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# Diagnosis, classification and treatment of gestational trophoblastic neoplasia

## *Diagnóstico, classificação e tratamento da neoplasia trofoblástica gestacional*

Review

**Keywords**
Gestational trophoblastic disease/diagnosis
Gestational trophoblastic disease/classification
Gestational trophoblastic disease/drug therapy
Choriocarcinoma/drug therapy

**Palavras-chave**
Doença trofoblástica gestacional/diagnóstico
Doença trofoblástica gestacional/classificação
Doença trofoblástica gestacional/quimioterapia
Coriocarcinoma/quimioterapia

## Abstract

Gestational trophoblastic neoplasia (GTN) is the term to describe a set of malignant placental diseases, including invasive mole, choriocarcinoma, placental site trophoblastic tumor and epithelioid trophoblastic tumor. Both invasive mole and choriocarcinoma respond well to chemotherapy, and cure rates are greater than 90%. Since the advent of chemotherapy, low-risk GTN has been treated with a single agent, usually methotrexate or actinomycin D. Cases of high-risk GTN, however, should be treated with multiagent chemotherapy, and the regimen usually selected is EMA-CO, which combines etoposide, methotrexate, actinomycin D, cyclophosphamide and vincristine. This study reviews the literature about GTN to discuss current knowledge about its diagnosis and treatment.

## Resumo

Neoplasia trofoblástica gestacional (NTG) é o termo que descreve o conjunto de anomalias malignas da placenta, incluindo a mola invasora, coriocarcinoma, tumor trofoblástico do sítio placentário e tumor trofoblástico epitelióide. Ambos a mola invasora e o coriocarcinoma respondem bem à quimioterapia, com taxas de cura superiores a 90%. Desde o advento da quimioterapia, NTG de baixo risco tem sido tratada com monoquimioterapia, pelo geral methotrexate ou actinomicina-D. Casos de NTG de alto risco, contudo, devem ser tratados com poliquimioterapia, e o regime usualmente escolhido é o EMA-CO que combina etoposide, methotrexate, actinomicina-D, ciclofosfamida e vincristina. Esse estudo revê a literatura sobre NTG a fim de discutir os conhecimentos atuais sobre seu diagnóstico e tratamento.

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**Received**
10/28/2014

**Accepted with modifications**
11/19/2014

**DOI:** 10.1590/S0100-720320140005198

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Conflict of interests: none.

## Introduction

Gestational trophoblastic neoplasia (GTN) is the term used to describe malignant lesions that originate in the chorionic villi and the extravillous trophoblast. This designation includes four different clinical entities, each with different degrees of proliferation, invasion and dissemination: invasive mole (IM), choriocarcinoma (CCA), placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (ETT)[1-5].

About 50% of all cases of GTN occur postmolar gestations, 25% after abortions or ectopic pregnancies and 25%, after term or preterm deliveries[4]. PSTT and ETT, however, develop after term deliveries or non-molar abortions in 95% of the cases[6].

The largest epidemiological study conducted in Brazil about trophoblastic disease found that GTN developed in 24.6% of the patients that had complete hydatidiform moles and in 7.6% of the cases of partial hydatidiform moles[7].

Most cases of GTN are IM and CCA. These diseases, characterized by high levels of human chorionic gonadotropin (hCG), are highly responsive to chemotherapy (ChT) and have cure rates greater than 90%[4]. In contrast, the rarer PSTT and ETT have low hCG levels[8] and are relatively resistant to ChT. Therefore, the first-line treatment in these cases is surgery, particularly in no metastatic cases[4].

The objective of this paper is to present an update of clinical aspects, diagnosis and treatment of GTN in order to guide the Brazilian gynecologists and obstetricians on the major advances in the management of patients affected by this neoplasm of pregnancy.

## Methods

A search was conducted in the PubMed and the Cochrane Library databases from January 2004 to June 2014, using the term "gestational trophoblastic neoplasia". The search retrieved 1,950 publications, 370 abstracts were read in detail, and 52 studies, preferably those published more recently and that focused on GTN diagnosis and treatment, were included in this review.

Although the priority was to select meta-analyses and methodologically well-designed studies, reviews conducted by organizations and institutions, as well as expert opinions, were also included because of the low prevalence of this disease. Although not published within the period defined for the search, the original Federation of Gynecology and Obstetrics (FIGO) 2002 study about GTN staging was also included because of its relevance, as its publication marked the beginning of the use of a universal GTN classification.

## Clinical presentation

The clinical presentation of GTN is variable and depends on the gestational event that originated the disease, as well as on its extension and histological diagnosis[1,4].

Enlarged uterus, vaginal bleeding and persistence of theca lutein cysts in the ovaries are suggestive of postmolar GTN[4]. However, over 50% of patients with GTN do not have any clinical findings, and the diagnosis is made only according to plateaued or rising serum hCG concentrations measured during postmolar follow-up after uterine evacuation[9].

When CCA is associated with a previous non-molar pregnancy, signs and symptoms are most often associated with tumor invasion in the uterus or sites of metastases, especially the lungs and the pelvis[1,4].

GTN metastases occur by hematogenous spread to the lungs (80%), vagina (30%), brain (10%) and liver (10%)[10]. Lung metastases are usually symptomless, but may be extensive and cause dyspnea, cough, hemoptysis and thoracic pain[1,4]. Vaginal metastatic nodules are more frequent in the fornices and suburethral region. They may cause purulent leucorrhea and difficult-to-control bleeding, as they are richly vascularized[1,11].

Bleeding due to uterine perforation or metastases is associated with abdominal pain, hemoptysis, melena and signs and symptoms of increased intracranial pressure, such as headaches, seizures, impaired speech, impaired vision and hemiplegia[1,4]. GTN perfusion involves anomalous and aberrant circulation in fragile vessels that tend to bleed. Metastatic site biopsies are not recommended because of the high risk of bleeding[11].

Almost all patients with PSTT and ETT have abnormal uterine bleeding a long time after the previous gestational event[8]. Virilization and nephrotic syndrome have also been rarely described[1,4,12].

As symptoms may be minimal or even absent and the antecedent gestational may be remote, a GTN diagnosis should be suspected in all reproductive age women who present with pulmonary symptoms or unexplained systemic symptoms, particularly in the case of metastases of a primary neoplasia whose site is unknown[11].

## Evaluation and management

When a GTN diagnosis is made or suspected, metastases and risk factors should be evaluated.

In addition to a detailed patient history and careful clinical examination, a complete blood count, blood type, Rh factor, coagulation tests, liver and renal function evaluation and serum hCG levels should be requested[2,4,13].

The concentration of serum hCG is the diagnostic pillar of postmolar GTN. The other diagnostic criteria for postmolar GTN are as follows[14]: 4 or more plateaued hCG concentrations over three weeks (that is, on days 1, 7, 14 and 21); increase of hCG concentrations for three or more consecutive measurements for at least two weeks (that is, on days 1, 7 and 14); histological diagnosis of choriocarcinoma and elevated hCG concentrations for six months or longer.

Agarwal et al.[15] evaluated the rigorous clinical and laboratory follow-up of patients with elevated hCG concentrations for six months or longer after molar evacuation. They found that a prolonged follow-up was acceptable and commonly precluded the use of chemotherapeutic drugs[15].

The clinical events listed as indications for treatment by the Charing Cross Trophoblastic Disease Center should also be included as GTN diagnostic criteria: abundant vaginal bleeding, signs of gastrointestinal or intraperitoneal hemorrhage, evidence of brain, liver or gastrointestinal metastasis and radiological opacities >2 cm on chest X-ray[5].

Transvaginal ultrasound (TVUS) imaging is a fundamental tool for the diagnosis of GTN, but different diseases may have similar appearances on imaging studies[16]. The most common finding is a focal myometrial mass. The image may be hypo- or hyperechoic, or complex and even multicystic. Intramyometrial anechoic spaces result from hemorrhage and tissue necrosis or vascular spaces[16,17].

In extensive disease, imaging may reveal a large, heterogenous and lobulated uterus or an undifferentiated pelvic mass[16,17]. Color Doppler ultrasound may demonstrate intense chaotic vascularity and loss of vessel discreteness. It demonstrates high-velocity, low-resistance flow in contrast with the flow usually detected in normal myometrial arteries. However, PSTT may be hypo- or hypervascular[16].

A chest X-ray is the imaging method recommended by FIGO to evaluate lung metastases[14]. However, up to 41% of the patients with lung metastases on computed tomography (CT) have a normal chest X-ray. Pulmonary micrometastases are better evaluated using chest CT, but its use is questionable because the presence of micrometastases does not seem to affect long-term survival[17].

Other imaging studies, such as magnetic resonance imaging (MRI) and CT, are not part of the routine assessment of GTN and are used only in equivocal cases or when metastatic disease is suspected[5,16].

CT is the most suitable method to evaluate the common sites of metastases, except for vaginal and brain lesions, which are accurately detected using MRI[16]. Although few studies have thoroughly investigated it, positron emission CT seems to be capable of detecting sites of metabolically active disease not found in other imaging studies. Moreover, it may be useful in differentiating uterine scars of fibrosis from active disease[16].

## Classification and staging

Several staging systems, classifications and prognostic systems have been used globally in the past for GTN, which has made it difficult to compare results of studies conducted in different reference centers.

Because of the need for a universal language, common treatment criteria and a staging system accepted worldwide, the FIGO published a new classification system for GTN in 2002 (Table 1). The system combined its former anatomic staging system with a modified scoring system with risk factors defined by the World Health Organization (WHO)[4,14].

This classification excluded blood type from the list of risk factors, assigned a score of four instead of three to liver metastases, and excluded the group of moderate risk neoplasia. According to this system, tumors may be classified into two groups: low-risk GTN, if the score ≤6; and high-risk, if the score ≥7[13,14]. Staging notation uses a Roman numeral followed by an Arabic numeral that indicate FIGO anatomic staging and the WHO modified score, respectively. PSTT and ETT are classified separately[4].

Treatment is defined according to the total score of risk factors, which represents the chance that the patient may develop resistance to first-line single-agent treatment[4,5].

## Treatment

Half a century ago, before the introduction of ChT in the management of GTN, mortality rates associated with invasive moles reached 15%, more frequently due to hemorrhage, sepsis, embolic phenomena or surgical complications. In the presence of metastases, CCA had a mortality rate of 100%, and of about 60% when hysterectomy was performed to treat apparent nonmetastatic disease[1].

Currently, cure rates are greater than 90% even in the case of widespread metastatic disease[1,4,7,18].

**Table 1.** International Federation of Gynecology and Obstetrics and World Health Organization staging and classification of gestational trophoblastic neoplasia[14]

| GTN: FIGO staging and classification (Washington, 2000) | | | | |
|---|---|---|---|---|
| **FIGO anatomic 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 | | | | |
| **Modified WHO prognostic scoring system as adapted by FIGO** | | | | |
| **Prognostic factors** | **Score** | | | |
| | **0** | **1** | **2** | **4** |
| **Age** | <40 | ≥40 | – | – |
| **Antecedent gestation** | mole | abortion | term | – |
| **Interval (months)** | <4 | 4–6 | 7–12 | >12 |
| **Pretreatment serum hCG (mIU/mL)** | $<10^3$ | $10^3$ to $<10^4$ | $10^4$ to $<10^5$ | $>10^5$ |
| **Largest tumor size (including uterus)** | <3 | 3 to 4 | ≥5 | – |
| **Site of metastases** | lung | spleen, kidney | GIT | brain, liver |
| **Number of metastases** | – | 1–4 | 5–8 | >8 |
| **Previous failed chemotherapy** | – | – | single drug | ≥2 |

*Interval (in months) between the end of antecedent gestation (when known) and symptom onset; FIGO: International Federation of Gynecology and Obstetrics; WHO: World Health Organization; GTN: gestational trophoblastic neoplasia.

A multicenter study conducted in Brazil found that 21.8% of 5,250 patients with molar pregnancy developed GTN, classified as low risk in 81.3%, high risk in 17.5% and PSTT in 1.2%. The overall cure rate was 96.4%, with a mortality of 0.4% for low-risk disease, 9.5% for high-risk and 21.4% for PSTT[7]. Methotrexate (MTX), actinomycin-D (ActD), cyclophosphamide, vincristine, etoposide, cisplatin and paclitaxel are some of the drugs used to treat GTN effectively[19].

After hCG returns to normal levels, additional ChT courses, called consolidation ChT, are repeated three to four times, especially in cases of high-risk disease, to avoid recurrence[20]. A recent study conducted by Lybol et al.[21] found a greater recurrence rate among patients with low-risk GTN treated with two instead of three ChT consolidation courses[21]. However, their data were retrospective, and further prospective randomized studies should be conducted to confirm their findings.

## Low-risk disease

Low-risk GTN includes nonmetastatic disease (stage I) and metastatic disease with FIGO/WHO scores <7[11,14]. These patients should be first treated with a single agent, either MTX or ActD[4,20,22]. A retrospective study found that 9,4% of women undergoing a second uterine evacuation did not need ChT to attain remission[23]. Benefits seem to be greater when hCG concentration is below 1500 IU/L at the time of evacuation[24]. However, this recommendation is controversial, and prospective randomized studies should be conducted to confirm the benefits of a repeat uterine evacuation.

In the group of patients with low-risk disease, the choice of the first line treatment depends on their wish to preserve fertility. Hysterectomy and an adjuvant single-agent ChT course may be recommended for patients that completed childbearing, because this choice treats any occult metastases[11].

Extensive experience has been accumulated in treating low-risk GTN over time, and over 14 different types of ChT regimens have been described, but no consensus has been reached about the preferred first-line treatment. As there is no strong evidence to confirm the superiority of any one method, several treatments have been arbitrarily used in different centers[22,25]. However, a consensus has been reached about the use of a single agent, such as MTX or ActD, for patients with low-risk disease[3]. These drugs have induction remission rates of 50 to 90%[5].

The three most common regimens are: (1) weekly low-dose intramuscular (IM) MTX; (2) pulsed doses of ActD every two weeks; and (3) several other dosing regimens of MTX with or without folinic acid (FA) rescue[25]. Table 2 shows primary remission rates according to ChT regimen.

Primary response variability results from differences in drug doses, times and administration modes, as well as patient selection. In general, weekly IM or intermittent IV infusion of MTX and biweekly ActD are less effective than MTX and ActD for five days or MTX/FA for eight days. However, almost all patients are cured and have their fertility preserved despite the differences in initial remission after primary ChT[3,4].

The weekly MTX 30–50 mg/m$^2$ regimen has the advantage of convenience and low cost and toxicity, but has the lowest complete response rate among all other regimens, and is not appropriate for the treatment of metastatic disease or CCA[3].

ActD has been used as primary therapy in case of renal or hepatic compromise or MTX contraindication and as secondary therapy when the patient develops resistance

**Table 2.** Primary remission rates of low-risk gestational trophoblastic neoplasia according to regimen used[3]

| ChT regimen | Primary remission rate (%) |
|---|---|
| 1) MTX 0.4 mg/kg (maximum 25 mg) IV or IM qd for 5 days, repeat every 14 days | 87–93 |
| 2) MTX 30-50 mg/m² IM weekly | 49–74 |
| 3) MTX 1 mg/kg IM d 1, 3, 5, 7; folinic acid 0.1 mg/kg IM d 2, 4, 6, 8; repeat every 15-18 d, or as needed | 74–90 |
| 4) MTX 100 mg/m2 IVP, then 200 mg/m² in 500 mL D5W over 12 h; folinic acid 15 mg IM or PO every 12 h for 4 doses beginning 24 h after start of MTX; repeat every 18 d, or as needed | 69–90 |
| 5) Act-D 10-13 mg/kg IV qd for 5 d; repeat every 14 d | 77–94 |
| 6) Act-D 1.25 mg/m2 IV every 2 weeks | 69–90 |
| 7) Alternating MTX/Act-D regimens 1 and 5 | 100 |

ChT; chemotherapy; Act-D: actinomycin-D; D5W: dextrose 5% in water; IM: intramuscular; IV: intravenous; IVP: intravenous push; MTX: methotrexate; PO: by mouth; qd: daily; d: day(s).

to MTX. It has more side effects (nausea, alopecia) than MTX and has the risk of local tissue injury in case of extravasation during IV infusion. The most effective regimens are ActD 10–12 mg/kg IV daily for five days every two weeks, or a single 1.25 mg/m² IV dose every two weeks[3,26].

Several studies, most retrospective and not randomized, have investigated the efficacy of MTX in comparison with ActD in the treatment of low-risk GTN.

A recent prospective randomized study conducted by the Gynecologic Oncology Group found that ActD 1.25 mg/m² IV every two weeks was significantly superior to MTX 30 mg/m² IM every week, with complete response rates of 70 and 53% (p=0.01). However, both regimens were less effective when the GTN score was five or six, or when there was a histologic diagnosis of choriocarcinoma[27].

Other studies also found greater primary remission rates for pulsed ActD than weekly MTX[28,29], MTX for five days[30] and MTX/FA for eight days[31].

A study about GTN treatment at the John I. Brewer Trophoblastic Disease Center in Chicago included 359 patients treated from 1979 to 2006 and found a rate of complete remission after treatment with a single agent of 79% (78% for MTX and 86% for ActD), and 92% complete response after treatment with a single sequential agent. The other 8% reached remission after treatment with multiple agents or adjuvant surgery[32].

A Brazilian study compared three ChT regimens for low-risk GTN: MTX for five days, ActD for five days and combined MTX and ActD (MACT). Primary remission rates were 69, 71.4 and 79.1% respectively, and the differences were not significant. Side effects were significantly more frequent in the MACT group than in the single-agent groups. The authors found that single-agent regimens are as effective as the combination of drugs under study and suggested that ActD is a less toxic drug with a better cost-effectiveness for the treatment of low-risk GTN. However, because of its ease of administration, MTX may be the first choice in areas where resources are limited[33].

Although the FIGO/WHO staging system is useful to define the type of ChT to be used, several authors have suggested that a few points should be clarified, such as the scores assigned according to hCG concentration before treatment[34].

A recent study found that resistance to first line ChT may develop when the FIGO/WHO score is six or when hCG is higher than 100,000 IU/L. Based on those findings, the authors suggested a change in the cut-off point for low-risk disease from six to five, or the assignment of a score of six, and not of four, to patients with hCG higher than 100,000 IU/L before treatment[35].

Evidence suggests that patients with hCG above 400,000 IU/L should begin ChT with multiple agents because of the significantly greater resistance to single-agent ChT[34].

A study conducted by the Charing Cross Trophoblastic Disease Center also found that the efficacy of the MTX/FA regimen decreased as the prognostic score increased. The rate of complete response in the group of patients with scores of 0 and 1 was 75%, but this rate fell to less than 50% when the score was 3 to 5 and to 31% when the score was 6[36].

Regardless of which single-agent ChT regimen is used, ChT should continue until hCG returns to normal values, and at least three more ChT cycles should be administered after the first normal hCG result. The drug in use should be replaced by another when hCG plateaus or when toxicity precludes the use of appropriate doses or treatment frequency. Multiagent ChT should be used when there is significant elevation of hCG concentrations, appearance of metastases or sequential resistance to single-agent ChT[3].

Findings suggest that any regimen with ActD has primary remission rates higher than those achieved with MTX regimens, but most studies have compared pulsed ActD with weekly MTX, a regimen found to be less effective than those in which treatment is administered along five to eight days[22].

The comparison of side effects between studies is difficult because of the differences between patients. The most common side effects for both agents are nausea, anemia

and fatigue[22], similar in both pulsed ActD and low-dose MTX regimens. However, Lertkhachonsuk et al.[31] found more severe side effects, such as alopecia and mucositis, in the group treated with ActD.

A prospective randomized study comparing 8-day MTX/FA and 5-day MTX with pulsed ActD is currently being conducted by the Gynecology Oncology Group. Its results, to be published in 2016, may help to define which drug should be used as first-line treatment[22].

## High-risk disease

Patients with high-risk GTN (FIGO stages II-III with score >7 and stage IV) should be treated with multiagent chemotherapy with or without adjuvant surgery and radiotherapy[3,4,11] .

The multiagent therapy of choice has changed over the years. In the 1970s and 1980s, MTX, ActD and cyclophosphamide or chlorambucil (MAC) were the first line treatment, and cure rates reached 63 to 71%. In the early 1980s, studies found that the regimen with cyclophosphamide, hydroxyurea, ActD, MTX/FA, vincristine and doxorubicin (CHAMOCA) increased primary remission to 82%. However, CHAMOCA had lower sustained primary remission rates, as well as greater toxicity, than the MAC regimen[3,4].

In 1980, etoposide was found to be a very effective agent in the treatment of GTN. Regimens using this drug in combination with high doses of MTX, FA ActD, cyclophosphamide and vincristine (EMA-CO) resulted in higher remission and survival rates[3]. The EMA-CO regimen (Table 3) became the first choice for the treatment of high-risk GTN because of its low toxicity and high complete response and survival rates[3-5].

Primary or secondary hysterectomy is not effective in reducing the need of ChT or improving remission rates in women with metastatic high-risk GTN, probably because of the higher load of extra uterine disease found in these patients[37].

Primary remission rates for the EMA-CO regimen range from 54 to 91%. Although EMA-CO is the most commonly used regimen in the treatment of patients with high-risk GTN, current evidence is not conclusive, as there are no high-quality studies in the literature to support the superiority of this regimen in comparison with other multiagent ChT regimens[38].

Induction ChT with EP (etoposide 100 mg/m$^2$ and cisplatin 20 mg/m$^2$) for one or two courses before the start of EMA-CO for selected high-risk patients (hCG>100,000 IU/L and FIGO/WHO>12) seems to increase overall survival and decrease early deaths[39].

**Table 3.** EMA-CO and EMA-EP protocols[4]

| EMA-CO and EMA-EP protocols | | |
|---|---|---|
| **Day** | **Drug** | **Dose** |
| **EMA-CO** | | |
| 1 | Etoposide<br>ActD<br>MTX | 100 mg/m$^2$ by infusion in 200 mL saline over 30 min<br>0.5 mg IVP<br>100 mg/m$^2$ IVP<br>200 mg/m$^2$ by infusion over 12 h |
| 2 | Etoposide<br>ActD<br>Folinic acid | 100 mg/m$^2$ by infusion in 200 mL saline over 30 min<br>0,5 mg IVP<br>15 mg IM or PO every 12 h for 4 doses starting 24 hours after start of MTX |
| 8 | Cyclophosphamide<br>Vincristine | 600 mg/m$^2$ by infusion in saline over 30 min<br>1 mg/m$^2$ IVP |
| **EMA-EP** | | |
| 1 | Etoposide<br>ActD<br>MTX | 100 mg/m$^2$ by infusion in 200 mL saline over 30 min<br>0.5 mg/m$^2$ IVP<br>100 mg/m$^2$ IVP<br>200 mg/m$^2$ by infusion over 12 h |
| 2 | Etoposide<br>ActD<br>Folinic acid | 100 mg/m$^2$ by infusion in 200 mL saline over 30 min<br>0.5 mg/m$^2$ IVP<br>15 mg IM or PO every 12 h for 4 doses starting 24 hours after start of MTX |
| 8 | Cisplatin<br>Etoposide | 60 mg/m$^2$ IV with prehydration<br>100 mg/m$^2$ by infusion in 200 mL saline over 30 min |

ActD: actinomycin (Cosmegan); EMA-CO: etoposide, actinomycin D, methotrexate, cyclophosphamide, vincristine; EMA-EP: etoposide, methotrexate, actinomycin D, cisplatin; FA: folinic acid; IM: intramuscular; IVP: intravenous push; MTX: methotrexate; PO: by mouth.

To define which treatment is more effective and less toxic for high-risk patients, carefully conducted multi-site studies should control variables that may affect remission and survival rates, such as risk score, liver and brain metastases and use of adjuvant treatments (surgery, radiotherapy, granulocyte colony-stimulating factor)[38].

## Placental site trophoblastic tumor and epithelioid trophoblastic tumor

Because of the rarity of placental site trophoblastic tumors and epithelioid trophoblastic tumors, their treatment is based on findings of small case series described retrospectively[12]. These tumors are relatively resistant to ChT and have a propensity for lymphatic spread. Therefore, hysterectomy with or without lymph node dissection and bilateral salpingo-oophorectomy plays a major role in their treatment when the disease is confined to the uterus[3,11,12] and is curative in two thirds of the cases[37].

There may be a response to the EP-EMA (Table 3) or the paclitaxel/cisplatin-paclitaxel/etoposide (TE-TP) regimen, protocols indicated for patients with unfavorable prognostic factors or metastatic disease[3,10].

## Resistant or recurrent disease

GTN is resistant to ChT when hCG levels plateau or increase, regardless of whether new metastases develop, while the patient is undergoing treatment. In contrast, a diagnosis of recurrence is made when there are two elevations of hCG concentrations in the absence of pregnancy after a normal hCG result[40]. Both conditions are challenging in the treatment of GTN.

Recent data indicate that the number of consolidation ChT administered, a clinical and histologic diagnosis of choriocarcinoma, a high pretreatment hCG concentration, disease spread (brain, liver and gastrointestinal metastases) and a high WHO score are associated with increased rates of resistant disease[26,41].

About 5% of the patients with low-risk GTN without metastases and 10% to 15% of those that have metastases develop resistance to primary ChT[42]. For low-risk disease, a different single-agent regimen (e.g., ActD after ChT with MTX) is usually enough when hCG levels plateau[4,43]. When there is no response to sequential single-agent therapy, multiagent ChT should be initiated, and the EMA-CO regimen is the most commonly used multiagent ChT[4].

Recent studies suggest that a uterine artery pulsatility index equal to or lower than one predicts an increase in the risk of resistance to MTX/FA in women with low-risk GTN and may be useful in patient staging for first line therapy[44,45]. Prospective studies are underway evaluate this finding.

Resistance to ChT and recurrent disease are more frequent in patients with high-risk GTN[25]. About 20 to 30% of the high-risk patients have an incomplete response to first line ChT or recurrence after remission and eventually need salvage ChT. Treatment with alternative agents, particularly those containing cisplatin, are usually necessary after failure of initial combined ChT[43].

Because of the few cases of resistance to ChT, most studies with this type of patients are retrospective and based on case series. Several salvage regimens (Table 4) are used all over the world, and it is unclear which regimens are more effective and less toxic[38], but the EP-EMA regimen is preferred and recommended by the FIGO. The rate of complete response to this regimen is higher among patients that develop resistance (81.8%) than in those with disease recurrence (42.9%), and the most common side effects are myelosuppression, nausea, vomiting and hepatotoxicity[46]. With divergent results, Powles et al.[47] found an overall 5-year survival of 93% for patients with recurrent disease and 43% for those with chemoresistant disease.

**Table 4.** Salvage chemotherapy for resistant or relapsed gestational trophoblastic neoplasia[40]

| Chemotherapy regimens |
|---|
| EMA-EP: Etoposide, Methotrexate, Actinomycin-D, Etoposide, Cisplatin |
| BEP: Bleomycin, Etoposide, Cisplatin |
| TP/TE: Paclitaxel, Cisplatin/Paclitaxel, Etoposide |
| FA: 5-Fluorouracil, Actinomycin-D |
| FAEV: Floxuridine, Actinomycin-D, Etoposide, Vincristine |
| MBE: Methotrexate, Bleomycin, Etoposide |
| VIP/ICE: Ifosfamide, Cisplatin, Etoposide |

Recent studies have suggested the use of hCG regression normograms to predict resistance to ChT with EMA-CO and the initiation of ChT with a platinum-containing drug instead of EMA-CO when pretreatment hCG concentrations are above the 90$^{th}$ percentile[41].

In addition to salvage ChT, associated procedures, such as hysterectomy, surgical resection of sites of resistant disease, radiotherapy and chemoembolization techniques, are part of the adjuvant treatment for these patients[43,48].

## Follow-up after gestational trophoblastic neoplasia treatment

After three consecutive normal weekly hCG measurements and ChT completion, serum hCG should be measured monthly for 12 months[20]. Some centers recommend additional follow-up procedures for this period. In the New England Trophoblastic Disease Center (Harvard Medical School), specialists recommend two years of follow-up for high-risk disease, and in the Charing Cross Trophoblastic Disease Center (United Kingdom) follow-up continues for the rest of life with urine hCG measurements every six months after five years of follow-up[4,49]. Overall risk of recurrence is 3 to 9% in the first year after treatment and is unusual after 12 months of normal hCG concentrations[4].

Contraception is obligatory during follow-up, preferably using combined oral contraceptives. Intrauterine devices should not be used before hCG levels become undetectable[4].

Women that develop GTN may have significant changes in mood, as well as sexual and marital problems, in addition to concerns with their reproductive future. They have to deal with the loss of a pregnancy and the threat of malignancy

simultaneously. Patients with active metastatic disease run greater risks of developing severe psychosocial problems and should receive counseling, psychological support and interventions that may mitigate these disturbances[50].

Most patients have a normal ovarian function after ChT, and numerous successful pregnancies have been reported, without any increase in abortions, stillbirths, congenital anomalies, prematurity or other serious obstetric complications[3].

A Brazilian study about the first pregnancy after single-agent and multiagent ChT found 68.2% normal term pregnancies and births of healthy newborns. Maternal adverse effects and abortions were significantly greater when conception occurred in up to six months after the end of ChT[51].

As there is a risk of 1 to 2% of a new molar pregnancy in subsequent pregnancies, the use of TVUS is recommended in the beginning of the first trimester to confirm that the pregnancy is normal. Moreover, the products of contraception or placentas of future pregnancies should be examined histologically. Serum hCG level should be measured six weeks after the end of any future pregnancy to detect occult GTN[3,4].

The introduction of regimens with etoposide in the treatment of GTN has been associated with an increase in the risk of secondary neoplasia, such as acute myeloid leukemia (1%), colon and breast cancer and melanoma. This increase of susceptibility seems to be dose dependent and to affect primarily patients that received doses that exceeded 2 g/m$^2$, who should be strictly followed[4].

## Conclusion

Early adequate treatment ensures an excellent prognosis for patients with GTN. The FIGO/WHO staging system (2002)[14] has provided a universal language for the discussion of this neoplasia and has been used to define prognostic factors more accurately and to compare different treatment protocols for low- and high-risk GTN in several parts of the world.

Because of the low frequency of this disease, current treatments are based on retrospective studies and small case series. Well-designed prospective and multi-site studies should be conducted to answer issues that remain controversial, such as the role of a second uterine evacuation in the progression of the disease, first-line ChT for low- and high-risk disease, when to discontinue ChT, when to end hCG monitoring and allow the patient to become pregnant again. It is essential that these patients be followed in Reference Centers where they will receive specialized care which directs impacts survival and quality of life[52].

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