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SUPPLEMENT ARTICLE

Diagnosis and management of gestational trophoblastic disease: 2025 update

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Abstract

Gestational trophoblastic disease (GTD) arises from abnormal placenta and comprises a spectrum of premalignant to malignant disorders. Changes in the epidemiology of GTD have been noted in various countries. In addition to histology, molecular genetic studies can help in the diagnostic pathway. Earlier detection of molar pregnancy by ultrasound has resulted in changes in clinical presentation and decreased morbidity from uterine evacuation. Follow-up with human chorionic gonadotropin (hCG) is essential for early diagnosis of gestational trophoblastic neoplasia (GTN). The duration of hCG monitoring varies depending on histological type and regression rate. Low-risk GTN (International Federation of Gynecology and Obstetrics [FIGO] Stages I–III: score <7) is treated with single-agent chemotherapy but may require additional agents. Although scores of 5–6 are associated with higher drug resistance, overall survival approaches 100%. High-risk GTN (FIGO Stages II–III: score ≥7 and Stage IV) is treated with multi-agent chemotherapy, with or without adjuvant surgery for excision of resistant foci of disease or radiotherapy for brain metastases, achieving a survival rate of approximately 90%. Gentle induction chemotherapy in ultra–high-risk disease helps reduce early deaths in patients with extensive tumor burden, but late mortality still occurs from recurrent treatment-resistant tumors. Immunotherapy can be considered in recurrence.

KEYWORDS
choriocarcinoma, epithelioid trophoblastic tumor, FIGO Cancer Report, gestational trophoblastic disease, gestational trophoblastic neoplasia, moles, placental site trophoblastic tumor

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1 | INTRODUCTION

Gestational trophoblastic disease (GTD) is a group of uncommon conditions associated with pregnancy. Histologically, it includes the premalignant partial hydatidiform mole (PHM) and complete hydatidiform mole (CHM), as well as the malignant invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT). The last three malignant forms can arise after any type of pregnancy and are collectively known as gestational trophoblastic neoplasia (GTN). The GTD spectrum has recently been expanded to include atypical placental site nodule (APSN). Although PSTT, ETT, and APSN have a more varied production of the pregnancy hormone human chorionic gonadotropin (hCG), all other forms of GTD produce this hormone. Indeed, hCG is an excellent biomarker of disease progression, response, and subsequent post-treatment surveillance. Thus, a plateaued or rising hCG level enables the early detection of progression of CHM and PHM to GTN that occurs in 13%–20% and 0.5%–5% of cases, respectively.[1,2] Use of this biomarker, together with the development of highly effective therapies, has transformed survival outcomes, so that today, nearly all women affected by GTN can expect to be cured if managed properly.

2 | EPIDEMIOLOGY

There are marked differences in the reported incidence of hydatidiform mole, ranging from 11.5 per 1000 deliveries in Indonesia to less than 1 per 1000 deliveries in the USA, with the prevalence being higher in Asia, Africa, and Central America than in the USA, Europe, and Australia.[3] Abnormalities of gametogenesis and fertilization are more frequent at the extremes of reproductive age and can explain the higher prevalence of hydatidiform mole among teenage girls and women older than 35 years. Teenage girls and women aged over 35 years have twice the risk of having a sporadic mole compared to that for women aged 20–35 years. The risk increases 5–7 times for women aged over 40 years. The risk of recurrence after complete mole is approximately 1%, which is not seen after partial mole.[4] Familial clustering and recurrent mole are the rule in biparental familial recurrent moles resulting from mutations of NLRP7 and KHD3CL genes.[5] The reported prevalence of choriocarcinoma is 3 per 100 000 deliveries in the USA and Europe compared to the high incidence of 23 per 100 000 deliveries in Southeast Asia.[6] PSTT and ETT are the rarest types of GTD, with a reported incidence of 0.2% of all GTD cases and 1%–2% of GTN cases.[7]

3 | GENETICS AND PATHOLOGY

3.1 | Molar pregnancy

Upon visual inspection, CHMs consist of hydropic villi forming semitransparent vesicles of varying sizes, with an absence of normal placental tissue. In early CHM, gross abnormalities may be minimal or absent.

Differential diagnoses of CHM include PHM, hydropic abortion, and early non-molar gestation with florid trophoblastic hyperplasia. The 5th edition of the WHO Classification of Female Genital Tumors introduces a new category of abnormal (non-molar) villous lesions that carry the same low risk of GTN as other non-molar conceptions. In the absence of genotyping studies, women in whom PHM is suspected because of the presence of atypical/dysmorphic villous morphology may be monitored by hCG surveillance.[8]

The histology of mole and partial mole have been described previously in 2021.[9] Immunohistochemical staining for cyclin-dependent kinase inhibitor p57 is recommended to help distinguish CHM without the maternal genome expression from that of PHM and non-molar abnormal gestations with maternal genome and strong nuclear p57 staining. However, p57 cannot differentiate PHM from non-molar gestations. The cytogenetics of CHM, PHM, and abnormal (non-molar) villous lesions are different. Typically, CHM is diploid and PHM is triploid. Abnormal non-molar villous lesions may harbor various chromosomal or genetic alterations, including trisomy syndromes and digynic triploid. Microsatellite short tandem repeat (STR) genotyping enables a precise diagnosis of CHM and PHM by identifying the absence of maternal genetic contribution and diandric triploidy, respectively. Cytogenetic studies also play a role in determining the index pregnancy leading to GTN by identifying the paternal genotype in GTN.[5]

Rarely, invasive and metastatic moles can be diagnosed by hysterectomy or biopsy of a metastatic lesion.

3.2 | Choriocarcinoma

Upon visual inspection, choriocarcinoma is bulky with hemorrhagic and necrotic areas. Aside from the uterus, it can also be found in the fallopian tubes, ovaries, lung, liver, spleen, kidneys, bowel, and brain.[9]

Histologically, choriocarcinoma is characterized by the absence of chorionic villi and the presence of proliferating intermediate trophoblasts, cytotrophoblasts, and syncytiotrophoblast. Genotyping analysis can identify unique paternal alleles, helping to confirm whether the tumor is of choriocarcinoma or germ cell origin, or a somatic carcinoma with trophoblast differentiation.[5]

3.3 | Placental site nodule (PSN)

A PSN is a benign lesion composed of chorionic-type intermediate trophoblastic cells and is typically an incidental finding in uterine or endocervical curettage specimens.

An atypical PSN (APSN) is considered a precursor to an epithelioid trophoblastic tumor. Approximately 10%–15% may co-exist with or develop into PSTT/ETT.[8–10] APSNs are larger and show more cytological atypia. The Ki-67 proliferation index is less than 5% for PSNs and in the range of 5%–10% for APSNs.[8]

3.4 | Placental site trophoblastic tumor (PSTT)

Upon visual inspection, PSTTs typically appear as nodular masses averaging 5 cm within the endomyometrium, with approximately half of the cases showing deep myometrial invasion. Histologically, PSTTs arise from placental site extravillous intermediate trophoblasts. Chorionic villi are absent. Tumor cells diffusely express different markers.[9] The proliferation index is generally increased, with Ki-67 expressed in 10%–30% of cells—higher than that of benign exaggerated placental site reaction.[9]

3.5 | Epithelioid trophoblastic tumor (ETT)

Upon visual inspection, the tumor appears as discrete nodules or cystic hemorrhagic masses invading deep into the surrounding tissue. Nearly half arise in the cervix or lower segment of the uterus, with some in the fundus and broad ligament.

Histologically, ETTs arise from chorionic-type intermediate trophoblasts. Extensive or "geographic" necrosis is often present. ETTs may co-exist with other trophoblastic neoplasms. The Ki-67 proliferation index is higher than 10%. Tumor cells diffusely express different markers.[9] ETTs may mimic choriocarcinoma (especially after chemotherapy), PSTT, and squamous cell carcinoma of the cervix.[9]

4 | CLINICAL PRESENTATION, INVESTIGATIONS, AND DIAGNOSIS

4.1 | Molar pregnancy

Since diagnosis is often made in the first trimester through ultrasound examination, complications such as hyperemesis gravidarum, pre-eclampsia, and hyperthyroidism are now much less common. If vaginal passage of gestational tissue occurs, vesicular structures may be seen.

The classic honeycomb appearance of a complete mole is rarely observed, especially in the first trimester. Typically, there is an absence of fetal parts and a cystic appearance of the placenta. In contrast, a partial mole may show a cystic placenta alongside a yolk sac or fetal tissue. Therefore, histologic examination after uterine evacuation—whether for spontaneous abortion or suspected molar pregnancy—is essential for accurate diagnosis.

4.2 | Gestational trophoblastic neoplasia

A post-molar GTN is usually diagnosed with hCG surveillance without symptoms. According to the FIGO Gynecology Oncology Committee meeting in 2000, the definition of post-molar GTN is based on changes in hCG level or choriocarcinoma histology, modified in 2021 (Box 1).[1]

Specific investigations have been updated in the 2024 EOTTD/ISSTD/GCIG guidelines (Box 2).[10]

BOX 1 FIGO criteria for diagnosis of post-molar gestational trophoblastic neoplasia.[9]

- When the plateau of hCG lasts for four measurements over a period of 3 weeks or longer; that is, days 1, 7, 14, 21.
- When there is a rise in hCG for three consecutive weekly measurements over a period of at least 2 weeks or more; days 1, 7, 14.
- If there is a histologic diagnosis of choriocarcinoma.

Abbreviation: hCG, human chorionic gonadotropin.

BOX 2 Imaging tools for investigation of gestational trophoblastic neoplasia.[10]

- Pelvic ultrasound and chest radiograph are the basic imaging tools for post-mole GTN scoring. Doppler is used to assess uterine vascularity in some centers. Chest radiographs should be used for counting the number of lung metastases to evaluate the risk score.
- Should lung CT be used, only metastases of 1 cm or more in size are counted to evaluate the risk score.
- Lung metastases of 1 cm or more should induce a thorough imaging investigation, including contrast-enhanced MRI of the brain, pelvis, and abdomen or abdominal CT.
- Whole-body imaging listed in the above bullet point is needed if choriocarcinoma, PSTT, or ETT are suspected or histologically diagnosed.
- Characterization of ultrasound or CT scanning of suspected liver metastases may need liver MRI.
- Brain metastases may be diagnosed by MRI or CT; however, MRI is more sensitive.
- Whole-body 18FDG-PET-CT may be helpful to identify sites of active disease for resection either in multi-drug–resistant cases or in patients with unexplained elevated hCG. Careful correlation with other imaging modalities is advised.

Abbreviations: CT, computed tomography; ETT, epithelioid trophoblastic tumor; GTN, gestational trophoblastic neoplasia; hCG, human chorionic gonadotropin; MRI, magnetic resonance imaging; PET, positron emission tomography; PSTT, placental site trophoblastic tumor.

4.3 | Human chorionic gonadotropin monitoring

For GTN monitoring, an hCG assay that detects all forms of hCG, including beta- hCG, core hCG, C-terminal hCG, nicked-free beta, beta core, and preferably the hyperglycosylated forms, should be

used when possible. A persistently low hCG level needs continuous monitoring as some may progress to GTN with rising hCG levels.[10] To exclude a false-positive result, retesting with another assay or measuring urine hCG may be used.

4.4 | Gestational trophoblastic neoplasia after non-molar pregnancy

Although approximately 75% of GTNs arise after a molar pregnancy, the remainder can occur after a spontaneous abortion, ectopic pregnancy, or, more rarely, a term pregnancy. In addition to abnormal postpartum vaginal bleeding, clinical presentations can include bleeding from metastatic sites such as the liver, spleen, intestines, lung, or brain. Pulmonary symptoms and neurological signs may also occur, particularly in cases of metastasis to the spine or brain.[1] GTNs should be included in the differential diagnosis for patients with atypical presentations. Measurement of serum hCG should be part of the diagnostic workup. In cases of suspected post-term pregnancy GTN, imaging studies should include contrast- enhanced pelvic and brain magnetic resonance imaging (MRI), chest computed tomography (CT), and abdominal CT or MRI.[10]

5 | TREATMENT

5.1 | Molar pregnancy

Assessment of the patient's clinical condition is essential, and any medical complications should be promptly identified and treated to avoid obstetric near-miss events.[11] Conventional suction evacuation—or manual aspiration in settings without electronic equipment—remains the preferred method for uterine evacuation, ideally performed under ultrasound guidance.[12] A 7–12 suction cannula is recommended for evacuation, and an intravenous oxytocin infusion may be initiated at the start of the procedure and continued for several hours postoperatively to promote uterine contractility and reduce blood loss. When available, hysteroscopic resection of residual tissue can serve as a complementary approach. Rh-negative women should receive Rh immune globulin at the time of molar evacuation. Improved outcomes are achieved through the careful use of appropriate equipment and techniques, access to blood products, close intraoperative monitoring, and early recognition and mangement of complications. A second curettage yields controversial results[2,11] and should not be routinely performed. However, it may be used in selected cases with uterine bleeding and ultrasound findings suggestive of molar remains in the endometrial cavity. For patients who have completed childbearing, hysterectomy with ovarian preservation is a viable alternative to suction curettage.[13] Medical induction of labor and hysterotomy are not recommended for molar evacuation, as these approaches are associated with increased maternal morbidity and the development of post-molar GTNs.[14]

Prophylactic chemotherapy at the time of or immediately after molar evacuation is associated with a reduction of 3%–8% in the incidence of post-molar GTNs. However, it should be limited to special situations in which the risk of post-molar GTN is much greater than normal or where adequate hCG follow-up is not possible.[15]

Follow-up hCG monitoring every 1–2 weeks is essential for the timely diagnosis and management of post-molar GTNs. If testing is carried out at 2-week intervals and a rise or plateau in hCG levels is detected, next sample should be obtained after 1 week. On the other hand, post-molar GTN rarely occurs after hCG levels have spontaneously returned to normal, which allows for a shortened follow-up period in most women.[16] Hence, for a PHM, a single confirmatory hCG test 1 month after initial normalization is recommended. For a CHM, monthly hCG monitoring should continue for 6 months after hCG normalization.[16] Hormonal contraception is considered safe during post-molar follow-up period.[17]

Adherence to hormonal monitoring is essential for the early detection of post-molar GTN. To support this, nursing care and psychosocial play a role in maximizing patient compliance and preventing loss to follow-up.[18] In regions where patients live far from medical facilities,[19] telemedicine has proven effective for monitoring during post-molar follow-up.[20] Whenever possible, cases of molar pregnancy should be managed and monitored in referral centers.[21]

The risk of recurrence in subsequent pregnancies is low (range of 0.6%–2%) after a single molar pregnancy but increases significantly after consecutive molar pregnancies.[22] Mutations in the *NLRP7* and *KHDC3L* genes have been identified in women with recurrent molar pregnancies.[23]

5.2 | Co-existing normal pregnancy with mole

Molar pregnancies rarely co-exist with normal pregnancies. The diagnosis is usually made via ultrasound. Although there is a high risk of spontaneous abortion, approximately 40%–60% result in live births. The risk of GTN in co-existing molar and normal pregnancies compared with singleton molar pregnancies is increased from 15%–20% to 27%–46%. In the absence of complications and typical genetic and ultrasound findings, the pregnancy can proceed.[23–25]

5.3 | Gestational trophoblastic neoplasia

The treatment of GTNs is typically by chemotherapy. The best regimen depends on the stage and classification of the tumor. In the 2000 FIGO staging and classification (Tables 1 and 2), a score of 6 and below is classified as low risk, whereas a score above 6 is considered high risk.[9]

TABLE 1 FIGO staging and classification for gestational trophoblastic neoplasia.

FIGO Stage	Description
I	Gestational trophoblastic tumors strictly confined to the uterine corpus
II	Gestational trophoblastic tumors extending to the adnexa or to the vagina, but limited to the genital structures
III	Gestational trophoblastic tumors extending to the lungs, with or without genital tract involvement
IV	All other metastatic sites

TABLE 2 WHO scoring system based on prognostic factors modified as FIGO score.[a]

FIGO score	0	1	2	4
Age (years)	<40	≥40		
Antecedent pregnancy	Mole	Abortion	Term	
Interval from index pregnancy (months)	<4	4–6	7–12	>12
Pre-treatment hCG (mIU/mL)	$<10^3$	$>10^3$–10^4	$>10^4$–10^5	$>10^5$
Largest tumor size, including uterus[b] (cm)	–	3–4	≥5	–
Site of metastases, including uterus	Lung	Spleen, kidney	Gastrointestinal tract	Brain, liver
Number of metastases identified	–	1–4	5–8	>8
Previous failed chemotherapy	–	–	Single drug	Two or more drugs

[a]To stage and allot a risk factor score, a patient's diagnosis is allocated to a Stage as represented by a Roman numeral I, II, III, or IV. This is then separated by a colon from the sum of all the actual risk factor scores expressed in Arabic numerals, e.g. Stage II:4, Stage IV:9. This Stage and score will be allotted for each patient.

[b]Size of the tumor in the uterus.

BOX 3 First-line single agent chemotherapy regimens for low-risk gestational trophoblastic neoplasia.[9,10]

- MTX-FA 8-day regimen (50 mg MTX IM on days 1, 3, 5, and 7 with folinic acid 15 mg orally 24 h after MTX on days 2, 4, 6, 8); repeated every 2 weeks.
- MTX 0.4 mg/kg (25 mg max) IV or IM for 5 days every 2 weeks.
- Actinomycin-D pulse 1.25 mg/m^2 IV every 2 weeks.
- Actinomycin-D 0.5 mg IV for 5 days every 2 weeks.
- Others: MTX 30–50 mg/m^2 IM weekly, MTX 300 mg/m^2 infusion every 2 weeks.

Abbreviations: IM, intramuscularly; IV, intravenously; MTX-FA, methotrexate–folinic acid.

5.4 | Role of systemic therapy

5.4.1 | Low-risk gestational trophoblastic neoplasia

Low-risk GTN patients should be treated with one of the single-agent protocols for methotrexate or actinomycin-D (Box 3).[9] Both the 2016 Cochrane Review and a 2021 meta-analysis suggest superior efficacy of actinomycin-D, with a complete remission rate of 80.2% versus 65.1% for methotrexate (odds ratio [OR] 2.15, 95% confidence interval [CI] 1.70–2.73)[26] but included some studies using inferior methotrexate regimens. Actinomycin-D may also be associated with a higher incidence of adverse effects, including some hair thinning, nausea, and vomiting.

Approximately 30% of low-risk GTN patients develop resistance after single-agent chemotherapy.[27] Primary resistance is defined as a rise or plateau in β-hCG levels (<10% decrease) during the first two cycles, while secondary resistance is defined as a plateaued or rising β-hCG after initial effective treatment.[10]

Chemotherapy should be changed to the alternative single agent if toxicity prevents adequate dosing or if the hCG level plateaus or rises during treatment, indicating resistance. Switching from methotrexate to actinomycin-D achieves a response of 76%–87%, particularly in patients with relatively low hCG levels.[28,29] The chance of curative treatment strongly depends on the hCG level when actinomycin-D is initiated. Cutoff levels are regularly updated and physicians should consult local guidelines. Otherwise, multiple agents should be considered.

The complete response rate for avelumab as second-line treatment for methotrexate-failed low-risk patients is only 53%, disappointingly lower than second-line actinomycin-D, and is not recommended as standard salvage treatment in low-risk cases.[30]

Patients with FIGO scores of 5–6, particularly with metastatic disease (OR 1.9, 95% CI 1.1–3.2; $P=0.018$), choriocarcinoma histology (OR 3.7, 95% CI 1.9–7.4; $P=0.0002$), or elevated pre-treatment hCG levels (≥411 000 IU/L without metastases or ≥149 000 IU/L with metastases/choriocarcinoma), have an increased risk of single-agent treatment failure[31] and should start multi-agent chemotherapy. The remaining patients with FIGO scores of 5–6 are still best treated with one or two sequential single agents to spare women from the more toxic multi-agent treatment.[31]

Although hysterectomy is an option for selecting low-risk patients who have completed childbearing,[32] postoperative chemotherapy and hCG monitoring are still required. As a result, single-agent chemotherapy remains the standard of care for low-risk non-metastatic GTN and is more cost-effective than hysterectomy, which is not highly recommended.

After hCG normalization, 2–3 additional chemotherapy cycles reduce the risk of recurrence. The overall complete remission rates approach 100%.[2,10]

5.5 | High-risk gestational trophoblastic neoplasia

High-risk GTN requires multi-agent chemotherapy, the most common of which is EMA-CO (etoposide, methotrexate, actinomycin-D, cyclophosphamide, vincristine) (Table 3), although the Cochrane Database review failed to conclude which combination was best.[33] Approximately 20% of patients fail EMA-CO, but most are salvaged with further therapy; therefore, overall survival rates for high-risk GTN patients now exceed 96%.[34] A number of adverse features predict poorer outcomes, including an interval longer than 2.8 years from the antecedent pregnancy,[35] liver and/or brain metastasis,[36–38] and the management of such patients, together with salvage therapies are discussed below.

5.5.1 | Ultra high-risk gestational trophoblastic neoplasia and salvage therapy

Patients with a FIGO score of 13 and above, typically with liver, brain, or extensive metastases, do poorly when treated with first-line multi-agent chemotherapy[38,39] and are considered ultra-high risk.

For those with massive disease, starting with standard chemotherapy may cause sudden tumor collapse with severe bleeding, metabolic acidosis, myelosuppression, septicemia, and multiple organ failure, any or all of which can result in early death. This is avoided by using initial gentle induction chemotherapy with etoposide 100 mg/m^2 and cisplatin 20 mg/m^2 on days 1 and 2, repeated weekly for 1–3 weeks before starting normal dose treatment.[38,39]

For patients with liver metastases, with or without brain involvement, or a very high- risk score, EP (etoposide and platinum)/EMA or another more intensive chemotherapy regimen (Box 4), rather than EMA-CO, may yield a better response and outcome.[36] For such high-risk patients, a longer consolidation with four cycles of chemotherapy should be considered.

For patients with brain metastases, an increase in the methotrexate infusion to 1 g/m^2 will help the drug cross the blood–brain barrier and intrathecal methotrexate 12.5 mg may be used in some centers.[40] This can be given at the time of CO when EMA-CO is used or with the EP in the EP/EMA regimen. Some centers may give whole brain radiotherapy (WBRT) 3000 cGy in 200 cGy daily fractions, concurrent with chemotherapy, or use stereotactic or gamma knife radiation to treat existing or residual brain metastases after chemotherapy.[40] However, there is no evidence that WBRT improves cure rates[41] and it does add to long-term toxicity; therefore, it is not recommended in the new ESGO/GCIG/EOTTD/ISSTD guidelines.[10] Patients with resistance to EMA-CO are mostly salvaged with paclitaxel and etoposide alternating with paclitaxel and cisplatin (TE/TP) or with EP/EMA. In China, the 5FU- based FAEV regimen is also an effective salvage treatment as well as being an alternative to EMA/CO as a first-line therapy.[42] When there is resistance to EP/EMA or TE/TP, emerging data have shown complete responses rates to pembrolizumab or other PD1 targeting checkpoint immunotherapy agents, either alone or in combination

TABLE 3 EMA-CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine) chemotherapy.

Regimen 1[a]	
Day 1	
Etoposide	100 mg/m^2 IV infusion over 30 min
Actinomycin-D	0.5 mg IV bolus
Methotrexate	100 mg/m^2 IV bolus
	200 mg/m^2 IV infusion over 12 h
Day 2	
Etoposide	100 mg/m^2 IV infusion over 30 min
Actinomycin-D	0.5 mg IV bolus
Folinic acid rescue	15 mg IM or PO every 12 hours for four doses (starting 24 h after beginning the methotrexate infusion)
Regimen 2	
Day 8	
Vincristine	1 mg/m^2 IV bolus (2 mg max)
Cyclophosphamide	600 mg/m^2 IV infusion over 30 min

Abbreviations: EMA-CO, etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine; IM, intramuscularly; IV, intravenous; PO, orally.

[a]The two regimens alternate each week.

BOX 4 Salvage therapies.

- EP-EMA (etoposide, cisplatin, etoposide, methotrexate- and actinomycin-D)
- TP/TE (paclitaxel, cisplatin/paclitaxel, etoposide)
- MBE (methotrexate, bleomycin, etoposide)
- VIP or ICE (etoposide, ifosfamide, and cisplatin or carboplatin)
- BEP (bleomycin, etoposide, cisplatin)
- FA (5-fluorouracil, actinomycin-D)
- FAEV (floxuridine, actinomycin-D, etoposide, vincristine)
- High-dose chemotherapy with autologous bone marrow or stem cell transplant
- Immunotherapy with pembrolizumab

with chemotherapy, of over 70%.[43] This is much higher than that seen using other standard or high-dose chemotherapy (HDC) regimens (Box 4).[44] Consequently, the ESGO/GCIG/EOTTD/ISSTD guidelines recommend immunotherapy before HDC in the management pathway. Finally, surgical salvage should not be overlooked.

5.6 | Role of surgery

Surgery may play an important role in the management of GTN. Hysterectomy can be considered in cases of uncontrolled uterine bleeding, although it can often be avoided by performing uterine artery embolization. Minimally invasive versus open abdominal hysterectomy appears to have comparable oncologic outcomes with less blood loss and shorter hospital stay.[45] Laparotomy may be needed to stop bleeding in organs such as the liver and spleen, whereas neurosurgery is needed if there is intracranial bleeding or increased intracranial pressure. The resection of an isolated drug-resistant tumor may also be curative.[46,47] This may be particularly important in patients with resistance to combination chemotherapy.[46,48]

5.7 | Role of radiotherapy

Radiotherapy has a limited role in GTN, except in the treatment of brain metastasis, although its efficacy compared with intrathecal methotrexate is controversial.[46,47]

5.8 | PSTT/ETT

Both PSTT and ETT are less chemo-sensitive. Hysterectomy is the primary mode of treatment and also plays an important role in metastatic disease, including solitary lung metastasis. A localized lesion that is easily removed may be considered if fertility preservation is desired. In advanced stages, EP-EMA or TE/TP are recommended and immunotherapy may be considered.[10] Interval between antecedent pregnancy of more than 48 months and/or Stage IV disease remain the most significant adverse prognostic factors and are considered more informative than using FIGO scoring for GTN.[49] For APSN, if there is no visible residual lesion, conservative management is considered for fertility-sparing, otherwise, hysterectomy is recommended.[10]

5.9 | Follow-up

After GTN treatment, monthly hCG monitoring for at least 12 months is essential for symptoms of relapse. Any type of reliable contraception must be used throughout this period. Re-imaging of initial abnormal areas should be considered after treatment as a baseline for comparison for future recurrence. Future fertility, pregnancy, and offspring are typically not affected.

6 | ESTABLISHMENT OF A (NATIONAL) GTD CENTER

Centralized care is needed for optimal management of a rare disease like GTD. Centralization allows for a multidisciplinary team approach to improve patient outcomes, develop evidence or consensus-based guidelines, and collect data; however, this needs to be balanced against cost and time. Without centralization, treatment decisions will be inconsistent. Many countries lack specialized centers, leading to inconsistent treatment decisions and preventable deaths.[50] Creating a center is not easy and requires considerable time and dedication. It requires support from the national obstetrics and gynecology governing body and creation of a multidisciplinary team comprising gynecology, gynecological and medical oncology, interventional radiology, nurses, geneticists, and an hCG biochemical laboratory. Expert pathology is essential and can enable centralized review for the entire region. The center needs a clear model of care with clinical guidelines, a database, and a website, and to promote the center at national meetings. Annual funding is needed to support these activities along with patient information materials and to provide training and education for staff. Establishing connections with other centers through the International Society for the Study for Trophoblastic Diseases (ISSTD) or the European Organization for Treatment of Trophoblastic Diseases (EOTTD) is essential. This allows for assistance in complex cases, collaboration of research projects, and education.

AUTHOR CONTRIBUTIONS

All authors contributed to different sessions as well as to the whole article.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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