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Gestational Trophoblastic Neoplasia, A Review

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Abstract

GTD is still an important reproductive health problem worldwide. The problem is that much information of GTD has come from less developed countries, where proper diagnostic tools and up to date treatment cannot be employed. Maternal age, previous hydatiform mole, race and geographical region have been identified as clear risk factors for GTD. Etiological factors of GTD have long been studied but no definite causes have yet been found.

As per latest ESMO guidelines post molar GTN needs different investigation profile compared with non-molar GTN. 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. Even if there are differences in initial remission rate among the regimens, salvage with alternate regimens is very effective.

INTRODUCTION

It is just 100 years since Marchand (1) identified choriocarcinoma as a tumour arising from placental villous trophoblast. Earlier description of similar tumours failed to identify their tissue of origin. Trophoblast populations of normal placenta are composed of cytotrophoblast, syncytiotrophoblast and intermediate trophoblast.

Villous trophoblast covers chorionic villi and consists predominantly of cytotrophoblast and syncytiotrophoblast. The cytotrophoblast is the trophoblastic stem cell. These rather primitive mononuclear cells have a clear cytoplasm. Syncytiotrophoblast differentiates from fusion of cytotrophoblast and is composed of multinucleated cells with abundant dense cytoplasm. It secretes abundant hCG, some human placental lactogen (hPL) and placental alkaline phosphatase (PLAP) but has little capacity for further proliferation. Inhibin alpha is highly expressed by syncytiotrophoblast in the first trimester but progressively decreases towards term. This links with the observation that serum levels of Inhibin peak at 7-8 weeks, decline in mid trimester and rise again towards term . Production of hCG decreases while hPL and PLAP increase as pregnancy advances and the amounts of villous trophoblast in relation to the amounts of villous stroma gradually decrease with increasing gestational age. Trophoblast also synthesizes estrogen and progesterone. Gestational trophoblastic disease (GTD) is the terminological umbrella now used to span the spectrum of cellular proliferations ranging from villous forms of hydatiform mole through invasive mole and choriocarcinoma to placental site tumours [(2).]Each form of GTD presents its own particular set of problems ranging frolm social to therapeutic.

These proliferations are unique in several aspects. In the first place there is no known homolog of hydatiform mole in any other species. The rare identification of choriocarcinoma like tumours remains restricted to a rhesus monkey [(3)] and an armadillo [(4)]. In the human, histologically characterized choriocarcinoma behaves in a broadly similar manner whether it is genetically identical with the host as in germ cell origin, or whether it arises from a normal conception or an androgenetic hydatiform mole.

It is now more than 35 years since the sensitivity of invasive mole and choriocarcinoma to cytotoxic drugs was first recognized [(5)]. They remain the most sensitive and most curable of all human cancers. Apart from speculation about the contribution of the immune response to this sensitivity there has been little expression of interest as to why choriocarcinoma should, in most cases, be so responsive.

GTD is still an important reproductive health problem worldwide. The problem is that much information of GTD has come from less developed countries, where proper diagnostic tools and up to date treatment cannot be employed. Maternal age, previous hydatiform mole, race and geographical region have been identified as clear risk factors for GTD. Etiological factors of GTD have long been studied but no definite causes have yet been found.

However, it can be speculated that during gametogenesis and fertilization, the Risk factors may act synergistically. Genetic subclassification may be helpful in this context. Geographic variations of incidence exist but are inextricably linked with above mentioned risk factors. Important prerequisites for accurate evaluation are common denominators, standard classification and definition of index cases. The developments and improvements in suction curettage, termination of

pregnancy, contraceptive techniques, diagnostic imaging and biochemical testing have been associated with not only fall in birth rate but also with a reduction in trophoblastic disease[6-14]

Gestational trophoblastic disease (GTD) can be benign or malignant. Histologically, it is classified into hydatidiform mole, invasive mole (chorioadenoma destruens), choriocarcinoma, and placental site trophoblastic tumor (PSTT). Those that invade locally or metastasize are collectively known as gestational trophoblastic neoplasia (GTN). Hydatidiform mole is the most common form of GTN. While invasive mole and choriocarcinoma are malignant, a hydatidiform mole can behave in a malignant or benign fashion.

In histologic section of a complete hydatidiform mole stained with hematoxylin and eosin, Villi of different sizes are present. The large villous in the center exhibits marked edema with a fluid-filled central cavity known as cisterna. Marked proliferation of the trophoblasts is observed. The syncytiotrophoblasts stain purple, while the cytotrophoblasts have a clear cytoplasm and bizarre nuclei. No fetal blood vessels are in the mesenchyme of the villi. CHMs are usually diploid and androgenetic in origin, ~80% resulting from duplication of the haploid genome of a single sperm while 20% arise by dispermic fertilisation of an ovum . In either case maternal chromosomes are lost before, or shortly after, fertilisation. However, while nuclear DNA is entirely paternal in CHM, mitochondrial DNA remains maternal in origin [15].No methods exist to accurately predict the clinical behavior of a hydatidiform mole by histopathology. The clinical course is defined by the patient's serum human chorionic gonadotropin (hCG) curve after evacuation of the mole. In 80% of patients with a benign hydatidiform mole, serum hCG levels steadily drop to normal within 8-12 weeks after evacuation of the molar pregnancy. In the other 20% of patients with a malignant hydatidiform mole, serum hCG levels either rise or plateau[16,17]

Hydatidiform mole is considered malignant when the serum hCG levels plateau or rise during the follow-up period and an intervening pregnancy is excluded. This occurs in 15-20% of hydatidiform moles[16,17].

A hydatidiform mole with a fetus or fetal tissue and a triploid karyotype is known as a partial or incomplete mole. Partial moles also have malignant potential, but only 2-3% become malignant(18,19,20). An invasive mole has the same histopathologic characteristics of a hydatidiform mole, but invasion of the myometrium with necrosis and hemorrhage occurs or pulmonary metastases are present.

Histologically, choriocarcinomas have no villi, but they have sheets of trophoblasts and hemorrhage. Choriocarcinomas are aneuploid and can be heterozygous depending on the type of pregnancy from which the choriocarcinoma arose. If a hydatidiform mole preceded the choriocarcinoma, the chromosomes are of paternal origin. Maternal and paternal chromosomes are present if a term pregnancy precedes the choriocarcinoma. Of choriocarcinomas, 50% are preceded by a hydatidiform mole, 25% by an abortion, 3% by ectopic pregnancy, and the other 22% by a full-term pregnancy[16].

Placental site trophoblastic tumor is a rare form of gestational trophoblastic neoplasia, with slightly more than 200 cases reported in the literature [21,22]. In patients with PSTT, intermediate trophoblasts are found infiltrating the myometrium without causing tissue destruction. The intermediate trophoblasts contain human placental lactogen (hPL) [23]. These patients have persistent low levels of serum hCG (100-1000 mIU/mL). However, serum hCG levels as high as 108,000 mIU/mL have been reported in patients with PSTT[24]. The most frequent sites of metastases of malignant gestational trophoblastic neoplasia are the lungs, lower genital tract, brain, liver, kidney, and gastrointestinal tract.

EPIDEMIOLOGY

The incidence is estimated at 1-3: 1000 pregnancies for CHM and 3: 1000 pregnancies for PHM, respectively [15]. GTD appears to be more frequent in Asia than in North America or Europe.

An increased risk of molar pregnancy is seen in the very young (<16 years), but is most associated with advanced maternal age (>45 years). Following a molar pregnancy, the risk of a further CHM or PHM increases to ~1%. After two molar gestations, the risk of a third mole is 15%–20% . The frequency of CC and PSTT is less clear, since these can arise after any type of pregnancy. CC develops after around 1:50 000 deliveries, while recent data suggest that PSTT represents 0.2% of UK GTD cases [25] . GTN risk may also relate to hormonal factors since women with menarche after 12 years of age, light menstrual flow and prior use of oral contraceptives are at increased risk.

DIAGNOSIS

CHMs and PHMs most commonly present with vaginal bleeding in the first trimester of pregnancy. Previously reported features such as anaemia, uterine enlargement, pre-eclampsia, hyperemesis, hyperthyroidism and respiratory distress are now rare [26] reflecting the introduction of routine ultrasonography in early pregnancy.

Characteristic sonographic findings for CHM in the second trimester, of a heterogeneous mass (‘snowstorm’), without foetal development and with theca lutein ovarian cysts, are not seen in the first trimester, and ultrasonography is not diagnostically reliable [27]. Indeed, false positive and negative rates are high with ultrasound, especially for PHM, and histological examination is essential to achieve a correct diagnosis [27] . All products of conception from nonviable pregnancies must undergo histological examination regardless of ultrasound findings [28].

The safest method of evacuation is suction dilation and curettage (D&C) under ultrasound control to ensure adequate emptying of uterine contents and to avoid uterine perforation [15]. A proportion of women who miscarry or who undergo medical terminations will have unsuspected molar pregnancies. As histological examination is not routinely requested, the diagnosis of GTN can be delayed resulting in significantly greater morbidity[29]. Histological examination of every termination is impractical, and perhaps a simple measurement of the urine or serum hCG level 3–4 weeks post-treatment to ens

ure return to normal is indicated [29].

The other malignant forms of GTD, CC and PSTT/ETT can be much more tricky to diagnose as the disease can develop months or many years after a prior pregnancy with protean presentations possible. Although change in menstruation is frequent, it does not always occur. It is therefore essential to measure the hCG in any woman of childbearing age who has unexplained metastatic disease. Biopsy of lesions without the ability to control bleeding is highly risky in this very vascular disease and is not essential before commencing chemotherapy. However, where complete excision is possible this can provide useful histological confirmation of the diagnosis and material for genetic analysis

INDICATIONS FOR TREATMENT

Table 1. indications for chemotherapy following the diagnosis of GTD.

- Plateaued or rising hCG after evacuation
- Heavy vaginal bleeding or evidence of gastrointestinal or intraperitoneal Haemorrhage
- Histological evidence of choriocarcinoma
- Evidence of metastases in the brain, liver or gastrointestinal tract, or radiological opacities of >2 cm on chest X-ray
- Serum hCG of ≥20 000 IU/l >4 weeks after evacuation, because of the risk of uterine perforation.

Staging investigations and treatment stratification after a molar pregnancy

Most patients developing GTN post-HM are detected early via hCG monitoring and so extensive investigation is rarely required. Information to determine therapy can be obtained from the clinical history, examination, measurement of serum hCG and a Doppler pelvic ultrasound to confirm the absence of a pregnancy, to measure the uterine size/volume, spread of disease within the pelvis and its vascularity. The latter assessed by the Doppler pulsatility index is an independent prognostic factor for resistance to single-agent methotrexate MTX) therapy [30] and is now being evaluated in a prospective trial. Pulmonary metastases are most common, so a chest radiograph is essential [31]

Computed tomography (CT) of the chest is not required if the chest X-ray (CXR) findings are normal, since discovery of micrometastases, which may be seen in ~40% of patients, does not influence outcome [32]. However, if lesions are noted on CXR, magnetic resonance imaging (MRI) of the brain and CT body are indicated to exclude more widespread disease involving, for example, the brain or liver, which would significantly alter management. FIGO reports data on GTN using prognostic scoring and anatomic staging systems [33] .

FIGO 2000 scoring system for GTN

Prognostic factor	Score			
	0	1	2	4
Age (years)	<40	≥40	–	–
Antecedent pregnancy (AP)	Mole	Abortion	Term	–
Interval (end of AP to chemotherapy in months)	<4	4–6	7–12	>12
hCG (IU/l)	$<10^3$	10^3–10^4	10^4–10^5	$>10^5$
Number of metastases	0	1–4	5–8	>8
Site of metastases	Lung	Spleen & kidney	GI tract	Brain &liver
Largest tumour mass	–	3–5 cm	>5 cm	-
Prior chemotherapy	–	–	Single drug	>2 drugs

The total score for a patient is obtained by adding the individual scores for each prognostic factor. Low risk, 0–6; high risk, ≥7. PSTT should not be scored and instead requires staging. Stage I, disease confined to the uterus; stage II, disease extending into the pelvis; stage III, disease spread to lungs and/or vagina; stage IV, all other metastatic sites including liver, kidney, spleen and brain.

Staging investigations for CC and PSTT/ETT

Women who present with an elevated hCG and suspected GTN (CC or PSTT/ETT) following a prior pregnancy require much more extensive staging investigations, which include a contrast enhanced CT of the chest and abdomen, MRI of the brain and pelvis, a Doppler ultrasound of the pelvis and may benefit from a lumbar puncture to assess the cerebrospinal fluid to serum hCG ratio. The latter if more than 1:60 suggests occult central nervous system disease . For CC, the FIGO scoring/staging system is the same as described above. However, PSTT/ETT has a discrete biological behaviour with less hCG production, slower growth, late metastasis and slightly less chemosensitivity. Consequently, the scoring system is not valid for PSTT/ETT, but FIGO staging is used to help adapt treatment intensity. Some investigators have recently started using positron emission tomography (PET)/CT imaging, but experience is still quite limited. It appears that this imaging modality is more helpful in relapsed disease to identify sites for resection and, as with other cancers, is prone to both false-positive and false-negative results [15].

MANAGEMENT OF LOW-RISK DISEASE

About 95% of patients with HM who develop GTN are low risk (score 0–6). In women with

stage I disease apparently confined to the uterine cavity, the role of second D&C in reducing the need for chemotherapy remains controversial. UK results indicate that this procedure is only valuable if the hCG is <5000 IU/l with disease in the cavity rather than myometrium. Indeed, the low efficacy of a second D&C, small risks of introducing infection, causing haemorrhage and uterine perforation should be balanced against the almost 100% cure rate and relative safety of chemotherapy [15]

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 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 two treatment cycles 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.[34] In that systematic review, four randomized controlled trials were identified.[35-38]

Three of the randomized trials [36-38] compared the same two commonly used regimens:

- Biweekly (pulsed) dactinomycin (1.25 mg/m2 intravenously [IV]).
- Weekly intramuscular methotrexate (30 mg/m2).

These three trials included a total of 392 patients. All three trials showed better primary complete response (CR) rates without the need for additional salvage therapy associated with pulsed dactinomycin (relative risk [RR] of cure, 3.00; 95% confidence interval [CI], 1.10–8.17), even though the magnitude of benefit showed substantial heterogeneity (I2 statistic = 79%).[36-38]·Fewer courses of therapy were needed to achieve CR and cure with dactinomycin treatment. 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. There was a statistically significant increase in dermatologic toxicity, including alopecia, associated with dactinomycin. However, in the largest study,[38] there was statistically significantly more low-grade gastrointestinal toxicity, grade 2 nausea, grade 1 to 2 vomiting, and grades 1 to 3 neutropenia in the dactinomycin group. In that study, choriocarcinoma patients and patients with a risk score of 5 to 6 had a worse CR

rate to initial treatment with single-agent therapy, and methotrexate was virtually ineffective.[38]

The fourth randomized trial was a very small study of 45 patients and compared a 5-day regimen of dactinomycin (10 μg/kg) with an 8-day regimen of methotrexate (1 mg/kg) and folinic acid (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).[35]·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·[34]

Commonly Used Treatment Regimens Include The Following:

1. The 8-day Charing Cross regimen. Methotrexate (50 mg intramuscularly [IM] on days 1, 3, 5, and 7) and folinic acid (7.5 mg orally on days 2, 4, 6, and 8). This may be the most common regimen worldwide,[34,39] but it has not been directly compared with other regimens.
2. Biweekly pulsed dactinomycin (1.25 mg/m2 IV).
3. Weekly methotrexate (30 mg/m2 IM). Efficacy of this regimen appears to be low for choriocarcinoma and for patients with Féderation Internationale de Gynécologie et d'Obstétrique (FIGO) risk scores of 5 to 6.

Other regimens in less-common use include the following:[34]

- An 8-day regimen of methotrexate (1 mg/kg IM days 1, 3, 5, and 7) and folinic acid (0.1 mg/kg IM days 2, 4, 6, and 8).
- Methotrexate 20 mg/m2 IM days 1 to5, repeated every 14 days.
- Dactinomycin 12 μg/kg/day IV days 1 to 5, repeated every 2 to 3 weeks. This regimen has fallen out of favor because of substantial alopecia and nausea.
- Methotrexate 20 mg IM daily, days 1 to 5; and dactinomycin 500 μg IV daily, days 1 to 5, repeated every 14 days.
- Dactinomycin 10 μg/kg/day, 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/m2/day IV on days 1 to 5, or 250 mg/m2 IV on days 1 and 3, at 10-day intervals.[40]

As gestational trophoblatic neoplasia is a highly curable disease, the aim of treatment should be to minimize the drug toxicity but not at the cost of treatment efficacy.

Management of High-Risk GTN

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.[41] In the trial, only 42 women were randomly assigned to either a CHAMOMA regimen (i.e., methotrexate, folinic acid,

hydroxyurea, dactinomycin, vincristine, melphalan, and doxorubicin) or MAC (i.e.,methotrexate, dactinomycin, and chlorambucil).[42] There was substantially more life-threatening toxicity in the CHAMOMA arm and no evidence of higher efficacy. However, there were serious methodologic 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.[41]. 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 below.[43-45]

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

Day	Drug	Dose
1	Etoposide	100 mg/m2 IV for 30 min
	Dactinomycin	0.5 mg IV push
	Methotrexate	300 mg/m2 IV for 12 h
2	Etoposide	100 mg/m2 IV for 30 min
	Dactinomycin	0.5 mg IV push
	Folinic Acid	15 mg or PO every 12 h × 4 doses, beginning 24 h after the start of methotrexate
8	Cyclophosphamide	600 mg/m2 IV infusion
	Vincristine	0.8–1.0 mg/m2 IV push (maximum dose 2 mg)

IV = intravenously; PO = orally.
aAdapted from Bower et al.[43]
bAdapted from Escobar et al.[44]
cAdapted from Lurain et al.[45]

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.[43] 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% CI, 81.9%–90.5%).[39]. 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.[46] Among the women who had an intact uterus, about 50% of them retained their fertility. Patients with documented brain metastases received higher doses of systemic methotrexate as part of the EMA component (i.e., etoposide, methotrexate,

folinic acid, and dactinomycin) of EMA/CO (1 g/m2 intravenously [IV] for 24 hours, followed by folinic-acid 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/m2 for 24 hours followed by folinic acid (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:[41]

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

Brain metastases are associated with poor prognosis, particularly when liver metastases are also present.[47-49] However, even patients with brain metastases may achieve long-term remission in 50% to 80% of cases.[43,44,49] Patients with central nervous system (CNS) metastases receive additional therapy simultaneously with the initiation of systemic chemotherapy. Some centers utilize whole-brain irradiation (30 Gy in 2 Gy fractions) with or without intrathecal methotrexate.[47] 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/m2 IV for 24 hours on the first day, as noted above, to achieve therapeutic CNS levels.[49]

MANAGEMENT OF DRUG-RESISTANT DISEASE

About 20% of high-risk GTN patients will progress on or after primary chemotherapy, but these individuals still have an excellent outcome with ~75%–80% still being salvaged. This is partly because relapse is detected early due to hCG monitoring so disease volume is small. Moreover, hCG monitoring enables the early detection of resistance during therapy. In relapsed patients, fluorine-18 fluorodeoxyglucose-PET (FDG-PET) scanning may help identify the site of active disease to facilitate surgical resection and cure. However, if surgery is not possible , several salvage regimens have been either created or adopted from the germ cell tumour setting. At Charing Cross Hospital, a regimen has been developed combining etoposide with cisplatin (EP) alternating weekly with EMA that omitted the second day of etoposide and Act D. Survival rates are >80% but toxicity is significant, and less toxic salvage therapies are required. Several cases of drug-resistant GTN have been reported to respond and/or be cured by paclitaxel-based single-agent or combination therapy, gemcitabine

and capecitabine

Of these, an alternating two weekly doublet of paclitaxel/cisplatin and paclitaxel/etoposide (TP/TE;) appears from non-randomised data to be much better tolerated than EP/EMA and is effective in patients with relapsed and/or refractory GTN. In view of these results, the International Society of the Study of Trophoblastic Diseases (ISSTD) has recently proposed a randomised trial of TE/TP versus EP/EMA to determine the optimal therapy for patients relapsing after non-cisplatin/paclitaxel-based combination therapies such as EMA/CO.

TP/TE schedule for relapsed GTN

Day 1	
Dexamethasone	20 mg
oral (12 h pre-paclitaxel)	
Dexamethasone	20 mg
oral (6 h pre-paclitaxel)	
Cimetidine	30 mg
in 100 ml NS over 30 min i.v.	
Chlorphenamine	10 mg
bolus i.v.	
Paclitaxel	135
mg/m2 in 250 ml NS over 3 h i.v.	
Mannitol	10% in
500 ml over 1 h i.v.	
Cisplatin	60
mg/m2 in 1 l NS over 3 h i.v.	
Post-hydration	1 l NS + KCl
20 mmol + 1 g MgSO4 over 2 h i.v.	
Day 15	
Dexamethasone	20 mg
oral (12 h pre-paclitaxel)	
Dexamethasone	20 mg
oral (6 h pre-paclitaxel)	
Cimetidine	30 mg
in 100 ml NS over 30 min i.v.	
Chlorphenamine	10 mg
bolus i.v.	
Paclitaxel	135
mg/m2 in 250 ml NS over 3 h i.v.	
Etoposide	150
mg/m2 in 1 l NS over 1 h i.v.	

Another approach in patients with refractory disease involves high-dose chemotherapy with peripheral stem-cell transplantation. However, cures are not common, so improved patient selection may be required to achieve better outcomes from this approach. PSTT differs from CC, growing more slowly, metastasising later, involving lymph nodes more commonly and producing less hCG [15]. However, like CC, it can arise after any type of pregnancy, including PHM, and usually presents with abnormal vaginal bleeding [16]. PSTT may be suspected if the hCG level is low for the volume of disease present on imaging combined with an elevated free beta form of hCG, but none of these features are diagnostic. Consequently histological confirmation is essential. A recent large population-based series of PSTT comprised 62 cases over 30 years, representing 0.2% of UK GTD cases, and examined prognostic features. On univariate analysis, stage, hCG, mitotic index and a duration of >4 years from the preceding pregnancy were prognostic, but the FIGO score was unhelpful. Only the duration from the prior pregnancy remained predictive of survival on multivariate

analysis with 100% (13 of 13) dying and 98% (48 of 49) surviving for those ≥48 and <48 months, respectively. This effect was not explained by differences in disease stage or hCG levels, but may reflect a biological switch in the tumours after this time. In the absence of sufficient data regarding adjuvant therapy, currently 8 weeks of EP/EMA or TE/TP are advocated when there are poor risk factors such as disease presenting beyond 4 years of the antecedent pregnancy. While uterine-sparing surgery is possible [15], Multifocal microscopic uterine disease can occur, which could compromise survival and careful counselling is required. Currently, it is thought that ETT behaves very similarly to PSTT but in reality, little data are available to be sure of this. PSTT and ETT are so rare that it is unlikely that their treatment will ever be fully optimised Very rarely, multi-drug resistant disease develops that is not amenable to surgical resection or any other existing treatment, so it is unclear whether anything can be done in this case. Since GTN is very vascular it is plausible that vascular targeting agents such as bevacizumab might be active. The tumours can also overexpress epidermal growth factor receptor, leading to the question whether erlotinib or gefitinib could demonstrate efficacy. The potential for an anti-hCG targeted therapy has not been explored and could be of interest in women who have completed their families or have run out of other options.

follow-up and long-term implications

The risk of relapse after chemotherapy is ~3% and most occur in the first year of follow-up. Therefore, careful hCG monitoring is required and pregnancy should ideally be delayed until beyond this period. Any method of contraception can be used including the oral contraceptive pill, as long as there are no other contraindications to their use.

UK follow-up protocol of GTN patients who have been treated with chemotherapy

	hCG concentration sampling	
	Urine	Blood
Year 1		
Week 1–6 after chemotherapy	Weekly	Weekly
Month 2–6	Two weekly	Two weekly
Month 7–12	Two weekly	–
Year 2	Four weekly	–
Year 3	Eight weekly	–
Year 4	Three monthly	–
Year 5	Four monthly	–
After Year 5	Six monthly	–

Fortunately, apart from EMA/CO bringing forward the menopause date by 3 years, fertility is not otherwise affected with 83% of women becoming pregnant after either MTX/FA or EMA/CO chemotherapy [15] . Moreover, there is no obvious increase in the incidence of congenital malformations. When a patient does become pregnant, it is important to confirm by ultrasound and other appropriate means that the pregnancy is normal. Follow-up is then discontinued, but the hCG should be rechecked at 6 and 10 weeks after the pregnancy to ensure no recurrence or new disease.

Late sequelae from chemotherapy have been remarkably rare. In 279 patient on 15 years of follow-up, there was no significant increase in the incidence of second tumours following MTX therapy. In contrast, 26 patients receiving combination chemotherapy for GTN developed another cancer when the expected rate was only 16.45, a significant difference. Most of this risk appears to occur if combination chemotherapy is continued beyond 6 months.

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