GESTATIONAL TROPHOBLASTIC NEOPLASIA:

A GUIDE TO MANAGEMENT

AT WESTON PARK HOSPITAL,

SHEFFIELD TEACHING HOSPITALS FOUNDATION TRUST (STHFT)

CONTENTS

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OBJECTIVE

The objective of this booklet is to provide a guide for all clinicians concerned with the management of patients with Gestational Trophoblastic Disease (GTD) at Weston Park Hospital (WPH).

These notes form recommendations only and junior clinicians should liaise closely with senior colleagues at all times.

INTRODUCTION

GTD comprises a range of related tumours arising from tissues of placental origin including complete hydatidiform mole, partial hydatidiform mole, invasive mole, choriocarcinoma and placental site trophoblastic tumour. The worldwide incidence of GTD varies considerably. In the U.K. it is around 1.5 cases per thousand live births whilst the incidence of choriocarcinoma is around 1 case in 50,000 live births. Placental site trophoblastic tumour accounts for approximately 0.2% of cases of GTD in the U.K.

The U.K. Trophoblastic Disease Registration and Surveillance scheme was established in 1973 by the Royal College of Obstetricians and Gynaecologists (RCOG) in conjunction with the Department of Health. Guidance on initial management of patients by gynaecologists prior to registration with GTD centres is provided by the RCOG green top guideline 38: 'The Management of Gestational Trophoblastic Neoplasia.'

Following diagnosis, patients with GTD are registered with and followed up by one of three Centres currently located at Weston Park Hospital, Sheffield, Charing Cross Hospital, London and Ninewells Hospital, Dundee. If subsequent treatment is required, those patients are treated in Sheffield or London (Charing Cross).

In Sheffield patients with GTD are followed up for six months (from date of evacuation if hCG normalises within 56 days, or for 6 months from the first normal reading if this is beyond 56 days). We currently receive approximately 600 registrations per annum.

All non English speaking patients are contacted using interpreter services provided by STHFT.

The onset of malignant change is termed persistent trophoblastic disease (PTD) or gestational trophoblastic neoplasia (GTN) and is represented by plateauing or rising hCG. Malignant change occurs in approximately 15% of complete moles and in 0.5-1% of partial moles (Seckl et al., 2010).

DEFINING PERSISTENT TROPHOBLASTIC DISEASE AND THE NEED FOR TREATMENT

The need for treatment is identified by 'evidence of persistent disease activity unlikely to resolve spontaneously.' This fundamental definition is generally accepted; however in Sheffield only 5-6% of patients receive chemotherapy whilst in Europe this figure is 12-15% and in North America 20-30%. These differences are explained by the fact that in Sheffield the criteria for treatment are significantly more stringent than elsewhere.

The surveillance scheme allows us to adopt a very conservative treatment philosophy. We now report high cure rates whilst exposing the minimum number of patients possible to cytotoxic chemotherapy.

WPH Criteria for staging and if clinically required Chemotherapy in Gestational Trophoblastic Neoplasia.

- hCG levels greater than 20,000 iu/L after one or two uterine evacuations.
- Static or rising hCG levels after one or two uterine evacuations.
- Persistent hCG elevation six months post uterine evacuation
- Persistent uterine haemorrhage with raised hCG levels
- Pulmonary metastases with static or rising hCG levels
- Metastases in: liver, brain, or GI tract.
- Histological diagnosis of choriocarcinoma.
- Placental Site Trophoblastic Tumour (PSTT)

The above list indicates the treatment criteria we adopt. By definition patients fulfilling any of these criteria have PTD. Patients who fulfil the treatment criteria should be reviewed at WPH for staging and treatment.

Registration

Registration with the surveillance scheme will normally have been undertaken by the referring gynaecologist. In urgent cases this may not be the case and registration should be completed on arrival.

CLINICAL ASSESSMENT AND STAGING INVESTIGATIONS

The following should be routine in all cases:

1. Full history

2. Full examination

3. Blood tests

   a) Endocrine:
      - hCG
      - Oestradiol
      - LH/FSH
      - TSH / T4 / T3

   b) Haematology:
      - FBC
      - 2 x group and save samples

   c) Biochemistry:
      - U & E
      - LFTs
      - Urate

4. Imaging

   - Chest X-ray (CXR)
   - Transvaginal Ultrasound of pelvis/ Ultrasound of the abdomen
   - Other investigations should be performed as clinically indicated.

5. Central nervous system assessment

   It is recognised that choriocarcinoma can readily metastasise to the brain. CNS assessment is performed in those patients with choriocarcinoma, PSTT, or where there is clinical suspicion.

   It is therefore recommended that patients in these categories have:
   - MRI brain
   - Lumbar puncture - provided there is no clinical evidence of raised intra-cranial pressure - in order to obtain the CSF for a hCG level (an abnormal CSF-hCG level is interpreted as one where the ratio with serum hCG value is > 1:60).

FIGO STAGING

Stage I: confined to uterus
Stage II: extends to genital tract
Stage III: spread to lungs with or without extension to genital tract
Stage IV: all other metastatic sites including liver, kidney, spleen and brain

HISTOLOGY REVIEW

A histopathological review will be arranged by the GTD team forwarding a completed histology review request form to the Department of Pathology, Royal Hallamshire Hospital (for the attention of Professor Michael Wells).

PROGNOSTIC RISK ASSESSMENT

Prior to treatment, a prognostic score should be calculated for each new patient using the international WHO/FIGO (2000) scoring system for GTN

	0	1	2	4
Age (years)	<40	≥40		
Antecedent pregnancy	Mole	Abortion	Term	
Interval Months from Index Pregnancy	<4	4-6	7-13	>13
Pre-treatment hCG concentration (IU/L)	<1000	1000 -10,000	10,000 – 100,000	>100,000
Largest tumour mass diameter		3-5cm	≥5cm	
Site of mets	Lung	Spleen, Kidney	GI tract	Brain, liver
Number of mets		1-4	5-8	>8
Previous chemotherapy			Monotherapy	Combined therapy

Patients are categorised into **low** (score $\leq$ 6) or **high** (score $\geq$ 7) risk prognostic groups for treatment purposes. Patients are treated with single agent intramuscular methotrexate if their score is 6 or less or multi-agent chemotherapy for scores of 7 or more. All prognostic scores must be discussed with senior colleagues prior to initiating treatment.

PRINCIPLES OF TREATMENT

All chemotherapy is given as an in-patient at Weston Park Hospital with the exception of second and subsequent courses of therapy in low risk patients (subject to adequate response).

Measurements of serum hCG are used to monitor treatment response. It is essential with all chemotherapy regimens that hCG is measured regularly. In general, an adequate treatment response is defined by a 50% reduction in hCG on serum analysis with every cycle of chemotherapy. The half-life of hCG is approximately 48-72 hours.

Our experience shows that the success of these regimens is at least in part schedule dependent and therefore every effort should be made to ensure there are no deviations from the following protocols. The level of hCG may reach normal or become undetectable when there is still a residual tumour burden of 10^5 - 10^6 cells. Therefore, with all regimens, treatment is continued for 6 weeks following biochemical remission.

CHEMOTHERAPEUTIC REGIMENS

The following pages describe the chemotherapy regimens employed at WPH for the management of the different categories of patients.

1. Low risk patients

2. Salvage of drug resistance in low risk patients

3. High risk patients

4. Salvage of drug resistance in high risk patients

5. Treatment of established CNS disease.

PRE CHEMOTHERAPY INVESTIGATIONS

- Serum hCG
- U & E/extended LFT's
- FBC
- Group and save if pt bleeding heavily
- For regimens where cisplatin or high dose methotrexate (>1g/m2) are being given, creatinine clearance should be calculated. Do not proceed if <60ml/min

LOW RISK PATIENTS

The majority of our patients will initially receive this regimen.

Low dose methotrexate regimen
Methotrexate: 50mg by intramuscular (IM) injection, alternate days x 4 doses per cycle (Days 1,3,5,7)
Folinic acid: 15mg, orally, 24 hours after each MTX injection (Days 2,4,6,8).
Seven day rest between treatment cycles

Common problems
All problems with the low dose MTX regimen can be ameliorated in part by adequate hydration during treatment and increasing the dose of folinic acid rescue.

(1) Oral mucositis
- Treatment - analgesic mouthwash (Difflam)

(2) Conjunctivitis
- Treatment - hypromellose eye drops

(3) Pleurisy / Peritoneal pain (due to serositis)
- Treatment - simple analgesia (avoid NSAIDs as these reduce renal excretion of methotrexate). On rare occasions this problem can be very severe and may necessitate alteration in therapy despite adequate tumour response.

(4) Other medications including some antibiotics can also affect excretion of methotrexate

SALVAGE OF DRUG RESISTANCE IN LOW RISK PATIENTS

Approximately 20-30% of all low risk patients will require additional treatment because of the development of MTX resistance. Such patients have been successfully treated with subsequent intravenous chemotherapy. Patients who develop resistance to methotrexate with hCG levels of <300 IU/L are treated with single agent actinomycin D (see below). Patients with hCG levels above 300 IU/L are treated with Carboplatin every 3 weeks as described below.

Note: a score of 6 is associated with an approximate 85% chance of having to change from methotrexate to intravenous chemotherapy. Some patients depending on age and preference may request hysterectomy as part of salvage treatment

Low risk salvage regimen when hCG <300IU/L
- Dactinomycin 1.25mg/m^2 i.v. repeated every 2 weeks
- Dexamethasone 8mg i.v.
- Granisetron 3mg i.v.

Supportive medication post chemotherapy

- Dexamethasone 4mg BD for 3 days post chemo
- Ondansetron 8mg BD for 2 days post chemo

Low risk salvage regimen when hCG >300IU/L

- Carboplatin AUC 6 iv
- Dexamethasone 8mg i.v.
- Granisetron 3mg i.v.
- Rantidine 50mg i.v.
- Chlorphenamine 10mg i.v.

Carboplatin is given every 3 weeks as a day case.
Supportive medication post chemotherapy

- Domperidone 10mg every 4-6 hourly when necessary
- Dexamethasone 4mg BD for 3 days post chemo
- Ondansetron 8mg BD for 2 days post chemo
- Cetirizine 10mg for 3 days starting the night before the next chemotherapy

Common problems

- Pancytopenia
- Nausea and constipation

  Increased infection risk and bone marrow toxicity
  Treatment - GCSF may be prescribed should this problem lead to delays in drug administration.

3rd level salvage regimen

- Dactinomycin 0.5mg day 1,2,3
- Etoposide 100mg/m^2 day 1,2,3
- Granisetron 3mg i.v.
- Dexamethasone 8mg i.v.

7 days interval between courses

- Domperidone 10mg every 4-6 hourly when necessary
- Dexamethasone 4mg BD for 3 days post chemo
- Ondansetron 8mg BD for 2 days post chemo

Common problems

- Dactinomycin : emesis
- Etoposide : hair loss
- Increased infection risk and bone marrow toxicity

HIGH RISK PATIENTS

The aim of the following regimen is to facilitate the rapid delivery of the five drugs proven most effective in the treatment of GTD. This is a regimen of alternating intravenous Etoposide, Methotrexate and Actinomycin D with Cyclophosphamide and Vincristine. This regimen is given weekly without a break. Alkalinisation of the urine is advised. Particular caution should be employed in patients with widespread pulmonary metastases who are at risk of developing respiratory failure following treatment with chemotherapy.

EMA:

Day 1
Dexamethasone 8mg i.v.
Granisetron 3mg i.v.
Sodium bicarbonate 2g qds po and urinary pH maintained above 7 for at least 24 hours
Actinomycin D 0.5mg IV bolus followed by
Etoposide 100mg/m^2 IV 1 hour infusion in 500mls normal saline followed by
Methotrexate 300mg/m^2 IV 12 hour infusion in one litre of normal saline

Day 2
Dexamethasone 8mg i.v.
Granisetron 3mg i.v.
Actinomycin D 0.5mg IV bolus followed by
Etoposide 100mg/m^2 IV, 1 hour infusion in 500mls normal saline
Folinic Acid 15mg, 6 hourly, commences 24 hours after the start of MTX. Eight doses are administered; these may be given i.v/oral

CO:

Day 8
Dexamethasone 8mg i.v.
Granisetron 3mg i.v.
Vincristine 0.8mg/m^2 IV in 50mls in normal saline over 10 mins
followed by
Cyclophosphamide 600mg/m^2 IV in 250mls normal saline over 30 mins

Day 9
Filgrastim 0.5mu/kg/day sc for 5 days

Note: once hCG levels normalise omit day 2 EMA

Problems
Dactinomycin : emesis,
Etoposide : hair loss
Increased infection risk and bone marrow toxicity
In addition with the increased dose of MTX careful attention should be paid to renal and liver function. Alkalinisation of the urine may be required. Particular caution

should be employed in patients with widespread pulmonary metastases who are at risk of developing respiratory failure following treatment with chemotherapy.

With our IV regimens patients are treated on a Monday or Thursday. Please note regimens containing dactinomycin are not started on a Friday due to expiry of dactinomycin over the weekend.

Occasionally these drugs have been given in combination as the EMA regimen (see below) following MDT review e.g. if responding better to one arm than the other

EMA regimen

- Dactinomycin 0.5mg days 1 and 2
- Etoposide 100mg/m^2 day 1 and 2
- Methotrexate 300mg/m^2 day 1
- **Calcium folinate 15mg 12 hourly orally for 4 doses commencing 24 hours after start of methotrexate**
- Dexamethasone 8mg i.v.
- Granisetron 3mg i.v.

Problems
Dactinomycin : emesis,
Etoposide : hair loss
Increased infection risk and bone marrow toxicity
In addition with the increased dose of MTX careful attention should be paid to renal and liver function. Alkalinisation of the urine may be required. Particular caution should be employed in patients with widespread pulmonary metastases who are at risk of developing respiratory failure following treatment with chemotherapy.

GCSF may be prescribed should bone marrow toxicity be a problem

SALVAGE OF DRUG RESISTANCE IN HIGH RISK PATIENTS

There is no chemotherapy regimen with a guaranteed outcome. However the cisplatin based combination described below has been shown to be active. In addition salvage surgery to remove foci of resistant disease e.g. hysterectomy, thoracotomy or craniotomy, may be required. There may also be a role for stereotactic radiosurgery and cases should be discussed with the neurosurgery team.

Salvage regimens of drug resistance in high risk patients

EP-EMA

EP:
Etoposide 150mg/m2 day1
Cisplatin 75mg/m2 day 1
Dexamethasone 8mg i.v.
Granisetron 3mg i.v.

Alternates weekly with **EMA**:

- Dactinomycin 0.5mg day 1
- Etoposide 100mg/m^2 day 1
- Methotrexate 300mg/m^2 day 1
- Dexamethasone 8mg i.v.
- Granisetron 3mg i.v.

Supportive medication post chemotherapy

- Domperidone 10mg every 4-6 hourly when necessary
- Dexamethasone 4mg BD for 3 days post chemo
- Ondansetron 8mg BD for 2 days post chemo

Note omission of second day of etoposide and dactinomycin

An alternative regimen is TP-TE, a 28 day cycle

TP – day 1
Dexamethasone 20mg po 12hr and 6hr before paclitaxel
Dexamethasone 8mg i.v.
Granisetron 3mg i.v.
Chlorpheniramine 10mg i.v.
Ranitidine 50mg i.v.
Paclitaxel 135mg/m^2
Cisplatin 60mg/m^2

Filgrastim 0.5mu/kg/day for 5 days starting on day 5

TE – day 15
Dexamethasone 20mg po 12hr and 6hr before paclitaxel
Dexamethasone 8mg i.v.
Granisetron 3mg i.v.
Chlorpheniramine 10mg i.v.
Ranitidine 50mg i.v.
Paclitaxel 135mg/m^2
Etoposide 150mg/m^2 day 15
Filgrastim 0.5mg/kg/day for 5 days starting on day 19

Supportive medication post chemotherapy

- Domperidone 10mg every 4-6 hourly when necessary
- Dexamethasone 4mg BD for 3 days post chemo
- Ondansetron 8mg BD for 2 days post chemo

Common problems
Nausea can be problematic and there may be a role for aprepitant pre and post cisplatin chemotherapy
A satisfactory creatinine clearance is required prior to each new cycle and the usual precautions for maintaining IV hydration during and after platinum therapy must be followed.
Magnesium levels should be checked routinely pre cisplatin chemotherapy.

HIGH DOSE CHEMOTHERAPY WITH AUTOLOGOUS STEM CELL TRANSPLANTATION
Potential role in patients with refractory disease, but patients need to be highly selected

PLACENTAL SITE TROPHOBLASTIC DISEASE
This rare form of GTD produces less hCG than choriocarcinoma and is typically less chemosensitive.

Management of disease localised to the uterus is usually hysterectomy. Uterine sparing surgery has been reported in the literature but multifocal microscopic disease is possible.

Patients presenting with metastatic disease need combination chemotherapy with EP-EMA or TP/TE. Recommendations would also then include hysterectomy and removal of residual masses that can contain microscopic disease.

TREATMENT OF ESTABLISHED CNS DISEASE

Wherever possible single cerebral metastases should be excised or treated by radiosurgery prior to chemotherapy. Cases should be discussed with the neurosurgery team.

The MAE high risk regimen is employed with alteration of MTX dosage and the addition of intrathecal MTX as described below. The aim is to ensure maximum penetration of MTX in the CNS.

Treatment of established CNS disease

A satisfactory creatinine clearance should be obtained prior to initiating treatment.

Arm A:

Methotrexate:
1g/m^2 in two litres of normal saline, infused over 24 hours.
Alkalisation of urine must be performed to maintain urinary PH >7

Folinic acid:
15mg, 6 hourly commencing at the end of the MTX infusion.
12 doses are administered, the first four being given by either IM or IV injection

Seven day interval

Arm B:

Dactinomycin and Etoposide: administered as previously described

Intrathecal Methotrexate: 12.5mg, intrathecal

Arm A is repeated after a seven day rest et seq.

Notes
Intrathecal MTX should be continued for four injections after CSF:serum ratios have returned to normal

MANAGEMENT OF ACUTE VAGINAL BLEEDING

This can be due to the disease itself or due to treatment. Patients with or at risk of vaginal bleeding need to be closely monitored and must have large bore intravenous access and if bleed be appropriately resuscitated with fluids and blood products. FBC should be monitored closely.

Pelvic examination and vaginal packing if required should be done by gynaecologists and therefore the gynaecology team should be contacted (Professor Tidy and team if available during office hours or the gynae on call team if after hours) **to be made aware of any patients bleeding significantly.** It may be more appropriate that the patient is transferred to the gynaecology wards at the RHH.

It is very rare but patients with uncontrolled bleeding may need urgent hysterectomy or embolisation.

Patients are all advised to use condoms for contraception rather than hormonal contraception until serum hCG has normalised.

MANAGEMENT OF HEALTHY WOMEN WITH PERSISTENTLY RAISED HCG

In the absence of pregnancy, an elevated hCG is highly suspicious of an underlying malignancy. The causes of a raised hCG in the absence of pregnancy are:

1. GTN
2. A non-gestational trophoblastic tumour
3. Pituitary-derived hCG e.g. in menopause or associated with premature ovarian failure
4. False-positive result
5. High normal level

Healthy women with persistently raised hCG in absence of pregnancy and overt tumour is a rare clinical scenario but should be seen at WPH for assessment.

Assessment should include:

- History and full examination including breasts
- Verification serum hCG is not false-positive by checking presence of hCG in urine
- Evaluation of other tumour markers as may indicate presence of non-gestational tumour – AFP, Ca125, LDH, CEA, CA19-9
- Pelvic ultrasound
- CXR
- Bilateral mammograms

If all scans negative, continue regular serum / urine hCG monitoring
If hCG levels continue to rise, repeat imaging and consider MRI pelvis, CT chest. Further investigation may also include PET scan

INFORMATION FOR PATIENTS

Each patient has her own information pathway that includes:

1. An information booklet entitled 'Molar Pregnancy' for all patients registered with the Screening and Treatment Centre

This informs them about:

- The GTD team, how to contact them and each individual's role
- What GTD is and the different types
- Who it may affect
- How it is diagnosed
- How it is initially treated by gynaecologists
- How they are monitored by Sheffield
- When they can try for another pregnancy
- Which contraception to use

2. A further booklet, entitled: 'Gestational Trophoblastic Neoplasia' for all patients attending WPH for staging investigations

This informs them about:

- The GTN team, each individual's role and contact details
- What GTN is
- What investigations they will have
- How they are informed of their results
- What is their treatment plan
- What is chemotherapy, types and possible side effects
- Contact details once discharged after treatment
- When may try for another pregnancy
- Risk of further problems
- Contraception advice
- Monitoring post chemotherapy

3. Printed cytotoxic drug information

The above booklets are available on-line from the Sheffield website:

www.chorio.group.shef.ac.uk

Patient support website: www.molarpregnancy.co.uk (run by patients)

FOLLOW UP OF PATIENTS TREATED AT WESTON PARK HOSPITAL

Completion of Treatment

After conclusion of treatment, serum hCG analysis should be performed weekly for the first 6 weeks and then monthly for the subsequent 6 months. If levels remain satisfactory patients will be followed up with periodic urinary hCG for life.

Contraception

Patients are all advised to use condoms for contraception. New guidelines for oral contraception - effective from 1st January 2014. Oestrogen and/ or progestogens taken between evacuation of the mole and the 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 the hCG returns to normal.

Pregnancy

Patients are advised not to conceive for 12 months from conclusion of their treatment. There is a risk of teratogenicity from cytotoxic chemotherapy and secondly, the risk of recurrent GTD is greatest during this time.

GESTATIONAL TROPHOBLASTIC DISEASE FOLLOW-UP PROCEDURES (patients not receiving chemotherapy treatment)

All patients registered with the GTD Screening Centre are monitored by sending urine samples by post for hCG measurement

If the hCG returns to normal within 56 days of the end of the molar pregnancy, the patient is monitored for 6 months from the end of the pregnancy

If the hCG does not return to normal within that 56 days then monitoring continues for six months from the date of the first normal result

Patients are advised to avoid a new pregnancy until monitoring is complete

Patients are advised to avoid hormonal contraception until hCG is normal, condoms only until then.

In some cases when the hCG is unknown but where the risk of conceiving a new pregnancy is thought to be great, progestogen contraception may be used

NATIONAL SCREENING CENTRES

1. Trophoblastic Screening and Treatment Centre,
   Weston Park Hospital
   Sheffield
   S10 2SJ

   Director - Professor R. E. Coleman
   Director of screening service – Professor John Tidy
   Consultant oncologist- Dr Matt Winter

   Tel: 0114 226 5205
   Fax: 0114 226 5511
   Website: www.chorio.group.shef.ac.uk/index.html

2. Trophoblastic Tumour Screening and Treatment Centre,
   Department of Medical Oncology,
   Charing Cross Hospital,
   Fulham Palace Road,
   London
   W6 8RF

   Director - Professor M. Seckl

   Tel: 020 88461409
   Fax: 020 87485665
   Website: www.hmole-chorio.org.uk

3. Trophoblastic Tumour Screening and Treatment Centre,
   Department of Obstetrics and Gynaecology,
   Ninewell Hospital,
   Dundee
   DD2 1UB

   Tel: 01382 632748
   Fax: 01382 632096

This service is funded by the Department of Health

FURTHER READING

Gestational Trophoblastic Disease
Hancock, B W et al
(Chapman & Hall, London,1997)

Palmieri C., et al. Management and outcome of healthy women with a persistently elevated hCG. Gynecologic Oncology 2007; 106, 35-43

RCOG Green-top Guideline No. 38 Feb 10: The Management of Gestational Trophoblastic Disease

Seckl, M.J. et al. Gestational Trophoblastic disease. Lancet 2010;376:717-29

Manuscripts/Abstracts detailing our experience and attitudes towards various aspects of Gestational Trophoblastic Disease are available through the Department of Clinical Oncology