GESTATIONAL TROPHOBLASTIC NEOPLASIA

Executive Summary

Gestational trophoblastic neoplasms (GTN) are malignant lesions that arise from placental villous and extra-villous trophoblast.[1-6] GTN occurs in 1:40,000 pregnancies and is more common in Asia than in Europe or North America.[6] Four clinicopathologic conditions make up this entity: 1) invasive mole (IM) that follows either a complete (CHM) or partial hydatidiform mole (PHM), 2) choriocarcinoma (CCA), 3) placental site trophoblastic tumor (PSTT) and 4) epithelioid trophoblastic tumor (ETT). Each of these conditions can perforate the uterine wall, metastasize and lead to death if left untreated. Approximately 50% of cases of GTN arise from molar pregnancy, 25% from miscarriage or tubal pregnancy, and 25% from term or preterm pregnancy. Invasive mole and choriocarcinoma, which make up the vast majority of these tumors, always produce substantial amounts of human chorionic gonadotropin (hCG) and are highly responsive to chemotherapy with an overall cure rate exceeding 90%, making it usually possible to achieve cure while preserving fertility.[1] This success is due to the unique sensitivity of these two trophoblastic neoplasms to chemotherapy and the use of hCG as a tumor marker for diagnosis, monitoring treatment and follow-up. In contrast, PSTT and ETT, which rarely occur, produce scant amounts of hCG and are relatively resistant to chemotherapy. [6]

In 2002, FIGO adopted a combined anatomic staging and modified WHO risk-factor scoring system (Tables I and II) for GTN. Treatment is based on the total score which signifies the risk of the patient developing single-agent drug resistance . Patients with non-metastatic disease (Stage I) and low-risk metastatic GTN (Stages II and III, score <7) can be treated initially with single-agent chemotherapy with either methotrexate or actinomycin D (Table III) with cure rates approaching 80-90%. Patients classified as having high-risk metastatic disease (stage IV and stages II-III with scores >6) require multiagent chemotherapy preferably with the EMA-CO regimen(Table IV), possibly with adjuvant radiation and/or surgery to achieve similar cure rates.[3] There is growing evidence that patients with low-risk GTN and prognostic scores of 5 or 6 are at increased risk of initial single-agent drug resistance and may require multiagent chemotherapy.[6] The use of the FIGO staging/scoring system has become the accepted basis for determining the optimal initial therapy that achieves the best outcome with the least morbidity.

Public Health Relevance

Global epidemiological data pertaining to gestational trophoblastic neoplasia (GTN) is limited. GTN is included in the group of pregnancy-related disorders that constitute gestational trophoblastic disease (GTD).[8] More specifically, GTN encompasses invasive moles, choriocarcinoma, and placental-site trophoblastic tumors. Epidemiological characteristics of

GTD and GTN are difficult to determine due to the rarity of the conditions, inconsistencies in case definitions, and lack of centralized databases.[8]

Certain studies have suggested a higher incidence of GTD in Asia than in North America or Europe. A review published in the *American Journal of Obstetrics and Gynecology* in 2010 indicates that choriocarinoma, a subset of GTN, affects 1 in 40,000 pregnancies in Europe and North America versus 9.2 in 40,000 pregnancies in Southeast Asia and Japan.[8] A seminar in *The Lancet* in 2010 estimated choriocarcinoma to occur in 1 in 50,000 deliveries in the UK.[9] The same seminar found that placental-site trophoblastic tumor accounted for about 0.2% of cases of gestational trophoblastic disease in the UK in 2010.

Requirements for diagnosis, treatment, and monitoring

Diagnostics:

1) Pathology laboratory analysis of surgically excised specimens.
2) Clinical laboratory facilities to perform routine hematological and chemical analyses required for monitoring the effects of chemotherapy.
3) Facilities for performing radioimmunoassay of hCG which serves as a tumor marker for GTN. The measurement of hCG is based on a radioimmunoassay and requires the use of a laboratory equipped with automated equipment and reagents designed for radioimmunoassay procedures and trained technicians. The serial quantitative measurement of hCG is essential for the diagnosis, monitoring the efficacy of treatment, and follow-up of patients with GTN. After evacuation of a molar pregnancy, hCG levels usually disappear in 8 to 10 weeks. After normal delivery or miscarriage, hCG levels become undetectable within 3-6 weeks. Persistence of hCG levels indicate local or metastatic disease, which allows for early detection and timely intervention. During treatment, hCG response is used as a guide to determine whether to continue treatment with an agent or switch to another agent. hCG monitoring after treatment allows for identification of patients who relapse and require additional therapy.

Testing: Once it is determined that a patient has an elevated and rising hCG level, a thorough evaluation is required to determine the extent of disease, including blood tests to assess renal and hepatic function, peripheral blood counts, and baseline serum hCG levels. A speculum examination should be performed to identify vaginal metastases, which may cause heavy bleeding. Radiologic evaluation should include a pelvic ultrasound , both to look for retained trophoblastic tissue and to evaluate local spread. Chest imaging is also required as the lungs are the most common site of metastases. In the absence of pulmonary and vaginal involvement, brain and liver metastases are rare and further radiologic testing may not be needed. However, magnetic resonance imaging of the brain with contrast is important in women with metastases and in all patients with a pathologic diagnosis of CCA. It is usually not necessary to obtain an histologic diagnosis because of the high vascularity of the tumor and the risk of hemorrhage.

Administration and care of patients: Administration requires intravenous infusion capacity, and requires the patient to have regular access to clinical care. Methotrexate can be administered

either intramuscularly or intravenously. Actinomycin D requires careful administration through a freely running infusion. All other chemotherapeutic agents are also administered intravenously. IV hydration and anti-emetics should accompany administration of most agents.

Monitoring requires that clinicians have access to laboratory facilities, as well as the ability to recognize and address potential toxicities caused by the treatment itself, including but not limited to bone marrow suppression, infection, allergic reactions, and gastrointestinal toxicity.

hCG Follow-Up and Relapse-All patients with GTN are followed with weekly hCG values until undetectable for 3 consecutive weeks, and then monthly until undetectable for 12 months. All patients must be encouraged to use effective contraception during the entire interval of monitoring. Relapse rates range from 3 to 9 percent for stages I to IV and the mean time to recurrence from the last non-detectable hCG level was 6 months.[3]

Subsequent Pregnancy after Treatment for GTN-Patients with GTN treated successfully with chemotherapy can expect normal future reproductive function with no increased risk of congenital anomalies.[3]

Psychosocial Issues-Women with GTN can experience significant mood disturbance, marital and sexual problems, and concerns over future fertility. Patients may therefore need emotional support and counseling during and after treatment.

Overview of Regimens

Standard Regimens

Table III. Single-Agent Regimens for Low-Risk Gestational Trophoblastic Neoplasms

MTX regimens	Primary Remission Rates(%)
1) MTX: 0.4-0.5 mg/kg IV or IM daily for 5 days	87-93
2) MTX: 30-50 mg/m^2 IM weekly	49-74
3) MTX-Leucovorin MTX 1 mg/kg IM or IV on days 1,3,5,7 Leucovorin 15 mg PO days 2,4,6,8	74-90
4) High dose IV MTX/FA MTX 100 mg/m^2 IV bolus MTX 200 mg/m^2 12 hr infusion Leucovorin 15 mg q 12hr in 4 doses IM or PO beginning 24 hr after starting MTX.	69-90

Actinomycin D regimens (Vesicant-If administered peripherally, give through free flowing IV)

ActD 10-12 mcg/kg IV push daily for 5 days	77-94
Act D 1.25 mg/m^2 IV push q 2 wks	69-90

MTX, methotrexate; ActD, actinomycin D; Leucovorin (a.k.a. folinic acid, calcium folinate)
IV, intravenous; IM, intramuscular; PO, by mouth

Table IV. EMA/CO Regimen for resistant Low-Risk GTN or as Primary therapy for High-Risk GTN

Day	Drug	Dose
1	Etoposide	100 mg/m^2 by infusion in 200 ml NS over 30 min
	ActD	0.5 mg IVP
	MTX	100 mg/m^2 IVP 200 mg/m^2 by infusion over 12 hr
2	Etoposide	100 mg/m^2 by infusion in 200 ml NS over 30 min
	ActD	0.5 mg IVP
	Leucovorin	15 mg q 12 hr x 4 doses IM or PO beginning 24 hr after starting MTX
8	Cyclophosphamide	600 mg/m^2 by infusion in NS over 30 min
	Vincristine	1 mg/m^2 IV

Review of Benefits and Harms

Benefits
GTN affects women in the reproductive age group. It is a highly curable malignancy. Chemotherapy is associated with cure rates >90% even in patients with widespread metastases. Furthermore, the efficacy of chemotherapy has made it possible for the vast majority of patients to preserve fertility.

Harms and Toxicity Considerations

Common

Chemotherapy regimens for GTN are associated with well-recognized toxicities including bone marrow suppression, increased risk of infection, hair loss, stomatitis, nausea and vomiting, neuropathy, and alterations in hepatic and renal function.

Specifically, dactinomycin is a highly emetogenic agent requiring prophylaxis with antiemetic regimens to reduce severity of nausea and vomiting. Patients treated with dactinomycin also commonly suffer reversible alopecia. Methotrexate regimens are associated with a higher incidence of diarrhea and stomatitis. [7]

The EMA/CO regimen can cause predictable and generally easily manageable adverse effects including reversible alopecia and myelosuppression, occasionally including severe neutropenia and anemia [4,6,7]

Serious

The use of etoposide in this patient population has also been associated with a small but increased risk of secondary cancers in <2% of patients, particularly leukemia.[5,7]

Systematic Reviews

Alazzam M, Tidy JA, Hancock BW, Osborne R. First line chemotherapy in low risk gestational trophoblastic neoplasia. Cochrane Database Syst Rev 2009; 1:CD007102.

Background: This is an update of a Cochrane review that was first published in Issue 1, 2009. Gestational trophoblastic neoplasia (GTN) is a rare but curable disease arising in the fetal chorion during pregnancy. Most women with low-risk GTN will be cured by evacuation of the uterus with or without single-agent chemotherapy. However, chemotherapy regimens vary between treatment centres worldwide and the comparable benefits and risks of these different regimens are unclear. **Objectives:** To determine the efficacy and safety of first-line chemotherapy in the treatment of low-risk GTN. **Search Methods:** In September 2008, we electronically searched the Cochrane Gynaecological Cancer Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL Issue 3, 2008), MEDLINE and EMBASE. In addition, we searched online trial registers, conference proceedings and reference lists of identified studies. We re-ran these searches in February 2012 for this updated review. **Selection Criteria:** For the original review, we included randomised controlled trials (RCTs), quasi-RCTs and non-RCTs that compared first-linechemotherapy for the treatment of low-risk GTN. For this updated version of the review, we included only RCTs. **Data Collection and Analysis:** Two review authors independently assessed studies for inclusion and extracted data to a pre-designed data extraction form. Meta-analysis was performed by pooling the risk ratio (RR) of individual trials. **Main Results:** We included five moderate to high quality RCTs (517 women) in the updated review. These studies all compared methotrexate with dactinomycin. Three studies compared weekly intramuscular (IM) methotrexate with bi-weekly pulsed intravenous (IV) dactinomycin (393 women), one study compared five-day IM methotrexate

with bi-weekly pulsed IV dactinomycin (75 women) and one study compared eight-day IM methotrexate-leucovorin (MTX-FA) with five-day IV dactinomycin (49 women).Overall, dactinomycin was associated with significantly higher rates of primary cure than methotrexate (five studies, 513 women; RR 0.64, 95% Confidence Interval (CI) 0.54 to 0.76). Methotrexate was associated with significantly more treatment failure than dactinomycin (five studies, 513 women; RR 3.81, 95% CI 1.64 to 8.86). We consider this evidence to be of a moderate quality. There was no significant difference between the two groups with respect to nausea (four studies, 466 women; RR 0.61, 95% CI 0.29 to 1.26) or any of the other individual side-effects reported, although data for all of these outcomes were insufficient and too heterogeneous to be conclusive. No severe adverse effects (SAEs) occurred in either group in three out of the five included studies and there was no significant difference in SAEs between the groups overall (five studies, 515 women; RR 0.35, 95% CI 0.08 to 1.66; $I^2 = 60\%$), however, there was a trend towards fewer SAEs in the methotrexate group. We considered this evidence to be of a low quality due to substantial heterogeneity and low consistency in the occurrence/reporting of SAEs between trials. **Authors' Conclusions:** Dactinomycin is more likely to achieve a primary cure in women with low-risk GTN, and less likely to result in treatment failure, compared with methotrexate. There is limited evidence relating to side-effects, however, the pulsed dactinomycin regimen does not appear to be associated with significantly more side-effects than the low-dose methotrexate regimen and therefore should compare favourably to the five- and eight-day methotrexate regimens in this regard.We consider pulsed dactinomycin to have a better cure rate than, and a side-effect profile at least equivalent to, methotrexate when used for first-line treatment of low-risk GTN. Data from a large ongoing trial of pulsed dactinomycin compared with five- and eight-day methotrexate regimens is likely to have an important impact on our confidence in these findings.

Alazzam M, Tidy J,Osborne R, et al. Chemotherapy for resistant or recurrent gestational trophoblastic neoplasia. Cochrane Database Syst Rev, 2012;12: CD008891.

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. **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.

Recommendations

The reviewers recommend the incorporation of GTN cancer treatment options into the WHO Model List of Essential Medicines. Drugs for all regimens are already included in the 2013 List.

Additions proposed for Section 8.2 of the EML

None.

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Table I: FIGO Staging of GTN

Stage I	Disease localized to uterus
Stage II	Disease localized to the pelvis and adnexa
Stage III	Pulmonary metastases
Stage IV	Distant organ involvement(i.e., liver, brain, kidney, GI tract, spleen, etc.)

TABLE II: **Modified WHO Prognostic Scoring System**

	Score			
Prognostic Factors	**0**	**1**	**2**	**4**
Age (yrs)	<40	>39	-	-
Antecedent pregnancy	Mole	Abortion	Term	-
Interval(months)*	<4	>3, <7	>6, <13	>12
Pretreatment serum hCG(mIU/ml)	$<10^3$	10^3 to$<10^4$	10^4 to $<10^5$	$>10^5$
Largest tumor, including uterine(cm)	-	3 to <5	>4	
Site of metastases	Lung	Spleen GI tract Kidney		Brain Liver
Number of metastases	-	1-4	5-8	>8
Prior failed Chemotherapy	-	-	Single drug	Two drugs