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REVIEW ON CURRENT MANAGEMENT OF GESTATIONAL TROPHOBLASTIC NEOPLASIA

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ABSRACT

Gestational Trophoblastic Neoplasia (GTN) arises from placental tissue and is one of the few human malignancies that can be healed even if it has spread widely. GTN refers to a group of cancers that include hydatidiform moles, invasive moles, choriocarcinoma, and placental site trophoblastic tumours, all of which have various propensities for local invasion and spread. The purpose of this study was to summarise current knowledge of the natural history of molar pregnancy and persistent gestational trophoblastic neoplasia (GTN), as well as recent improvements in their treatment.

KEYWORDS: EMACO chemotherapy, Stages of GTN.

INTRODUCTION

GTN (gestational trophoblastic neoplasia) is a malignant lesion caused by aberrant placental trophoblast growth. GTN occurs in around 50% of instances due to molar pregnancy, 25% due to miscarriage or tubal pregnancy, and 25% due to term or preterm pregnancy.[1] [8] The majority of these tumours, invasive mole and CCA, always produce measurable quantities of human chorionic gonadotropin (hCG). They are highly sensitive to chemotherapy, with a cure rate of more than 90%. 90% of the time, a treatment can be achieved while maintaining reproductive function. GTN diagnosis is one of the most important steps in its treatment

because these tumours can almost always be treated and fertility can be maintained in the majority of cases.

- **STAGES OF GESTATIONAL TROPHOBLASTIC DISEASE[6]**

Stage 1 - Disease confined to the uterus

Stage 2 - GTN extends outside of the uterus, but is limited to the genital structures

Stage 3 - GTN extends to the lungs, with or without known genital tract involvement

Stage 4 – All other metastatic sites

Single-agent chemotherapy can be used to treat patients with nonmetastatic disease (Stage I) and low-risk metastatic GTN (Stages II and III, score 7) with cure rates of 80 percent to 90 percent. Patients with high-risk metastatic disease (Stage IV and Stages II–III with scores >6), on the other hand, require multiagent chemotherapy, possibly with adjuvant radiation and/or surgery when indicated, to attain comparable cure rates.

- **INDICATIONS FOR CHEMOTHERAPY AFTER GTN[4]**

A 10% increase in HCG in two consecutive serum samples over at least two weeks (days 1, 7 and 14)

HCG plateau in four or more consecutive serum samples following at least three weeks of evacuation (days 1, 7, 14 and 21)

More than 4 weeks after evacuation, serum HCG 20,000 IU/l

On a chest X-ray, there are >2 cm of brain, liver, gastrointestinal, or lung metastases.

Choriocarcinoma histological evidence

Gastrointestinal/intraperitoneal bleeding or heavy vaginal bleeding

Unless the HCG level is dropping, pulmonary, vulval, or vaginal metastases are possible.

PRIMARY THERAPY FOR LOW RISK OF GTN

Patients with non-metastatic (Stage I) and metastatic (Stage II) GTN who have a prognosis score of b7 have low risk GTN. The primary therapy for people with stage I GTN is determined by the severity of the disease. `If the patient has finished having children, a hysterectomy with one course of adjuvant single-agent chemotherapy may be advised for the treatment of any occult cancer. Adjuvant chemotherapy hasn't been found to raise the risk of perioperative problems in this situation. Patients with stage I GTN who want to keep their fertility and patients with low-risk metastatic GTN should receive single-agent chemotherapy with sequential methotrexate (MTX)/actinomycin D (ACTD). In both non-metastatic and

low-risk metastatic GTN, single-agent chemotherapy with either MTX or ACTD has achieved excellent and comparable remission rates.[1] A second round of chemotherapy is given under the following circumstances: 1) the HCG level remains stable for more than 3 weeks or re-elevates, or 2) the HCG level does not drop by 1 log within 18 days following the first therapy.

SALVAGE THERAPY OF LOW RISK GTN

Patients with low-risk GTN who acquire resistance to single-agent chemotherapy can usually achieve remission with combination treatment, such as MAC (MTX, ACTD, and cyclophosphamide) or EMACO (methotrexate, acetate, and cyclophosphamide) (etoposide, MTX, ACTD, cyclophosphamide, and Oncovin). Because etoposide is linked to an increased risk of second malignancies, including a 1% chance of leukaemia, MAC is chosen as the first combination chemotherapy. Hysterectomy or local resection may be recommended if the disease is resistant to both single-agent and combination chemotherapy.

Table 1: Treatment protocol for stage I gestational trophoblastic disease.[1]

Initial	Sequential MTX/ACT-D Hysterectomy (with adjunctive single – agent chemotherapy)
Resistant to both single agents	MAC EMACO, if MAC fails Hysterectomy (with adjunctive multiagent chemotherapy Local uterine resection(for localized lesion, to preserve, fertility)
Follow up	12 consecutive months of normal HCG levels Contraception mandatory

ACT-D: Actinomycin; EMACO: Etoposide, Methotrexate, Actinomycin D, Cytoxan, Oncovin; MAC: Methotrexate, Actinomycin D, Cytoxan; MTX: Methotrexate.

PRIMARY THERAPY OF HIGH RISK GTN

Women with high-risk stages II and III should receive EMACO as a first-line treatment. Mtx, actD, and cyclophosphamide or chlorambucil (MAC) were the favoured first-line multiagent regimens, with cure rates ranging from 50% to 71% in this group of patients. When used alone in patients with low-risk disease 55 or in combination with Mtx, actD, cyclophosphamide, and vincristine (EMA/CO), etoposide was shown to be a highly effective treatment for GTN in the 1980s[1] With an 80% to 90% remission rate in high-risk metastatic GTN patients, EMA/CO is now the chosen main combination chemotherapy regimen.

Combination chemotherapy resulted in complete remission in 6 of 6 high-risk high-risk stage stage II GTN patients and 36 of 37 high-risk stage III GTN patients (97.3 percent).

SALVAGE THERAPY OF HIGH RISK GTN

Patients with illness resistant to EMACO can be treated by adding cisplatin and etoposide (EMAEP) to the regimen. In patients who were resistant to EMACO, EMAEP alone or with surgery produced remission.

Table 2: Treatment protocol for stages II and III of gestational trophoblastic disease.[1]

Low risk Initial therapy Resistant therapy	Sequential MTX/ACT-D MAC Or EMA/CO Surgery, as indicated
High risk Initial therapy Resistant therapy	EMACO EMAEP VBP Surgery, as indicated
Follow up	12 consecutive months of undetectable HCG levels Contraception for 12 months

Other regimens include MEA (methotrexate, etoposide, and actinomycin-D); MAC (methotrexate, actinomycin-D, and cyclophosphamide or chlorambucil); CHAMOMA (cyclophosphamide, hydroxyurea, actinomycin-D, methotrexate with folinic acid, vincristine, melphalan, and doxorubicin); the response rate was 60 to 80 percent when used as a primary treatment. To avoid life-threatening complications such as pulmonary, cerebral, or liver decompensation from tumour oedema or haemorrhage, patients with advanced cancer involving organs such as the lungs, brain, and/or liver may be started on reduced-dose chemotherapy, such as etoposide 100 mg/m2 and cisplatin 20 mg/m2 on days 1 and 2 and repeated weekly for 1e3 weeks before returning to the usual chemotherapy regimen.

EMACO CHEMOTHERAPY[4]

Regimen 1 Day 1	Etoposide Actinomycin – D Methotrexate	100mg/m^2 intravenous infusion over 30 min 0.5 mg intravenous bolus 300mg/m^2 intravenous infusion over 12h
Day 2	Etoposide Actinomycin – D Folinic acid rescue	100mg/m^2 intravenous infusion over 30 min 0.5 mg intravenous bolus 15mg IM or PO every 12hr for 4 doses

Regimen 2 Day 8	Vincristine Cyclophosphamide	1mg/m^2 intravenous bolus 600mg/m^2 intravenous infusion over 30 min

These 2 regimens alternate each week

TREATMENT OF STAGE IV GTD

EMACO is the most commonly used combination chemotherapy to treat stage IV cancer. Treatment for women with brain metastases might be difficult. To guarantee appropriate coverage of brain tissue, the initial change to the EMACO regimen in these patients is to raise the MTX dose on day 1 to 1 gm/m^2.[3]

Table 3: Treatment protocol for stage IV gestational trophoblastic disease.[1]

Initial	EMACO: Radiation Therapy for Brain Metastases For peripheral lesions, a cranialotomy is performed. Metastases to the liver: Embolization To avoid complications, a resection is performed.
Resistant	EMAEP VBP as a salvage chemotherapy Protocols for experiments As needed, surgery As needed, hepatic artery infusion or embolization
Follow up	HCG levels are measured weekly for 3 weeks until undetectable, then monthly for 24 months. 24 months' contraception

PSYCHOSOCIAL CONSEQUENCES OF GTN

GTN can cause severe mood swings, marital and sexual issues, and concerns about future fertility in women.[1] GTN can cause severe mood swings, marital and sexual issues, and concerns about future fertility in women. Anxiety, exhaustion, anger, disorientation, sexual issues, and worry about future pregnancy can all linger for a long time. Beyond remission, the psychological and social stressors associated with persistent GTN may linger for many years.[2] Finally, it is widely known that a GTN diagnosis can have a major emotional impact on the patient and her family.[3]

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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