Molar pregnancy clinic guide for clinicians

Gestational trophoblastic disease (GTD) service at Charing Cross Hospital

Introduction

The abnormal proliferation of gestational trophoblast tissue forms a spectrum of disease from the generally benign partial hydatidiform mole through to malignant forms of the illness, choriocarcinoma and placental site trophoblast tumours. The biology, diagnosis and treatment of these diseases make trophoblast disease an extremely important and interesting area of gynaecological and oncology care. Although these illnesses are all rare, patients generally have successful outcomes with total cure rates in excess of 95 per cent. In this clinic guide we will give some background information, but mainly concentrate on the assessment and treatment of these rare patients.

Further advice and contacts

Clinicians and patients are welcome to contact us by email for further advice on their treatment. We would welcome feedback regarding the contents of this clinic guide, any omissions or areas of debate.

ICHC.HMOLE@NHS.NET.

Registering patients for hCG follow-up after molar pregnancy evacuation

Clinicians can register their patients online. Users must be logged into an NHS computer in order to use this service. Please note that most browsers will redirect from http to https, users may need to manually edit the address in the address bar of their browser to http://nww.h-mole.nhs.uk/.

Alternatively clinicians can register patients by sending this form by email to **ICHC.HMOLE@NHS.NET** or by post to their nearest laboratory:

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Ninewells Hospital, Dundee

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Please note that fax is not a secure method of communication.

Classification

The World Health Organisation classification divides trophoblast disease into the pre-malignant and malignant forms as shown below:-

- **Pre-malignant**
  - partial molar pregnancy
  - complete molar pregnancy

- **Malignant**
  - invasive mole
  - choriocarcinoma
  - placental site trophoblastic tumour

Pre-malignant trophoblast disease

Molar pregnancy

The incidence of molar pregnancies in Europe and North America is in the order of 0.2-1.5 per 1,000 live births although these figures are of limited accuracy (Smith and Kim 2003). There may be a higher incidence of molar pregnancies in Africa and Asia, however the varying standards in the frequency and accuracy of pathology and demographics make accurate comparisons difficult.

The relative risk of molar pregnancy is highest in those pregnancies at the extremes of the reproductive age group. There is a modestly increased incidence in teenagers (1.3 fold) but a 10 fold increased risk in those aged 40 and over. The risk of a complete molar pregnancy increases more than the risk of developing a partial mole (Sebire 2002).

Historically the relative incidence of partial and complete molar pregnancies have been reported as approximately 3:1,000 and 1:1,000. This situation may well represent an over diagnosis of partial mole, as data from Charing Cross Hospital demonstrates that nearly 40 per cent of partial moles referred for expert review are reclassified as either complete moles or non-molar pathologies (Paradinas 1994).

Partial mole (PM)

Partial moles are triploid with two sets of paternal and one set of maternal chromosomes as shown in Fig 1. Macroscopically PM may resemble the normal products of conception with initially an embryo present, which dies by week eight or nine. The histology shows less swelling of the chorionic villi than in complete mole and there are usually only focal changes. As a result the diagnosis of PM can often be missed after an apparently straightforward miscarriage or termination.

The clinical presentation of partial mole is most frequently via irregular bleeding or by detection on routine ultrasound. The obstetric management is by suction or medical evacuation and these all PM patients should be followed up with serial hCG measurement arranged through the trophoblast service in the UK.

Fortunately PM rarely becomes malignant with generally only one or two cases of malignant disease seen per year at Charing Cross Hospital with an overall risk of 0.5 per cent requiring chemotherapy after a PM (Seckl 2000).

Complete mole (CM)

In most complete moles the genetic material is entirely male in origin and results from the fertilisation of an empty ovum lacking maternal genes. The chromosome complement is most commonly 46XX, which results from one sperm that duplicates its DNA, or less frequently 46XX or 46XY from the presence of two different sperm. On very rare occasions CM can be biparental with genetic contributions from both the mother and father (ref). Whilst this type is extremely rare, biparental mole is associated with a high risk of further molar pregnancies and patients who have had more than two molar pregnancies may benefit from investigation at an expert centre. At Charing Cross Hospital we are able to perform genetic tests to investigate if this rare condition is present and to offer appropriate advice.

The diagnosis of CM is most often made as a result of bleeding, a large for dates uterus, or an abnormal ultrasound. Macroscopically there is no foetus and the histology shows the characteristic oedematous villous stroma. However the textbook 'bunch of grapes' appearance is seen in the second trimester and as now most cases are diagnosed earlier, this is rarely seen in the UK. The obstetric management is by suction evacuation followed by serial hCG measurement and surveillance registration.

In contrast to PM, CM more frequently proceeds to invasive disease with eight to 20 per cent of patients requiring chemotherapy.

Malignant trophoblast disease

Invasive mole (chorioadenoma destruens)

Invasive mole is a very rare condition in the UK. The use of routine ultrasound, the early evacuation of complete moles and effective hCG surveillance mean that very few women have this diagnosis.

Invasive mole usually arises from a complete mole and is characterised by invasion of the myometrium, which can lead to perforation of the uterus. Microscopically invasive mole has a similarly benign histological appearance as complete mole but is characterised by the ability to invade in to the myometrium and the local structures if untreated.

The usual presentation is with hCG elevations following a previous molar pregnancy, other clinical features can include abnormal bleeding, abdominal pain or swelling.

Gestational choriocarcinoma

Choriocarcinoma is clinically and histologically overtly malignant and presents the most common emergency medical problems in the management of trophoblast disease.

The diagnosis most frequently follows a CM when the patients are usually in a surveillance programme but can also arise in unsupervised patients after a non-molar abortion or a normal pregnancy.

The clinical presentation of choriocarcinoma can be from the disease locally in the uterus leading to bleeding, or from distant metastases that can cause a wide variety of symptoms with the lungs, central nervous system and liver the most frequent sites of distant disease.

Choriocarcinoma presenting with distant metastases can present some diagnostic challenges, however the combination of the reproductive/gynaecology history and elevated serum hCG usually makes the diagnosis apparent and so avoid a biopsy which can be hazardous from the risk of haemorrhage.

On the occasions that pathology is available the characteristic findings show the structure of the villous trophoblast but with sheets of syncytiotrophoblast or cytotrophoblast cells, haemorrhage, necrosis and intravascular growth is common.

In contrast to molar pregnancies the genetic profile of choriocarcinoma gives a range of gross abnormalities without any specific characteristic pattern.

Placental site trophoblastic tumour (PSTT)

Placental site trophoblast tumours were first described in 1976 (Kurman 1976) and are the least common form of gestational trophoblast disease comprising less than two per cent of all cases. PSTT most commonly follows a normal pregnancy but may occur after a non-molar abortion or a complete molar pregnancy and recently a case was reported following a partial mole.

In contrast to the other types of trophoblast disease which characteristically present fairly soon after the index pregnancy, in PSTT the average interval between the prior pregnancy and presentation is 3.4 years. The clinical presentation of PSTT can range from slow growing disease limited to the uterus to more rapidly growing metastatic disease that is similar in behaviour to choriocarcinoma.

The most frequent presentations are abnormal bleeding or amenorrhea. Usually the hCG levels, whilst elevated, are relatively low in PSTT relative to the volume of the disease compared to the other types of GTT.

PSTT is diploid and arises from the non-villous trophoblast and the pathology is characterised by intermediate trophoblastic cells with vacuolated cytoplasm, the expression of PLAP rather than hCG and the absence of cytotrophoblast and villi.

Pre-Charing Cross Hospital management

Molar evacuation

Suction evacuation is recommended for complete and partial molar pregnancies. If evacuation is followed by excessive bleeding, a single dose of oxytocin can be used after complete evacuation.

For persistent disease repeated evacuations bring reducing results and repeated procedures are rarely advised. We suggest referring teams discuss this with the team at Charing Cross prior to repeated evacuation. The table below shows the results of an audit of second evacuations in the treatment of molar pregnancy and shows that the procedure is rarely of benefit when the hCG level is >1500IU/L. The figure shows the number of patients who required chemotherapy after their second evacuation.

hCG at 2nd evac	hCG Plateau	Rising hCG	Chemo/Total	%
< 1500	4/8	nil	4/8	50%
1500-5000	4/11	1/2	5/13	38%
5000-10000	5/5	5/7	10/12	83%
10000-20000	10/12	8/12	18/24	75%
20000-50000	8/9	7/13	15/22	68%
> 50000	11/12	19/20	30/32	94%
Total	42/57	40/54	82/111	74%

Assessment and hCG surveillance

Following diagnosis patients should be registered and followed by serial serum hCG levels. For confirmed partial moles patients will be monitored with serum and urine samples every two weeks until hCG levels are normal. Once confirmed with a normal sample four weeks later, follow up will be complete. For complete moles if the hCG falls to normal within eight weeks of evacuation the monitoring can be stopped at six months post evacuation. If the hCG falls more slowly, monitoring can stop at six months after the first normal value. After normalisation of the serum hCG the monitoring is by urine hCG monthly.

The role of hCG in trophoblast disease diagnosis and management

Produced predominantly by the syncytiotrophoblast cells, hCG is a glycosylated heterodimer protein consisting of the non-covalently bonded alpha and beta units. Whilst in pregnancy the hCG molecule is intact and full size, in malignant disease a number of variants can occur including; hyperglycosylated hCG, nicked hCG, hCG missing the beta subunit C terminal peptide and the free beta subunit. With the exception of a few atypical cases of PSTT, hCG is always expressed by malignant trophoblast cells. The measurement of the hCG level allows an estimation of the number of proliferating cells, forms a key part of the assessment of the patient's disease risk and provides the simplest method following the response to treatment.

In the absence of tumour hCG production the serum half life of hCG is 24 to 36 hours, however in the clinical situation total hCG levels characteristically show slower falls as the tumour cells continue to produce some hCG while their number decreases with treatment.

Advice to patients regarding contraception during the monitoring phase

Oestrogen and/or progestogen taken between evacuation of the mole and return to normality of hCG values appear not to increase the risk of invasive mole or choriocarcinoma developing. Therefore, women may use oral contraceptives after molar evacuation, before hCG returns to normal. Pregnancy should be avoided until after the completion of the surveillance period.

Charing Cross Hospital molar pregnancy indications for chemotherapy treatment during surveillance

1. Brain, liver, GI mets or lung mets >2cm on CXR
2. Histological evidence of choriocarcinoma
3. Heavy PV bleeding or GI/intraperitoneal bleeding
4. Pulmonary, vulval or vaginal mets unless the hCG level is falling
5. Rising hCG in two consecutive serum samples
6. hCG > 20,000 IU/L more than four weeks after evacuation
7. hCG plateau in 3 consecutive serum samples
8. Raised hCG level six months after evacuation (even if falling)

Patients in this last group are reviewed at Charing Cross and individualised decisions are made regarding treatment or further observation.

FIGO indications for chemotherapy treatment

1. hCG plateau of four values +/- 10% over a three week period
2. hCG increase of >10 per cent of three values over a two week period
3. Persistence of hCG for more than six months after molar evacuation.

Charing Cross Hospital initial assessment at admission

For patients admitted for treatment after a documented molar pregnancy

- Full history to include: details of the antecedent and all other pregnancies, LMP date, evacuation date and method, OCP usage, bleeding and other symptoms particularly respiratory and CNS.
- Investigations: FBC, biochem, clotting, HIV, HBV serology, hCG serum levels are measured twice a week during treatment, group and save.
- Doppler ultrasound of the pelvis to confirm disease presence and volume and to rule out the possibility of a new pregnancy and CXR.

For patients admitted for treatment for presumed choriocarcinoma or PSTT

- As above plus
- CT scan thorax, abdomen and liver
- MRI brain scan
- Diagnostic CSF hCG level if lung or brain metastases,
- GFR prior to EP/EMA or CNS EMA/CO chemo

Prognostic factors and treatment groups

Data from the early days of chemotherapy treatment for trophoblast disease shows clearly that there is a relationship between the level of elevation of hCG at presentation, the presence of distant metastases and the reducing chances of cure with single agent chemotherapy. This relationship and the impact on treatment choice and cure rate was first codified at Charing Cross Hospital with the Bagshawe scoring system published in 1976 (Bagshawe 1976).

Subsequently there have been a number of revisions and parallel systems introduced that are broadly similar to this original. In the revised 2000 FIGO prognostic score table is shown below.

From these parameters, an estimate of the risk category can be obtained and patients offered initial treatment either with single agent chemotherapy if their score is six or less or multi-agent combination chemotherapy for scores of seven and over (FIGO 2002).

Scores	0	1	2	4
Age	<40	≥40	-	-
Antecedent pregnancy	Mole	Abortion	Term	-
Months from index pregnancy	<4	4-6	7-13	>13
Pre-Treatment hCG	<1,000	1000-10,000	10,000-100,000	>100,000
Largest Tumour Size	-	3-5cm	≥5cm	-
Site of mets	Lung	Spleen, kidney	Gastro-Intestinal	Brain, Liver
Number of Mets	-	1-4	5-8	> 8
Previous chemotherapy	-	-	Single agent	Two or more drugs

WHO/FIGO scores

Low risk 0–6
High risk >7

Gestational trophoblast tissue treatment plans

Low risk disease management

Our standard treatment for patients with low risk trophoblast disease is methotrexate given intra-muscularly with oral folinic acid rescue following the schedule shown below. The first course of treatment is administered in hospital, with the subsequent courses administered at home. However patients with a high hCG level of >10,000 iu/ml may need to stay in for three weeks as they have a higher risk of bleeding, particularly as the tumour shrinks rapidly with the initial chemotherapy. Bleeding usually responds well to bed rest and less than one per cent of our low risk patients have required emergency interventions such as vaginal packing, embolisation or hysterectomy.

The low risk chemotherapy treatment is generally well tolerated without much major toxicity. Methotrexate does not cause alopecia or significant nausea and myelosuppression is extremely rare. Of the side effects that do occur, the most frequent problems are from pleural inflammation, mucositis and asymptomatic elevation of liver function tests.

For low risk patients with lung metastases on their chest X rays, our policy is to add CNS prophylaxis with intra-thecal methotrexate (12.5mg) administration on three occasions two weeks apart to minimise the risk of development of CNS disease (ref).

Results of treatment in low risk disease

The data shows that 67 per cent of the low risk group patients will be successfully treated with methotrexate and we monitor their disease response by twice weekly serum hCG measurement. Following normalisation of the serum hCG level it is usual to continue treatment for another 3 cycles (six weeks) to ensure eradication of any residual disease that is below the level of serological detection (McNeish 2002).

Patients who have an inadequate response to methotrexate therapy as shown by an hCG plateau or rise have their treatment changed to second line therapy. This is either single agent Actinomycin D, given at 0.5mg for days one to five every two weeks if the hCG is below 300iu/L, or EMA/CO combination chemotherapy if the hCG is above 300 iu/L.

An individual example of the pattern of hCG levels during the course of management is shown in Fig X. This demonstrates the rise in hCG that lead to the introduction of methotrexate chemotherapy, following this the hCG initally fell rapidly but after two cycles appeared to plateau. The introduction of second line treatment with EMA/CO chemotherapy lead to a rapid fall in the hCG to normal and the discontinuation of chemotherapy after six weeks further treatment. Overall the survival in the low risk group approaches 100 per cent and the sequential introduction of additional chemotherapy as necessary minimises the potential long term carcinogenic risks of excess treatment.

High risk disease management

Historical data that pre-dates the use of multi-agent chemotherapy schedules demonstrates that only 31 per cent of the high risk patients would be cured with single agent chemotherapy (Bagshawe 1989).

The introduction of combination chemotherapy treatments in the 1970s transformed this situation and modern series shows a cure rate for high risk patients of 86 per cent using EMA/CO chemotherapy (Newlands 1991, Bower 1997). This combination of drugs delivers a dose of intense treatment with the five chemotherapy agents, delivered in two groups one week apart as shown in Table 3b. This approach to chemotherapy, rather than the more usual three or four weekly cycles used in other malignancies, appears to be the most effective approach to this rapidly proliferating malignancy. However, these drugs are fairly myelosuppressive and G-CSF support is frequently helpful.

Fortunately serious or life threatening toxicity is rare and the majority of patients tolerate treatment without any major problems. As in the low risk situation, treatment is continued for six weeks after the normalisation of the hCG. In selected patients we reduce the dose of etoposide after the hCG falls to normal, to contain the total dose exposure and so minimise the potential risk of developing secondary malignancies.

Of the high risk patients treated with EMA/CO, approximately 17 per cent develop resistance to this combination and require a change to second line drug treatment. In this situation we generally use the EP/EMA regimen as shown in Table 3c which incorporates cisplatin and a further dose of etoposide replacing the vincristine and cyclophosphamide. This treatment combined with surgery mostly to the uterus for defined areas of drug resistant disease, produces a cure rate approaching 90 per cent in this relatively small group of patients (Newlands 2000).

With the aim of minimising short term infective risks and that of long term bone toxicity we avoid the routine use of dexamethasone in the anti-emetics, as this can be associated with both pneumocystis infection and avascular necrosis of the femoral head.

CNS metastases

Approximately 4 per cent of patients presenting with trophoblast disease have cerebral metastases at the time of diagnosis. In contrast to most other malignancies where cerebral metastases are associated with a very poor prognosis, trophoblast patients with CNS disease can routinely be cured of their disease. Treatment may include an initial surgical resection if the disease is superficial and then chemotherapy with modified EMA/CO containing a higher dose of methotrexate, which enhances penetration into the CNS.

This treatment, combined with intra-thecal methotrexate administration, has produced a cure rate of 86 per cent for patients with CNS disease who were fit enough at presentation to commence effective treatment (Newlands 2002).

The management of placental site trophoblast disease (PSTT)

The original description of placental site trophoblast disease suggested a relatively benign malignancy, however further data demonstrated that this is a malignancy that can often metastasise but can still be cured with effective therapy.

The management depends on careful staging, when the disease is limited to the uterus, curative treatment can be achieved with hysterectomy alone. For patients with disseminated disease we recommend treatment with EP/EMA chemotherapy, which is continued for six to eight weeks after the normalisation of the hCG level. Following successful chemotherapy treatment we usually recommend hysterectomy. Our data for patients with PSTT treated between 1975 and 2001 demonstrates a 100 per cent cure rate for those presenting within four years of the antecedent pregnancy, but a poorer prognosis for those presenting after a longer interval (Papadopoulos 2002).

EP/EMA (note the EMA in EP/EMA is the one day version) is the standard treatment for PSTT at Charing Cross Hospital.

The role of CNS prophylaxis in PSTT is unclear. An approach based on the results of brain MRI and CSF/serum hCG ratio may be prudent.

Common treatment issues

hCG monitoring during chemotherapy treatment

During chemotherapy the serum and urine hCG is checked twice a week. Once the hCG becomes normal the markers are checked weekly until the treatment stops.

Dose delays and reductions for haematological toxicity

Guidelines for chemotherapy administration: We are keen to maintain the intensity of chemotherapy treatment. It is very rare for there to be appreciable myelosuppression with single agent Methotreaxtae.

In high risk disease with EMA-CO chemotherapy myelosuppression is fairly common and we frequently use G-CSF support (G-CSF 30mU for 3-4 days per week) to keep treatment on time.

As a general rule we use the following results obtained on the day of treatment to give the go ahead for chemotherapy:-

Neutrophils >1.0
Platelets > 75

Bleeding

PV or intraperitoneal bleeding can occur. Moderate bleeding usually responds to bed rest and chemotherapy treatment. Torrential bleeding may require treatment with a vaginal pack, emergency embolization and very rarely with hysterectomy. Overall less than 1.5 per cent of GTD treated at Charing Cross patients have required one of these interventions over the past 25 years.

Choriocarcinoma emergency treatment of unwell patients

Patients who are acutely unwell from liver or CNS disease and particularly those with large lung metastases who are at risk of respiratory failure should be treated with emergency chemotherapy given a soon after admission as possible. Treatment should be given at night or weekends as these patients can deteriorate very rapidly.

We usually give emergency treatment with can be started with 1-2 days of EP. (Etoposide 100mg/m2 D 1+2, Cisplatin 20mg/m2 D1 + 2 the doses are as in BEP given for testicular cancer)

This treatment can be repeated weekly and then altered to EMA/CO or EP/EMA at a later point.

Hepatic metastases

Due to their poorer overall response rate and higher risk of relapse, patients with hepatic metastases should be treated with using the EP/EMA protocol and continued for eight weeks after the normalisation of the hCG level.

Cerebral metastases

In GTT the outlook for patients with brain mets is good with a survival rate of over 80 per cent.

The Charing Cross Hospital treatment for this is the high dose EMA(CNS)/CO, using an increased methotrexate dose (1gm/m2) combined with longer folinic acid rescue. In CNS disease the EMA(CNS)/CO chemotherapy is continued for eight weeks after the hCG normalisation.

Intrathecal MTX is also given 12.5mg + 15mg FA on the EMA week until the serum hCG is normal at which point it is discontinued.

In the emergency situation with cerebral metastases, hi-dose dexamethasone is given followed by two day EP as above.

Surgery can be indicated for isolated superficial lesions or for cerebral haemorrhage.

CNS prophylaxis

Charing Cross Hospital policy is to give prophylaxis to low risk patients with lung mets and all of the high risk patients.

Treatment is I-T MTX 12.5 mg (followed by oral FA 15mg at 24 hrs) on three occasions during the first three MTX courses, for the high risk patients it usually coincides with the CO treatment.

Respiratory failure

In patients with large volume pulmonary lung mets oxygen support can be given but ventilation is contra-indicated, due to the risk of traumatic haemorrhage from the tumour vasculature.

Respiratory compromise can also result from tumour within the pulmonary vasculature, this can respond promptly to chemotherapy. Consideration can be given to anti-coagulation in these rare patients with tumour emboli.

Tumour Lysis Syndrome

This is rare in GTT and no special precautions need to be taken.

Post chemotherapy follow-up

Assessment at the end of treatment

We review patients six weeks after the completion of therapy. This is to do the following;

- Recheck the sites of original disease
- Doppler US of pelvis
- CXR or CT/MRI if abnormal at presentation
- To advise on the need for contraception for 12 months
- To advise re avoidance of excess sunlight exposure
- To outline the risk of relapse 5 per cent following Methotrexate, 3 per cent following EMA-CO or the chance of a new molar pregnancy (1:75)

All patients have routine marker follow-up for life.

Post treatment hCG follow-up

Year 1: 2-weekly serum and urine hCG for 1-6 months
2 weekly urine hCG for 7-12 months
Year 2: 4 weekly urine hCG
Year 3: 8 weekly urine hCG
Year 4: 3-monthly urine hCG
Year 5: 4-monthly urine hCG
Year 6-life: 6-monthly urine hCG

Risk of relapse and late treatment complications

For the majority of patients with trophoblast disease who achieve a serological remission the outlook is very bright in terms of future risks of relapse, the possibility of further pregnancy and only modest long term health risks from the chemotherapy exposure. Once the hCG has fallen to normal, the risk of relapse is less than five per cent for patients treated with the low risk protocols and only three per cent for patients treated with the high risk EMA/CO regimen. Generally these recurrences occur within the first 12 months after treatment but may occur many years later. Even in this situation trophoblast disease retains the possibility of cure, with further chemotherapy and on occasion surgery to sites of disease often providing satisfactory outcomes.

Subsequent fertility after chemotherapy

Following either low or high risk chemotherapy treatment fertility is usually maintained and regular menstruation restarts two to six months after the end of chemotherapy. However chemotherapy treatment does bring the average age of the menopause forward, by approximately one year for those treated with methotrexate and three years for those treated with EMA/CO (Bower 1996).

We normally recommend for 12 months after treatment that further pregnancy is avoided to minimise any teratogenic effects on developing oocytes and to minimise the possible confusion from the rising hCG between a new pregnancy and disease relapse. The modest impact on future fertility is reflected in the data demonstrating that 83 per cent of women wishing to conceive after chemotherapy treatment have been able to have at least one live birth. Despite the frequent long exposure to cytotoxic chemotherapy in the high risk group there does not appear to be any significant increase in foetal abnormalities.

Many patients after experiencing one molar pregnancy and particularly those who require chemotherapy are anxious of the problem occurring again in any subsequent pregnancy. Whilst the data suggests that the risk of a further molar pregnancy is about 10 fold higher than in the normal population this only equates to an approximate one in 70 risk (Bagshawe 1986). This risk appears to be independent of chemotherapy exposure, being similar for those patients who required chemotherapy and those where the molar pregnancy was cured by evacuation alone.

Other long term toxicities

With the prolonged follow-up data available from trophoblast disease patients treated from the 1970s onwards, it is clear that the exposure to combination chemotherapy carries some long-term health risks. Data from a study of 1377 patients treated at CXH show that those receiving combination chemotherapy have enhanced risks of developing a second malignancy. From our series of patients the overall relative risk (rr) was increased 1.5 fold and is particularly marked for myeloid leukaemia (rr 16.6), colon cancer (rr 4.6), breast cancer (rr 5.8) and melanoma (rr 3.41) malignancies (Rustin 1996). This database is being updated and as the cohorts of treated patients get older, these risks may further increase. In contrast the patients treated with single agent methotrexate do not appear to have increased risks of second malignancies.

This long-term health concern from the use of combination chemotherapy reinforces the benefits from surveillance, allowing treatment to be commenced with single agent methotrexate whilst the patient falls within the low risk group.

Personal and psychological issues

Despite the very high cure rates and the low long-term toxicity from chemotherapy treatment, it is perhaps unsurprising that the diagnosis of a molar pregnancy and particularly treatment with chemotherapy can result in a number of psychological sequelae. The areas that lead to stress in the short term are the loss of the pregnancy, the impact of the 'cancer' diagnosis, the treatment process and the delay of future pregnancy. During chemotherapy treatment issues regarding potential side effects, emotional problems and fertility concerns are frequent. Other studies have shown that the concerns can remain for many years, with feelings regarding the wish for more children, a lack of control of fertility and an on-going mourning for the lost pregnancy still frequently reported five to 10 years after treatment (Wenzel 2002). Additionally issues regarding self-esteem and loss of sexual desire can be troublesome for many years after treatment, however overall marital happiness does not seem to be impaired for trophoblast patients and their partners (Wenzel 1992). A number of surveys have demonstrated the wish of many patients to have more support through counselling and support both at diagnosis and continuing after treatment, through the appointment of a clinical nurse specialist we hope to have enhanced the support we are routinely able to give.

Other background information

hCG levels in a normal pregnancy

Weeks from the Last Menstrual Period (LMP)	Amount of hCG in mIU/ml
3	5 - 50
4	3 - 426
5	19 - 7,340
6	1,080 - 56,500
7-8	7,650 - 229,000
9-12	25,700 - 288,000
13-16	13,300 - 254,000
17-24	4,060 - 165,400
25 - 40	3,640 - 117,000

Chemotheraphy regemens for trophoblast disease

Methotrexate/folinic acid treatment schedule

Day 1: Methorexate 50mg im at 12.00
Day 2: Folinic acid 15mg po at 18.00
Day 3: Methorexate 50mg im at 12.00
Day 4: Folinic acid 15mg po at 18.00
Day 5: Methorexate 50mg im at 12.00
Day 6: Folinic acid 15mg po at 18.00
Day 7: Methorexate 50mg im at 12.00
Day 8: Folinic acid 15mg po at 18.00

EMA-CO chemotherapy

Week 1
- Day 1 Actinomycin-D 0.5mg iv
  - Etoposide 100mg/m2 iv
  - Methotrexate 300mg/m2 iv
- Day 2 Actinomycin-D 0.5mg iv
  - Etoposide 100mg/m2 iv
  - Folinic acid 15mg po 12 hourly x 4 doses
  - Starting 24hrs after commencing methotrexate

Week 2
- Day 8 Vincristine 0.8mg/m2 (max 2mg)
  - Cyclophosphamide 600mg/m2

EP/EMA chemotherapy

Week 1
- Day 1 Actinomycin-D 0.5mg iv
  - Etoposide 100mg/m2 iv
  - Methotrexate 300mg/m2 iv
- Day 2 Folinic acid 15mg po 12 hourly x 4 doses
  - Starting 24hrs after commencing methotrexate

Week 2
- Day 8 Etoposide 150mg/m2 iv
  - Cisplatin 75 mg/m2 iv

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Publications

GTT scientific and clinical publications

The GTT unit at Charing Cross Hospital has been closely involved in developing the treatment of GTT. We have listed below the most recent publications along with their PubMed links. Also lower down the page are some of the key historical publications from Charing Cross that have helped develop the current successful management of GTT.

Historical interest

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Agarwal R, Teoh S, Short D, Harvey R, Savage PM, Seckl MJ (2012) Elevated human chorionic gonadotrophon levels six months after uterine evacuation of molar pregnancy- is chemotherapy necessary? A retrospective cohort study. Lancet Mar 13;106(6):1089-94

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Demographics

Savage PM, Sita-Lumsden A, Dickson S, Iyer R, Everard J, Coleman R, Fisher RA, Short D, Casalboni S, Catalano K, Seckl MJ (2013) The relationship of maternal age to molar pregnancy incidence, risks for chemotherapy and subsequent pregnancy outcome. J Obstet Gynaecol. 2013 May;33(4):406-11

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Newlands ES, Holden L, Seckl MJ, McNeish I, Strickland S, Rustin GJ. Management of brain metastases in patients with high-risk gestational trophoblastic tumors J Reprod Med. 2002 Jun;47(6):465-71

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PSTT

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