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[Intervention Review]

Chemotherapy for resistant or recurrent gestational trophoblastic neoplasia

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ABSTRACT

Background

Gestational trophoblastic neoplasia (GTN) is a highly curable group of pregnancy-related tumours; however, approximately 25% of GTN tumours will be resistant to, or will relapse after, initial chemotherapy. These resistant and relapsed lesions will require salvage chemotherapy with or without surgery. Various salvage regimens are used worldwide. It is unclear which regimens are the most effective and the least toxic.

Objectives

To determine which chemotherapy regimen/s for the treatment of resistant or relapsed GTN is/are the most effective and the least toxic.

Search methods

We searched the Cochrane Gynaecological Cancer Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL, Issue 4), MEDLINE and EMBASE up to October 2011. In addition, we handsearched the relevant society conference proceedings and study reference lists. For the updated review, we searched Cochrane Group Specialised Register, CENTRAL, MEDLINE and EMBASE to 16 November 2015. In addition, we searched online clinical trial registries for ongoing trials.

Selection criteria

Only randomised controlled trials (RCTs) were included.

Data collection and analysis

We designed a data extraction form and planned to use random-effects methods in Review Manager 5.1 for meta-analyses.

Main results

The search identified no RCTs; therefore we were unable to perform any meta-analyses.

Authors' conclusions

RCTs in GTN are scarce owing to the low prevalence of this disease and its highly chemosensitive nature. As chemotherapeutic agents may be associated with substantial side effects, the ideal treatment should achieve maximum efficacy with minimal side effects. For methotrexate-resistant or recurrent low-risk GTN, a common practice is to use sequential five-day dactinomycin, followed by MAC (methotrexate, dactinomycin, cyclophosphamide) or EMA/CO (etoposide, methotrexate, dactinomycin, cyclophosphamide, vinblastine) if further salvage therapy is required. However, five-day dactinomycin is associated with more side effects than pulsed dactinomycin, therefore an RCT comparing the relative efficacy and safety of these two regimens in the context of failed primary methotrexate treatment is desirable.

For high-risk GTN, EMA/CO is the most commonly used first-line therapy, with platinum-etoposide combinations, particularly EMA/EP (etoposide, methotrexate, dactinomycin/etoposide, cisplatin), being favoured as salvage therapy. Alternatives, including TP/TE (paclitaxel, cisplatin/ paclitaxel, etoposide), BEP (bleomycin, etoposide, cisplatin), FAEV (floxuridine, dactinomycin, etoposide, vincristine) and FA (5-fluorouracil (5-FU), dactinomycin), may be as effective as EMA/EP and associated with fewer side effects; however, this is not clear from the available evidence and needs testing in well-designed RCTs. In the UK, an RCT comparing interventions for resistant/recurrent GTN will be very challenging owing to the small numbers of patients with this scenario. International multicentre collaboration is therefore needed to provide the high-quality evidence required to determine which salvage regimen/s have the best effectiveness-to-toxicity ratio in low- and high-risk disease. Future research should include economic evaluations and long-term surveillance for secondary neoplasms.

PLAIN LANGUAGE SUMMARY

Anti-cancer drug treatment for gestational trophoblastic neoplasia (GTN) that does not respond to first-line treatment or that re-occurs

This review concerns anti-cancer drug treatment for women with GTN that does not respond to first-line treatment or that re-occurs. GTN is the name given to a type of cancer that arises from placental tissue following pregnancy, most frequently a molar pregnancy. Molar pregnancies are benign abnormal growths of placental tissue inside the womb. Most are cured by evacuation (D&C) of the womb, however, in up to 20% of cases they become malignant. GTN is usually very responsive to anti-cancer drugs (chemotherapy), however, these drugs can be toxic, therefore the aim of treatment is to achieve a cure with the least side effects. To help doctors select the most appropriate treatment for women with GTN, the disease is classified as low- or high-risk according to specific risk factors.

Chemotherapy treatment for low-risk GTN usually only requires a single drug, whereas high-risk tumours are treated with a combination of drugs. The most common combination consisting of five drugs is abbreviated as EMA/CO. Doctors assess the response to treatment by checking the levels of the pregnancy hormone (hCG) in the blood. If the chemotherapy is deemed not to be working an alternative (or salvage) treatment must be started. This is necessary in about 25% of cases and a variety of drug combinations are in use.

We undertook this review because it was unclear which of the various salvage combinations, if any, was the most effect and the least toxic. We searched the literature up to November 2015 to find all relevant studies. Unfortunately, we were unable to find any good quality studies that compared the different types of salvage treatments. This is partly because the disease has a high cure rate with several combination chemotherapy options, but is also owing to the rarity of the disease that makes recruiting for large studies difficult. Hence we were unable to draw conclusions about how these drug combinations compare with regard to their effectiveness and side effects, and we urge researchers in this field to collaborate to provide this important evidence.

BACKGROUND

Description of the condition

Gestational trophoblastic disease (GTD) encompasses a spectrum of pregnancy-related disorders that includes benign, pre-malignant disorders (complete and partial hydatidiform mole), and persistent, malignant disorders of invasive mole, choriocarcinoma, placental site trophoblastic tumour (PSTT) and epithelial trophoblastic tumour (ETT). Gestational trophoblastic neoplasia (GTN) is a term used for the persistent/malignant disorders.

The incidence of GTD varies across the world. In North America and Europe it is less than two per 1000 pregnancies, whereas higher rates have been reported in parts of Asia, Africa and South America (Lee 2009; Palmer 1994; Tham 2003). GTD can affect women at any reproductive age; however, the risk is higher in women under 16 years and over 45 years of age (Sebire 2002).

Persistent disorders or GTN usually arise following molar pregnancies, but may occur after any antecedent pregnancy (Seckl 2009). Complete moles (CMs) are paternally derived and have a diploid karyotype, whereas partial moles (PMs) are usually triploid, deriving two sets of haploid genes paternally and one maternally. Molar pregnancies usually resolve spontaneously following one or more uterine evacuations, with or without chemotherapy. However, in approximately 6% to 20% of CMs and 0.5% to 1% of PMs the disease persists and transforms to GTN (Hancock 2006; Seckl 2009), which usually requires chemotherapy. The most common forms of GTN are invasive mole and choriocarcinoma; PSTT and ETT are rare.

Various scoring systems have been used to stratify GTN according to risk (Bagshawe 1976; Hammond 1973; WHO 1983). Most recently the combined WHO-FIGO system (Table 1; Table 2; FIGO 2009; Nagan 2002) was adopted in 2002 by the International Society for the Study of Trophoblastic Diseases (ISSTD) (Kohorn 2000; Nagan 2002). The revised scoring system differs from the WHO system in that the ABO blood group risk factor has been eliminated and the risk factor for liver metastases has been upgraded from two to four. Low-risk is defined as a score of six or less (FIGO stages I-III) owing to the merging of the old intermediate-risk group (scores five and six) into the low-risk category (score zero to four). A score of seven or more (or FIGO stage IV) is classed as high risk.

Invasive moles and choriocarcinomas are highly chemosensitive tumours and chemotherapy (with or without surgery) will cure virtually all low-risk lesions and 80% to 90% of high-risk lesions. However, approximately 25% of these tumours will be resistant to primary treatment or relapse after cure and will require salvage chemotherapy. Low-risk GTN is more common than high-risk GTN and more easily salvaged. Treatment failure or drug-resistance is variably defined in the literature and may be considered to have developed if three consecutive serum hCG values decline by less than 10% over two weeks or by one log hCG level over six weeks, if two consecutive hCG values rise, or if new metastases develop (Covens 2006; Homesley 2009; McGrath 2010). These criteria may not be clinically helpful for patients with low hCG levels (Covens 2006; Homesley 2009). Relapse or recurrence has occurred if there is a rise in serum hCG levels after reaching normal values with treatment.

Description of the intervention

Chemotherapy regimens differ for low-risk and high-risk lesions:

Low-risk GTN

Women with low-risk GTN are usually treated with single-agent chemotherapy, methotrexate (with or without folinic acid) or dactinomycin. However, 5-fluorouracil (5-FU) has been used in China for many years and is considered very effective and less toxic (Song 1998). Five- and eight-day methotrexate regimens are the first-line treatment of choice at many centres in Europe and the North America (May 2011; McGrath 2010). Dactinomycin is generally considered to be associated with more side effects than methotrexate, particularly alopecia and nausea; however, one Cochrane review of first-line chemotherapy for low-risk GTN found that dactinomycin was more likely to result in primary cure than methotrexate with comparable side effects, especially when bi-weekly pulsed dactinomycin was used (Alazzam 2012a).

Tumour resistance to first-line chemotherapy has been reported in up to 45% of women with low-risk GTN, depending on the regimen used (Homesley 1988; Khan 2003; Lurain 1995; McNeish 2002; Osborne 2011), with higher primary cure rates reported with the five- and eight-day methotrexate regimens (10% to 33%) than with weekly low-dose methotrexate. Resistance in low-risk GTN is more likely to develop when pre-treatment hCG levels are high (Hammond 1973; Lurain 1995; McGrath 2010). A study from Charing Cross hospital (London, UK) found that single-agent chemotherapy (methotrexate) only cured 30% of low-risk women with hCG levels greater than 100,000 mIU/mL and was futile in low-risk lesions where hCG levels were greater than 400,000 mIU/mL (McGrath 2010). Other risk factors for drug resistance in low-risk GTN include higher risk scores (i.e. five or six) (El-Helw 2009; Osborne 2011), non-molar antecedent pregnancy and a histological diagnosis of choriocarcinoma (Hammond 1973; Lurain 1995). Drug resistance to primary therapy is associated with higher relapse rates (Matsui 2005).

When first-line chemotherapy fails, secondary chemotherapy, with or without surgery, is used to achieve remission. Several secondary treatment regimens have been described with various success rates and toxicity profiles, including:

- single-agent pulsed dactinomycin (Covens 2006) (where first-line therapy has been methotrexate);
- five-day dactinomycin (McNeish 2002);
- etoposide and dactinomycin (EA) (Dobson 2000);
- methotrexate, dactinomycin, cyclophosphamide (MAC) (Goldstein 2012);
- etoposide, methotrexate, dactinomycin/cyclophosphamide, vincristine (EMA/CO) (McNeish 2002).

High-risk GTN

Women with high-risk GTN are at a higher risk of first-line treatment failure and therefore require multi-agent combination chemotherapy to achieve a cure. Various combinations are and have been used as first-line treatment of high-risk GTN, including:

- EMA/CO, as reported in Newlands 1986, whereby EMA and CO are given on alternate weeks, is the most widely used;

- MEA (methotrexate, etoposide, dactinomycin), is reported to have comparable success rates with relatively reduced toxicity (Dobson 2000; Matsui 2004);
- MAC or methotrexate, dactinomycin, chlorambucil (Curry 1989; Hammond 1973);
- FA (5-FU, dactinomycin) or FAV (5-FU, dactinomycin, vincristine) are commonly used regimens in China (Feng 2011; Zhao 2009);
- MEF (methotrexate, etoposide, 5-FU) (Wang 2006);
- EMA/EP (etoposide, methotrexate, dactinomycin/etoposide, cisplatin) whereby EMA and EP are alternated weekly (Cyriac 2011; Ghaemmaghami 2004);
- CHAMOCA (methotrexate, dactinomycin, cyclophosphamide, doxorubicin, melphalan, hydroxyurea, vincristine) (Bagshawe 1976) was found to be more toxic and less effective than MAC (Curry 1989) and has been superseded by EMA/CO.

PSTT and ETT are less chemo-sensitive than GTN owing to invasive mole or choriocarcinoma and more likely to relapse. The first-line treatment for these rare tumours is usually surgery (hysterectomy with pelvic lymph node sampling), with the administration of adjuvant chemotherapy to women with metastatic disease (Goldstein 2012; Seckl 2010).

Deng 2009 conducted a systematic review of chemotherapy for high-risk GTN and were unable to draw any firm conclusions about the best primary treatment regimen as only one small RCT was found (EMA/CO versus CHAMOCA; Curry 1989). EMA/CO is the most widely used primary combination therapy for high-risk GTN, however 30% to 40% of women will develop resistance or will relapse after remission and need salvage chemotherapy (Goldstein 2012; Lurain 2011). Salvage chemotherapy in high-risk GTN is a much more difficult clinical scenario than salvage chemotherapy in low-risk GTN. Risk factors for resistance to treatment in high-risk GTN include the number and sites of metastases (brain, liver and gastrointestinal metastases have a worse prognosis), incomplete previous treatments, and the age of the tumour (Kim 1998). Salvage therapy is more likely to fail in heavily pre-treated patients (Feng 2011; Theodore 1989; Wang 2008), hence hysterectomy and other adjuvant treatments play an important role in the management of these women. Several salvage regimens have been reported in the literature, mostly small case series (see Table 3), including:

- EMA/EP (Lurain 2005; Lu 2008; Mao 2007; Newlands 2000);
- BEP (bleomycin, etoposide, cisplatin) (Lurain 2005; Zhao 2009);
- VBP or PVB (cisplatin or carboplatin, vinblastine, bleomycin) (Azab 1989; Rodriguez 2010)
- VIP or ICE (ifosfamide, etoposide, cisplatin) (Lurain 2005);
- EP (etoposide, cisplatin) (Soper 1995; Theodore 1989);
- TP/TE (paclitaxel, cisplatin/paclitaxel, etoposide) whereby TP and TE are alternated weekly (Wang 2008);
- FAEV (floxuridine, dactinomycin, etoposide, vincristine) every 21 days (Feng 2011; Wan 2007).

Approximately 90% of high-risk patients treated initially with EMA/CO, followed by salvage therapy with a platinum-etoposide combination if required, will survive (Lurain 2010). In three series of EMA/EP salvage treatment following EMA/CO treatment failure, cure rates of 75% (nine out of 12 women; Newlands 2000) 66.6% (12 out of 18 women; Mao 2007) and 84.9% (11 out of 13 women; Lu 2008) were reported; however, EMA/EP was associated with significant myelosuppression and hepatotoxicity, leading to

treatment delays and dose reductions. Myelosuppression may be minimised by administering granulocyte-colony stimulating factor (G-CSF) (El-Helw 2005; Lurain 2005; Seckl 2010).

In another small series, the taxane-containing regimen, TP/TE, was found to be associated with comparable cure rates to EMA/EP (70% of 10 patients who had not been exposed to previous EP treatment were cured) but with relatively reduced toxicity and no dose delays or reductions (Wang 2008).

Regimens including 5-FU are favoured in some parts of China. In a study of 222 patients, FA was found to be effective as primary treatment for low- and high-risk GTN (with remission rates of 99% and 84%, respectively), except in patients with extensive metastases (Zhao 2009). FA has also been used as salvage therapy in a Japanese study in which it was shown to be a well-tolerated active regimen, resulting in an cure rate of eight of 10 patients (80%) at one year (Matsui 2002); however, two of these women subsequently relapsed and were cured with MEA.

BEP is favoured by Zhao 2009 as salvage therapy in FA-resistant GTN, citing greater convenience compared with EMA/CO, and reporting a remission rate of 80% (10 out of 12) in high-risk cases. One study of 91 women with resistant or relapsed high-risk GTN, who had been heavily pre-treated before commencing salvage therapy, reported a 60.4% cure rate and 75% three-year overall survival rate with FAEV (Feng 2011). Reported myelosuppression with this regimen was lower than those reported with EMA/EP and TP/TE.

Patient characteristics in these case series vary widely with regard to the type and number of previous regimens administered, risk scores and other factors (see Table 3), hence direct comparisons of these results do not provide good evidence of the relative effects of these treatments.

Why it is important to do this review

Several salvage chemotherapeutic regimens are used for treating resistant or recurrent GTN; however, it is not known which regimens are the most effective and the least toxic. Furthermore, other considerations relating to salvage chemotherapy, such as quality of life (QoL), cost and convenience, are important and require clarification. To our knowledge, there have been no other systematic reviews in this field.

OBJECTIVES

To assess the efficacy and safety of the various salvage chemotherapy regimens in the treatment of women with resistant or recurrent GTN.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs comparing different chemotherapy regimens following failed first-line treatment for GTN.

Types of participants

Women with GTN (staged and risk scored) who developed resistance (as defined by investigators, e.g. hCG plateau or decline

by less than 10% over three weeks or a rise in hCG or new metastases) to first-line chemotherapy or who relapsed after cure (as defined by investigators, e.g. normalisation of hCG levels, undetectable hCG or hCG less than 5 IU/L).

Types of interventions

Any chemotherapy regimen used to treat recurrent or resistant GTN in any dose, duration, combination or frequency.

For example, possible intervention comparisons for resistant or recurrent low-risk GTN would include:

1. pulsed dactinomycin versus five-day dactinomycin;
2. dactinomycin (pulsed or five-day) versus EA;
3. EA versus MAC or EMA/CO;
4. dactinomycin (pulsed or five-day) versus MAC or EMA/CO.

Possible intervention comparisons for resistant or recurrent high-risk GTN would include:

1. EMA/EP versus TP/TE;
2. EMA/EP versus BEP.

Types of outcome measures

Primary outcomes

- Remission/complete response (CR) rate.
- Treatment failure.
- Overall survival (OS).

Secondary outcomes

- Toxicity graded according to [CTCAE 2010](#), including: haematological (anaemia, neutropenia, abnormal liver function); gastrointestinal (pain, nausea, vomiting); genitourinary (vaginal bleeding); skin (stomatitis, mucositis, alopecia, allergy); neurological (peripheral and central) and respiratory (pain, shortness of breath, pleural effusion).
- Mean number of courses (time) to cure.
- Mean number of courses (time) to failure.
- QoL.
- Secondary cancers.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Gynaecological Cancer Group Specialised Register (October 2011), Cochrane Central Register of Controlled Trials (CENTRAL, Issue 4, 2011) ([Appendix 1](#)), MEDLINE (1950 to October week 3, 2011) ([Appendix 2](#)) and EMBASE (1980 to 2011, week 43) ([Appendix 3](#)). For this update we searched Cochrane Central Register of Controlled Trials (CENTRAL, Issue 10, 2015), MEDLINE (2011 to 2015, week 46) and EMBASE (2011 to 2015, week 46).

Searching other resources

We searched the following for ongoing trials: National Research Registry, National Cancer Institute (www.cancer.gov/), Metaregister of Controlled Trials (www.controlled-trials.com/mrct/), Medical Research Council Clinical Trial Directory (www.ctu.mrc.ac.uk/), Australian New Zealand Clinical Trial Registry (www.anzctr.org.au/).

We handsearched conference proceedings of the following societies: ISSTS, International Gynecological Cancer Society, European Gynaecological Cancer Society, Society of Gynecologic Oncologist, American Society of Clinical Oncology and British Gynaecological Cancer Society.

In addition, we searched the reference lists of relevant articles/reviews, and used the 'related articles' feature in PubMed, to identify additional articles. We sought expert opinion to identify relevant but unpublished studies.

Data collection and analysis

Selection of studies

Two review authors (MA and TL) sifted the search results and identified no RCTs to include in this review.

Data extraction and management

There were no data to extract for meta-analysis using [RevMan 2011](#) software. For future versions of this review, two review authors will independently extract data from new RCTs to a pre-designed data collection sheet. We will also record the following information:

- study methodology: description of randomisation, blinding, number of study centres, study duration, length of follow-up and number of study withdrawals;
- participants: number, mean age, mean risk score;
- intervention: type of intervention; dose and schedule;
- outcomes:
 - data will be extracted to allow intention-to-treat (ITT) analysis where possible;
 - for dichotomous outcomes (e.g. cure, adverse events and number of patients who relapsed or died), we will extract outcome rates to estimate a risk ratio (RR);
 - for continuous outcomes (e.g. QoL measures and duration of treatment) we will extract means and standard deviations (SD) to estimate a mean difference (MD);
 - for time-to-event outcomes (e.g. OS) we will extract the log of the hazard ratio [log(HR)] and its standard error from trial reports. If these are not reported, we will attempt to estimate the log (HR) and its standard error using Parmar's methods ([Palmer 1998](#)).

Assessment of risk of bias in included studies

Risk of bias in included RCTs in future versions of this review will be assessed using The Cochrane Collaboration's tool ([Higgins 2011](#)) and the following criteria:

1. selection bias: random sequence generation and allocation concealment;
2. performance bias: blinding of participants and personnel (patients and treatment providers);
3. detection bias: blinding of outcome assessment;
4. attrition bias: incomplete outcome data;
5. reporting bias: selective reporting of outcomes;
6. other possible sources of bias.

Subgroup analysis and investigation of heterogeneity

We had planned to subgroup data according to low- and high-risk groups. For future meta-analysis, random-effects models will be used (DerSimonian 1986) and we will perform sensitivity analyses to investigate the impact of bias or poor-quality trials on our results.

RESULTS

Description of studies

Our search identified no RCTs for classification.

Results of the search

Our electronic searches produced 1970 records after de-duplication (see Figure 1 for search flow diagram). Two review authors (MA and TL) sifted the search and identified no RCTs for evaluation. For the 2015 update an additional 274 records were identified, however, we did not find any studies eligible for inclusion.

Figure 1. Study flow diagram of search results.

Risk of bias in included studies

Not applicable as there were no included studies.

Effects of interventions

Not applicable as there were no included studies.

DISCUSSION

GTN is a highly chemosensitive disease with almost all low-risk lesions and 80% to 90% of high-risk lesions eventually attaining cure (Khan 2003; McNeish 2002). However, owing to its chemosensitivity and low prevalence in developed countries, very few RCTs have been conducted to evaluate and compare primary treatments, and no RCTs have been conducted to compare salvage treatments for GTN.

Low-risk GTN

From the limited available evidence, the most suitable first-line options for low-risk GTN appear to be methotrexate (five- and eight-day regimens) or pulsed dactinomycin; however, in China, 5-FU is considered highly effective (Song 1998). In one meta-analysis of four RCTs, bi-weekly pulsed dactinomycin was shown to be at least as effective and safe as methotrexate, although this evidence was downgraded from high to moderate quality as most of the included trials utilised the weekly low-dose methotrexate regimen (Alazzam 2012a). Bi-weekly pulsed dactinomycin may also have other benefits compared with methotrexate with regard to cost and convenience (Covens 2006). An ongoing trial of pulsed dactinomycin versus five- or eight-day methotrexate for first-line treatment in low-risk GTN should provide the vital 'missing' evidence (NCT01535053). However, administered alone, both interventions are considered to achieve primary remission

approximately 75% of the time ([McNeish 2002](#); [Osborne 2011](#)). This means that approximately 25% of women with low-risk GTN will require salvage treatment.

Women with GTN should be treated with the least toxic and most effective therapy ([Goldstein 2012](#)). However, no RCTs have been conducted to compare the various treatment options for salvage therapy, and non-RCTs are subject to differing selection criteria and other biases that render them incomparable. Sequential methotrexate/dactinomycin (MA) single-agent therapy is considered to be the least toxic route, as well as being highly effective. Indeed, this sequential treatment (usually with five-day dactinomycin) is considered as the 'initial' treatment (before multi-agent therapy) for low-risk GTN, achieving a cure in approximately 85% of cases ([Goldstein 2012](#)). Furthermore, one small phase II study found that, when methotrexate was the primary treatment and pulsed dactinomycin was used as salvage therapy, a cure rate of 94% was achieved ([Covens 2006](#)).

In RCTs comparing first-line MA for low-risk GTN, salvage therapy is often the comparison intervention (e.g. [Lertkhachonsuk 2009](#); [Yarandi 2008](#)). However, the optimal order of the single-agent sequence remains unclear. Since there may be additional benefits to administering bi-weekly pulsed dactinomycin as the primary treatment (followed by methotrexate as initial salvage therapy), not only with regard to efficacy and toxicity, but particularly with regard to cost and convenience, these sequential treatment options need further evaluation in a multicentre RCT.

If sequential single-agent therapy fails, multi-agent chemotherapy must be used to achieve a cure; this is necessary in 6% to 15% of cases ([Covens 2006](#); [Goldstein 2012](#)). The multi-agent therapy used most frequently at Charing Cross (one of two treatment centres in the UK) is EMA/CO. The New England Trophoblastic Disease Center (NETDC, USA) prefers to use MAC before EMA/CO owing to concerns that etoposide may be associated with an increased risk of secondary tumours ([Goldstein 2012](#)); this treatment strategy, with or without hysterectomy, has resulted in a 100% cure rate in low-risk GTN at NETDC between 1965 and 2010.

High-risk GTN

EMA/CO is the most widely used primary chemotherapy for high-risk GTN and is considered to have the best effectiveness to toxicity ratio. The less toxic MAC regimen is considered to be substantially less effective than EMA/CO in high-risk disease and is therefore not recommended ([May 2011](#)). 5-FU combination regimens (e.g. FA) are favoured in China, with excellent primary remission rates reported and FA resistance occurring mainly in cases with widespread metastases ([Zhao 2009](#)). In two studies of EMA/EP as first-line chemotherapy for high-risk GTN ([Ghaemmaghani 2004](#)) and very high-risk GTN (risk scores of 12 or more) ([Cyriac 2011](#)), EMA/EP was considered to compare favourably with EMA/CO, with remission rates of 88% and 67%, respectively. However, a high proportion of all high-risk patients will fail first-line therapy or will relapse after remission. Although high-risk GTN is less frequent than low-risk GTN, drug resistance and relapse in high-risk GTN is inherently much more difficult to treat.

[Lurain 2005](#) studied various combinations of drugs for salvage therapy and concluded that a platinum-etoposide component was essential. In a subsequent study, 36 out of 40 patients (90%) with high-risk metastatic disease who were treated initially with

EMA/CO, followed by salvage therapy with a platinum-etoposide combination if necessary, survived; the four patients who died all had risk scores of 12 or more ([Lurain 2010b](#)). Currently, the most commonly used salvage regimen in North America and the UK for the treatment of resistant or recurrent high-risk GTN is EMA/EP ([May 2011](#)) whereas BEP and 5-FU combination regimens appear to be favoured in China ([Feng 2011](#); [Zhao 2009](#)). TP/TE may be better tolerated than EMA/EP ([Wang 2008](#)) and it is understood that the ISSTD has an RCT planned, comparing these two salvage regimens. Comparisons of BEP versus EMA/EP would also be helpful. In addition, given that there is a wide discrepancy in chemotherapeutic practice between Western and Asian GTN treatment centres, comparisons between the commonly used regimens in these regions is desirable.

To our knowledge, there is currently no comparative data on the relative cost, convenience and QoL relating to any of the regimens in use.

AUTHORS' CONCLUSIONS

Implications for practice

Limited evidence from retrospective case series suggest that EMA/EP, BEP, TP/TE, FAEV and other combinations may all be effective as salvage therapy for recurrent or resistant GTN. However, reported efficacies and toxicities vary, as do patient characteristics in the various studies. Since no randomised comparative studies have been conducted, it is not possible to draw any conclusions with regard to these important outcomes, based on the available evidence. Current treatment protocols in use in various UK and US GTD treatment centres can be found in [Seckl 2010](#) and [Goldstein 2012](#), respectively.

Implications for research

Multicentre collaboration with centres in Asia, Latin America and Africa that experience a higher prevalence of this disease is required to produce the high-quality evidence needed in this field.

For low-risk GTN, [NCT01535053](#) is currently underway to determine whether the pulsed dactinomycin or five- or eight-day methotrexate regimen is the best primary treatment (see [Alazzam 2012a](#)). Trials such as these would benefit from a cross-over design, whereby, in the event of treatment failure, the alternative intervention is administered, with pre-specified outcomes. Furthermore, an RCT of pulsed dactinomycin versus five-day dactinomycin would be helpful to determine whether the more toxic five-day treatment is warranted in women with low-risk GTN that is resistant to methotrexate treatment.

For high-risk GTN, much work is needed to optimise treatment for these women. It is hoped that the proposed trial of EMA/PE versus TP/TE for salvage therapy is commenced soon and is able to provide the necessary high-quality evidence to guide clinical practice that is currently lacking in this field. Randomised comparisons of the floxuridine- or 5-FU-based regimens favoured in China with the EMA/EP regimen, following failed EMA/CO primary treatment, would be interesting.

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ADDITIONAL TABLES

Table 1. FIGO anatomical staging *

Stage I	Disease confined to the uterus
Stage II	GTN extends outside of the uterus, but is limited to the genital structures (adnexa, vagina, broad ligament)
Stage III	GTN extends to the lungs with or without known genital tract involvement
Stage IV	All other metastatic sites

*FIGO 2009.

Table 2. Modified WHO Prognostic Scoring System as adapted by FIGO for GTN

Scores	0	1	2	4
Age (years)	< 40	≥ 40	–	–
Antecedent pregnancy	mole	abortion	term	–
Interval months from index pregnancy	< 4	4 to 6	7 to 12	> 12
Pre-treatment serum hCG (IU/L)	< 10 ³	10 ³ –10 ⁴	10 ⁴ to 10 ⁵	> 10 ⁵
Largest tumour size (including uterus)	< 3	3 to 4 cm	≥ 5 cm	–
Site of metastases	lung	spleen, kidney	gastrointestinal	liver, brain
Number of metastases	–	1 to 4	5 to 8	> 8
Previous failed chemotherapy	–	–	single drug	≥ 2 drugs

To stage and allot a risk factor score, a patient's diagnosis is allocated to a stage as represented by a Roman numeral I, II, III and IV. This is then separated by a colon from the sum of all the actual risk factor scores expressed in Arabic numerals, i.e. stage II:4, stage IV:9. This stage and score will be allotted for each patient (FIGO 2009). A score ≤ 6 indicates low risk; > 6 indicates high risk.

Table 3. Retrospective studies of salvage chemotherapy for resistant or recurrent GTN

Study	Dates	Participants	Characteristics	Primary treatment	Salvage treatment	Complete response	Severe adverse effects (≥ G3)	Investigators' conclusions
Theodore 1989	1977 to 1985	22 women	Drug-resistant high-risk GTN (14 women; WHO scores ≥ 8). Also included 8 women who underwent primary treatment for high-risk GTN	Methotrexate/vincaloid with or without sequential dactinomycin (12/14 women)	EP with dactinomycin (APE; 8) or without (EP; 6) every 4 weeks	CR = 13/14 (93%) and 11/14 were cured (79%; defined as CR sustained for 12 months). 1 woman died	Data for the drug-resistant group could not be separated. Leukopenia 11/22 (50%); thrombocytopenia 8/22 (36%); alopecia 22/22 (100%); sepsis 3/22 (14%); renal 4/22 (18%); nausea and vomiting 6/22 (27%). SAEs were more likely to occur with the APE than with the EP regimen	APE/PE regimens compare favourably with other regimens such as MAC and EMA/CO
Azab 1989	1977 to 1985	8 women	Drug resistant high-risk GTN (WHO score > 11)	Methotrexate/vincristine alternated with vincristine/dactinomycin weekly (6/8 women)	PVB (every 21 days)	CR = 6/8 (75%; including 2 women who had a partial response initially but a CR following hysterectomy). 1 woman relapsed and 5/8 were cured	All toxicities were grade 1/2	PVB is a well-tolerated regimen. Hysterectomy plays an important role in the treatment of drug resistant GTN
Soper 1995	1984 to 1992	7 women	Median WHO score = 16 (range 10 to 20). Heavily pre-treated women	Not reported in detail. Various regimens of which 6/7 included etoposide	EP (days 1 to 5; 14 to 21 day cycles)	CR = 6/7 (86%) but only 3/7 had sustained remissions, and 4 died within 18 months	Neutropenia = 5/7 (71%); neutropenic sepsis = 4/7 (57%); thrombocytopenia = 2/7 (29%); renal toxicity = 2/7 (29%)	EP therapy is an active salvage regimen for GTN but has significant haematological and renal toxicity
Newlands 2000	1980 to 1997	42 women	34/42 women had relapsed/resistant high-risk GTN; 8 women had PSTT. 22/34 relapsed/resistant women had hCG levels approaching normal	EMA/CO	EMA/EP	The 22 women with low levels of hCG could not be assessed for response. Of the remaining 12 relapsed/resistant women, CR =	Neutropenia (68%); anaemia (21%); thrombocytopenia (40%). (These data may include data from women with PSTT.) Myelosuppression caused delays in chemotherapy in 88%	EMA/EP is an effective regimen for relapsed/resistant high-risk GTN (with surgery in selected cases) but toxicity is significant

Table 3. Retrospective studies of salvage chemotherapy for resistant or recurrent GTN (Continued)

						9/12 (75%). OS = 30/34 (88%)	of patients and dose reductions in 38%	
Matsui 2002	1985 to 2001	10 women	7 women had resistant high-risk GTN and 3 women had relapsed after treatment	EMA/CO (2) and MEA (8)	FA	OS = 8/10 (80%). Mean follow-up of 11.5 years. 2 patients died of multidrug resistance and 2 relapsed subsequently and were treated successfully with MEA	Neutropenia (6.4% of cycles) and thrombocytopenia (3.8% of cycles)	FA is an effective and well-tolerated salvage therapy
Xiang 2004	Unclear	15 women	12 women had resistant high-risk GTN and 3 had PSTT	Unclear	EMA/EP	CR = 11/15 (73.3%)	Myelosuppression and gastrointestinal SAEs	EMA/EP is an effective salvage therapy for chemo-refractory GTN
Lurain 2005	1980 to 2001	26 women	Relapsed or resistant high-risk GTN	EMA/CO (10). MA-based without E (16)	All salvage treatment contained E + P. BEP (19), EMA/EP (3), VIP/ICE (3), PVB. Repeated every 21 days	CR = 73%; OS = 61.5%	Not reported	BEP is first choice for high-risk patients with drug resistance or relapse following treatment with EMA/CO and EMA/EP. This regimen resulted in a 74% CR and 58% OS in this study
Wang 2006	1992 to 2003	26 women	9 women had relapsed or resistant high-risk GTN. Also included 17 women undergoing primary treatment. Risk score range was 7 to 12	MA (4); MEA (2); MAC (1); EMA/CO (2)	MEF	CR = 7/9 (78%); OS = 8/9 (96%) at mean follow-up of 37 months (range 14 to 124 months)	1 death occurred owing to multi-drug resistant GTN. Toxicity data could not be separated (reported as % of 167 cycles): neutropenia (26.4%); nausea/vomiting (39%); thrombocytopenia (5.6%). G-CSF given as necessary	MEF is a well-tolerated, less-toxic regimen that is effective as salvage therapy
Mao 2007	1999 to 2005	18 women	11 women had resistant high-risk GTN and 7 women	EMA/CO	EMA/EP	CR = 12/18 (66.6%) including 9/11 (82%) resistant patients	Neutropenia (28% of cycles); nausea/vomiting 15% of cycles). Myelosuppression and	EMA/EP was more effective in patients with drug resistance than those who have re-

Table 3. Retrospective studies of salvage chemotherapy for resistant or recurrent GTN (Continued)

			had relapsed after treatment			and 3/7 (43%) re-lapsed patients	hepatotoxicity led to dose reductions and delays in 43% of cycles despite the use of G-CSF as necessary	lapsed after treatment with EMA/CO. Toxicity caused treatment delays that might have been prevented with prophylactic G-CSF
Wan 2007	2001 to 2004	11 women	Resistant high-risk GTN with median risk score of 9 (range 7 to 13)	Various	FAEV	CR = 7/11 (63.6%)	Myelosuppression was treated with G-CSF in 98.4% of courses	FAEV could be an effective treatment for drug-resistant GTN
Lu 2008	1996 to 2005	13 women	10 woman had resistant high-risk GTN and 3 women had relapsed after treatment	EMA/CO	EMA/EP	CR = 11/13 (84.6%); 5 patients had adjuvant surgery/brain irradiation	Not reported	EMA/EP is a highly effective salvage therapy for those patients failing EMA/CO treatment
Wang 2008	1999 to 2006	24 women	Group A: 16 women with relapsed/resistant GTN (9 high-risk, 5 low-risk and 2 PSTT) Group B: 8 women switched owing to toxicity on previous regimen (4 high-risk, 1 low-risk and 3 PSTT). 10/24 women (42%) had received 2 or more previous chemotherapy regimens	Group A: EMA/CO or EMA/EP, or both (5) or BEP (1) Group B: EMA/EP (5), EMA/CO (2), EMA/EP + EMA/CO (1)	TP/TE	Group A: CR = 3/16 (19%); OS = 7/16 (44%; median follow up of 25 months) Group B: CR = 2/4 assessable (50%); OS = 6/8 (75%; at median of 19 months follow up)	Neutropenia = 10/24 (42%); neuropathy = 1/24 (4%); thrombocytopenia = 3/24 (13%). Treatment discontinued in 1 patient owing to neuropathy (grade 2). No dose reductions or delays	TP/TE was more likely to fail if previous chemotherapy had included a platinum agent. Out of 10 patients who had not previously received EMA/EP, 7/10 survived (70%). TP/TE is relatively less toxic than EMA/EP
Zhao 2009	1995 to 2007	12 women	High-risk drug-resistant GTN	FA	BEP	CR = 10/12 (83%)	Not reported	BEP is more convenient than EMA/CO and is well tolerated
Feng 2011	2005 to 2008	91 women	80/91 women had relapsed or resistant high-risk GTN; 11/91 had relapsed or resistant	Mainly FAV (60), EMA/CO (29) and 5-FU (22) but sever-	FAEV	CR = 55/91 (60.4%); NR = 29/91 (31.9%)	Neutropenia 24/91 (26.4%); febrile neutropenia 6/91 (6.6%); thrombocytopenia 3/91 (3.3%). 7/91	FAEV is an effective salvage regimen in this cohort of heavily pre-treated patients. It is more convenient (21-

Table 3. Retrospective studies of salvage chemotherapy for resistant or recurrent GTN (Continued)

			low-risk GTN. 63/91 women (69.1%) had received 2 or more previous chemotherapy regimens	al other regimens administered		OS at 3 years = 74.9%	(7.7%) discontinued FAEV owing to toxicity. No neutropenic sepsis or treatment-related deaths	day cycle) and less toxic than other regimens
Manopunya 2012	2009 to 2011	5 women	Heavily pre-treated high-risk women (≥ 3 previous regimens; risk scores of 9, 10, 17, 17 and 18)	Various including EMA, EMA/CO, ICE, VAC, EMA/EP, TP/TE, PT, PI	FA	CR = 1/5 (20%)	Neutropenia 3/12 cycles (25%); diarrhoea 1/12 cycles (8%); mucositis 8/12 cycles (67%)	FA had modest efficacy with tolerable side effects in this group of heavily pre-treated patients

5-FU: 5-fluorouracil; APE: etoposide, cisplatin, dactinomycin; BEP: bleomycin, etoposide, cisplatin; CR: complete response; E: etoposide; EMA: etoposide, methotrexate, dactinomycin; EMA/CO: etoposide, methotrexate, dactinomycin/cyclophosphamide, vincristine; EMA/EP: etoposide, methotrexate, dactinomycin/etoposide, cisplatin; EP: etoposide, cisplatin; FA: 5-fluorouracil, dactinomycin; FAEV: floxuridine, dactinomycin, etoposide, vincristine; FAV: 5-fluorouracil, dactinomycin, vincristine; G-CSF: granulocyte colony stimulating factor; GTN: gestational trophoblastic neoplasia; hCG: human chorionic gonadotrophin; MA: methotrexate, dactinomycin; MAC: methotrexate, dactinomycin, cyclophosphamide; MEA: methotrexate, etoposide, dactinomycin; MEF: methotrexate, etoposide, 5-fluorouracil; NR: no response; OS: overall survival; PI: cisplatin, ifosfamide; PSTT: placental site trophoblastic tumour; PT: carboplatin, paclitaxel; PVB: cisplatin, vinblastine, bleomycin; SAE: severe adverse effects; TP/TE: paclitaxel, cisplatin/paclitaxel, etoposide; VAC: vincristine, actinomycin, cyclophosphamide; VIP/ICE: ifosfamide, etoposide, cisplatin; WHO: World Health Organization.

APPENDICES

Appendix 1. CENTRAL search strategy

- #1 MeSH descriptor Trophoblastic Neoplasms explode all trees
- #2 invasive mole*
- #3 hydat* mole*
- #4 choriocarcinoma*
- #5 gestational trophoblastic and (tumo* or disease* or neoplas*)
- #6 persistent trophoblastic disease*
- #7 (#1 OR #2 OR #3 OR #4 OR #5 OR #6)
- #8 Any MeSH descriptor with qualifier: DT
- #9 MeSH descriptor Antineoplastic Agents explode all trees
- #10 MeSH descriptor Antineoplastic Combined Chemotherapy Protocols explode all trees
- #11 chemo*
- #12 antineoplastic agent*
- #13 methotrexate
- #14 dactinomycin
- #15 etoposide
- #16 cyclophosphamide
- #17 cisplatin
- #18 vincristine
- #19 chlorambucil
- #20 doxorubicin
- #21 melphalan
- #22 hydroxyurea
- #23 CHAMOCA
- #24 EMA-CO
- #25 MAC
- #26 EMA
- #27 VPB
- #28 EMACE
- #29 5-fluorouracil or 5-fu
- #30 EPEMA
- #31 BEP
- #32 ICE
- #33 ifosfamide
- #34 TP-TE
- #35 (#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34)
- #36 (#7 AND #35)

Appendix 2. MEDLINE search strategy

- 1 exp Trophoblastic Neoplasms/
- 2 invasive mole*.mp.
- 3 hydat* mole*.mp.
- 4 choriocarcinoma*.mp.
- 5 (gestational trophoblastic and (tumo* or disease* or neoplas*)).mp.
- 6 persistent trophoblastic disease*.mp.
- 7 1 or 2 or 3 or 4 or 5 or 6
- 8 drug therapy.fs.
- 9 exp Antineoplastic Agents/
- 10 exp Antineoplastic Combined Chemotherapy Protocols/
- 11 chemo*.mp.
- 12 antineoplastic agent*.mp.
- 13 methotrexate.mp.
- 14 dactinomycin.mp.
- 15 etoposide.mp.
- 16 cyclophosphamide.mp.

17 cisplatin.mp.
 18 vincristine.mp.
 19 chlorambucil.mp.
 20 doxorubicin.mp.
 21 melphalan.mp.
 22 hydroxyurea.mp.
 23 CHAMOCA.mp.
 24 EMA-CO.mp.
 25 MAC.mp.
 26 EMA.mp.
 27 VPB.mp.
 28 EMACE.mp.
 29 (5-fluorouracil or 5-fu).mp.
 30 EPEMA.mp.
 31 BEP.mp.
 32 ICE.mp.
 33 Ifosfamide.mp.
 34 TP-TE.mp.
 35 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
 or 32 or 33 or 34
 36 randomized controlled trial.pt.
 37 controlled clinical trial.pt.
 38 randomized.ab.
 39 placebo.ab.
 40 drug therapy.fs.
 41 randomly.ab.
 42 trial.ab.
 43 groups.ab.
 44 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43
 45 7 and 35 and 44
 46 (animals not (humans and animals)).sh.
 47 45 not 46

key:

mp=title, original title, abstract, name of substance word, subject heading word, unique identifier

pt=publication type

ab=abstract

sh=subject heading

Appendix 3. EMBASE search strategy

1 exp trophoblastic tumor/
 2 invasive mole*.mp.
 3 hydat* mole*.mp.
 4 choriocarcinoma*.mp.
 5 (gestational trophoblastic and (tumo* or disease* or neoplas*)).mp.
 6 persistent trophoblastic disease*.mp.
 7 1 or 2 or 3 or 4 or 5 or 6
 8 dt.fs.
 9 exp antineoplastic agent/
 10 exp chemotherapy/
 11 chemo*.mp.
 12 antineoplastic agent*.mp.
 13 methotrexate.mp.
 14 dactinomycin.mp.
 15 etoposide.mp.
 16 cyclophosphamide.mp.
 17 cisplatin.mp.
 18 vincristine.mp.
 19 chlorambucil.mp.
 20 doxorubicin.mp.
 21 melphalan.mp.

22 hydroxyurea.mp.
 23 CHAMOCA.mp.
 24 EMA-CO.mp.
 25 MAC.mp.
 26 EMA.mp.
 27 VPB.mp.
 28 EMACE.mp.
 29 (5-fluorouracil or 5-fu).mp.
 30 EPEMA.mp.
 31 BEP.mp.
 32 ICE.mp.
 33 ifosfamide.mp.
 34 TP-TE.mp.
 35 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31
 or 32 or 33 or 34
 36 7 and 35
 37 random*.mp.
 38 factorial*.mp.
 39 (crossover* or cross over* or cross-over*).mp.40 placebo*.mp.
 41 (doubl* adj blind*).mp.
 42 (singl* adj blind*).mp.
 43 assign*.mp.
 44 allocat*.mp.
 45 volunteer*.mp.
 46 crossover procedure/
 47 double blind procedure/
 48 randomized controlled trial/
 49 single blind procedure/
 50 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49
 51 36 and 50

key:

mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer

WHAT'S NEW

Date	Event	Description
30 September 2019	Review declared as stable	Most recent search 19 August 2019. No potentially relevant new studies identified. The conclusions of this Cochrane Review are therefore still considered up to date for this topic. No new studies expected in this topic area.

HISTORY

Protocol first published: Issue 12, 2010

Review first published: Issue 12, 2012

Date	Event	Description
1 April 2015	Amended	Contact details updated.
11 February 2015	Amended	Contact details updated.
27 March 2014	Amended	Contact details updated.

CONTRIBUTIONS OF AUTHORS

MA conceived the idea, registered the title and wrote the first draft of the protocol. JT helped to write the protocol. MA and TL wrote the first draft of the review. BH, RO and RC critically appraised the manuscript. All the authors approved the final draft.

DECLARATIONS OF INTEREST

All the authors have no interest to declare.

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- No sources of support supplied

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- National Institute for Health Research (NIHR), UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

None.

INDEX TERMS

Medical Subject Headings (MeSH)

*Drug Resistance, Neoplasm; Gestational Trophoblastic Disease [*drug therapy]; Neoplasm Recurrence, Local [*drug therapy]

MeSH check words

Female; Humans; Pregnancy