding villous structure with trophoblast hyperplasia, stromal karyorrhectic debris, and collapsed villous blood vessels. By contrast, early partial moles show patchy villous hydrops with scattered abnormally shaped irregular villi, trophoblastic pseudoinclusions, and patchy trophoblast hyperplasia (figure 3).40–42 Morphological distinction of non-molar miscarriage from partial hydatidiform mole can be difficult, since villous dysmorphism can be present but without the characteristic trophoblast hyperplasia that is noted in partial mole. Ancillary techniques are needed in some cases to differentiate non-molar miscarriage from hydatidiform mole, including immunostaining for P57kip2, the product of CDKN1C. P57kip2 is expressed by the maternal allele and is visible on histology as nuclear staining of cytotrophoblast and villous mesenchyme in placenta of all gestations except androgenetic complete mole.43,44 Additionally, ploidy analysis by in-situ hybridisation or flow cytometry can distinguish diploid from triploid conceptions, helping to diagnose partial mole, but is unable to distinguish complete mole from diploid non-molar miscarriage, or molar versus non-molar triploidy, which necessitate molecular investigations.18,45–47

Choriocarcinomas are malignant hCG-producing epithelial tumours with central necrosis and a characteristic biphasic architecture recapitulating cytotrophoblast-like
cells and multinucleate, pleomorphic syncytiotrophoblast-like regions; however, mononuclear cells predominate in some cases, especially after chemotherapy. Intraplacental choriocarcinoma does occur and is probably the source of metastatic disease after term pregnancies. Most cases of neonatal choriocarcinoma result from metastatic spread from an intraplacental choriocarcinoma. Placental-site trophoblastic tumours are the malignant equivalent of extravillous, interstitial implantation site-like trophoblast and form uterine lesions with less haemorrhage and necrosis, and lower hCG concentrations than does choriocarcinoma. Epithelioid trophoblastic tumour—a variant of placental-site trophoblastic tumour with similar clinical behaviour but distinctive hyalinisation—has been reported, but data for this disease are sparse.

Accurate measurement of hCG is key to effective management of gestational trophoblastic disease, several cancers, and pregnancy. Panel 1 summarises some of the issues related to hCG measurements.

**Diagnostic ultrasound for molar pregnancy**

Patients with complete hydatidiform mole most commonly present with vaginal bleeding in early pregnancy. Previously reported features such as anaemia, uterine enlargement, pre-eclampsia, hyperemesis, hyperthyroidism, and respiratory distress are now rare, probably because routine use of ultrasonography leads to diagnosis in the first rather than late-second trimester. Partial hydatidiform moles grow more slowly and present slightly later in the first or early second trimester than do complete moles, but also manifest with vaginal bleeding or missed or incomplete miscarriages. Characteristic ultrasonographic scans of complete mole show a uterine cavity filled with a heterogeneous mass (so-called snowstorm), without associated fetal development and with theca lutein ovarian cysts. However, these features are not visible in the first trimester and, although some investigators have suggested that ultrasound can be diagnostic of complete mole in early pregnancy, large studies have shown that only 40–60% of cases are detected as molar by sonography in routine clinical practice. Moreover, 10% of cases that are thought to be molar on sonography were diagnosed as non-molar hydropic abortions on histological review.

Findings from other reports are similar and emphasise...
Panel 1: 

**hCG measurement in gestational trophoblastic disease and cancer**

hCG comprises an α subunit (shared with other members of the glycoprotein hormones, including thyroid-stimulating hormone and luteinising hormone) and a β subunit that confers specificity. Consequently, assays designed to specifically detect hCG have to target the β subunit. In healthy pregnancy, hCG is intact and is hyperglycosylated during the first trimester. However, in cancer, many other subtypes of β-hCG can exist, including free-β-hCG, β-core, nicked free-β, or c-terminal peptide. Therefore, hCG assays used in cancer need to detect all forms of hCG and not only those found in healthy pregnancy. Moreover, the different β-hCG forms should be detected equally well.

Unfortunately, most commercial assays fail to or variably detect all forms of β-hCG and therefore are prone to false-negative results in patients with cancer. Additionally, every assay is susceptible to false-positive results, usually caused by cross-reacting heterophile antibodies. These antibodies do not pass into the urine, so if hCG is present, a false-positive serum value can be excluded in most cases, although other approaches to this problem might be necessary.

However, the false-negative issue cannot be easily resolved and is potentially clinically important, since a false-negative finding could result in delayed diagnosis or premature withdrawal of chemotherapy, or both. No commercial assay is licensed for use in cancer diagnosis or management at present, although many are used for this purpose.

In the UK, we use a non-commercial rabbit polyclonal antibody that detects all forms of hCG for monitoring of patients with gestational trophoblastic disease. By comparison with other assays, our assay seems to have a low false-negative rate and, since we routinely measure hCG in serum and urine, false-positive results are rare. This assay is not available worldwide and, to our knowledge, the only commercial assay that seems comparable is the Siemens Immulite (Deerfield, IL, USA). Therefore, a new generation of cancer-specific hCG assays is urgently needed.

Findings from recent studies that used a hyperglycosylated hCG assay suggest that a high ratio of this variant to total hCG can detect malignant forms of gestational trophoblastic disease. These findings correlate with some biological evidence suggesting that hyperglycosylated hCG induces an invasive phenotype in trophoblast and choriocarcinoma cells. Additionally, some preliminary studies suggest that free-β-hCG is a marker for placental-site trophoblastic tumour and seminomatous germ cell tumours. Prospective studies in large patient cohorts are needed to define the role of hyperglycosylated hCG and free-β-hCG in the management of gestational cancers.

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**Surgical evacuation**

Suction curettage is the preferred method of evacuation irrespective of uterine size in patients with suspected hydatidiform mole who want to preserve fertility. Intraoperative ultrasonography can reduce the risk of uterine perforation. Patients who are rhesus-negative should receive rhesus immunoglobulin at the time of evacuation because rhesus D factor is expressed on trophoblast. Women who are nulliparous should not be given prostanooids to ripen the cervix since these drugs can induce uterine contractions and might increase the risk of trophoblastic embolisation to the pulmonary vasculature. Hysterectomy is rarely recommended but might be considered for women who do not want further children or have life-threatening haemorrhage. Patients should be counselled that, although hysterectomy stops the risk of local invasion, it does not eliminate the possible need for chemotherapy, and monitoring of hCG concentrations should still be done.

A healthy co-twin can develop alongside a complete or partial hydatidiform mole in one per 20000–100000 pregnancies (figure 4). Some investigators have suggested that such pregnancies should be terminated because of the low probability of successful outcome and the increased risk of development of malignant disease. However, evidence from a case series of 77 pregnancies suggests that about 40% of women will deliver a healthy baby without a significant increase in the risk of malignant transformation of the complete hydatidiform mole. Findings from a study of 2800 singleton molar pregnancies lent support to the notion that late evacuation of complete hydatidiform mole is not associated with an increased rate of malignant disease.

**Registration for hCG surveillance**

All patients with hydatidiform mole should be registered with a specialist centre for hCG surveillance, preferably one that is coordinated nationally. The UK established the first national service for gestational trophoblastic disease through a combined agreement of the Royal College of Obstetricians and Gynaecologists and the Department of Health’s National Commissioning Group. Since 1973, all women with hydatidiform mole or other forms of gestational trophoblastic disease have been registered with one of three centres for hCG monitoring and, if subsequent treatment is necessary, are treated at the Sheffield Trophoblastic Disease Centre (Sheffield, UK) or Charing Cross Hospital Trophoblast Disease Centre (London, UK).

Onset of malignant change, termed persistent gestational trophoblastic disease or post-mole neoplasia, is signified by a plateaued or rising hCG concentration. Studies in the UK show that malignant change arises after 15% of complete and 0.5–1.0% of partial hydatidiform moles. Rates are probably higher in other countries than the UK, possibly because of...
differences in hCG criteria and overdiagnosis of neoplasia, scarcity of whole-population demographics, or a difference in disease biology, although this explanation is unlikely. Precise surveillance protocols vary by country but principles are alike. In the UK, serum and urine hCG concentrations are measured every 2 weeks until the values are within the normal range, and then urine hCG concentrations are recorded monthly. Patients with normal hCG values within 56 days of uterine evacuation have a reduced risk of development of malignant disease, and are monitored for 6 months from evacuation date. When the first hCG reading within the normal range is noted after 56 days, monthly monitoring continues for 6 months. Some investigators suggest shortened hCG surveillance, with discontinuation after the first value within the normal range is measured, especially for women with partial mole in whom the risk of neoplasia is reduced. Shortened surveillance could enable women to attempt a subsequent pregnancy sooner, but could result in late development of neoplasia with increased morbidity and mortality.

Data reported at the 2009 International Society for the Study of Trophoblastic Diseases (ISSTD) world congress from 22,000 women with complete and partial hydatidiform moles in the UK suggest that either form can occasionally develop post-mole neoplasia after the hCG has returned to normal; however, the risk of missed gestational trophoblastic neoplasia can be reduced from one in 800 women to one in 1400 by following present UK guidelines. Consequently, UK practice seems good for young women, but older nulliparous women should be made aware of the relative risks and benefits of an early pregnancy. During hCG follow-up, patients are encouraged to use reliable contraception, including a combination of methods, although data are conflicting about whether oral contraceptives increase the risk for gestational trophoblastic neoplasia. In the UK, practitioners avoid recommending oral contraceptives until hCG is in the normal range. After completion of hCG monitoring, serum or urine hCG concentrations should be checked 6 weeks and 10 weeks after every pregnancy to ensure no reactivation of previous molar disease.

**Panel 2: Indications for chemotherapy for gestational trophoblastic disease in the UK**

- Plateaued or rising hCG concentration after evacuation
- Heavy vaginal bleeding or evidence of gastrointestinal or intraperitoneal haemorrhage
- Histological evidence of choriocarcinoma
- Evidence of metastases in brain, liver, or gastrointestinal tract, or radiological opacities larger than 2 cm on chest radiograph
- Serum hCG concentration of 20,000 IU/L or more, 4 weeks or more after evacuation, because of the risk of uterine perforation
- Raised hCG concentration 6 months after evacuation, even when still decreasing

hCG=human chorionic gonadotropin. A plateaued hCG concentration is defined as four or more equivalent values of hCG for at least 3 weeks (days 1, 7, 14, and 21), and rising as two consecutive increases in hCG concentration of 10% or more for at least 2 weeks (days 1, 7, and 14).

**Treatment Indications**

Panel 2 shows the UK indications for treatment of gestational trophoblastic disease with chemotherapy. These recommendations are similar to those suggested by the International Federation of Gynecology and Obstetrics (FIGO) and include a plateaued or rising hCG (the most common reason for treatment), a persistently raised hCG at 6 months after evacuation, or histological diagnosis of choriocarcinoma. However, our experience suggests that the disease is unlikely to remit spontaneously when: the hCG concentration is more than 20,000 IU/L, 1 month after evacuation (also associated with an increased risk of uterine perforation); or there are lung or vaginal metastases more than 2 cm in diameter (small lesions can spontaneously regress), or spread to other organs. Additionally, in the UK, chemotherapy is started to help to stop heavy bleeding that necessitates transfusion, even when the hCG concentration is falling.

**Staging and stratification**

Most patients who develop gestational trophoblastic neoplasia after hydatidiform mole are detected early by hCG monitoring so detailed investigation is rarely needed. Information on which to base therapy decisions can be obtained from clinical histories, examination, and measurement of serum hCG. Additionally, patients should have doppler pelvic ultrasonography to confirm absence of pregnancy, and to measure the uterine size and volume, spread of disease within the pelvis, and disease vascularity (figure 5). Disease vascularity can
suggest patients who are at risk of treatment resistance. Pulmonary metastases are most common, so chest radiography is essential. Chest CT is not needed when findings from chest radiography is normal, since discovery of micrometastases, which can be seen in about 40% of patients, does not affect outcome. However, if lesions are noted on chest radiograph, brain MRI and body CT are recommended to exclude more widespread disease affecting, for example, the brain or liver, which would substantially change management.

FIGO report data for gestational trophoblastic neoplasia by use of prognostic scoring and anatomical staging systems (table 1). Since 2002, all physicians treating gestational trophoblastic neoplasia should use this system to allow comparison of data. The combined prognostic score predicts potential for development of resistance to monochemotherapy with methotrexate or dactinomycin. A score of 0–6 suggests low risk of resistance and 7 or more indicates high risk. Such disease has almost no chance of being cured with monochemotherapy and needs multidrug treatment. Anatomical staging does not aid therapeutic choices but helps clinicians to compare results between centres.

**Low-risk disease**

About 95% of patients with hydatidiform mole who develop neoplasia are at low risk of resistance (score 0–6). In patients with stage I disease that is seemingly confined to the uterine cavity, the use of second dilatation and curettage to reduce the need for chemotherapy is controversial. Results from the UK suggest that secondary surgery is of no value when hCG concentrations are greater than 5000 IU/L, since more than 50% of such patients will need chemotherapy. The low effectiveness of second surgery and small risks of infection, haemorrhage, and uterine perforation should be measured against the almost 100% cure rate and comparative safety of chemotherapy. Some patients with stage I neoplasia who do not want further children request hysterectomy, which can be technically difficult with these highly vascular tumours and does not completely obviate the need for chemotherapy.

For most low-risk patients with gestational trophoblastic neoplasia, monochemotherapy with methotrexate or dactinomycin is the preferred treatment. Many regimens have been used, showing a 50–90% chance of induction of remission in non-randomised, mostly retrospective, studies. The wide variability results from differences in dose, frequency, route of administration, and the criteria used to select patients for therapy. Some investigators suggest that intensive therapy given daily for 5–8 days every 2 weeks is better than treatments given once every 2 weeks; others suggest that dactinomycin is more likely to induce remission than is methotrexate. The few randomised studies that addressed some of these issues were underpowered and compared regimens that are not frequently used internationally. Patients in whom first-line therapy fails—generally because of resistance—can be easily salvaged with second-line or occasionally third-line chemotherapy, so overall survival is nearly 100%. Since survival is so high, patients should be given the least toxic therapy first to avoid exposure to more harmful treatments.

The regimen of methotrexate (50 mg intramuscularly every 48 h for four doses) with calcium folinate (folinic acid) rescue (15 mg orally 30 h after methotrexate) regimen developed at our UK institute is effective and is well tolerated. Courses are repeated every 2 weeks. Unlike dactinomycin, this regimen does not induce hair loss; thus
pleuritic or peritoneal pains from serositis. Patients who About 2% of women have mouth ulcers, sore eyes, or rarely
home after a short stay in hospital to monitor any bleeding.
universal, so unless clinicians consider gestational
disease in the pulmonary vasculature might have a
combination of haemoptysis, shortness of breath, or
drugs to prevent life-threatening haemorrhage. Chemotherapy
should be continued until hCG is within the normal range
and then for a further 6 weeks (figure 6), helping to
eliminate any residual tumour cells and reduce the chance
of relapse.

Only 30% of patients scoring 5–6 can be cured with low-
risk therapy. Therefore, revision of the FIGO scoring system would be helpful for early identification of the 70% of women in this group who develop resistance to methotrexate with folinic acid rescue and who need more intensive therapy. The amount of vascularisation as detected on doppler ultrasonography could help to provide the necessary additional information. Furthermore, data suggest that women in this category with an hCG concentration of more than 400 000 IU/L are unlikely to be cured by methotrexate with folinic acid rescue, so multidrug treatment should be given from the outset.

High-risk disease
Most high-risk patients with gestational trophoblastic neoplasia present with many metastases months or years after the causative pregnancy of any type. Symptoms and signs vary with disease location. Patients with brain metastases (figure 5) present with seizures, headaches, or hemiparesis, whereas those with lung metastasis or disease in the pulmonary vasculature might have a combination of haemoptysis, shortness of breath, or pleuritic chest pain. Menstrual irregularity is not universal, so unless clinicians consider gestational trophoblastic neoplasia in the differential of metastatic disease and measure the serum or urine hCG the diagnosis can be missed. If hCG concentrations are raised, the treating physician should consult the nearest gestational trophoblastic disease centre about management. Imaging investigations should include body CT, brain MRI, and pelvic MRI and Doppler ultrasonography (figure 5). If the brain scan is normal, a lumbar puncture to measure the ratio of cerebrospinal fluid to serum hCG (normal <1:60) can help to exclude occult CNS disease.

Investigators should avoid taking a biopsy sample of these highly vascular tumours to prevent life-threatening haemorrhage. However, when a lesion is easily accessible and bleeding can be controlled, taking an excision biopsy sample can be helpful. This is especially important when placental-site or non-gestational tumours might exist, since their management differs from that of gestational choriocarcinoma.

Fortunately, placental-site trophoblastic tumour has a distinct histological appearance and comparison of microsatellite polymorphisms in the tumour with DNA from the patient and her partner can establish whether the tumour is gestational. The phenotypic appearance of the tumour is not always reliable and rarely non-gestational carcinomas can look morphologically very similar to gestational choriocarcinomas and, conversely, these carcinomas can occasionally mimic other epithelial tumours. Chemotherapy is effective for cure of gestational tumours, whereas the chance of survival from a non-gestational tumour depends on the primary site.

Patients scoring 7 or more on the FIGO system (table 1) are at high risk of developing drug resistance and are very unlikely to be cured with monochemotherapy. Consequently, several different multidrug therapies have been investigated, including methotrexate, folinic acid, and dactinomycin (MFA); methotrexate, dactinomycin, cyclophosphamide, doxorubicin, melphalan, hydroxy-carbamide, and vincristine (CHAMOCA); methotrexate, dactinomycin, and cyclophosphamide (MAC); and etoposide, methotrexate, and dactinomycin (EMA). At our UK institute, a regimen was developed consisting of alternating EMA every week with cyclophosphamide and
trophoblastic disease service has increased the hCG concentration at which combination chemotherapy is started to more than 300 IU/L, to reduce the number of women being exposed to greater toxicity. Chemotherapy should be continued until hCG is within the normal range and then for a further 6 weeks (figure 6), helping to eliminate any residual tumour cells and reduce the chance of relapse.
Figure 6: Response to low-risk chemotherapy measured by hCG tumour marker concentration

After uterine evacuation of a complete hydatidiform mole, hCG remained plateaued, suggesting persistent gestational trophoblastic disease or neoplasia, so the patient started treatment with methotrexate and folinic acid. Time and type of intervention are shown above the line. Therapy was continued for 6 weeks after normal hCG gestational trophoblastic disease or neoplasia, so the patient started treatment with methotrexate and folinic acid. After uterine evacuation of a complete hydatidiform mole, hCG remained plateaued, suggesting persistent gestational trophoblastic disease or neoplasia, so the patient started treatment with methotrexate and folinic acid. Therapy was continued for 6 weeks after normal hCG gestational trophoblastic disease or neoplasia, so the patient started treatment with methotrexate and folinic acid.

Table 2: EMA-CO chemotherapy regimen for patients at high risk of monochemo resistance

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Day 1 (EMA)</th>
<th>Day 2 (EMA)</th>
<th>Day 8 (CO)</th>
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<tbody>
<tr>
<td>Etoposide</td>
<td>100 mg/m² by intravenous infusion for 30 min</td>
<td>100 mg/m² by intravenous infusion for 30 min</td>
<td>1 mg/m² intravenous bolus (maximum 2 mg)</td>
</tr>
<tr>
<td>Dactinomycin</td>
<td>0.5 mg intravenous bolus</td>
<td>0.5 mg intravenous bolus</td>
<td>600 mg/m² intravenous infusion for 30 min</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>300 mg/m² by intravenous infusion for 12 h</td>
<td>Folinic acid rescue†</td>
<td>15 mg intramuscular or orally every 12 h for four doses</td>
</tr>
<tr>
<td>EMA-epoetin, methotrexate, and dactinomycin</td>
<td>EMA alternates with CO every week.* Reduction of the EMA by omission of the day 2 dose of etoposide and dactinomycin is only exceptionally needed to avoid extended intervals between courses caused by myelosuppression. This problem is usually overcome with filgrastim and increased frequency (four doses daily) and duration (up to 4 days) of folinic acid rescue.† Rescue begun 24 h after start of methotrexate infusion.</td>
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vindesine (CO; table 2). This regimen is widely used worldwide,116 since it seems effective with predictable and easily managed short-term toxic effects. The Korean gestational trophoblastic disease centre noted in a retrospective comparison20 that MFA had a remission rate of 63% (31 of 49 patients), MAC 68% (27 of 40), CHAMOCA 71% (32 of 45), and EMA-CO 91% (87 of 96). The EMA-CO regimen necessitates one overnight stay every 2 weeks, causes reversible alopecia, and is myelosuppressive (although support with filgrastim helps to maintain neutrophil count and treatment intensity, and avoids neutropenic febrile episodes).20

Cumulative 5-year survival of patients given EMA-CO is between 75% and 90%,119–121 and was 86.2% (95% CI 81.9–90.5) in 272 patients at our UK institute.119 Although these results were good, long-term survival was only 27% when there were metastases in the liver, 70% with brain metastases, and 10% with both sites of metastasis.119–122 Why these patients have adverse outcomes is unclear, but most had not had previous hydatidiform mole, were not registered for follow-up, and therefore presented with widespread disease. Furthermore, many deaths happened soon after admission from haemorrhage or metabolic results of overwhelming disease. Indeed, when deaths within 4 weeks (before adequate chemotherapy can be given) were excluded, survival of patients with brain metastases was equivalent to that for other patients.119 This effect may also apply to liver metastases; of 37 patients with liver metastases treated between 1977 and 2005 at our UK institute, overall survival increased to about 50% at 5 years, but when early deaths were excluded, survival was nearly 70%.123 Besides disease extent, type and duration of antecedent pregnancy and previous chemotherapy are associated with poor outcome.127,124

To reduce early deaths in patients with very advanced disease, we noted that starting chemotherapy with low-dose etoposide (100 mg/m²) and cisplatin (20 mg/m²) for 2 days, combined with dexamethasone 24 mg in 24 h is helpful to reduce tumour oedema. Further details about management and modifications to treatment needed for patients with very advanced disease and difficult clinical situations such as brain metastasis and pulmonary failure have been reviewed elsewhere.116,117

As in low-risk disease, therapy is continued for 6 weeks of normal hCG values in patients with high-risk disease or 8 weeks if poor prognostic features such as liver or brain metastases are present.18 Reimaging is then done to document the post-treatment appearance for future comparison. Removal of residual masses is unnecessary since it does not reduce risk of recurrence, which is less than about 3%.126–128

Drug-resistant disease

Patients with gestational trophoblastic neoplasia who progress during or after primary chemotherapy still have excellent outcomes, with about 100% of low-risk and 84% of high-risk patients being cured,119 partly because relapse is detected early by hCG monitoring so disease volume is small. PET scanning with ¹⁸F-Fluorodeoxyglucose can help to identify the site of active disease to aid surgical resection and cure.119 The half-life for hCG is 48 h or less after surgery if the disease has been completely removed.119 However, when surgery is not possible or hCG concentrations decrease inappropriately, several salvage regimens have been created or adapted from the germ-cell tumour setting.119 At our UK institute we developed a regimen combining etoposide with cisplatin (EP) alternating every week with EMA that omitted the second day of etoposide and dactinomycin.119 Survival is more than 80% but toxic effects are substantial.119 Several patients with drug-resistant tumours have responded to gemcitabine119 or
platin-based single-agent or combination therapy. An alternating combination of paclitaxel-cisplatin and paclitaxel-etoposide (TP-TE) every 2 weeks (table 3) seems to be much better tolerated than is EP-EMA, and is effective in patients with relapsed or refractory neoplasia. On the basis of these results the ISSTD has recently proposed a randomised trial of TE-TP versus EP-EMA to assess optimum therapy for patients relapsing after non-cisplatin-based combination therapies such as EMA-CO. High-dose chemotherapy with peripheral stem-cell transplantation does not cure many patients with refractory disease, so selection of patients needs to improve.

Placental-site trophoblastic tumour

Placental-site trophoblastic tumours grow more slowly, metastasise later, more commonly involve lymph-nodes, and produce less hCG than do choriocarcinomas. However, as with choriocarcinoma, this disease can happen and could compromise survival. Management of placental-site trophoblastic tumour differs from that for choriocarcinoma. Patients with metastatic disease need combination chemotherapy (eg, EP-EMA) until 8 weeks of normal hCG concentrations are recorded. Unlike choriocarcinoma, residual masses are removed surgically, including the uterus, which can contain microscopic disease. The need for surgery might cause difficulties for management of stage I disease. The safest option is hysterectomy with sampling of pelvic lymph nodes and ovarian conservation, unless the patient has a family history of ovarian cancer or is postmenopausal. In the absence of sufficient data for adjuvant therapy, we advocate 8 weeks of EP-EMA or TE-TP when there are poor risk factors such as disease presentation beyond 4 years from the antecedent pregnancy. However, young nulliparous women generally have a strong desire to preserve fertility, especially when there seems to be a focal abnormality in the uterus. Although uterine-sparing surgery is possible, multifocal microscopic uterine disease can happen and could compromise survival. Appropriate counselling is needed. Placental-site disease is so rare that the optimum treatment will probably never be identified, but the ISSTD has formed an international database to pool information about cases.

Postchemotherapy sequelae and follow-up

Most patients recover from even intensive chemotherapy within weeks or months, and nearly all side-effects such as alopecia are reversible. Fertility is an important issue for patients with gestational disease. Fortunately, although EMA-CO advances the menopause date by 3 years, fertility is not otherwise affected by either methotrexate with folinic acid rescue or EMA-CO chemotherapy. Furthermore, the pregnancy rate is more than 83% after either treatment, and the incidence of congenital malformations is not increased.

Table 3: Sampling protocol for hCG concentration in all patients after initial chemotherapy (monotherapy or combination) and following relapse treatment with gestational trophoblastic neoplasia in the UK

<table>
<thead>
<tr>
<th>Urine</th>
<th>Blood</th>
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<tr>
<td>Year 1</td>
<td>Every week</td>
</tr>
<tr>
<td>1-6 weeks</td>
<td>Every 2 weeks</td>
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<tr>
<td>2-6 months</td>
<td>Every 2 weeks</td>
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<tr>
<td>7-12 months</td>
<td>Every 2 weeks</td>
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<td>Year 2</td>
<td>Every 4 weeks</td>
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<td>Year 3</td>
<td>Every 8 weeks</td>
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<td>Year 4</td>
<td>Every 3 months</td>
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<tr>
<td>Year 5</td>
<td>Every 4 months</td>
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<tr>
<td>After year 5</td>
<td>Every 6 months</td>
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<table>
<thead>
<tr>
<th>Day 1 (TP)</th>
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<th>Blood</th>
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<tbody>
<tr>
<td>Dexamethasone 20 mg orally (12 h before paclitaxel)</td>
<td>Every week</td>
<td>Every week</td>
</tr>
<tr>
<td>Dexamethasone 20 mg orally (6 h before paclitaxel)</td>
<td>Every 2 weeks</td>
<td>Every 2 weeks</td>
</tr>
<tr>
<td>Cimetidine 30 mg in 100 mL normal saline intravenous for 30 min</td>
<td>Every 2 weeks</td>
<td>Every 2 weeks</td>
</tr>
<tr>
<td>Chlorphenamine 10 mg intravenous bolus</td>
<td>Every 2 weeks</td>
<td>Every 2 weeks</td>
</tr>
<tr>
<td>Paclitaxel 135 mg/m² in 250 mL normal saline intravenous for 3 h</td>
<td>Every 2 weeks</td>
<td>Every 2 weeks</td>
</tr>
<tr>
<td>Mannitol 10% in 500 mL intravenous for 1 h</td>
<td>Every 2 weeks</td>
<td>Every 2 weeks</td>
</tr>
<tr>
<td>Cisplatin 60 mg/m² in 1 L normal saline intravenous for 3 h</td>
<td>Every 2 weeks</td>
<td>Every 2 weeks</td>
</tr>
<tr>
<td>Post-hydration 1 L normal saline, 20 mmol potassium chloride, and 1 g magnesium sulphate intravenous for 2 h</td>
<td>Every 2 weeks</td>
<td>Every 2 weeks</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Day 15 (TE)</th>
<th>Urine</th>
<th>Blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone 20 mg oral (12 h before paclitaxel)</td>
<td>Every week</td>
<td>Every week</td>
</tr>
<tr>
<td>Dexamethasone 20 mg oral (6 h before paclitaxel)</td>
<td>Every 2 weeks</td>
<td>Every 2 weeks</td>
</tr>
<tr>
<td>Cimetidine 30 mg in 100 mL normal saline intravenous for 30 min</td>
<td>Every 2 weeks</td>
<td>Every 2 weeks</td>
</tr>
<tr>
<td>Chlorphenamine 10 mg intravenous bolus</td>
<td>Every 2 weeks</td>
<td>Every 2 weeks</td>
</tr>
<tr>
<td>Paclitaxel 135 mg/m² in 250 mL normal saline intravenous for 3 h</td>
<td>Every 2 weeks</td>
<td>Every 2 weeks</td>
</tr>
<tr>
<td>Etoposide 150 mg/m² in 250 mL normal saline intravenous for 1 h</td>
<td>Every 2 weeks</td>
<td>Every 2 weeks</td>
</tr>
</tbody>
</table>

Table 4: TP-TE schedule for relapsed gestational trophoblastic neoplasia
However, patients are advised not to become pregnant until 12 months after completion of chemotherapy to reduce the potential teratogenicity and to avoid confusion between a new pregnancy and relapsed disease as the cause of increasing hCG values. Between 1973 and 1997, 230 women at our UK centre became pregnant during the first year of follow-up, despite the advice to avoid pregnancy. The risk of relapse, fetal morbidity, and maternal death were not increased; more than 70% continued their pregnancies to term, but one patient relapsed with advanced disease.\textsuperscript{12} Thus, although we advise women to avoid pregnancy for 1 year after completing chemotherapy, those who do become pregnant will probably have a favourable outcome. Any form of contraception is suitable provided there are no other medical contraindications to their use. When a patient does become pregnant, ultrasonography and other appropriate methods should be used to ensure that the pregnancy is healthy. Follow-up therapy is then discontinued but hCG concentrations should be rechecked 6 weeks and 10 weeks after delivery to ensure no recurrence or new disease. In the UK, we follow up patients for life (table 4), since monitoring is easy to do (urine samples only), cheap, and we are uncertain about when stopping is safe.

Late sequelae from chemotherapy are very rare. Findings from a study\textsuperscript{13} of 15,279 patient-years of follow-up showed no significant increase in incidence of second tumours after methotrexate therapy. By contrast, 26 patients receiving combination chemotherapy for second tumours after methotrexate therapy. By contrast, follow-up showed no significant increase in incidence of delayed termination has no increased risk of malignant and in pregnancies with a healthy twin suggest that delayed evacuation of complete hydatidiform mole alone is possible. However, evidence comparing early versus changes after evacuation, such a test might never be provided there are no other medical contraindications to their use. When a patient does become pregnant, ultrasonography and other appropriate methods should be used to ensure that the pregnancy is healthy. Follow-up therapy is then discontinued but hCG concentrations should be rechecked 6 weeks and 10 weeks after delivery to ensure no recurrence or new disease. In the UK, we follow up patients for life (table 4), since monitoring is easy to do (urine samples only), cheap, and we are uncertain about when stopping is safe.

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Conclusions

Although outcomes for more than 98% of women with gestational trophoblastic neoplasia are excellent, a few women die from the disease, mainly because of late presentation and diagnosis or drug resistance. Consequently, novel therapies with improved efficacy and reduced toxic effects need to be identified. Additionally, after diagnosis of molar pregnancy, women have to wait many weeks or months to find out whether they need chemotherapy. Therefore, a new prognostic test at the time of initial molar diagnosis is needed to identify those who might develop malignant disease. Of course, if residual complete hydatidiform mole acquires additional genetic changes after evacuation, such a test might never be possible. However, evidence comparing early versus delayed evacuation of complete hydatidiform mole alone and in pregnancies with a healthy twin suggest that delayed termination has no increased risk of malignant disease.\textsuperscript{14,15} This finding suggests that hydatidiform moles are probably pre-programmed to behave malignantly at an early stage of development and before uterine evacuation.

The optimum management strategy for women with repetitive molar pregnancies to allow healthy pregnancy is unknown; even though the causative gene has been identified for many cases, its function is unknown. The successful UK model of centralised care for rare diseases should be established worldwide to improve outcomes for gestational trophoblastic disease.

Contributors

All authors did a detailed review of published work and contributed to the writing, review, and editing of the report. MJ S had access to all the data used to write the report and had final responsibility for submission. All authors saw and approved the final version.

Conflicts of interest

We declare that we have no conflicts of interest.

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Seminar


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