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REVIEW



The role of chemotherapy in high-risk gestational trophoblastic neoplasia

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ABSTRACT

Introduction: Gestational trophoblastic neoplasia (GTN) comprises a group of rare malignant disorders arising from placental trophoblastic tissue. Despite the remarkable chemosensitivity of high-risk GTN, delays in diagnosis, inadequate risk stratification, or inappropriate chemotherapy regimens remain the primary determinants of adverse outcomes. Understanding the role of chemotherapy is essential to ensure optimal management, maximize cure rates, and ultimately eliminate preventable mortality associated with this disease.

Areas covered: A narrative review of the literature was conducted using PubMed/MEDLINE, Scopus, and Web of Science, from database inception through July 2026, supplemented by manual review of reference lists and international guidelines. Study selection was based on clinical relevance, methodological rigor, and contribution to the understanding of chemotherapy strategies in high-risk disease. The evidence was qualitatively synthesized, focusing on risk stratification, first-line and salvage chemotherapy, treatment outcomes, mechanisms of chemoresistance, emerging therapies, and the management of relapsed disease.

Expert opinion: Although multiagent chemotherapy remains the cornerstone of treatment, future advances in molecular diagnostics, predictive biomarkers, targeted therapies, and immunotherapy, together with continued centralization of care, have the potential to further personalize treatment, reduce toxicity, and improve outcomes.

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Gestational trophoblastic neoplasia; high-risk; chemotherapy; immunotherapy; choriocarcinoma; placental site trophoblastic tumor; epithelioid trophoblastic tumor

1. Introduction

Gestational trophoblastic neoplasia (GTN) comprises a group of rare malignant disorders arising from placental trophoblastic tissue, representing the malignant end of the spectrum of gestational trophoblastic disease. These tumors include invasive mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor, entities that differ in their biological behavior, degree of invasion, and sensitivity to chemotherapy [1].

GTN is uniquely characterized by its direct relationship with prior gestation. Although most cases develop following a hydatidiform mole, accounting for approximately 50% of cases, a substantial proportion arises after nonmolar pregnancies, including spontaneous or induced abortions, ectopic pregnancies, and term or preterm deliveries. This broad spectrum of antecedent gestations underscores the need for clinical vigilance in any woman of reproductive age presenting with abnormal bleeding or metastatic disease, regardless of obstetric history [2–5].

One of the most distinctive and clinically valuable features of GTN is the presence of a highly sensitive and specific biological marker: human chorionic gonadotropin (hCG). Produced by trophoblastic cells, hCG enables a unique paradigm in oncology in which diagnosis can be established without histological confirmation, based solely on serial serum measurements. Beyond diagnosis, hCG serves as a robust tool for monitoring therapeutic

response, confirming remission, and detecting relapse at a very early stage, often before clinical or radiologic manifestations become evident [6,7].

Historically, GTN was a highly lethal disease, particularly in metastatic cases. However, the introduction of effective chemotherapy transformed its natural history, making GTN one of the most curable solid tumors in oncology, even in the presence of widespread metastatic disease. Cure rates exceeding 80–90% in high-risk disease have been consistently reported when patients are treated appropriately in specialized centers [8,9].

This remarkable chemosensitivity confers a unique responsibility upon clinicians: maternal deaths from GTN are largely preventable. Delays in diagnosis, inadequate risk stratification, or inappropriate chemotherapy regimens remain the primary determinants of adverse outcomes. Therefore, understanding the role of chemotherapy, particularly in high-risk GTN, is essential to ensure optimal management, maximize cure rates, and ultimately eliminate preventable mortality associated with this disease [10].

In this context, the present review aims to provide a comprehensive and clinically oriented overview of the role of chemotherapy in high-risk GTN, integrating historical perspectives, contemporary treatment strategies, and emerging therapeutic approaches. By situating chemotherapy within the

Article highlights

- High-risk gestational trophoblastic neoplasia (GTN) is a highly curable malignancy, with cure rates exceeding 80–90% when promptly diagnosed, appropriately risk-stratified, and managed in specialized reference centers.
- EMA/CO remains the standard first-line multiagent chemotherapy regimen for most patients with high-risk GTN and represents the therapeutic backbone against which alternative regimens are evaluated.
- Patients with ultra-high-risk GTN (FIGO score ≥ 13 or extensive visceral disease) require individualized management, including low-dose etoposide–cisplatin induction chemotherapy before full-dose multiagent treatment to reduce the risk of early treatment-related death.
- Chemoresistant or relapsed GTN remains potentially curable, and salvage treatment should be individualized according to prior chemotherapy exposure, disease distribution, and clinical status, with regimens such as EP/EMA and TP/TE playing important roles.
- Immune checkpoint inhibitors, particularly pembrolizumab, have emerged as highly effective therapeutic options for multidrug-resistant or relapsed GTN and are reshaping the salvage-treatment landscape.
- Centralization of care in specialized GTN centers is a critical determinant of treatment success and survival, facilitating accurate risk assessment, standardized chemotherapy, early recognition of resistance, and timely access to salvage strategies.

broader framework of GTN management, including diagnosis, risk stratification, and follow-up, this article seeks to highlight key principles that underpin optimal care, as well as current challenges and future directions in the treatment of this highly curable yet potentially lethal disease.

2. Methods

This study was designed as a narrative review aimed at providing a comprehensive and clinically oriented synthesis of the current evidence regarding the role of chemotherapy in high-risk GTN.

A structured literature search was conducted to identify relevant studies addressing epidemiology, pathophysiology, risk stratification, and, particularly, chemotherapy regimens and outcomes in high-risk GTN. The following electronic databases were consulted: PubMed/MEDLINE, Scopus, and Web of Science, from database inception through July 2026. Additional articles were identified through manual review of reference lists of key publications and consultation of international guidelines.

The search strategy included combinations of the following keywords: ‘*gestational trophoblastic neoplasia*,’ ‘*high-risk GTN*,’ ‘*chemotherapy*,’ ‘*EMA-CO*,’ ‘*EMA-EP*,’ ‘*immunotherapy*,’ ‘*choriocarcinoma*,’ ‘*trophoblastic disease*,’ and ‘*human chorionic gonadotropin*.’ Emphasis was placed on studies published in English, prioritizing seminal articles, large cohort studies, and contemporary guidelines from international organizations.

Given the rarity of GTN and the consequent scarcity of randomized controlled trials, evidence from retrospective series, institutional experiences from reference centers, and consensus guidelines was also considered essential and therefore included in the analysis.

Study selection was based on clinical relevance, methodological rigor, and contribution to the understanding of

chemotherapy strategies in high-risk disease. Data were qualitatively synthesized, with particular attention to treatment regimens, response rates, mechanisms of chemoresistance, and management of relapsed disease.

As a narrative review, this study did not follow a formal systematic review protocol, and no meta-analysis was performed. However, key principles of transparency and reproducibility were adopted, including explicit description of the search strategy, sources, and selection criteria, in order to provide a balanced and comprehensive overview of the topic.

3. Epidemiology of gestational trophoblastic neoplasia

GTN is a rare malignancy, with an estimated global incidence of approximately 22,000 cases annually [11], of which approximately 10–20% are classified as high-risk disease [12]. The epidemiology of GTN closely reflects the distribution of antecedent molar pregnancies, with higher incidence rates observed in low- and middle-income countries, particularly in regions of Southeast Asia, Latin America, and parts of Africa. Socioeconomic disparities and challenges in post-molar surveillance contribute to both increased incidence and delayed diagnosis in these settings [13,14].

Although GTN most commonly arises after a hydatidiform mole, a substantial proportion follows nonmolar gestations, including spontaneous or induced abortions, ectopic pregnancies, and term or preterm deliveries. Notably, GTN arising after nonmolar pregnancies is more often associated with delayed diagnosis and advanced-stage disease at presentation, thereby contributing disproportionately to the burden of high-risk GTN.

Population-based data further highlight important demographic disparities in GTN. Analyses from large national databases have shown that the disease is disproportionately represented at the extremes of reproductive age, with higher incidence observed among adolescents and women over 40 years. In addition, racial disparities have been identified, with Black women presenting more frequently at these age extremes and being overrepresented compared with national birth rates. These findings suggest that both biological and social determinants may influence disease occurrence and presentation [15].

Several clinical and biological factors are associated with the development of high-risk GTN. Among the most important are a long interval (>12 months) between the antecedent pregnancy and diagnosis, markedly elevated pretreatment hCG levels (particularly $>10^5$ IU/L), and a high tumor burden, reflected by large tumor size or the presence of multiple metastatic sites. The site of metastasis is also critical, with brain and liver involvement conferring a particularly poor prognosis [6].

Patient-related factors also play a role. Advanced maternal age and antecedent term pregnancy have been associated with more aggressive disease biology. Furthermore, delays in diagnosis, often due to lack of access to specialized care or inadequate hCG monitoring, remain a key determinant of progression to high-risk disease, particularly in resource-limited settings [6,10].

Importantly, health system factors significantly influence outcomes. Data from the United States have demonstrated that care for GTN remains highly fragmented, with the majority of institutions treating very few cases per year and only a small proportion of patients receiving care at high-volume centers. This lack of centralization is associated with worse outcomes and reinforces the need for the establishment of dedicated reference centers to optimize management of this rare but highly curable disease [15].

In this context, the epidemiology of high-risk GTN reflects not only intrinsic biological aggressiveness but also the influence of health system factors, including access to early diagnosis, structured follow-up, and specialized care. Recognition of these determinants is essential for timely identification, appropriate risk stratification, and early initiation of multiagent chemotherapy – key elements to optimize outcomes and prevent avoidable mortality.

4. Pathology of gestational trophoblastic neoplasia

A unique and defining feature of GTN is that, unlike most malignancies, its diagnosis is primarily established based on serial serum hCG measurements, rather than histopathological diagnosis. In clinical practice, rising or plateauing hCG levels following a gestational event are sufficient to initiate treatment, and biopsy is generally avoided due to the highly vascular nature of these tumors and the associated risk of severe hemorrhage [16].

Nevertheless, a thorough understanding of the histopathological spectrum of GTN remains essential [17]. Histologic subtype is closely related to biological behavior, metastatic potential, and, importantly, sensitivity to chemotherapy. This is particularly relevant in distinguishing tumors that are highly chemosensitive from those that may require alternative or multimodal approaches.

GTN encompasses four principal histologic entities: invasive mole, choriocarcinoma, placental site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT) [18].

Invasive mole is the most common form of GTN following a molar pregnancy. It is characterized by the presence of hydropic chorionic villi that invade the myometrium, often accompanied by proliferation of cytotrophoblast and syncytiotrophoblast. Despite its locally invasive behavior and occasional metastatic potential, invasive mole generally retains the biological features of molar tissue, including robust hCG production and high sensitivity to chemotherapy [18].

Choriocarcinoma represents the most aggressive and highly malignant form of GTN. Histologically, it is characterized by the absence of chorionic villi and the presence of anaplastic cytotrophoblast and syncytiotrophoblast with extensive hemorrhage and necrosis. This tumor demonstrates a marked propensity for early hematogenous dissemination, particularly to the lungs, brain, and liver, which occurs in approximately 20% of cases. Despite its aggressive clinical course, choriocarcinoma is highly sensitive to chemotherapy, and cure rates remain high even in metastatic disease [19].

In contrast, PSTT arises from intermediate (extravillous) trophoblast and is characterized by infiltrative growth within the myometrium composed of mononuclear trophoblastic

cells. PSTT produces relatively low levels of hCG compared to other forms of GTN, often secreting human placental lactogen (hPL) instead. Importantly, PSTT is less sensitive to chemotherapy than other forms of GTN [20,21].

Similarly, ETT is a rare variant derived from chorionic-type intermediate trophoblast. Histologically, it consists of nodular growth of epithelioid trophoblastic cells with eosinophilic cytoplasm and geographic necrosis, often mimicking carcinoma. Like PSTT, ETT is relatively chemoresistant [20,21].

In summary, while GTN is uniquely managed based on biochemical diagnosis and monitoring, the underlying histopathological diversity of these tumors has critical implications for prognosis and treatment. Recognizing these histopathological distinctions is essential because they reflect important differences in tumor biology, clinical behavior, and chemosensitivity.

5. Diagnosis, staging, and risk score of gestational trophoblastic neoplasia

The diagnosis of GTN is unique in oncology, as it relies primarily on biochemical criteria based on serial measurements of hCG, rather than histopathological confirmation. This paradigm reflects both the biology of trophoblastic tumors and the risks associated with invasive diagnostic procedures. According to FIGO (International Federation of Gynecology and Obstetrics), GTN can be diagnosed in the presence of a plateau in hCG levels over at least three weeks, defined by four consecutive values with minimal variation, or a rise in hCG levels across at least two weeks, defined by three consecutive increasing measurements [6,7]. In addition, histopathological diagnosis of gestational choriocarcinoma, PSTT, or ETT establishes the diagnosis of GTN [6,7]. International consensus recommendations emphasize that radiologic evidence of metastases in the setting of elevated hCG warrants immediate evaluation and treatment, even in the absence of classical postmolar surveillance patterns, a scenario that is particularly common in GTN arising after nonmolar pregnancies. Biopsy is generally contraindicated due to the highly vascular nature of these tumors and the associated risk of severe hemorrhage.

Once the diagnosis is established, accurate staging is essential to define disease extent and guide management. Initial evaluation typically includes a thorough clinical examination, with particular attention to pelvic and speculum assessment to identify vaginal metastases, in addition to pelvic ultrasound with Doppler and chest X-ray, which remain the foundation of staging. Although computed tomography (CT) has greater sensitivity for detecting pulmonary metastases, its routine use in all patients is not recommended. CT-based staging may lead to overestimation of disease burden, artificially increasing the FIGO score and resulting in upstaging of patients from low- to high-risk categories. Importantly, this may translate into the use of more intensive and potentially more toxic chemotherapy regimens without clear improvement in overall outcomes. Accordingly, chest X-ray-based assessment remains the standard approach for initial staging, balancing adequate risk stratification with avoidance of over-treatment [22,23].

When pulmonary metastases are identified or suspected, further imaging with chest computed tomography is recommended, and in patients with lung metastases of significant size or high-risk features, brain magnetic resonance imaging and abdominal imaging should be performed to assess for additional metastatic sites. Although advanced imaging modalities such as positron emission tomography may have a role in selected scenarios, they are not routinely indicated for staging.

GTN staging is based on the FIGO anatomic classification, which categorizes disease according to its extent of spread. In the revised FIGO 2026 system, stage I comprises tumors confined to the uterine corpus and cervix; stage II includes extension to the adnexa, vagina, or broad ligaments, but remains limited to genital structures; stage III comprises lung metastases, with or without genital tract involvement, and lymph-node metastases below the diaphragm; and stage IV encompasses all other metastatic sites, including lymph-node metastases above the diaphragm. For lymph-node involvement, a short-axis diameter ≥ 10 mm on imaging is used to define likely metastatic nodes, and the notation 'r' (imaging) or 'p' (pathology) should indicate the method by which nodal involvement was established [7].

This anatomic classification is complemented by the modified WHO (World Health Organization) prognostic scoring system adopted by FIGO, which integrates clinical and laboratory variables to refine risk stratification and guide therapeutic decision-making. The variables include patient age, type of antecedent pregnancy, interval since the index gestation, pre-treatment hCG level, largest tumor size, site of metastases, and number of metastases. Importantly, previous chemotherapy, which was included in the former scoring system, has been removed from the FIGO 2026 score. The revised classification formally stratifies patients into three risk groups: low-risk GTN (score 0–6), high-risk GTN (score 7–12), and ultra-high-risk GTN (score ≥ 13), as shown in Table 1 [7].

High-risk GTN is clinically significant because it is intrinsically associated with an increased likelihood of resistance to

single-agent chemotherapy, thereby necessitating the use of primary multiagent regimens to achieve cure. Although overall survival rates remain high with appropriate treatment, outcomes are less favorable than in low-risk disease, particularly among patients with very high prognostic scores. Within this group, a subset of patients with scores ≥ 13 has been recognized as having ultra-high-risk disease, characterized by a markedly increased risk of early complications and mortality [6]. The identification of this subgroup has important therapeutic implications, as it has driven the development of adapted treatment strategies aimed at reducing early deaths and improving overall outcomes [24,25].

In this context, the integration of biochemical diagnosis, imaging-based staging, and prognostic scoring represents one of the most sophisticated risk-adapted treatment models in oncology. Early identification of high-risk disease is critical, as delays in diagnosis or inadequate risk stratification may result in suboptimal therapy and preventable mortality. Within this framework, the classification of GTN is not merely descriptive but directly determines treatment strategy, with high-risk disease requiring prompt initiation of multiagent chemotherapy, a principle that underpins the management of these patients.

6. Treatment of high-risk gestational trophoblastic neoplasia

6.1. Hysterectomy

Although chemotherapy remains the cornerstone of treatment in GTN, hysterectomy may play a relevant adjunctive role in selected patients. Surgical management can be considered in women with completed childbearing, particularly in the presence of significant uterine disease burden, uncontrolled uterine bleeding, or localized chemoresistant disease. In such scenarios, hysterectomy may reduce tumor burden, facilitate more rapid normalization of hCG levels, and potentially decrease the number of chemotherapy cycles required [26,27].

Table 1. Staging and classification of gestational trophoblastic neoplasia according to the International Federation of Gynecology and Obstetrics.

GTN: FIGO staging and classification

FIGO anatomic staging

Stage I: GTN strictly confined to the uterine corpus and cervix

Stage II: GTN extending to the adnexa or to the vagina or broad ligaments, but limited to the genital structures

Stage III: GTN extending to the lungs, with or without genital tract involvement, or lymph node metastases below the diaphragm*

Stage IV: All other metastatic sites, including lymph node metastases above the diaphragm*

*For lymph node metastases, the notation 'r' (imaging) or 'p' (pathology) should be added to indicate the method used for stage allocation. A lymph node short-axis diameter ≥ 10 mm on imaging should be used to define likely metastatic involvement. Surgical lymph node staging is not recommended.

Modified WHO prognostic scoring system as adapted by FIGO#

Scores	0	1	2	4
Age	<40	≥ 40	–	–
Antecedent pregnancy	Mole	Abortion	Term	–
Interval months from index pregnancy	<4	4– <7	7– <13	≥ 13
Pre-treatment serum hCG (IU/L)	<10 ³	10 ³ – <10 ⁴	10 ⁴ – <10 ⁵	$\geq 10^5$
Largest tumor size (including uterus)	–	3– <5 cm	≥ 5 cm	–
Site of metastases	Lung	Spleen, kidney	Gastro-intestinal	Liver Brain
Number of metastases	–	1–4	5–8	>8

#Reproduced from Ngan HYS, Seckl MJ, Horowitz N, et al. FIGO staging for gestational trophoblastic neoplasia: 2026. *Int J Gynecol Obstet.* 2026; 00: 1–9. doi: 10.1002/ijgo.71229. Published by John Wiley and Sons as an open access article under the Creative Commons CC BY license.

GTN, gestational trophoblastic neoplasia; FIGO, International Federation of Gynecology and Obstetrics; hCG, human chorionic gonadotropin; IU/L, International units per liter; WHO, World Health Organization.

However, it is essential to emphasize that hysterectomy does not replace systemic therapy, even in cases of apparently localized disease, given the high propensity for occult micro-metastatic dissemination. Therefore, chemotherapy remains mandatory in virtually all cases of GTN, including those undergoing surgical intervention.

6.2. Chemotherapy in high-risk gestational trophoblastic neoplasia

6.2.1. EMA/CO regimen

Multiagent chemotherapy is the standard of care for high-risk GTN, with the EMA/CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine) regimen being the most widely used first-line treatment [28]. The efficacy of EMA/CO has been confirmed in a large multinational multicenter study, which demonstrated a remission rate of 76.1% and an overall survival of 89% in patients treated with this regimen. Notably, remission rates increased to over 87% in patients requiring salvage therapy after initial resistance, highlighting the effectiveness of subsequent treatment lines [29].

Importantly, the study also identified key predictors of resistance, including the presence of two or more metastatic organs, elevated pretreatment hCG levels, and a longer interval from the antecedent pregnancy. Furthermore, resistance to EMA/CO emerged as the strongest independent predictor of disease-specific mortality, reinforcing the need for early identification and appropriate escalation of therapy [29].

There is growing interest in treatment de-escalation strategies in high-risk GTN, particularly the potential use of EMA without the CO component in selected patients. Historically, regimens such as M-EA (methotrexate, etoposide, and actinomycin D) and EMA/CO have demonstrated comparable survival outcomes, supporting the concept that the core EMA backbone is highly effective. More recent retrospective data suggest that, when adjusted for baseline prognostic factors, outcomes with EMA alone may be similar to those achieved with EMA/CO, despite the latter being preferentially used in patients with more adverse features. In addition, EMA/CO has been associated with increased toxicity, including higher rates of neutropenia, infection, peripheral neuropathy, and treatment delays, which may negatively impact patient experience. These observations raise the possibility that selected patients with high-risk GTN, particularly those at the lower end of the high-risk spectrum, could be effectively treated with less intensive regimens. However, given the retrospective nature of the available evidence and the risk of selection bias, EMA/CO remains the standard of care. Prospective studies are warranted to better define the role of EMA-based de-escalation strategies, with the aim of maintaining excellent cure rates while reducing treatment-related toxicity [30,31].

Regarding toxicity, EMA/CO is generally well tolerated, although adverse events are common. In the largest multinational multicenter study of EMA/CO to date, grade ≥ 2 toxicities occurred in 62.7% of patients. Hematologic toxicity was particularly frequent, with anemia and neutropenia reported in 59.7% and 31.6% of patients, respectively; other common adverse events included oral mucositis (34.9%), abnormal liver function tests (19.4%), neuropathy (11.0%), and

thrombocytopenia (9.9%). These toxicities are generally manageable with appropriate supportive care; G-CSF prophylaxis was administered to 76.0% of patients. Nevertheless, treatment delays due to toxicity occurred in 53.8% of patients with available data [29]. For this reason, the prophylactic use of granulocyte colony-stimulating factor is strongly recommended, ideally initiated before the first episode of neutropenia, to maintain dose intensity and avoid delays in chemotherapy cycles [1].

An important point of discussion in the management of high-risk GTN concerns central nervous system (CNS) prophylaxis. Although intrathecal methotrexate has historically been used in some centers, particularly in patients with high tumor burden or pulmonary metastases, its routine use remains controversial. Increasing evidence suggests that systemic therapy with adequate CNS penetration is sufficient in most cases, and many reference centers have moved away from routine intrathecal administration, reserving it for selected patients with confirmed or high suspicion of CNS involvement [1].

In contrast, the use of high-dose intravenous methotrexate, typically at doses of 1 g/m^2 , plays a well-established role in specific clinical scenarios. This approach is particularly indicated in patients with brain metastases or at high risk of CNS dissemination, as it ensures adequate penetration across the blood–brain barrier and improves intracranial disease control. In such cases, high-dose methotrexate is incorporated into treatment protocols with appropriate leucovorin rescue and careful monitoring to mitigate toxicity [32,33].

Treatment should be continued until complete remission is achieved, as defined by sustained normalization of serum hCG levels. Once remission is reached, the administration of consolidation chemotherapy with an additional three to four cycles is recommended, as this approach has been associated with a reduced risk of relapse.

6.2.2. FAEV regimen

Alternative multiagent regimens have been explored, particularly in specific geographic contexts. The FAEV regimen (floxuridine, actinomycin D, etoposide, and vincristine) has been reported primarily in Chinese cohorts, where it has shown promising efficacy in high-risk GTN [34–36].

However, it is important to recognize that the experience with FAEV remains largely regional, and its use has not been widely adopted in Western centers. Differences in patient populations, treatment protocols, and reporting standards limit direct comparisons with EMA/CO, which remains the global standard.

7. Chemoresistance and salvage therapy for high-risk gestational trophoblastic neoplasia

Resistance to chemotherapy represents the principal therapeutic challenge in high-risk GTN. It is defined by plateauing or rising hCG levels over at least two consecutive treatment cycles, or the appearance of new metastatic lesions, reflecting failure of tumor response.

In such cases, prompt modification of therapy is required. Several salvage regimens have been developed for patients with chemoresistant disease, each with distinct pharmacologic rationale and clinical indications. Among the most widely used

is EP/EMA, which consists of etoposide and cisplatin alternating with the EMA backbone (etoposide, methotrexate, and actinomycin D) [37]. This regimen is commonly employed as a second-line strategy following resistance to EMA/CO and has demonstrated high efficacy, particularly in patients with persistent but chemosensitive disease. The addition of cisplatin enhances cytotoxic activity and may overcome resistance to prior regimens, although at the expense of increased hematologic and renal toxicity [1].

Another important salvage option is the TP/TE regimen, which alternates paclitaxel and cisplatin (TP) with paclitaxel and etoposide (TE). This combination is particularly useful in patients with more advanced or heavily pretreated disease, offering a non-cross-resistant mechanism of action compared to traditional EMA-based regimens. Paclitaxel-based combinations have shown meaningful activity in refractory GTN and are often better tolerated in selected patients, although cumulative neurotoxicity and myelosuppression require careful monitoring [1,38].

In patients with highly aggressive or rapidly progressive disease, particularly those with multiply relapsed or refractory GTN after failure of conventional platinum-based salvage chemotherapy, further chemotherapy intensification may be considered, especially when immune checkpoint inhibitors are unavailable, contraindicated, or have failed [1]. One approach is escalated EP, consisting of etoposide 500 mg/m² and cisplatin 60 mg/m² administered on one day every 2 weeks [39,40]. Although clinical experience remains limited, escalated EP represents a potentially more accessible dose-intensification strategy because, unlike high-dose chemotherapy (HDC), it does not require autologous hematopoietic stem-cell support [41]. HDC, most commonly employing dose-intensive platinum- and etoposide-based regimens with autologous peripheral blood stem-cell support, has historically been reserved for highly selected patients with multiply refractory disease. In the largest reported series, 13 of 32 patients (41%) remained disease-free following HDC with or without additional treatment, while 7 of 32 (22%) achieved sustained complete remission attributable to HDC alone [41]. Both approaches require careful patient selection, close supportive care, and management in specialized centers because of their substantial toxicity. In the contemporary era, the favorable activity and lower treatment complexity of immune checkpoint inhibitors have moved these intensive chemotherapy strategies later in the treatment pathway; nevertheless, escalated EP and HDC remain relevant salvage options, particularly in settings where immunotherapy is unavailable or after immunotherapy failure [1,39–41]. The choice among these regimens depends on several factors, including prior treatment exposure, extent of disease, patient performance status, and the urgency of disease control. Importantly, management of chemoresistant GTN requires expertise and should ideally be conducted in reference centers with experience in complex, multimodal treatment strategies.

8. Immunotherapy in resistant high-risk gestational trophoblastic neoplasia

More recently, immunotherapy has emerged as a promising option for patients with multidrug-resistant high-risk GTN [42–46]. Checkpoint inhibitors targeting the PD-1/PD-L1 axis have

demonstrated encouraging results, particularly pembrolizumab, which has shown high rates of durable remission in heavily pretreated patients [47].

Pembrolizumab has been most commonly administered at a dose of 200 mg intravenously every 3 weeks, although weight-based dosing at 2 mg/kg every 3 weeks has also been reported in earlier studies. Treatment is typically continued until normalization of serum hCG levels, with some centers administering an additional three consolidation cycles after complete biochemical remission to reduce the risk of relapse. Response to therapy is monitored through serial hCG measurements, often demonstrating a rapid decline within the first few cycles [47].

Clinical data suggest that approximately 70–80% of patients with multidrug-resistant GTN may achieve sustained remission with pembrolizumab, even after failure of multiple prior chemotherapy regimens. Responses are frequently durable, and treatment discontinuation after remission has been associated with long-term disease control in a substantial proportion of patients [47,48].

More recently, pembrolizumab has also been explored in combination with chemotherapy, particularly in patients with high-risk or ultra-high-risk disease, with the aim of enhancing early tumor control and potentially reducing chemotherapy-related toxicity. Preliminary reports suggest that this combined approach may accelerate hCG decline and improve response rates, although robust prospective data are still lacking [40,49].

The toxicity profile of pembrolizumab in GTN is generally favorable and more manageable compared to conventional multiagent chemotherapy. Most adverse events are mild to moderate and include fatigue, rash, and thyroid dysfunction, while immune-related toxicities affecting endocrine, hepatic, or pulmonary systems are less frequent but require prompt recognition and management [47].

In addition, emerging data from Chinese cohorts using combinations such as Camrelizumab plus antiangiogenic agents (Apatinib) further support the role of immunotherapy as a salvage strategy in refractory disease, reinforcing the paradigm shift toward immune-based therapies in the management of resistant GTN [50].

9. Treatment of ultra-high-risk gestational trophoblastic neoplasia

Ultra-high-risk GTN, FIGO/WHO score ≥ 13 , represents a distinct subgroup of patients characterized by an exceptionally high tumor burden, frequent visceral metastases, particularly involving the liver and brain, and a substantially increased risk of early mortality. In these patients, the major threat is not only chemoresistance but also early death related to tumor hemorrhage, organ failure, or rapid disease progression during the initial phases of treatment [24,25].

For this reason, the management of ultra-high-risk GTN differs from that of standard high-risk disease and requires a carefully staged therapeutic approach. Immediate initiation of full dose multiagent chemotherapy may precipitate rapid tumor necrosis, leading to catastrophic complications such as hemorrhage, particularly in highly vascular metastatic sites.

To mitigate this risk, induction chemotherapy with low-dose etoposide and cisplatin (EP) has been adopted in many specialized

centers. This strategy typically consists of short-course, reduced-intensity EP administered over the first 1–2 weeks, aiming to achieve gradual tumor cytoreduction and clinical stabilization before escalation to definitive therapy. This approach has been associated with a reduction in early mortality, particularly in patients with extensive pulmonary, hepatic, or central nervous system involvement [51].

Following initial stabilization, patients are transitioned to standard multiagent chemotherapy, most commonly EMA/CO, which remains the backbone of treatment. In cases of liver and/or brain metastases, suboptimal response or early evidence of resistance, escalation to more intensive regimens such as EP/EMA (or TP/TE) are recommended. This sequential strategy allows for both safer initiation of therapy and maintenance of therapeutic intensity once the immediate risk of treatment-related complications has been reduced [1].

The management of ultra-high-risk GTN requires meticulous supportive care. Patients are at high risk for complications including severe hemorrhage, respiratory compromise, sepsis, and metabolic disturbances. Close monitoring in high-dependency or intensive care settings may be necessary during the initial phases of treatment. Early involvement of multidisciplinary teams, including critical care, interventional radiology, and surgical specialists, is often essential [1].

Central nervous system involvement requires particular attention. In patients with brain metastases, treatment strategies may include high-dose intravenous methotrexate to ensure adequate CNS penetration, in addition to systemic chemotherapy.

Stereotactic radiotherapy has a limited but important role in the management of GTN, particularly in patients with central nervous system involvement. In selected cases of brain metastases, stereotactic radiosurgery may be used as an adjunct to systemic chemotherapy to achieve local control, reduce the risk of hemorrhage, and manage residual or refractory lesions. This approach is especially valuable for patients with a limited number of well-defined intracranial metastases, offering precise, high-dose radiation while minimizing damage to surrounding brain tissue [52]. Radiotherapy may also be considered in cases of persistent or symptomatic metastatic disease not fully responsive to chemotherapy. However, its use should be individualized and integrated within a multidisciplinary treatment strategy, as chemotherapy remains the cornerstone of management in GTN.

Despite the severity of presentation, ultra-high-risk GTN remains a potentially curable condition when managed in experienced centers. Outcomes have improved significantly with the adoption of induction strategies, optimized chemotherapy sequencing, and advances in supportive care. More recently, immunotherapy has emerged as a promising option in patients with refractory disease, offering an additional therapeutic avenue in this highly challenging subgroup.

10. Treatment for relapsed gestational trophoblastic neoplasia

Relapse in GTN is defined as the re-elevation of serum hCG levels after achieving complete remission, in the absence of a new pregnancy and after exclusion of other causes of false-positive hCG, such as pituitary secretion or assay interference. Most relapses occur within the first 12 months following

remission, reinforcing the importance of strict post-treatment surveillance.

The management of relapsed GTN requires prompt reassessment of disease extent and careful therapeutic planning. A comprehensive evaluation should be undertaken to identify new or previously undetected metastatic sites, including repeat imaging of the chest, abdomen, pelvis, and central nervous system when clinically indicated. This step is critical, as relapse may be associated with changes in disease distribution and tumor biology.

Treatment of relapsed high-risk GTN depends primarily on prior chemotherapy exposure and the pattern of disease recurrence. In general, therapeutic escalation is required, with selection of regimens that are non-cross-resistant to those previously administered. Patients who relapse after first-line multiagent chemotherapy, typically EMA/CO, are managed with second-line or salvage regimens such as EP/EMA or TP/TE, both of which have demonstrated meaningful activity in this setting. The choice of regimen should be individualized based on prior treatment tolerance, extent of disease, and clinical urgency, with the goal of achieving rapid disease control while minimizing cumulative toxicity [38].

In cases of recurrent disease following multiple lines of chemotherapy, further escalation strategies may be necessary, including high-dose platinum-based regimens or, increasingly, immunotherapy with checkpoint inhibitors such as pembrolizumab, which has shown encouraging efficacy in multidrug-resistant GTN [1].

Surgery may also play an important role in the management of relapse, particularly in patients with localized, chemotherapy-resistant lesions. Resection of isolated metastatic foci, such as pulmonary nodules, uterine masses, or, less commonly, brain or hepatic lesions, can contribute to disease control and facilitate subsequent systemic therapy. Careful patient selection is essential, and surgical intervention should be performed in specialized centers with experience in the management of GTN [1]. In this setting, relapse in GTN remains a highly treatable condition when managed appropriately. The combination of accurate biochemical monitoring, timely imaging reassessment, strategic escalation of chemotherapy, and selective use of surgery allows for high rates of salvage and long-term survival, even in patients with recurrent disease.

Table 2 summarizes the landmark and practice-changing studies that have shaped the systemic treatment of high-risk GTN, encompassing first-line multiagent chemotherapy, induction strategies for ultra-high-risk disease, salvage chemotherapy, and immune checkpoint inhibition for chemoresistant or relapsed disease.

11. Management of placental site trophoblastic tumor and epithelioid trophoblastic tumor

PSTT and ETT represent rare variants of GTN characterized by distinct biological behavior, including lower proliferative activity, reduced hCG production, and relative resistance to chemotherapy. These features differentiate them fundamentally from other forms of GTN and have important implications for diagnosis, prognostic assessment, and treatment [21].

Table 2. Landmark and practice-changing studies in the systemic treatment of high-risk gestational trophoblastic neoplasia.

Study design / population	N	Treatment	Main outcomes	Key clinical implication
FIRST-LINE MULTIAGENT CHEMOTHERAPY				
Jareemit et al. [29] Multinational, multicenter retrospective study of GTN treated at reference centers in the USA, Thailand, Hungary, and Brazil (1986–2019)	335 (266 primary EMA/CO; 69 EMA/CO after prior single-agent treatment)	EMA/CO	Overall remission 76.1%; survival 89%. Remission was 73.3% with primary EMA/CO and 87.0% after prior single-agent therapy. Among EMA/CO-resistant patients, subsequent salvage treatment increased sustained remission to 87.2%.	Largest multinational experience with EMA/CO; confirms its effectiveness as a standard multiagent regimen and highlights resistance as a major determinant of disease-specific mortality.
Singh et al. [31] Retrospective cohort of high-risk GTN treated first-line at the Sheffield Trophoblastic Disease Center (1998–2018)	79 (M-EA 59; EMA/CO 20)	M-EA vs EMA/CO	Primary hCG complete response: 84.7% with M-EA and 70% with EMA/CO. Overall survival: 96.6% with M-EA and 100% with EMA/CO. EMA/CO was associated with greater hematologic, infectious, and neurologic toxicity and more treatment delays/hospitalizations.	Both regimens achieved excellent survival; highlights opportunities to refine treatment intensity and toxicity.
Ji et al. [36] Randomized controlled trial comparing first-line multiagent chemotherapy for high-risk GTN	94 randomized; 89 analyzed (FAEV 46; EMA/CO 43)	FAEV vs EMA/CO	Complete remission: 89.1% vs 79.1% ($p = 0.193$); relapse: 8.7% vs 9.3% ($p = 0.604$). No disease-related deaths. Grade 4 myelosuppression was initially more frequent with FAEV, but the difference disappeared with G-CSF support.	Prospective randomized evidence that FAEV can provide efficacy comparable to EMA/CO and may represent an alternative first-line regimen in experienced centers.
ULTRA-HIGH-RISK DISEASE / INDUCTION CHEMOTHERAPY				
Alifrangis et al. [51] Retrospective cohort from Charing Cross Hospital of high-risk GTN treated from 1995–2010	140 high-risk patients; 33 received low-dose EP induction	Low-dose EP induction followed by EMA/CO in selected patients with high disease burden	Overall survival 94.3%. Early mortality was 0.7% (1/140), compared with approximately 7.2–7.8% in the historical pre-1995 cohort.	Landmark evidence establishing low-dose etoposide–cisplatin induction before full-dose EMA/CO as a strategy to reduce early deaths in patients with very high disease burden.
SALVAGE CHEMOTHERAPY				
Wang et al. [38] Salvage-treatment series of heavily pretreated relapsed/refractory GTN	24 (16 with Wangfailed previous chemotherapy; 8 switched because of treatment toxicity)	TP/TE	Among 16 refractory/relapsed patients: CR 19%, PR 31%, overall response 50%, OS 44%; OS was 70% when patients previously resistant to cisplatin were excluded. Among 8 patients switched because of toxicity, OS was 75%.	Established TP/TE as an active, relatively well-tolerated, non-cross-resistant salvage option, particularly in patients without established platinum resistance.
Frijstein et al. [41] Retrospective international series of refractory choriocarcinoma and poor-prognosis PSTT/ETT	32	High-dose chemotherapy with peripheral blood stem-cell support	Sustained complete response after high-dose chemotherapy alone in 7 patients; 13/32 (41%) remained disease-free after high-dose chemotherapy with or without subsequent treatment.	High-dose chemotherapy can salvage a selected minority of heavily pretreated patients, but its toxicity and limited efficacy restrict its role to highly selected refractory cases.
IMMUNE CHECKPOINT INHIBITION				
Ghorani et al. [45] Case series of patients with genetically confirmed, multidrug-resistant GTN after failure of multiple prior treatment lines, including high-dose chemotherapy in two patients	4	Pembrolizumab	Sustained complete remission in 3/4 patients (75%); one patient had progressive disease. All three responders received five consolidation cycles after hCG normalization.	First clinical series demonstrating that PD-1 blockade can induce durable remission in otherwise highly treatment-refractory GTN, providing proof-of-concept for immune checkpoint inhibition in this disease.
Cheng et al. [50](CAP-01) Single-arm, open-label phase II trial in high-risk chemorefractory or relapsed GTN after at least two unsuccessful multidrug regimens	20	Camrelizumab + apatinib	Objective response 55% (11/20; 95% CI 32–77); complete response 50% (10/20; 95% CI 27–73). Median follow-up 18.5 months; median PFS approximately 9.5 months. No grade 4–5 treatment-related adverse events.	Prospective phase II evidence demonstrating substantial activity of PD-1 blockade combined with antiangiogenic therapy in heavily pretreated GTN.
Barcellos et al. [48] Systematic review and meta-analysis of published studies evaluating pembrolizumab for GTN	15 studies	Pembrolizumab, alone or combined with other treatment	Pooled sustained complete remission 71.59% (95% CI 53.27–84.78%), without significant heterogeneity. Response did not significantly differ according to age, histologic subtype, interval before immunotherapy, or concomitant chemotherapy.	Provides a contemporary quantitative synthesis supporting pembrolizumab as an effective treatment for multidrug-resistant or relapsed GTN, including PSTT and ETT.

Abbreviations: CI, confidence interval; CR, complete response; EMA/CO, etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine; EP, etoposide and cisplatin; ETT, epithelioid trophoblastic tumor; FAEV, floxuridine, actinomycin D, etoposide, and vincristine; G-CSF, granulocyte colony-stimulating factor; GTN, gestational trophoblastic neoplasia; hCG, human chorionic gonadotropin; M-EA, methotrexate, etoposide, and actinomycin D; OS, overall survival; PFS, progression-free survival; PR, partial response; PSTT, placental site trophoblastic tumor; TP/TE, paclitaxel/cisplatin alternating with paclitaxel/etoposide.

The relative chemoresistance of PSTT and ETT is supported by clinical outcome data, although the rarity of these tumors and the predominantly retrospective nature of the available evidence limit direct comparisons. In a large UK cohort of PSTT/ETT, 6 of 13 patients (46%) treated with chemotherapy alone failed to achieve long-term remission and died from their disease, while two additional patients initially achieving remission subsequently relapsed and required surgery [53]. For ETT, a systematic review of 147 reported cases showed that first-line chemotherapy resulted in complete and partial responses in 60.0% and 24.2% of patients, respectively, while 15.8% had no response; among patients treated with EMA/CO, complete remission was achieved in 56.8% [54]. These findings quantitatively support the lower chemosensitivity of PSTT and ETT compared with conventional GTN, particularly choriocarcinoma, and reinforce the central role of surgery in the management of these rare histologic subtypes. The FIGO 2026 classification formally establishes a distinct staging approach for PSTT and ETT, for which the modified WHO prognostic scoring system is no longer used. Instead, anatomical stage is combined with the interval from the antecedent pregnancy for stages I–III: an interval < 48 months is classified as a good prognostic factor, whereas an interval ≥ 48 months is classified as a poor prognostic factor. Stage IV disease is considered to have a poor prognosis irrespective of this interval. This revision formally incorporates into the FIGO staging system the well-established prognostic importance of the interval from the antecedent pregnancy in these tumors [7]. Surgical management plays a central role in the treatment of PSTT and ETT. For patients with stage I disease, hysterectomy is the standard of care and is often curative, given the predominantly localized nature of these tumors at presentation. In contrast to other forms of GTN, chemotherapy alone is generally insufficient in this setting due to the intrinsic chemoresistance of intermediate trophoblastic cells [1].

In patients with more advanced disease, combined modality treatment is required. For stage II and III disease, hysterectomy followed by multiagent chemotherapy, most commonly the EMA/CO regimen, is recommended. In stage IV disease, more intensive regimens such as EP/EMA are typically employed, reflecting the more aggressive clinical course and reduced chemosensitivity observed in metastatic PSTT and ETT [1].

Given the lower levels of hCG production in these tumors, biochemical monitoring alone is insufficient for surveillance. As such, prolonged follow-up with greater emphasis on imaging is required, including periodic radiologic assessment to detect recurrence. This approach reflects the potential for clinically significant disease progression in the setting of only minimal or modest elevations in hCG [1].

Fertility-sparing surgery may be considered in highly selected patients with localized disease who strongly desire future fertility. However, this approach remains exceptional and should only be undertaken in specialized centers with extensive experience in GTN. When conservative surgery is performed, achieving adequate oncologic margins is critical. A margin of at least 1 cm of healthy tissue is generally considered a key criterion for surgical success, as incomplete resection is associated with a high risk of recurrence [55].

PSTT and ETT require a fundamentally different therapeutic approach compared to other forms of GTN, with primary surgical management, limited reliance on prognostic scoring

systems, and tailored use of chemotherapy based on disease stage. Careful long-term surveillance is essential, given the potential for late recurrence and the limitations of hCG as a sole biomarker in these subtypes.

12. Follow-up for high-risk gestational trophoblastic neoplasia

Monitoring of serum hCG is central to the management of high-risk GTN and represents the primary tool for assessing treatment response, defining remission, and detecting relapse. Follow-up should be based primarily on serial hCG measurements, as biochemical monitoring is more sensitive and clinically relevant than imaging in this disease. During chemotherapy, hCG levels are typically measured biweekly, with remission defined as normalization sustained over three consecutive measurements.

Following remission, long-term surveillance is mandatory, with serial hCG monitoring for at least 12 months. This period is critical, as the majority of relapses occur within the first year after completion of treatment. Data from large national cohorts have shown that over 70–85% of recurrences occur during this interval, with a median time to relapse of approximately four months. The risk of recurrence declines substantially thereafter and becomes exceedingly low over time, with no relapses observed beyond seven years of follow-up. These findings support a more tailored approach to surveillance duration and suggest that lifelong hCG monitoring may be unnecessary in most patients after prolonged remission [56].

In patients with metastatic disease, imaging should be interpreted with caution during follow-up. Radiologic reassessment is generally not recommended at short intervals after completion of treatment, as metastatic lesions – particularly in the lungs – may take several months to regress completely. In this context, imaging performed earlier than 6–12 months after treatment completion may show persistent abnormalities that do not reflect active disease [57].

Residual pulmonary lesions after completion of chemotherapy are relatively common and do not necessarily indicate persistent or recurrent disease. Available evidence suggests that the presence of residual lung lesions is not significantly associated with an increased risk of relapse, despite a numerically higher recurrence rate observed in some cohorts. These findings reinforce that clinical decision-making should be guided primarily by hCG trends rather than imaging alone, and that residual radiologic abnormalities should not prompt additional treatment in the absence of biochemical evidence of disease activity [58].

Strict contraception is strongly recommended during the first 12 months after completion of chemotherapy to avoid confusion between rising hCG levels due to pregnancy and disease recurrence. Importantly, hormonal contraception has been shown to be safe in this setting and does not adversely affect prognosis or increase the risk of relapse [59].

13. Impact of chemotherapy on reproductive outcomes in high-risk GTN

Despite the use of intensive multiagent chemotherapy, reproductive outcomes in patients treated for high-risk GTN are generally favorable. Most women retain ovarian function

after treatment, and menstrual cycles typically resume within a few months following completion of therapy, particularly in younger patients [60,61]. Although multiagent chemotherapy may hasten the onset of natural menopause by approximately three years and frequently induces temporary amenorrhea, the risk of permanent ovarian failure or infertility remains low [60]. The EMA/CO regimen, despite its transient gonadal toxicity, does not appear to significantly compromise long-term fertility, and subsequent pregnancies are common, with a high likelihood of resulting in live and healthy newborns. Importantly, there is no consistent evidence of increased rates of congenital abnormalities, miscarriage, or obstetric complications attributable to prior chemotherapy exposure [62].

However, certain factors may influence reproductive outcomes. Increasing age at the time of treatment and cumulative exposure to alkylating agents, such as cyclophosphamide, are associated with a higher risk of diminished ovarian reserve and, in rare cases, premature ovarian insufficiency. These risks, although relatively low, should be discussed with patients, particularly those nearing the end of their reproductive lifespan. Importantly, given the low overall risk of long-term ovarian insufficiency and the urgency of initiating treatment in high-risk GTN, chemotherapy should not be delayed for the purpose of oocyte retrieval or fertility preservation procedures. In contrast, high-dose chemotherapy is associated with a substantial risk of permanent amenorrhea, and successful pregnancies following such treatment have not been consistently reported [60,61].

More recently, immunotherapy has emerged as a promising therapeutic option and may offer effective disease control with potentially reduced gonadotoxicity compared to conventional chemotherapy. Although experience remains limited, the first successful pregnancy following immunotherapy for GTN has been described, suggesting a favorable reproductive profile [60,61].

Another critical aspect is the timing of subsequent pregnancy. Conception is generally discouraged during the first 12 months following completion of chemotherapy, as this period corresponds to the highest risk of relapse and may complicate the interpretation of rising hCG levels. Pregnancies occurring within the first 6 months after treatment have been associated with an increased risk of miscarriage, further supporting the recommendation to delay conception [63,64]. After the recommended interval, pregnancy is considered safe and does not appear to increase the risk of recurrence. In addition, a prior history of molar pregnancy is associated with a modestly increased risk of recurrence in subsequent pregnancies, with an estimated incidence of approximately 1–2%. For this reason, early ultrasound evaluation and careful monitoring of hCG levels are recommended in all future pregnancies.

Data on fertility-sparing approaches in PSTT and ETT remain limited, and such strategies should be pursued with caution in highly selected patients. Continued systematic collection of long-term reproductive data, particularly in high-risk GTN, remains essential to further refine patient counseling and optimize care.

Accordingly, the prognosis for future fertility in patients treated for high-risk GTN is excellent. The combination of

high cure rates and preservation of reproductive potential represents one of the most remarkable aspects of trophoblastic disease management, underscoring the importance of balancing oncologic efficacy with long-term quality of life.

14. Long-term consequences of chemotherapy in gestational trophoblastic neoplasia

Although the prognosis of high-risk GTN is excellent, with high cure rates even in cases of multimetastatic disease and resistance to multiple lines of treatment, the long-term consequences of chemotherapy warrant careful consideration, particularly in patients exposed to multiagent regimens.

One of the most relevant late toxicities is the risk of secondary malignancies, especially therapy-related acute leukemia associated with etoposide exposure. This risk is dose-dependent and has been reported to increase with cumulative doses exceeding approximately 2–4 g/m², with most cases occurring within a few years after treatment. Although the absolute risk remains low, generally estimated at less than 0.5%, it represents a serious and potentially life-threatening complication that should be discussed with patients undergoing prolonged or repeated courses of etoposide-containing regimens [65].

Despite these potential late effects, it is important to emphasize that the benefits of chemotherapy in GTN overwhelmingly outweigh the risks, given the high likelihood of cure. Nonetheless, awareness of these long-term consequences is essential to inform treatment decisions, guide survivorship care, and ensure appropriate counseling and follow-up.

15. Psychosocial aspects and the importance of care in reference centers

GTN affects predominantly women of reproductive age and is frequently preceded by a desired pregnancy, which confers a unique psychosocial burden. The abrupt transition from a gestational event to a cancer diagnosis, often requiring prolonged chemotherapy and strict reproductive restrictions, may lead to significant emotional distress. Patients commonly experience anxiety, depressive symptoms, grief related to pregnancy loss, fear of death, and concerns regarding future fertility. The need for continuous hCG monitoring and the uncertainty surrounding treatment response further contribute to psychological vulnerability, particularly in patients with high-risk or prolonged disease courses [66].

These psychosocial challenges are compounded by the demands of treatment, including frequent hospital visits, potential toxicity, and the requirement for strict contraception during follow-up. In this context, multidisciplinary care, including psychological support, plays a critical role in improving adherence, quality of life, and overall outcomes [67,68].

Beyond individual factors, health system-related variables have a profound impact on prognosis. Access to specialized care in reference centers has been consistently associated with improved survival in GTN. These centers provide standardized treatment protocols, centralized hCG monitoring, experienced

multidisciplinary teams, and the ability to rapidly escalate therapy when needed. In contrast, fragmented care and delayed referral may lead to inadequate initial treatment, increased rates of chemoresistance, and preventable mortality [8,69].

Geographic distance to reference centers represents a particularly important barrier. A multicenter retrospective cohort study conducted across eight Brazilian GTN reference centers evaluated the impact of geographic distance on clinical outcomes in 1,055 patients treated between 2000 and 2017. The study demonstrated that distance from the patient's residence to the reference center is a significant determinant of prognosis. Notably, receiver operating characteristic analysis identified a threshold distance of 56 km from a GTN reference center as the best predictor of adverse outcomes, providing a clinically relevant quantitative measure of the impact of geographic barriers on access to specialized care. After adjustment for demographic and regional factors, patients residing at distances ≥ 56 km had a markedly increased risk of presenting with metastatic disease, requiring multiagent chemotherapy to achieve remission, and experiencing loss to follow-up during treatment. Importantly, greater distance was also associated with higher rates of chemoresistance, relapse, and death due to GTN. These findings highlight that geographic barriers are not merely logistical challenges but directly influence disease severity at presentation, treatment complexity, and survival. Ensuring timely referral to specialized centers and implementing strategies to support follow-up, particularly in geographically underserved regions, are therefore essential components of effective GTN care [70]. In this context, the role of social services is fundamental in addressing logistical and socioeconomic barriers, facilitating patient transportation, accommodation, and continuity of care. Likewise, integration across different levels of the health-care system is critical to ensure coordinated management, allowing local services to support initial assessment and follow-up while maintaining close linkage with reference centers. The incorporation of telemonitoring strategies, particularly during intervals between chemotherapy cycles and in the surveillance phase, represents a promising approach to enhance adherence, enable early identification of complications, and reduce the negative impact of geographic distance on outcomes [71].

Data from studies evaluating lethality in GTN further reinforce that these deaths are largely preventable when appropriate care is delivered [8,72]. In a large multicenter Brazilian cohort including 2,186 patients treated at ten reference centers between 1960 and 2017, overall mortality was 4%, with 95.7% survival. After adjustment for FIGO/WHO score, among patients with low-risk disease, factors associated with increased lethality included choriocarcinoma (RR: 12.40); metastatic disease (RR: 12.57); chemoresistance (RR: 3.18), and initial treatment outside a Reference Center (RR: 12.22). In high-risk GTN, the following variables were significantly associated with death: interval between the antecedent pregnancy and initiation of chemotherapy (RR: 4.10); metastatic disease (RR: 14.66), particularly brain (RR: 8.73) and liver metastases (RR: 5.76); absence of chemotherapy (RR: 10.58) or initial treatment with single-agent chemotherapy (RR: 1.81); chemoresistance

(RR: 3.20), and initial treatment outside a Reference Center (RR: 28.30). Notably, among these variables, the only clearly modifiable factor is whether initial management occurs within a specialized Reference Center. Inadequate treatment, delays in initiating chemotherapy, and lack of follow-up remain the principal determinants of adverse outcomes, underscoring that early referral to, or direct management within, a Reference Center is the most effective strategy to reduce mortality [8,72]. Conversely, when managed in experienced centers with established protocols, even high-risk GTN achieves cure rates exceeding 80–90%, underscoring the curable nature of this disease.

In this setting, the centralization of care is not merely an organizational preference but a critical determinant of survival. The integration of clinical expertise, structured follow-up, and psychosocial support within reference centers represents a key strategy to reduce mortality and optimize outcomes in patients with GTN.

16. Expert opinion

A critical first step in improving outcomes in high-risk GTN is strengthening early detection strategies. Expanding access to serum hCG monitoring, improving recognition of disease presentation, and integrating diagnostic pathways across health-care systems are essential to ensure timely diagnosis and referral, particularly in low-resource settings.

In parallel, advances in molecular diagnostics represent an important frontier. Improved genomic and epigenetic characterization of trophoblastic tumors may enhance diagnostic precision, particularly in distinguishing gestational from non-gestational neoplasms and refining the classification of PSTT and ETT [73,74]. The identification of novel biomarkers beyond hCG and the development of predictive models of chemoresistance may enable more personalized treatment strategies and earlier identification of patients at risk of treatment failure.

However, translating these advances into routine practice remains challenging. The rarity of GTN limits the feasibility of large randomized trials, while biological heterogeneity and the concentration of cases in relatively few specialized centers restrict the development and external validation of predictive biomarkers. International prospective registries, harmonized biobanking, standardized molecular characterization, and collaborative multicenter trials will therefore be essential to generate sufficiently robust evidence for biomarker-driven treatment selection. In our view, international collaboration is not merely desirable in GTN research but necessary to overcome the intrinsic limitations imposed by the rarity of the disease.

With respect to therapy, the development of novel strategies, including targeted agents and immunotherapy, represents a major area of progress. The integration of immune checkpoint inhibitors with chemotherapy is under active investigation and may enhance response rates while reducing cumulative toxicity. Moreover, the incorporation of immunotherapy earlier in the disease course, including in low-risk GTN, may allow for treatment de-escalation and avoidance of multiagent chemotherapy in selected patients [75–78]. However, as immune checkpoint inhibitors become

more widely incorporated into GTN treatment, primary and acquired resistance are likely to emerge as increasingly relevant challenges. Although the underlying mechanisms remain poorly characterized specifically in GTN, potential mechanisms of immune escape include heterogeneous or reduced PD-L1 expression, impaired antigen presentation, an increasingly immunosuppressive tumor microenvironment, and activation of alternative immune checkpoints. Addressing immunotherapy resistance will require prospective translational studies aimed at identifying predictive biomarkers and characterizing longitudinal changes in the tumor immune microenvironment, as well as the evaluation of rational combination strategies with chemotherapy, anti-angiogenic agents, or other immunomodulatory approaches [46]. In parallel, emerging therapeutic classes such as antibody-drug conjugates offer another promising avenue for overcoming treatment resistance. Given that trophoblastic tumors express specific surface receptors that may serve as targets for these agents, such approaches could enable more selective drug delivery, maximizing antitumor efficacy while minimizing systemic toxicity [7]. Fertility preservation remains a key priority, especially in younger patients. Although fertility-sparing surgery has been described in highly selected cases, particularly in PSTT and ETT, further research is needed to better define patient selection criteria, optimal surgical approaches, and oncologic safety. Expanding the evidence base in this area may allow for broader application of conservative strategies without compromising outcomes.

Important questions also remain regarding the optimal duration of therapy, particularly the number of consolidation chemotherapy cycles required after remission. Refining this aspect of treatment may help reduce toxicity while maintaining the excellent cure rates that characterize GTN. In parallel, the optimal duration and intensity of post-treatment surveillance warrant further evaluation, as emerging data suggest that the risk of relapse declines markedly after the first year and becomes exceedingly low after prolonged remission. Future research should also focus on the identification of novel biomarkers of recurrence beyond hCG, which may allow for more precise monitoring strategies and potentially enable de-escalation of follow-up in selected patients.

Beyond therapeutic advances, increasing awareness of GTN within the medical community is essential. Delays in diagnosis, inadequate initial management, and failure to refer patients to specialized centers remain key contributors to preventable morbidity and mortality. Expanding education and disseminating standardized management principles are critical steps to ensure that all patients benefit from the high curability of this disease.

At the system level, the centralization of care remains a cornerstone of optimal GTN management. The establishment and consolidation of dedicated reference centers are critical to ensure access to specialized expertise, standardized protocols, and coordinated multidisciplinary care. In parallel, improved integration between different levels of the healthcare system is necessary to facilitate early referral and ensure continuity of care. In this context, strategies such as telemonitoring, combined with locally collected hCG samples analyzed in centralized reference laboratories, represent a robust model to mitigate geographic

barriers and improve adherence to follow-up, while preserving laboratory standardization and centralized clinical oversight.

Finally, patient advocacy and the active involvement of patients in care organization are increasingly recognized as essential components of modern GTN management. Patient support groups and advocacy initiatives play a key role in promoting awareness, improving access to care, supporting adherence to long-term follow-up, and addressing the psychosocial impact of the disease. Empowering patients as active participants in their care contributes to the development of more responsive, equitable, and patient-centered healthcare systems.

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Author contributions

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