Gestational trophoblastic disease: an update on pathology, diagnosis and state-of-the-art management

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ABSTRACT

Gestational trophoblastic disease (GTD) is a spectrum of disorders originating from the placenta, including premalignant forms, such as complete and partial hydatidiform mole, and the malignant invasive mole, choriocarcinoma, placental site trophoblastic tumor and epithelioid trophoblastic tumor. The incidence of GTD varies between countries and the prevalence depends on maternal age, previous GTD history, socioeconomic factors. Histology and molecular genetic studies can help in the diagnostic pathway. Diagnosis of GTD is based on a multifactorial approach consisting of clinical features, serial human chorionic gonadotropin titers, and imaging findings. GTD can result in significant morbidity and mortality if left untreated; early diagnosis of GTD is essential for prompt and successful management while preserving fertility.

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Key words
Gestational trophoblastic disease; epidemiology; diagnosis; management; review.

SOMMARIO

La malattia trofoblastica gestazionale (GTD) rappresenta uno spettro di patologie derivanti dalla placenta, che include forme premaligne, come mola idatidiforme completa e parziale, e forme maligne quali mola invasiva, coriocarcinoma, tumore trofoblastico del sito placentare e tumore trofoblastico epiteliode. L’incidenza di GTD varia, la prevalenza dipende dall’età materna, dalla precedente storia di GTD e dai fattori socio-economici. Istologia e genetica molecolare possono aiutare nel percorso diagnostico. La diagnosi di GTD si basa su un approccio multifattoriale costituito dalla clinica, valutazioni di gonadotropina corionica umana e diagnostica per immagini. GTD se non trattata può provocare morbilità e mortalità significative; la diagnosi precoce di GTD è essenziale per una gestione ottimale che preservi la fertilità.
INTRODUCTION

Gestational trophoblastic disease (GTD) comprises a spectrum of tumors with a wide range of biologic behavior and potential for distant metastases, all arising from abnormal placenta (1). GTD includes the pre-malignant conditions of complete (CHM) and partial (PHM) hydatidiform mole and the malignant invasive mole, choriocarcinoma (CC) and the very rare placental site trophoblastic tumor and epithelioid trophoblastic tumor (PSTT/ETT) (2). The last four are referred to as gestational trophoblastic neoplasia (GTN) that often arises after molar pregnancy but can occur after any gestation including miscarriages and term pregnancies (3).

Epidemiology

The most common form of GTD is hydatidiform mole, which accounts for 80% of all cases, while invasive mole accounts for 15% and CC for 5%. PSTT represents only 0.2% of GTD cases within UK (4, 5). The prevalence of GTD varies depending on geography, maternal age, previous GTD history, socioeconomic factors, dietary factors, and possibly blood grouping (6, 7). A wide global variation in the prevalence of molar pregnancy has been reported (8). GTD arises more frequently in Asia than in North America or Europe. Hydatidiform mole occurs in 0.5-1 over 1000 pregnancies in North America and Europe, 1.5-6 over 1000 pregnancies in South America and 12 over 1000 pregnancies in Southeast Asia (8, 9). The incidence of choriocarcinoma is 1 in 40000 pregnancies in North America and Europe, 9.2 in 40000 pregnancies in Southeast Asia and 3.3 in 40000 pregnancies in Japan (10). Geographic differences in prevalence may be due to discrepancies between hospital-based and population-based data or in availability of central pathology review (11). Molar pregnancies are more frequent at the extremes of maternal age, i.e., under 16 years old and over 45 years old. In these age ranges, gametogenesis and fertilization abnormalities are more frequent (12, 13). Furthermore, the risk of PHM and CHM increases by 1-2% after a molar pregnancy, and by 15-20% after two molar gestations. The risk does not decrease with a change of partner (14-16). Dietary deficiency of beta-carotene and animal fat has been advocated as a risk factor for CHM (17). Moreover, there may be an increased risk of choriocarcinoma in women who have used long-term oral contraceptives and with blood group A (18-20).

Pathophysiology and genetics

GTD identifies a group of tumors of gestational origin. Soon after implantation, placental trophoblasts differentiate into cytotrophoblasts, syncytiotrophoblasts, and intermediate trophoblasts. While CHM, PHM and CC originate from cytotrophoblasts and syncytiotrophoblasts, PSTT and ETT arise from intermediate trophoblasts. In 90% of cases, CHM develops when an empty ovum that lost its maternal chromosomes is fertilized by one sperm, which then duplicates its DNA, resulting in a 46, XX karyotype with a complete paternally-derived set of chromosomes. About 10% of CHMs have a 46, XY karyotype, resulting from dispermic fertilization (21, 22). A rare form of CHM can result from a recurrent autosomal recessive disorder. In this case, CHM is diploid but of biparental origin. This condition is associated with mutations of two genes: NLRP7 and, rarely, KHDC3L (23-25). PHMs are almost always triploid, resulting from fertilization of a healthy ovum by two sperms or by one sperm that duplicates itself, resulting in the genotypes 69, XXX, 69, XXY, or 69, XY. Rarely, PHMs can be tetraploid with a 92, XXXY genotype. Diploid PHM is unlikely, most reported cases representing misdiagnosed complete moles or twin pregnancies (21, 22). The malignant invasive mole and CC follow CHM in 15%-20% of cases and PHM in less than 5% of cases. Invasive mole is the most common form of GTN and always occurs after CHM. Therefore, it usually has a diploid karyotype that is completely paternal in origin (26). It is a clinical rather than pathological diagnosis based on persistent human chorionic gonadotropin (hCG) elevation after molar evacuation (3).

Pathology

Complete and Partial Hydatidiform mole

CHM and PHM have distinctive morphological characteristics. CHM is characterized by the absence of fetal parts, abnormal villous structure, trophoblast hyperplasia, stromal hypercellularity, stromal karyorrhectic debris and collapsed villous blood vessels. In contrast, PHMs have less pronounced histopathologic features, with irregular and scalloped villi as proplile showing trophoblast inclusions and less pronounced hyperplasia. Also, in PHM fetal tissue might be present, like nucleated red blood cells and fetal membranes (1). Morphological distinction between PHM and CHM can in some cases be difficult. Immunos-
Gestational trophoblastic disease

Pregnancies may result in the development of gestational trophoblastic disease (GTD) which can be classified into non-molar and molar pregnancies. Molar pregnancies may be partial or complete hydatidiform moles (PHMs). CHMs are associated with hypersecretion of beta-human chorionic gonadotropin (β-hCG), with levels typically significantly higher than in normal pregnancies. PHMs are associated with a 50% increase in β-hCG, while CHMs can have levels 1000 times higher. The disease may occur in the absence of a pregnancy or be associated with a molar pregnancy.

Molecular genetic analysis with in-situ hybridization/flow cytometry, or molecular genotyping may be useful to rule out difficult cases. p57KIP2 gene is localized on chromosome 11p15.5 and it encodes an inhibitor of G1 cyclin/Cdk complexes. It acts as a negative regulator of cell proliferation. This gene is paternally imprinted and maternally expressed, thus its protein is a surrogate marker for the nuclear maternal genome. PHMs and non-molar normal and abnormal gestations with maternal genome display a strong nuclear p57 staining, while CHM is almost always p57-negative. Rare types of CHM carrying a maternal copy of chromosome 11 are p57-positive. However, p57 cannot differentiate PHM from non-molar gestation.

Choriocarcinoma

CC may manifest after a hydatidiform mole, a normal pregnancy, or an abortion. Histologically, CC shows absence of chorionic villi and presence of abnormal intermediate trophoblast and cytotrophoblast, surrounded by syncytiotrophoblasts. CC has numerous and large areas of necrosis of haemorrhagic type; viable tumor can be scant. CC is characterized by numerous atypical mitoses and by an high Ki-67 Index. Moreover, it is characterized by the production of high levels of β-hCG.

Placental Site Trophoblastic tumor and Epithelioid Trophoblastic tumor

PSTT and ETT are tumors that typically occur after non-molar gestations and may manifest many years after a full-term delivery. They usually produce lower levels of β-hCG compared to other forms of GTN. Histologically, PSTT lake origine from intermediate trophoblast of implantation side, organized in small cords with intertwining stroma, with absence of villar structures and with a low mitotic count in contrast to CC. PSTT is characterized by the absence of chorionic villi and low mitotic count. Tumor cells diffusely express hPL, MUC-4, HSD3B1, HLA-G and CD-146. Ki-67 is expressed in 10% to 30% of cells. ETT is composed by islands of intermediate trophoblastic cells that are surrounded by extensive necrosis and hyaline matrix. CC can be differentiated from PSTT and ETT also by SALL4 positivity. SALL4 is a zinc finger transcription factor involved in embryonal development. Its expression in CC could reflect the low level of differentiation of CC compared to PSTT and ETT and cannot be observed in CHM.

Clinical presentation

Complete and Partial Hydatidiform mole

Patients with molar pregnancies most commonly present with vaginal bleeding and markedly elevated β-hCG values in the first or early second trimester. Vaginal bleeding is attributed to the rapid growth of trophoblastic tissue that separates blood vessels from the decidua bed damaging their wall. Due to routine use of ultrasonography in first-trimester examination and in the investigation of vaginal bleeding, diagnosis usually occurs before the classic clinical presentation can arise. Previously reported clinical signs and symptoms such as hyperemesis, excessive uterine enlargement for gestational age, pre-eclampsia, anemia, respiratory distress and hyperthyroidism, are now rare. Such symptoms were generally related to CHM, whereas in PHM they were less evident. Depending on the age of the woman, clinical presentation can be different. Symptoms tend to be more pronounced in older women, where clinical features are often misinterpreted, leading to a delay in correct diagnosis and a higher incidence of disease-related complications. However, despite the earlier diagnoses and the consequent reduction in the frequency of major clinical symptoms, the rate of progression to GTN reported in literature has not changed over time.

Gestational trophoblastic neoplasia

Clinical presentation of GTN can vary and depends on the condition determining its onset, the extent of the disease and histopathology. GTN can happen after a molar pregnancy: in these cases, diagnosis is clinical and is defined by plateaued or rising levels of β-hCG during follow-up. Furthermore, there are diagnostic criteria that are not always recognized such as: β-hCG > 20000 U/L to one year; histology of choriocarcinoma; positive β-hCG for 4-6 months. The most frequent symptom of postmolar GTN is irregular bleeding after uterine evacuation; less frequently, it develops without symptoms. Occasionally, a metastatic vaginal lesion may cause uncontrolled bleeding. CC after a non-molar gestation (spontaneous abortion, ectopic pregnancy or term pregnancy) is characterized by a heterogeneous clinical presentation which is related to invasion of tumor in the uterus or at metastatic sites such as lung, liver, spleen or brain. Symptoms related to bleeding from metastatic sites may occur, resulting in abdominal pain, hemoptyisis, dyspnea,
cough, chest pain, melena, or symptoms related to increased intracranial pressure from intracerebral hemorrhage. In 1/3 of cases CC can present without gynecological symptoms. In all cases of metastatic disease of unknown origin in a woman of childbearing age with a positive history of pregnancy CC diagnosis must be considered (39).

PSTT and ETT generally occur with irregular uterine bleeding long after the non-molar pregnancy from which they originate. They often present with relatively low levels of serum ß-hCG despite the volume of disease seen at imaging (40, 41).

**Diagnosis**

**Partial and Complete Hydatidiform mole**

Ultrasonography is a critical exam in posing the early clinical suspicion of GTD. Ultrasound (US) morphological features allow differential diagnosis between PHM and CHM. However, PHM presents subtler US features so that its diagnosis is less common than CHM during first trimester. Early PHMs are characterized by cystic changes and increased echogenicity of the decidua and placenta in presence of embryonic tissue that can be identified as amorphous echoes (42, 43). In those few cases that proceed above 11 weeks (late PHMs), US features are characterized by enlarged and irregular molar placenta with focal villous edema and an abnormal triploid fetus carrying severe abnormalities (ventriculomegaly, hydrocephalus, holoprosencephaly, increased nuchal translucency, renal defects). CHMs are characterized by trophoblastic hyperplasia displayed as diffuse cystic spaces within the placenta (“snowstorm”) in the absence of a fetus or embryonic tissue (1). The high levels of ß-hCG can lead to excessive stimulation of the ovaries with theca lutein cysts, however this occurs in less than 20% of cases (44).

When US features are suspicious for HM, ß-hCG levels, a blood group and screen/save must be determined. Histological examination after suction curettage is essential for diagnosis (3).

**Gestational trophoblastic neoplasia (GTN)**

**Invased mole**

Postmolar GTN is usually diagnosed by hCG follow-up after histological diagnosis of HM. Invasive trophoblast can be identified at US by the presence of heterogeneous myometrial nodules or masses, which can be echogenic or hypoechoic, usually hypervascular (45). US findings of vascularized myometrial nodules after uterine evacuation can correlate with a high risk of malignant evolution (46). Arteriovenous shunts are also common due to neoangiogenesis phenomena occurring within the tumor (43).

**Placental site trophoblastic tumor (PSTT) and epithelioid trophoblastic tumor (ETT)**

The diagnosis of PSTT and ETT, which are the rarest forms of GTN, requires histopathologic examination. Their rarity makes diagnosis particularly challenging. US features are similar to other forms of GTN, i.e., the presence of myometrial nodules with a heterogeneous structure consisting of cystic cavities and solid masses (43). At US, they show different patterns of myometrial invasion: while ETT expands with sharp borders, PSTT penetrates between myometrium muscle fibers (47).

**Management**

**Hydatidiform mole**

Treatment of hydatidiform mole consists of uterine evacuation by suction and curettage. US control is recommended to ensure a thorough evacuation and to minimize the risk of uterine perforation (48). When gestational age is higher than 16 weeks and the uterus is particularly enlarged, the procedure carries a significant risk of bleeding and embolization of molar tissue to the lungs but the treatment must always be done (3). Ergometrine or other sustained uterotonic must be started at the onset of suction curettage and continued postoperatively to enhance uterine contractility (48). In women with no childbearing desire, hysterectomy is a valid alternative to uterine curettage, but it requires careful hCG surveillance because these women could still develop GTN (49). Diagnosis should always be confirmed by histology and, whenever possible, genetic testing for karyotype determination. Rh-negative patients should be given anti-D prophylaxis. Repeated uterine curettages did not prove to be effective in reducing the need for subsequent chemotherapy or the risk of relapse (50). If mole diagnosis is confirmed, hCG follow-up should be started 3 to 4 weeks after evacuation with a frequency of once a week and continued until at least 2 consecutive negative tests. Subsequently, a single confirmatory hCG measurement is recommended for a PHM over 1 month, and monthly measurements are recommended for a CHM for 6 months. Oral contraceptives may be useful in this timeframe to avoid interferences with hCG measurements due to a new pregnancy or elevated
levels of luteinizing hormone (LH) (48). Figure 1 reports the diagnostic pathway for HM.

**Coexisting normal pregnancy with mole (CHM coexisting with a Healthy Fetus)**

A multiple pregnancy consisting of a complete hydatidiform mole with a coexisting fetus (CHMCF) is very rare, complicating 1 per 20000 to 100000 pregnancies. This condition is normally diagnosed at the end of the second trimester (between 15 and 18 weeks) of pregnancy. Its US features are characterized by a complex cystic pattern adjacent to a normal placenta and a structurally normal fetus (43). In early first trimester, misdiagnosis with subchorionic hematoma is frequent (51). A recent meta-analysis including 244 cases reported that the incidence of antenatal maternal complications is around 80%, including vaginal bleeding (70%), hyperthyroidism (23%), and pre-eclampsia (14%). Live birth rate was 50% in ongoing pregnancies, with 78% pre-term births. Evolution into GTN happened in 34% of the patients whether pregnancy is stopped or continued. Therefore, these pregnancies should receive adequate counselling and be managed in a GTD center (52).

**Gestational Trophoblastic Neoplasia**

Prophylactic chemotherapy after HM diagnosis is not advisable (53). Indications for chemotherapy after a molar pregnancy (see table I) include an hCG rise for at least 3 consecutive measurements for a period of at least 2 weeks or a plateau for at least 4 consecutive measurements over a period of at least 3 weeks (2). Chemotherapy is also indicated in case of hCG level greater than 20000 IU/L more than 4 weeks after uterine evacuation (54). Elevated but falling hCG values 6 months after evacuation are no longer treated by chemotherapy, since in most cases a spontaneous normalization occurs (55). Postpartum GTN can be diagnosed by histological examination or by evidence of multiple metastases in a woman of childbearing age with elevated hCG values (3). Histological diagnosis of CC is no longer considered an absolute indication to start chemotherapy, since spontaneous regression with falling hCG levels has been reported (56, 57).

**Staging**

GTN should be staged by transvaginal US, chest X-ray and body CT scan (48). These exams allow the definition of FIGO 2000 staging and scoring system (see tables II and III). Only metastases detected by X-ray are included in the FIGO 2000 score, as micro-metastases are not associated with a worse prognosis (58). However, lung micrometastases are associated with a higher incidence of chemo-resistance (59). If lung meta-

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**Figure 1.** Diagnostic pathway for HM to GTN.
Gestational trophoblastic disease

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Ses are present, brain MRI is also recommended (3). In staging, PET cannot replace conventional imaging and does not show any information in addition to that shown by conventional imaging. However, it could have an additional value in patients with high-risk disease to identify unconventional metastatic locations (60). Scoring system by prognostic factors is necessary to identify patients at risk to develop chemoresistant disease. Patients scoring below 6 are considered at low risk and can be treated by monotherapy, while patients scoring 7 or higher are at high risk of developing resistance to single-drug regimens and therefore should receive combination-agent chemotherapy as first line treatment (1). FIGO scoring system is less predictive of resistance for intermediate risk patients. Over 50% of patients who score 5-6 develop chemoresistance and need to switch to multiagent regimens, but almost all are eventually cured (11). Other factors have been advocated to be prognostic of drug resistance in this group of patients, such as uterine artery pulsatility index measured by Doppler ultrasonography (43). At diagnosis, all patients should at least be discussed with a GTD referral center. High-risk patients must be referred at a GTD center (48).

Low-risk GTN

Low-risk GTN can be treated either with methotrexate (MTX) or actinomycin-D (act-D) (see Table IV). Act-D is probably the most effective treatment, being associated with higher primary response rates than MTX (61, 62). Nevertheless, in most centers MTX is preferred over act-D as first-line treatment because of the lower toxicity profile (no hair loss, less nausea and myelosuppression) (63) and cost-effectiveness (64). It is estimated that approximately 70% of low-risk patients will develop chemoresistance, but these patients will respond to salvage treatment with multiagent chemotherapy and will eventually be cured (3). Many different treatment schedules exist. The most widely used protocol consists of a 8-day regimen where MTX is administered on days 1, 3, 5, 7 alternated with a folinic acid (FA) rescue (generally 7.5 to 15 mg) on days 2, 4, 6, 8, repeated every 14 days. Some centers prefer to adjust MTX dose by body weight, although this is probably unnecessary (4). MTX can be also administered intravenously at the dose of 0.4 mg/kg for 5 days every 2 weeks. Act-D can be administered intravenously at the dose of 0.5 mg for 5 days, repeated every 14 days (1). Patients

Table I. Indications for chemotherapy after a molar pregnancy.

<table>
<thead>
<tr>
<th>Weekly hCG rising for at least 3 consecutive measurement for a period of at least 2 week (day 0-7-14)</th>
<th>Weekly hCG plateauing for at least 4 consecutive measurements for a period of at least 3 week (day 0-7-14-21)</th>
<th>Persistence of hCG more than 6 months after evacuation</th>
<th>Histological diagnosis of choriocarcinoma*</th>
<th>Serum hCG level greater than 20000 IU/L more than 4 weeks after evacuation*</th>
</tr>
</thead>
</table>

*Criteria non absolute.

Table II. FIGO 2000 scoring system for GTN.

<table>
<thead>
<tr>
<th>Prognostic factors</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>&lt; 40</td>
<td>≥ 40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antecedent pregnancy</td>
<td>Mole</td>
<td>Abortion</td>
<td>Term</td>
<td></td>
</tr>
<tr>
<td>Interval from antecedent pregnancy</td>
<td>&lt; 4</td>
<td>4-6</td>
<td>7-12</td>
<td>&gt; 12</td>
</tr>
<tr>
<td>hCG (IU/L)</td>
<td>&lt; 10³</td>
<td>10³-10⁴</td>
<td>10⁴-10⁵</td>
<td>&gt; 10⁵</td>
</tr>
<tr>
<td>No of metastases</td>
<td>0</td>
<td>1-4</td>
<td>5-8</td>
<td>&gt; 8</td>
</tr>
<tr>
<td>Site of metastases</td>
<td>Lung</td>
<td>Spleen, kidney</td>
<td>Gastrointestinal tract</td>
<td>Brain, liver</td>
</tr>
<tr>
<td>Largest tumor mass</td>
<td>&lt; 3</td>
<td>3-5 cm</td>
<td>&gt; 5 cm</td>
<td></td>
</tr>
<tr>
<td>Prior chemotherapy</td>
<td>Single drug</td>
<td>≥ 2 drugs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table III. FIGO staging for GTN.

| Stage I | Disease confined to the uterus |
| Stage II | Disease extending into the pelvis and/or vagina |
| Stage III | Disease spread to lungs and/or vagina |
| Stage IV | All other metastatic sites |
with disease confined to the uterus not wishing to maintain fertility can be treated by hysterectomy; however, this does not eliminate the need for subsequent chemotherapy (49). Serum hCG measurements should be repeated at least every 2 weeks to monitor response to treatment. In case of resistance, re-imaging and a therapy switch should be considered. Primary resistance occurs if hCG rises after 2 courses or plateaus (< 10% change between measurements) after 3 courses. Acquired resistance is defined by a plateau over 2 courses (4 weeks) or rise over at least 2 weeks (48). In case of MTX resistance, if hCG ≤ 1000 IU/L patient should receive act-D, if hCG > 1000 IU/L a multiagent regimen is recommended (48). The overall cure rate for low-risk disease patients is close to 100% (1). After normalization of hCG levels, 3 consolidation treatments will decrease the chance of recurrence (65).

### Table IV. Treatment of low-risk GTN.

| 8-day regimen: MTX (50 mg total dose intramuscular) day 1-3-5-7 with FA (15 mg) days 2-4-6-8; repeated every 14 day termed MTX/FA regimen* | Act-D 0.5 mg for 5 days repeated every 14 days |

| *First choice treatment. |

### High-risk GTN

High-risk patients with a FIGO score comprised between 7 and 12 should receive multiagent chemotherapy (see Table V). The most used regimen is a combination of etoposide 100 mg/m², MTX 300 mg/m² and ActD 0.5 mg (EMA) with repeated doses of etoposide and Act-D on day 2, alternated weekly to cyclophosphamide 600 mg/m² and vincristine 0.8 mg/m² (CO). This schedule requires a folinic acid rescue 24 hours after MTX administration 12 hourly for 4 doses (3). Chemotherapy should be administered weekly until hCG normalization and for 6-8 weeks of consolidation (48). EMA/CO-resistant disease can be salvaged with alternative platinum-based regimens: EMA (omitting the second day to reduce myelotoxicity) alternating weekly with etoposide and cisplatin (EP); paclitaxel and etoposide (TE) alternating every 2 weeks with paclitaxel and cisplatin (TP); etoposide, ifosfamide and cisplatin every 3 weeks; bleomycin, etoposide, and cisplatin every 3 weeks. In a study including over 400 patients, survival after treatment with these regimens was 94% in high-risk patients and 99% in the resistant low-risk group, with a median follow-up time of 4 years (66).

### Table V. Treatment of High-risk GTN.

| EMA-CO |
| Day 1: |
| · Actinomycin-D 0.5 mg iv. |
| · Etoposide 100 mg/m² iv. |
| · Methotrexate 300 mg/m² iv. |
| Day 2: |
| · Actinomycin-D 0.5 mg iv. |
| · Etoposide 100 mg/m² iv. |
| · Folinic acid 15 mg postoperatively 12 hourly x 4 doses Starting 24 hours after methotrexate. |
| Day 8: |
| · Vincristine 0.8 mg/m² (maximum, 2 mg). |
| · Cyclophosphamide 600 mg/m². |

| EP/EMA |
| Day 1: |
| · Actinomycin-D 0.5 mg iv. |
| · Etoposide 100 mg/m² iv. |
| · Methotrexate 300 mg/m² iv. |
| Day 2 |
| · folinic acid 15 - 30 mg po 12 hourly x 4 doses Starting 24 h after methotrexate week 2. |
| Day 8 |
| · Etoposide 150 mg iv. |
| · Cisplatin 75 mg/m² iv. |

| TP/TE schedule for relapsed GTN |
| Day 1 |
| · Paclitaxel 135 mg/m². |
| · Cisplatin 60 mg/m². |
| Day 15 |
| · Paclitaxel 135 mg/m². |
| · Etoposide 150 mg/m². |

### Ultra-high risk GTN

Patients scoring 13 or higher should immediately be referred to a GTD center. The presence of liver and/or brain metastases is considered a risk factor for poor prognosis (11). Early deaths due to respiratory compromise and hemorrhage secondary to rapid tumor destruction with full-dose chemotherapy used to be frequent before the introduction of low-dose induction etoposide-cisplatin (EP) in patients with a high burden of disease at presentation (66). Induction therapy consists of the administration of etoposide 100 mg/m² and cisplatin 20 mg/m² on days 1 and 2 weekly for 1-3 cycles. After induction, patients should be treated with EMA/EP or EMA/CO (see Table VI). In case of brain metastatic disease, the MTX dose in the EMA should be increased to 1 g/m² alternating weekly with CO. Intra-thecal MTX can be considered with CO. Patients with liver metastases should receive EMA/EP. With liver and brain involvement, the second day of etopo-
side and actinomycin D in EMA should be omitted. Treatment delays should be avoided by using G-CSF (granulocyte colony stimulating factor) support each week (48). Stereotactic radiotherapy or gamma-knife treatment at the end of chemotherapy could be used to treat residual lesions that are unsuitable for resection. Drug-resistant disease in a single site can be surgically removed (67, 68).

**High-Dose chemotherapy and Immunotherapy as salvage treatment**

Patients failing multiple lines of chemotherapy with unresectable disease could be salvaged by high-dose chemotherapy with peripheral blood stem cell support (69). Due to positive outcomes in selected patients with drug-resistant GTN, the use of pembrolizumab is a promising approach as salvage treatment (70). Genotyping of trophoblastic tumors with unusual presentations or atypical responses to therapy is recommended, to rule out non-gestational origin (67). Also, PSTT/ETT diagnosis should be suspected in case of chemoresistant disease.

**Follow up after remission**

After consolidation therapy is completed, weekly hCG measurements should be continued for at least 6 weeks, then monthly for at least 12 months. Follow-up should be continued for a few years; the recurrence risk drops off steeply after 3 years and no recurrences have been reported after 7 years (71). Since most relapses occur in the first 12 months, pregnancy seeking should be delayed for at least 1 year by the end of treatment.

**Placental site trophoblastic tumor (PSTT) and Epithelioid trophoblastic tumor (ETT)**

FIGO scoring does not apply to PSTT and ETT for treatment determination. The only recognized prognostic factors for these rare tumors are the interval from index pregnancy and presence of metastatic disease (72, 73). A stage-adapted, personalized approach is recommended for PSTT and ETT. In all cases, surgery remains the cornerstone of treatment. An interval ≥ 48 months from antecedent pregnancy is the most significant independent predictor of poor outcome and requires an intensification of treatment, generally with adjuvant platinum-based chemotherapy (i.e., EMA/EP) (73).

**Fertility after chemotherapy**

After a CHM, the risk of another CHM is 1 in 100; after one or two consecutive CHMs the risk of a further CHM is 1 in 4. Women with a PHM have only a small increase in risk for further molar pregnancies (74). In a recent meta-analysis, the pregnancy rate among women treated with chemotherapy for GTN was 86% (75). Adverse pregnancy outcomes were similar to those of general population (75). The cumulative risk of early menopause after EMA-CO reaches 13% by age 40 years and 36% by age 45 years (76). Except for this risk of premature ovarian failure, which rarely happens in younger women and is only associated with multiagent regimens, both single-agent and multiagent chemotherapy do not compromise pregnancy rates and outcomes among women wishing to conceive. In our series, high-risk patients showed worse reproductive outcomes only because the rate of salvage hysterectomies was higher in their cohort compared to low-risk patients (77).

**CONCLUSIONS**

Gestational trophoblastic disease (GTD) is a rare and heterogeneous group of disorders characterised by abnormal proliferation of trophoblastic tissue. Outcomes for most women with GTD are excellent but 2% of them die from the disease, because of late presentation and diagnosis or drug resistance. Indeed, early diagnosis and effective therapeutic strategies with reduced toxicity are essential. Morbidity and mortality for GTD can be reduced by referring patients in specialised centres with multidisciplinary teams, that participate in clinical trials and national registrations to evaluate quality of care. Guideline development is an on-going process, therefore it is important to provide a basis for standardisation of definitions, treatment and follow-up protocols. These specialized centres are needed to avoid inappropriate treatment strategies.

**CONFLICT OF INTERESTS**

The authors declare that they have no conflict of interests.
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