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RESEARCH ARTICLE

Clinicopathological Features and Treatment Outcomes of Gestational Trophoblastic Disease: A Retrospective Study From A Tertiary Care Center in Türkiye

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Abstract

Introductıon: This research aimed to evaluate the clinical features, treatment modalities, and outcomes in patients with gestational trophoblastic disease (GTD).

Methods: A retrospective study was performed on 27 patients diagnosed with GTD. Data were collected from hospital records, including demographic details, clinical presentations, FIGO staging, and chemotherapy regimens. Treatment outcomes were assessed based on complete remission (CR) rates, treatment duration, and resistance to therapy.

Results: The median age of the patients was 27 (18–53) years, and the majority were FIGO stage I (77.8%). Chemotherapy regimens included weekly methotrexate in 11 patients (40.7%), five-day methotrexate (14.8%) in four patients, and etoposide,methotrexate and dactinomycin (EMA) / cyclophosphamide and vincristine (CO) in six patients (22.2%), while six (22.2%) patients achieved spontaneous remission without chemotherapy. CR rates were high across all regimens, with 81.8% for weekly methotrexate, 75% for five-day methotrexate, and 83.3% for EMA-CO. Resistant disease was observed in four (14.8%) patients. The median duration to CR varied by regimen, ranging from 5 to 10 weeks.

Conclusion: GTD is a highly chemotherapy-sensitive disease with excellent CR rates in both low- and high-risk patients. Accurate risk stratification and individualized treatment remain key to optimizing outcomes. Further studies are needed to address challenges in resistant cases and explore emerging therapies.

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Introduction

Gestational trophoblastic disease (GTD) encompasses a category of neoplasia that can be classified as either benign or malignant, originating from atypical trophoblastic tissue proliferation. Hydatidiform mole (HM), the most common form of GTD, is considered a benign, premalignant disease. HM is characterized by trophoblastic proliferation and increased human chorionic gonadotropin (HCG) levels. HM has two histological subtypes: complete mole and partial mole. In complete mole, HCG levels may rise above 100,000 IU/L, whereas in partial mole, HCG levels are relatively low because trophoblastic proliferation is less.[1,2] The incidence of HM varies among countries in the world, with an incidence of 1-2 per 1000 pregnancies in developed countries [3] and it develops most frequently in people under 15 and over 45 years of age, and the risk is higher in people over 45 years of age.[1,4] Endometrial curettage is the initial treatment for HMs in women who want to preserve fertility.[5,6] For women who have completed childbearing, hysterectomy serves as another treatment option.

As stated above, HM is a premalignant disease and it may transform into a malignant form called gestational trophoblastic disease (GTN). There are different types of GTN including invasive mole, choriocarcinoma, epithelioid trophoblastic tumor (ETT), and placental-site trophoblastic tumor (PSTT). GTN is usually diagnosed by HCG surveillance. The most common GTN after a normal pregnancy is choriocarcinoma. It can progress very rapidly to metastatic disease and is considered the most aggressive GTN subtype. Its incidence varies by country, but it is seen in approximately 3 per 100,000 births in Europe and North America.[3,7] PSTT and ETT are relatively rare compared to other GTN subtypes.[3,8,9] While endometrial curettage and hysterectomy are the mainstays of management for HM, GTN mostly requires chemotherapy.[10]

Gestational trophoblastic neoplasia (GTN) is classified into low-risk and high-risk categories based on the International Federation of Gynecology and Obstetrics (FIGO) staging and the modified WHO prognostic scoring system. According to this system, patients with FIGO stage I–III disease and a WHO risk score of less than 7 are considered to have low-risk GTN, which is associated with an excellent prognosis and nearly 100% cure rates.[11,12] These patients are typically managed with single-agent chemotherapy, such as methotrexate or actinomycin D.[13] In contrast, high-risk GTN is defined as a WHO prognostic score of 7 or higher, or any disease classified as FIGO stage IV.[11,12] These cases carry a greater risk of resistance to single-agent therapy and are therefore treated with multiagent chemotherapy, most commonly the etoposide,methotrexate and dactinomycin (EMA) / cyclophosphamide and vincristine (CO) regimen (etoposide, methotrexate, actinomycin D, cyclophosphamide, and vincristine).[13] Accurate risk stratification is essential for guiding treatment decisions and optimizing outcomes.

Despite its rarity, GTD remains a significant clinical challenge, particularly in cases involving high-risk disease or resistance to treatment. We conducted a retrospective analysis of clinical characteristics, therapeutic strategies, and outcomes in GTD patients treated at a tertiary healthcare institution in Turkey. By evaluating real-world data, we aim to provide insights into the effectiveness of different chemotherapy regimens and identify factors associated with treatment response and resistance in this population.

Material and Methods

This retrospective study was performed at Ankara City Hospital, Turkey, and included patients diagnosed with GTD. Demographic and clinical data were collected from hospital records, including age, gravida, parity, antecedent pregnancy type, presenting symptoms, serum β-hCG levels, tumor characteristics such as size, metastasis, FIGO stage, and chemotherapy regimens received by patients. The study was approved by the local ethics committee under the approval number TABED-1-25-1023.

The chemotherapy regimens applied to the patients were recorded, including weekly methotrexate (MTX), five-day MTX, and EMA-CO. Weekly MTX was administered as a single-agent therapy at a dose of 50 mg/m² intravenously, given once per week. Five-day MTX involved administering MTX at a dose of 0.4 mg/kg daily for five consecutive days, repeated every two weeks. EMA-CO, a combination chemotherapy regimen, consisted of etoposide (100 mg/m²), MTX (100 mg/m² intravenously, followed by 200 mg/m² over 12 hours), and actinomycin-D (0.5 mg) on days 1 and 2, combined with cyclophosphamide (600 mg/m²) and vincristine (1.0 mg/m²) on day 8. This regimen was typically administered in 14-day cycles. These regimens were selected based on disease severity, FIGO risk score, and clinical judgment to

ensure optimal therapeutic efficacy.

Treatment outcomes were assessed based on complete remission (CR), defined as normalization of serum β-hCG levels over three consecutive weekly measure. Patients with resistant disease were identified based on failure to achieve CR or recurrence.

Comprehensive descriptive statistical analysis of all patient demographic and clinical characteristics was performed using the IBM SPSS 25.0 software package. Summary statistics were calculated either as mean with standard deviation or as median with interquartile range, depending on how the data were distributed.

Results

This study included a total of 27 participants. Table 1 provides an overview of the patients' baseline characteristics. The participants' median age was 27 years (range: 18–53). Regarding antecedent pregnancy outcomes, nine patients (33.3%) had a complete mole, two patients (7.4%) had a partial mole, 12 patients (44.4%) had a term pregnancy, and four patients (14.8%) experienced an abortion. Among the presenting symptoms, vaginal bleeding was the most frequent, observed in 18 patients (66.7%), followed by abdominal pain in 7 patients (25.9%). Backache and incidental findings on imaging were each reported in 1 patient (3.7%) (Table 1).

The histopathological subtypes of GTD included complete mole in 12 patients (44.4%), partial mole in 5 patients (18.5%), invasive mole in 9 patients (33.3%), and choriocarcinoma in 1 patient (3.7%). Metastases were identified in 6 patients (22.2%), most commonly in the lungs (4 patients, 14.8%) and liver (2 patients, 7.4%). The number of metastatic lesions varied from 1–4 in 2 patients (7.4%), 5–8 in 1 patient (3.7%), and >8 in 3 patients (11.1%) (Table 1).

Most patients were classified as FIGO stage I (21 patients, 77.8%), with four patients (14.8%) in stage III and two patients (7.4%) in stage IV. Based on the FIGO risk scoring system, 20 patients (74.1%) were categorized as low risk (scores 0–6), while seven patients (25.9%) were classified as high risk (scores ≥7). Resistant disease was observed in 4 patients (14.8%) (Table 1).

Table 1. Baseline characteristics of patients with gestational trophoblastic disease

	n=27
Variables	**Medium (Minimum-Maximum)**
Age (years)	**27 (18-53)**
Gravida	**3 (1-8)**
Parity	**1 (0-5)**
Variables	**n (%)**
Antecedent pregnancy	
Complete mole	9 (33.3)
Partial mole	2 (7.4)
Term	12 (44.4)
Abortion	4 (14.8)
Presenting symptom	
Bleeding	18 (66.7)
Abdominal pain	7 (25.9)
Backache	1 (3.7)
On imaging for another condition	1 (3.7)
Serum β-hCG at diagnosis (mIU/mL)	
$<10^3$	4 (14.8)
10^3 -10^4	3 (11.1)
10^4 -10^5	11 (40.7)
$>10^5$	9 (33.3)
Subtype of GTD	
Complete mole	12 (44.4)
Partial mole	5 (18.5)
Invasive mole	9 (33.3)
Choriocarcinoma	1 (3.7)
Largest tumor size	
<4 cm	11 (40.7)
4-8 cm	9 (33.3)
>8 cm	7 (25.9)
Site of metastases	
Lung	4 (14.8)
Liver	2 (7.4)
Number of metastases	
1-4	2 (7.4)
5-8	1 (3.7)
>8	3 (11.1)
FIGO stage	
I	21 (77.8)
II	0 (0)
III	4 (14.8)
IV	2 (7.4)
Pretreatment serum β-hCG (mIU/mL)	
$<10^3$	6 (22.2)
10^3 -10^4	8 (29.6)
10^4 -10^5	9 (33.3)
$>10^5$	4 (14.8)
FIGO risk score, number	
0-6	20 (74.1)
≥7	7 (25.9)
Resistant disease, number	4 (14.8)

Table 2 summarizes treatment modalities, chemotherapy regimens, and resistant disease for hydatidiform moles and low-risk (FIGO score <7) and high-risk (FIGO score ≥7 or stage 4) GTD patients. Chemotherapy after uterine evacuation was applied to 15 (75%) patients diagnosed with hydatidiform mole or classified as having low-risk disease and five (71.4%) patients with high-risk disease. Hysterectomy alone was performed in two (10%) patients with hydatidiform mole or low-risk disease and one patient (14.3%) with high-risk disease. Uterine evacuation without additional treatment was observed in three (15%) patients with hydatidiform mole or low-risk disease, while it was not used in high-risk cases. Chemotherapy alone was applied to one (14.3%) patient with high-risk disease but not in hydatidiform mole or low-risk cases. Regarding chemotherapy regimens, 5-day MTX was used in four (20%) patients with hydatidiform mole or low-risk disease, while weekly MTX was given to 11 patients (55%) with hydatidiform mole or low-risk disease. EMA-CO was administered to six (85.7%) patients with high-risk disease but was not used in hydatidiform mole or low-risk cases. No chemotherapy was received by five (25%) patients with hydatidiform mole or low-risk disease and one (14.3%) patient with high-risk disease. In terms of disease resistance, three (15%) patients with hydatidiform mole or low-risk disease and one (14.3%) patient with high-risk disease exhibited resistance. One patient diagnosed with high-risk GTD died before receiving chemotherapy due to pulmonary embolism at the time of diagnosis.

Table 2. Treatment modalities for GTD groups

		Hydatidiform mole or low-risk GTN	High-risk GTN
		n (%)	
		20 (74.1)	n (%)
		7 (25.9)	
Treatment modality	Chemotherapy after uterine evacuation	15 (75)	5 (71.4)
	Hysterectomy only	2 (10)	1 (14.3)
	Uterine evacuation only	3 (15)	0 (0)
	Chemotherapy only	0 (0)	1 (14.3)
Chemotherapy regimen	5-day MTX	4 (20)	0 (0)
	Weekly methotrexate	11 (55)	0 (0)
	EMA-CO	0 (0)	6 (85.7)
	No chemotherapy	5 (25)	1 (14.3)
Resistant disease	Yes	3 (15)	1 (14.3)
	No	17 (85)	6 (85.7)

The median duration of treatment to achieve complete remission (CR) varied by regimen. Weekly MTX required a median of 7 weeks (5-10), while five-day MTX achieved CR in a median of 5 (4–13) weeks. For EMA-CO, the median duration was 10 (7–24) weeks, and for patients who did not receive chemotherapy, CR was reached in a median of 10 (6–20) weeks (Table 3).

CR rates were high across all groups, with the highest observed in the no-chemotherapy group (100%, 6/6 patients). The CR rates for weekly MTX, five-day MTX, and EMA-CO were 81.8% (9/11), 75% (3/4), and 83.3% (5/6), respectively. The median number of chemotherapy cycles administered was comparable between weekly MTX and EMA-CO, both requiring a median of 6 cycles (range: 1–9 for weekly MTX and 1–10 for EMA-CO). Patients treated with five-day MTX required a median of 4 (1–8) cycles (Table 3).

Table 3. Comparison of treatment regimens

	MTX Weekly	Five-day MTX	EMA-CO	No chemotherapy
n (%)	11 (40.7)	4 (14.8)	6 (22.2)	6 (22.2)
The duration of treatment to CR (weeks), Median (Min-Max)	7 (5-10)	5 (4-13)	10 (7-24)	10 (6-20)
CR rates (%)	81.8 (9/11)	75 (3/4)	83.3 (5/6)	100 (6/6)
Number of total cycles, Median (Minimum-Maximum)	6 (1-9)	4 (1-8)	6 (1-10)	-

Discussion

This retrospective analysis of patients with GTD highlights the diverse clinical presentations and treatment outcomes of this rare malignancy. While the study demonstrates the effectiveness of tailored chemotherapy regimens, it also underscores the importance of individualized management strategies based on patient risk profiles.

In this study, the median age of the GTD patients was 27 (18-53) years, which aligns with values reported in the literature. Anuj Gupta et al.[14] reported a median age of 28 years (20–51), while another study conducted in China found a median age of 32 years (22–49 years).[15] This demographic similarity underscores the need for fertility-preserving strategies in treatment planning. The most frequent presenting symptom was vaginal bleeding, observed in 66.7% of patients, followed by abdominal pain (25.9%), backache (3.7%), and incidental findings during imaging for another condition (3.7%). These symptoms are typical of GTD presentations, and patients have reported vaginal bleeding as the most common symptom in the literature.[16] In this study, metastatic sites included the lungs (14.8%) and liver (7.4%), with the number

of metastases being 1–4 in 7.4% of patients, 5–8 in 3.7%, and more than 8 in 11.1%. In a meta-analysis, the most common metastasis site was reported as the lungs, which is consistent with our study.[17]

The incidence of high-risk GTN in our study was 25.9%. The incidence of high-risk GTN varies across studies. A study conducted in India reported the high risk-disease incidence of 65.1% [14], while another epidemiologic study conducted in Japan reported a high-risk disease incidence of 16.6%.[18] These variations may reflect variations in healthcare access, referral patterns, and differences in early detection rates. For instance, regions with more advanced screening programs and specialized centers may detect and treat GTD earlier, potentially reducing the proportion of high-risk cases. Additionally, referral bias in tertiary care centers may lead to a higher proportion of severe cases being reported.

Patients with low-risk GTN commonly receive single-agent chemotherapy as the first-line approach.[19] Besides low-risk GTN, some patients with HM in our study also received chemotherapy. Prophylactic chemotherapy after uterine evacuation in HM is controversial.[20] Research indicates that prophylactic chemotherapy (MTX or dactinomycin) can be administered to patients who are deemed to be at high risk for gestational trophoblastic neoplasia (GTN) following a hydatidiform mole (HM). Factors that may categorize patients as high risk include being over the age of 40, having human chorionic gonadotropin (hCG) levels exceeding 100,000 mIU/mL, exhibiting abnormal uterine growth, and/or having theca lutein cysts exceeding 6 cm.[1,16,20,21] In our study, 15 (75%) (4 patients 5-day MTX, 11 patients weekly MTX) of the hydatidiform mole or low-risk GTN patients received chemotherapy after uterine evacuation, 3 (15%) underwent only uterine evacuation, and 2 (10%) underwent only hysterectomy. Methotrexate or dactinomycin may be given as chemotherapy agents for low-risk GTN.[19] There are numerous studies comparing these agents, but a clear comparison cannot be made because of differences in patient characteristics, drug doses, and schedules.[5,22-25] One analysis showed that dactinomycin was more effective than MTX; however, this analysis showed that the majority of patients received weekly intramuscular MTX, which is known to be less effective than 5- or 8-day MTX regimens.[25] The reason why weekly MTX administration was more common in our patients was that this application was used more commonly in the past.

EMA-CO regiment is used most frequently for high-risk GTN.[26] EMA-EP (etoposide, methotrexate, and etoposide alternating with dactinomycin and cisplatin) regimen is also included in the first-line treatment of high-risk GTD.[27,28] However, EMA-CO is preferred over EMA-EP due to its high toxicity and inability to provide adequate salvage chemotherapy in recurrence.[22,29] In our study, all high-risk patients receiving chemotherapy received EMA-CO. Five (71.4%) patients with high-risk disease received chemotherapy after uterine evacuation, and one (14.3%) patient underwent hysterectomy and died immediately after diagnosis due to pulmonary embolism without receiving chemotherapy. In one case of high-risk GTD, uterine evacuation was not performed because of the risk of uterine perforation. This patient initially received EMA-CO. Complete remission was achieved only after 24 weeks in this patient. This highlights the critical role of uterine evacuation in the treatment of GTD, as it can significantly accelerate β-hCG normalization and reduce the need for long-term chemotherapy in appropriate cases.

In our study, complete remission (CR) rates were notably high in the non-chemotherapy group. However, these patients predominantly had HM that requires no treatment unless it harbors any risk factors for transforming into GTN, as mentioned above. CR rates were 81.8% and %75, with weekly and five-day MTX regimens, respectively. Our findings were consistent with the literature since approximately %75 of patients with low-risk GTN achieve complete marker remission following first-line treatment.[25] Despite the generally favorable outcomes associated with single-agent MTX in low-risk patients, one case in our study developed severe toxicity, manifesting as pancytopenia. This case underscores that, while MTX is often considered a safe and effective option for low-risk disease, it is not without risks. Clinicians should remain vigilant for potential toxicities and carefully weigh the benefits against the risks, even in seemingly straightforward cases.

Resistant disease was observed in a small subset of all patients (%15 for hydatidiform mole or low-risk GTN and %14.3 for high-risk GTN). This finding was aligned with the expected rates since a study conducted among 877 patients with GTD reported 17.4% of patients with resistant disease.[30] These cases often necessitate multi-agent regimens such as EMA-CO, which, although effective, require close monitoring for cumulative toxicity. Additionally, the potential role of emerging therapies, including targeted treat-

ments, warrants further exploration to address these challenges.

The limitations of the study were its retrospective nature and small sample size. Nonetheless, it contributes to the growing evidence supporting risk-adapted treatment strategies in GTD and highlights the importance of considering both efficacy and safety in patient management.

Conclusion

The successful management of gestational trophoblastic disease requires a patient-centered approach that balances treatment efficacy with safety considerations. Our findings emphasize the importance of individualized risk assessment in guiding therapeutic decisions. While single-agent chemotherapy remains the cornerstone for low-risk GTN, multi-agent regimens such as EMA-CO play a crucial role in high-risk cases. Additionally, uterine evacuation has been shown to facilitate treatment response by shortening chemotherapy duration and improving remission rates. Despite the generally high success rates, clinicians must remain vigilant for treatment resistance and potential toxicities, reinforcing the need for close monitoring and timely intervention. Looking ahead, optimizing existing protocols and integrating novel treatment modalities will be essential to further improving patient outcomes. Continued research and interdisciplinary collaboration are vital for refining therapeutic strategies and addressing the challenges associated with complex or high-risk cases.

Statements & Declarations

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Declaration of Conflict Interests

No author has any financial or personal relationships that could inappropriately influence this work.

Ethics approval

Approval for the study was granted by the Clinical Research Ethics Committee of Ankara City Hospital (decision no: TABED-1-25-1023), and the research was performed according to the the principles of the Declaration of Helsinki.

Author Contribution

Ugur Ozberk: Data Curation and Analysis, Investigation, Writing—original draft. Selin Akturk Esen, Ismet Seven and Burak Bilgin: Data Curation and Analysis. Oznur Bal, Efnan Algın and Dogan Uncu: Conceptualization, Methodology, Supervision, Writing—review & editing

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