Gestational trophoblastic neoplasia (GTN) – EML

The application sought specific endorsement of the following medicines, currently included on the complementary list of the Model List of Essential Medicines, for the treatment of gestational trophoblastic neoplasia: methotrexate, calcium folinate, dactinomycin, etoposide, cyclophosphamide and vincristine.

The application, amended to include details of the Expert Committee's considerations and decision, is presented in this section.

Introduction

Gestational trophoblastic disease (GTD) is a range of pregnancy-related premalignant and malignant disorders; the malignant forms are termed gestational trophoblastic neoplasia (GTN). The most common form of this disease is the hydatidiform mole, which occurs in 1–3 of every 1000 pregnancies and more frequently in Asia than in Europe or North America *(1)*. Five clinicopathological forms make up this entity. Hydatidiform mole – partial or complete – is the benign form. About 10% of hydatidiform moles transform into one of the malignant forms: invasive hydatidiform mole (IHM), choriocarcinoma (CCA), placental site trophoblastic tumour (PSTT) and epithelioid trophoblastic tumour (ETT) *(2)*. 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 tumours, always produce substantial amounts of human chorionic gonadotropin (hCG) and are highly responsive to chemotherapy; overall cure rate exceeds 90% and it is usually possible to preserve fertility while achieving cure *(3)*. This success is due to the unique sensitivity of these two trophoblastic neoplasms to chemotherapy and the use of hCG as a tumour marker for diagnosis, monitoring treatment and follow-up. In contrast, PSTT and ETT, which occur only rarely, produce scant amounts of hCG and are relatively resistant to chemotherapy *(1)*.

In 2002, the International Federation of Gynecology and Obstetrics adopted a combined anatomical staging and modified WHO risk-factor scoring system for GTN (see Tables 7 and 8). 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 – either methotrexate or dactinomycin – with cure rates approaching 80–90%. Patients classified as having high-risk metastatic disease (stage IV, and stages II–III with scores >6) require a multidrug chemotherapy regimen, preferably with etoposide, methotrexate dactinomycin, cyclophosphamide, and vincristine (EMA/CO), possibly with adjuvant radiation and/or surgery to achieve similar cure rates *(4)*. 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 multi-agent chemotherapy *(1)*.

The use of the FIGO staging/scoring system has become the accepted basis for determining the optimal initial therapy, achieving the best outcome with the least morbidity.

Table 7
FIGO staging of GTN

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

Table 8
Modified WHO prognostic scoring system

Prognostic factor	Score			
	0	1	2	4
Age (years)	< 40	≥40	–	–
Antecedent pregnancy	Mole	Abortion	Term	–
Interval months from index pregnancy	< 4	4–6	7–12	> 12
Pretreatment serum hCG (IU/L)	< 10^3	10^3–10^4	10^4–10^5	> 10^5
Largest tumour size (including uterus)	< 3 cm	3–4 cm	≥5 cm	–
Site of metastases	Lung	Spleen, kidney	Gastrointestinal	Liver, brain
Number of metastases	–	1–4	5–8	> 8
Previous failed chemotherapy	–	–	Single drug	≥ 2 drugs

Public health relevance

Global epidemiological data pertaining to gestational trophoblastic neoplasia are limited. Epidemiological characteristics of GTD and GTN are difficult to determine because of the rarity of the conditions, the inconsistencies in case definitions, and the lack of centralized databases *(5)*.

Certain studies have shown a higher incidence of GTD in Asia than in North America or Europe. In the United Kingdom, all patients are included on a national register, with central pathology review; the incidence of partial and complete hydatidiform mole is around 4 per 1000 pregnancies and GTN is diagnosed in 15% of patients with complete hydatidiform mole and 0.5–1% with partial hydatidiform mole *(1)*. A review published in the American Journal of Obstetrics and Gynecology in 2010 indicates that choriocarcinoma, a subset of GTN, affects 1 in 40 000 pregnancies in Europe and North America compared with 9.2 in 40 000 pregnancies in south-east Asia and Japan *(5)*. A seminar in *The Lancet* in 2010 estimated CCA to occur in 1 in 50 000 deliveries in the United Kingdom *(1)*. The same seminar found that placental-site trophoblastic tumour accounted for about 0.2% of cases of gestational trophoblastic disease in the United Kingdom in 2010.

Requirements for diagnosis, treatment, and monitoring

Diagnostics

- Pathology laboratory analysis of surgically excised specimens.
- Clinical laboratory facilities to perform the routine haematological and chemical analyses required for monitoring the effects of chemotherapy.
- Facilities for performing radioimmunoassay of hCG which serves as a tumour marker for GTN. The measurement of hCG requires trained technicians and a laboratory with automated equipment and reagents designed for radioimmunoassay procedures. The serial quantitative measurement of hCG is essential for diagnosis, monitoring the efficacy of treatment, and follow-up of patients with GTN. After evacuation of a molar pregnancy, hCG levels usually become undetectable within 8–10 weeks (compared with 3–6 weeks after normal delivery or miscarriage). Persistence of hCG levels indicates local or metastatic disease, which allows for early detection and timely intervention. During treatment, hCG response is used as a guide for deciding whether to continue treatment with a particular agent or switch to another. After treatment, hCG monitoring allows 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. Radiological 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 radiological 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 pathological diagnosis of CCA. It is usually not recommended to obtain a histological diagnosis because of the high vascularity of the tumour and the risk of haemorrhage.

Administration and care of patients

Administration of chemotherapy requires intravenous infusion capacity, and the patient must have regular access to clinical care. Methotrexate can be administered either intramuscularly or intravenously. Dactinomycin is a vesicant and requires careful administration through a freely running infusion. All other chemotherapeutic agents are also administered intravenously. Antiemetics and intravenous hydration should accompany the 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 levels are undetectable for 3 consecutive weeks, and then monthly until undetectable for 12 months. The use of effective contraception must be encouraged during the entire period 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 is 6 months *(4)*.

Subsequent pregnancy after treatment for GTN

Patients who have been successfully treated for GTN with chemotherapy can expect normal future reproductive function with no increased risk of congenital anomalies *(4)*.

Psychosocial issues

Women with GTN can experience significant mood disturbance, marital and sexual problems, and concerns about future fertility. They may therefore need emotional support and counselling during and after treatment.

Overview of regimens

Standard regimens

- **Single-agent regimens for low-risk gestational trophoblastic neoplasms**

Methotrexate (MTX) regimens	*Primary remission rates (%)*

MTX: 0.4-0.5 mg/kg IV or IM daily for 5 days	87–93
MTX: 30–50 mg/m^2 IM weekly	49–74
MTX/calcium folinate MTX 1 mg/kg IM or IV on days 1, 3, 5, 7 Calcium folinate 15 mg orally on days 2, 4, 6, 8	74–90
High-dose IV MTX/calcium folinate MTX 100 mg/m^2 IV bolus MTX 200 mg/m^2 12-hour infusion Calcium folinate 15 mg every 12 hours in 4 doses IM or orally beginning 24 hours after starting MTX	69–90

Dactinomycin regimens	*Primary remission rates (%)*
Dactinomycin 10–12 μg/kg IV push daily for 5 days	77–94
Dactinomycin 1.25 mg/m² IV push every 2 weeks	69–90

- **EMA/CO regimen for resistant low-risk GTN or as primary therapy for high-risk GTN**

Day	*Drug*	*Dose*
1	Etoposide	100 mg/m² by infusion in 200 ml normal saline over 30 min
	Dactinomycin	0.5 mg IV push
	MTX	100 mg/m² IV push; 200 mg/m² by infusion over 12 hours
2	Etoposide	100 mg/m² by infusion in 200 ml normal saline over 30 min
	Dactinomycin	0.5 mg IV push
	Calcium folinate	15 mg every12 hours x 4 doses IM or orally beginning 24 hours after starting MTX
8	Cyclophosphamide	600 mg/m² by infusion in normal saline over 30 min
	Vincristine	1 mg/m² IV

Review of benefits and harms

Benefits

Women with GTN are classified as having low- or high-risk GTN using the FIGO scoring system. After undergoing dilatation and curettage of the womb, the absolute majority (>90%) of women with low-risk GTN are cured by treatment with chemotherapy. Methotrexate and dactinomycin are the two most commonly used drugs for first-line treatment of low-risk GTN. A Cochrane systematic review of five randomized controlled trials comparing single-agent chemotherapy with methotrexate and dactinomycin in women with low-risk GTN found that, overall, dactinomycin was associated with higher rates of primary cure than methotrexate (risk ratio RR 0.64; 95% CI: 0.54–0.76), while methotrexate was associated with significantly more treatment failure than dactinomycin (RR 3.81; 95% CI: 1.64–8.86) (moderate-quality evidence) *(6)*. If the first-line treatment fails to cure the disease or is associated with adverse events that require it be discontinued, a secondary treatment has to be used. If methotrexate is the first drug used, dactinomycin is usually the secondary treatment, and vice versa.

High-risk tumours are treated with combination chemotherapy (e.g. EMA/CO), with or without adjuvant radiotherapy and surgery. Various drug combinations may be used for high-risk tumours; however, no experimental studies comparing different chemotherapy regimens are available and the comparative efficacy and safety of these regimens is unknown. The EMA/CO regimen has been widely adopted because of its efficacy and easily manageable short-term toxicity. In cohort studies five-year overall survival has been reported to range from 75% to 90% *(7-9)*.

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. Toxic side-effects are more likely to occur when chemotherapy agents are used in combination.

Specifically, dactinomycin is a highly emetogenic agent requiring prophylaxis with antiemetics to reduce the severity of nausea and vomiting. Patients treated with dactinomycin also commonly suffer reversible alopecia. Methotrexate regimens are associated with a higher incidence of diarrhoea and stomatitis *(10)*.

The EMA/CO regimen can cause predictable, and generally easily manageable, adverse effects including reversible alopecia and myelosuppression, occasionally with severe neutropenia and anaemia *(1, 10, 11)*.

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 leukaemia *(10, 12)*. The risk of etoposide-induced acute myeloid leukaemia is increased when the cumulative drug dose is high or when etoposide is used with concomitant radiotherapy or high-dose platinum agents *(13)*.

Recommendations

The Expert Committee acknowledged that gestational trophoblastic neoplasia is a rare, but highly curable, malignancy. On the basis of the evidence presented in the application, the Committee recommended endorsement of the following medicines for the treatment of GTN on the complementary list of the Model List of Essential Medicines: dactinomycin, methotrexate, calcium folinate, etoposide, cyclophosphamide and vincristine. However, the Committee noted that availability of dactinomycin is poor.

The Committee noted that the treatments are highly effective and the benefit is clinically obvious – high cure rates (greater than 90%) and preservation of fertility in the majority of patients.

1. Seckl MJ, Sebire NJ, Berkowitz RS. Gestational trophoblastic disease. Lancet. 2010;376(9742):717-29.
2. Sebire NJ, Seckl MJ. Gestational trophoblastic disease: current management of hydatidiform mole. BMJ. 2008;337:a1193.
3. Berkowitz RS, Goldstein DP. Current management of gestational trophoblastic diseases. Gynecol Oncol. 2009;112(3):654-62.

4. Goldstein DP, Berkowitz RS. Current management of gestational trophoblastic neoplasia. Hematol Oncol Clin North Am. 2012;26(1):111-31.
5. Lurain JR. Gestational trophoblastic disease I: epidemiology, pathology, clinical presentation and diagnosis of gestational trophoblastic disease, and management of hydatidiform mole. Am J Obstet Gynecol. 2010;203(6):531-9.
6. Alazzam M, Tidy J, Hancock BW, Osborne R, Lawrie TA. First-line chemotherapy in low-risk gestational trophoblastic neoplasia. Cochrane Database Syst Rev. 2012;7:CD007102.
7. Bower M, Newlands ES, Holden L, Short D, Brock C, Rustin GJ, et al. EMA/CO for high-risk gestational trophoblastic tumors: results from a cohort of 272 patients. J Clin Oncol. 1997;15(7):2636-43.
8. Kim SJ, Bae SN, Kim JH, Kim CT, Han KT, Lee JM, et al. Effects of multiagent chemotherapy and independent risk factors in the treatment of high-risk GTT--25 years experiences of KRI-TRD. Int J Gynaecol Obstet. 1998;60 Suppl 1:S85-96.
9. Turan T, Karacay O, Tulunay G, Boran N, Koc S, Bozok S, et al. Results with EMA/CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine) chemotherapy in gestational trophoblastic neoplasia. Int J Gynecol Cancer. 2006;16(3):1432-8.
10. Garner EIO. Gestational trophoblastic neoplasia: staging and treatment. In: UpToDate [website]. Waltham, MA: UpToDate; 2014.
11. Lurain JR. Gestational trophoblastic disease II: classification and management of gestational trophoblastic neoplasia. Am J Obstet Gynecol. 2011;204(1):11-8.
12. Ngan S, Seckl MJ. Gestational trophoblastic neoplasia management: an update. Curr Opin Oncol. 2007;19(5):486-91.
13. Ezoe S. Secondary leukemia associated with the anti-cancer agent, etoposide, a topoisomerase II inhibitor. Int J Environ Res Public Health. 2012;9(7):2444-53.