Article published online: 2023-03-02

Genitourinary Cancer

Gestational Trophoblastic Neoplasia—A Retrospective Analysis of Patients Treated at a Tertiary Care Oncology Center in North India

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South Asian J Cancer 2023;12(2):153–158.

Abstract

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Objectives The aim of this study was to do a retrospective analysis of patients of gestational trophoblastic neoplasia (GTN) treated at our center concerning their clinical features and treatment outcomes.

Materials and Methods Patients diagnosed and treated from May 2018 to December 2021 were included. All relevant information pertaining to eligible patients was retrieved from the electronic medical records. Patients were risk-stratified based on the World Health Organization (WHO) risk scoring system with a score of seven and above being classified into the high-risk category. Patients were monitored for response by measuring β-human chorionic gonadotrophin (β-HCG) levels before each consecutive cycle.

Statistical Analysis Appropriate statistical analysis was performed using SPSS version 26.

Results Records of 39 eligible patients were analyzed for clinical features out of which 38 were eligible for response assessment. The median age of presentation was 28 years with the majority of patients (79.4%) diagnosed based on β-HCG levels and clinical history alone. The most common symptom was bleeding per vagina (64%), while the majority of antecedent pregnancies were abortions (59%).

Of the 14 low-risk category patients, 12 received single-agent methotrexate/actinomycin D, while 2 received etoposide, methotrexate actinomycin D (EMACO) regimen. Overall response rates were 85.7% with the others responding to the second-line EMACO regimen. Five patients in this group had a WHO score of 5 or 6 and all of them responded to single-agent treatment. Among the 25 high-risk category patients, all received the EMACO regimen with high-dose methotrexate added to those with brain metastasis. The response rate was 87.5% with all the nonresponders having features of

Keywords

- β-HCG
- choriocarcinoma
- gestational trophoblastic neoplasia
- methotrexate
- WHO score

DOI https://doi.org/10.1055/s-0042-1758356 ISSN 2278-330X

How to cite this article: Gupta A, Kapoor A, Mishra BK, et al. Gestational Trophoblastic Neoplasia—A Retrospective Analysis of Patients Treated at a Tertiary Care Oncology Center in North India. South Asian J Cancer 2023;12(2):153–158

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

ultra-high risk of liver/brain metastasis and/or a WHO score of more than 12. While one nonresponder had expired despite treatment, the other two responded to the etoposide methotrexate and actinomycin D/ etoposide and cisplatin regimen.

Conclusion Our results are in consonance with other reported studies. The subcategories of low-risk GTN with a WHO score of 5 and 6 and high-risk GTN with ultra-high-risk features deserve further research in the form of multicenter prospective studies.

Introduction

Gestational trophoblastic neoplasia (GTN) incorporates the spectrum of invasive mole, choriocarcinoma, placental site trophoblastic tumor, and epithelioid trophoblastic tumor, which can occur following any type of pregnancy. Of these, the first two are associated with significantly elevated levels of serum β-human chorionic gonadotrophin (β-HCG) and occur at a short interval following the pregnancy. On the other hand, the latter two are associated with lower levels of β-HCG and occur at a much longer interval following the pregnancy.[1,2]

These are a group of rare but highly curable malignancies if appropriate treatment is instituted early and judiciously. Further, the fact that these occur in young women of reproductive age group makes them a high priority for society.[2] Of note, the incidence of these diseases is higher in the Asians, particularly the South-Asian population.[3]

Thus, it is important to be aware of the treatment policies followed and the results obtained in different regional settings. However, due to their rare nature, there is a paucity of prospective data on this topic from our country. Here, we have attempted to analyze the records of patients with this group of diseases at a tertiary care oncology center in north India.

Materials and Methods

This is a retrospective analytical study conducted at our center with the timeframe being from May 2018 to December 2021. Registration numbers of patients were retrieved from the electronic medical records by using the keywords "Gestational trophoblastic neoplasia," "Invasive mole," "choriocarcinoma," and "GTN."

Case records were studied in detail and evaluated for a complete history and physical examination as well as investigational reports. Data was acquired about patients' age, antecedent pregnancy interval (in months), history of abortion or molar pregnancy, pretreatment β-HCG levels, largest tumor dimension (in centimeters), site and number of metastases, and the number of prior failed lines of chemotherapy (if any). Based on the above details, patients were categorized into the low-risk group and the high-risk group as per the World Health Organization (WHO) risk stratification.[4]

Those with a score of 6 or less were deemed to have a low risk of resistance to single-agent chemotherapy and they were treated with single-agent methotrexate 1mg/kg intravenous on days 1,3,5 and 7 along with leucovorin per orally 15 mg on days 2, 4, 6, and 8 given to these patients. This cycle was repeated every 2 weeks. β-HCG was monitored before each consecutive cycle.

Those with a score of 7 and more (the high-risk patients) were considered a high probability of resistance to single-agent chemotherapy and therefore were treated with combination chemotherapy, that is, EMACO regimen (etoposide, methotrexate actinomycin D on day 1 and cyclophosphamide and vincristine given on D8, respectively). β-HCG was similarly monitored before every consecutive cycle. Chemotherapy was continued for three more cycles after the normalization of β-HCG levels. High-dose methotrexate was added to EMACO regimen for the patients with brain metastases.

Patients not responding in terms of serial decrement in β-HCG values with first-line EMACO or relapse were treated with second-line EMAEP (etoposide, methotrexate, actinomycin D given on day 1 and etoposide and cisplatin given on day 8, respectively) regimen.

After completion of treatment, patients were kept under regular follow-up with monitoring of β-HCG levels every 3 months. Patients were also counseled on standard contraceptive methods and the need for the same.

The response to treatment was standardized in the following manner—complete response when β-HCG values have normalized for a period of 3 consecutive weeks, partial response when more than 50% decline in β-HCG levels is noted concerning the baseline, and no response when there is less than 50% decrease from the baseline. Progressive disease is deemed when there is an increase in the size of any measurable lesion by at least 25% or the appearance of any new lesion on imaging and/or progressively increasing β-HCG levels. Recurrence was defined as an increase in β-HCG levels after more than three values in the normal range while excluding a confirmed pregnancy.

Statistics

The data were analyzed by SPSS Version 26 using appropriate statistical tools for the parameters mentioned in the results.

Results

A total of 42 patients were diagnosed with GTN and evaluated further. Of these, 39 patients started treatment at our

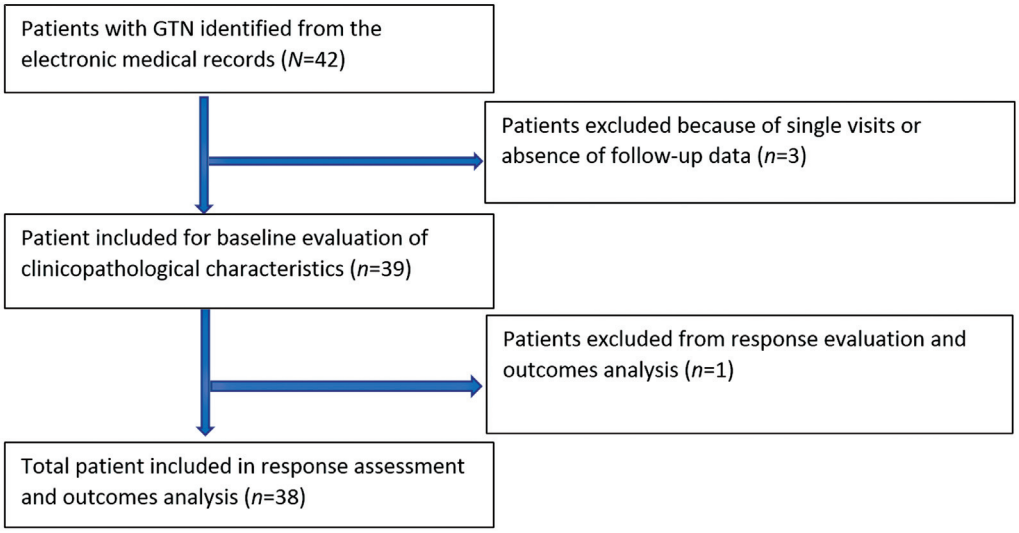

Fig. 1 Scheme of the inclusion of patients with gestational trophoblastic neoplasia (GTN) in the study.

center and 38 completed the treatment and were included in the analysis as shown in ►Fig. 1. The salient characteristics of these patients are provided in ►Table 1.

The median age of patients diagnosed with GTN at our center is 28 years with the range being from 20 to 51 years. The diagnosis was made only based on elevated β-HCG levels and clinical history in 31 (79.4%) patients, while 8 (20.5%) patients had a histologically proven diagnosis.

The most common symptom was bleeding per vagina in 25 patients (64.1%), while pain abdomen was present in 20 (51.3%) patients. A few patients (4; 10.3%) presented with hemoptysis, while headache and seizures were also present in one patient.

The majority of antecedent pregnancies were abortions, as reported in 23 (59%) patients, while molar pregnancy and term pregnancy were recorded in 11 (28.2%) and 5 (12.8%) cases, respectively. The median interval between pregnancy and the development of GTN was 3.5 months (range: 1–8 months). The median β-HCG levels were 90203 IU/L (range: 1300–6,52,318 IU/mL).

Twenty-eight (71.8%) patients also had distant metastasis on presentation. The lung was the most common site of distant metastasis reported in 22 (56.4%) patients. Other sites of metastasis were mediastinal nodes, liver, and omentum. Brain metastases were recorded in 5(12.8%) patients.

As per the WHO risk category, 14 (35.9%) patients were categorized as low risk, while the remaining 25 (65.1%) patients came under the high-risk category. Overall, 11 (78.6%) patients in the low-risk category were treated with single-agent methotrexate. One patient was treated with single-agent actinomycin D and two were treated with the EMACO regimen.

Twelve (85.7%) of these low-risk category patients attained complete response, while two of them had no response and were later switched to the EMACO regimen to attain complete response. Among the 25 high-risk category patients, 20 patients were treated with EMACO regimen, while five patients who had brain metastases were treated with EMACO + high-dose methotrexate regimen.

Twenty-one (87.5%) out of 24 of these high-risk category patients completed treatment at our center and went into complete response at a median of eight cycles of chemotherapy. Two among these had progression despite being on treatment, while one patient died during the course of treatment.

Among the seven (17.9%) patients with brain and/or liver metastasis, three achieved complete response, while two of them progressed on the first-line EMACO regimen and were later treated with EMAEP with high-dose methotrexate regimen. The other treatment nonresponding patient expired while on treatment.

Salvage Therapy

Out of 14 patients at low risk, two patients could not attain complete response and were later treated with the EMACO regimen. Two patients in the high-risk group with brain and/or liver metastases did not achieve complete response and were later treated with EMAEP + high-dose methotrexate regimen. Both of them responded but one of them expired later after defaulting on regular hospital follow-ups.

Toxicities

Chemotherapy was tolerated fairly well in all the patients. The most common toxicity noted was neutropenia. Other notable toxicities reported were thrombocytopenia and mucositis as shown in ►Table 1.

Follow-Up

The median follow-up was 26 months. Median overall survival was not reached due to low number of events. Two-year overall survival was 94.7% as shown in ►Fig. 2.

Discussion

In our study, the major chunk of cases of GTN has occurred after pregnancies resulting in abortion. In most of the other

Table 1 Clinical characteristics and treatment outcomes in GTN

Characteristics	Results in number (percentage)
Age (in years)	Median: 28 (range: 20–51)
Median follow-up	26 months (range: 8–42 months)
Baseline symptoms at presentation	
Bleeding per vagina Abdominal pain Hemoptysis Dyspnea Headache Seizure	25 (64.1%) 20 (51.3%) 4 (10.3%) 4 (10.3%) 1 (2.6%) 1 (2.6%)
Histopathological confirmation	8 (20.5%)
Antecedent pregnancy	
Abortion Mole Term	23 (59%) 11 (28.2%) 5 (12.8%)
The interval from the last pregnancy	3.5 months (range: 1–8 months)
Baseline β-HCG in mIU/mL	90,000 (1300–6,52,318)
Tumor size (in cm) median (range)	3.3 cm (0–13)
Number of patients with distant metastasis	28 (71.8%)
Sites of metastasis	
Lung Brain Omentum Liver Mediastinal node	22 (56.4%) 5 (12.8%) 8 (20.5%) 5 (12.8%) 10 (25.6%)
Number of metastases	4.4 (0–16)
Failed chemotherapy previously	None
FIGO stage	
1 2 3 4	7 4 11 17
WHO risk score	8.5 (range: 3–15)
WHO risk category	
Low risk High risk	14 (35.9%) 25 (65.1%)
Chemotherapy protocol received at our center	
Methotrexate Actinomycin D EMACO EMAEP HD methotrexate	11 1 29 2 5
The median number of cycles	8 (range: 3–16)
Response	
Low risk High risk	85.7% 87.5%
Toxicity	
Grade 3 neutropenia Grade 3 thrombocytopenia Grade 3 oral mucositis	10 (26.3%) 5 (15.2% 2 (5.3%)

Abbreviations: EMACO, etoposide, methotrexate actinomycin D; EMAEP, etoposide methotrexate and actinomycin D/ etoposide and cisplatin; FIGO, The International Federation of Gynecology and Obstetrics; GTN, gestational trophoblastic neoplasia; β-HCG, β-human chorionic gonadotrophin; HD, high-dose; WHO, World Health Organization.

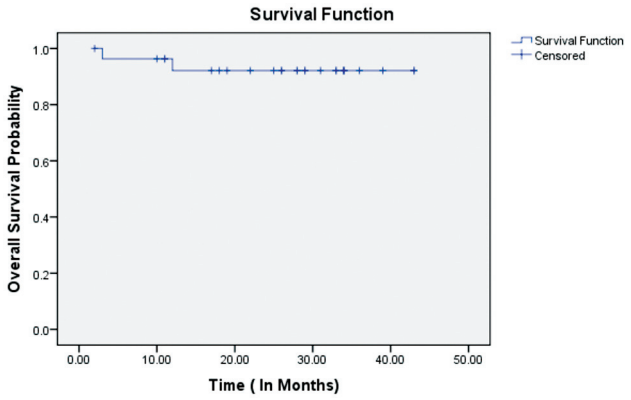

Fig. 2 Overall survival curve.

studies, the highest incidence had occurred after molar pregnancies.[5] But, in another study from the eastern part of our country, abortions were the commonest type of pregnancy preceding GTN.[6] We hypothesize that this may be due to the very high numbers of abortions performed outside of appropriate healthcare facilities in India where there is a very high chance of the diagnosis of molar pregnancy being missed.[7]

The percentage of patients with lung and brain and/or liver metastasis is similar to that reported by Gulia et al that is the largest published database from our country. The median β-HCG value in our study is 90,000 mIU/mL that is significantly higher than this study probably as our study has a higher proportion of high-risk GTN patients.[5] Again, this may be due to different referral patterns or maybe because more patients from our region come at a later stage. Also, variation in β-HCG levels may occur if samples are tested without dilution at levels more than 1000 mIU/mL.[8]

In the patients with low-risk GTN, the response rate with single-agent methotrexate or actinomycin-D is 85.7% with a small percentage of nonresponding patients achieving complete response with the EMACO regimen. This is comparable to the figures reported widely in literature.[9]

A recent study has tried to identify the risk factors for resistance to single-agent chemotherapy among patients of low-risk GTN but with a score of 5 or 6.[10] They identified metastatic disease, choriocarcinoma, and pretreatment β-HCG levels of more than 4,11,000 mIU/mL in those without metastasis and choriocarcinoma and levels of more than 1,49,000 mIU/mL in those with metastasis or choriocarcinoma, respectively, as identifiers for the same. Our study had only five patients with a WHO score of 5 or 6. But, none of them had any of these features predicting resistance to single-agent chemotherapy, and all of them responded. This is in resonance with the findings of the mentioned study. Thus, this group of patients represents a separate subgroup among low-risk GTN and should be considered for initial combination chemotherapy when mentioned features of resistance to single-agent chemotherapy are present.

In our patients with high-risk GTN, there was an 87.5% response rate to combination chemotherapy. This is higher than other similar studies. A definite reason for the same could not be established as the number of patients is relatively small.

Some of the factors that predict early death and poor response in high-risk GTN patients include a WHO score of more than 12, brain and/or liver metastasis, and extensive lung metastasis.[11] This seems to be an ultra-high-risk category among these patients. In our study, out of the six patients with a WHO score of more than 12, four (66%) responded, while one expired during treatment. Among those with brain and/or liver metastasis, only 57.1% out of the seven patients responded initially, while one patient expired. Although the numbers are small, early deaths in these ultra-high-risk patients remain one of the few unmet needs for this malignancy. Hence, the use of low-dose etoposide and cisplatin in the first cycle as a prephase to reduce the disease burden and to avoid the risk of early mortality as advocated by this study should be adapted.

The median follow-up of our patients was 26 months. Median overall survival and progression-free survival were not reached due to the low number of events. This is as expected for a highly curable malignancy.[5]

The toxicity profile was favorable. As most of the patients with these malignancies are young, this is as expected and in tune with other studies.[6]

The limitation of our study is the small sample size and retrospective nature of the study. However, this is true for all rare malignancies.

Conclusion

Our results of treatment for low- and high-risk category GTN patients align with other available national and international studies. Low-risk GTN with scores of 5 and 6 and ultra-high-risk GTN patients represent subcategories needing further research to improve treatment outcomes. This may be feasible by conducting multicenter studies in our country to achieve results of significance.

Conflict of Interest

None declared.

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