

**Original Article**

## A Retrospective Observational Study of Patients with High-Risk Gestational Trophoblastic Neoplasm treated at Chittagong Medical College Hospital

Authors

**Dr Jannatun Nisa<sup>1\*</sup>, Prof. Dr MD. Mokhles Uddin<sup>2</sup>, Dr Syeda Umma Tasmia<sup>3</sup>,  
Dr Fahmida Alam<sup>4</sup>, Dr Sajjad Mohammad Yusuff<sup>5</sup>**

<sup>1</sup>MBBS, FCPS (Radiotherapy), Resident surgeon, Department of Radiation Oncology, Chittagong Medical College & Hospital

<sup>2</sup>MBBS, MPhil, FCPS (Oncology and Radiotherapy), Ex Head of the Department of Radiation Oncology, Chittagong Medical College & Hospital

<sup>3,4</sup>MBBS, Radiotherapist, Department of Radiation Oncology, Chittagong Medical College & Hospital

<sup>5</sup>MBBS, MCPS, FCPS (Oncology and Radiotherapy), Head of the Department of Radiation Oncology, Chittagong Medical College & Hospital

\*Corresponding Author

**Dr Jannatun Nisa**

Resident Surgeon, Chittagong Medical Collage and Hospital

**Abstract**

**Objective:** Gestational trophoblastic tumors are a spectrum of interrelated conditions arising from an abnormal fertilization, most of them are highly sensitive to chemotherapy & curable in metastatic disease also. The aim of the study was to observe the outcome of high-risk Gestational trophoblastic neoplasia in Bangladeshi perspective.

**Methods:** This is a retrospective observational study of 31 women of high-risk gestational trophoblastic neoplasia conducted at Radiotherapy Department of Chittagong Medical College Hospital over a period of 4.5 years from January 2013 to June 2018. Only the patients with high-risk characteristics were included in this study. All patients were treated with EMA-CO chemotherapy regimen as first line chemotherapy. Second line chemotherapy with EP/EMA was given to patients having poorer response to primary chemotherapy or showing progression of disease.

**Results:** Of the 31 patients 3 were lost to follow up during treatment & 28 patients were evaluated. Among 28 patients 22 (79%) patients achieved complete remission with EMA-CO regimen & 6(21%) patients become refractory to EMA-CO & received subsequent chemotherapy with EP/ EMA, VIP regimen. 5 more patients achieved complete remission with 2nd and 3rd line chemotherapy. Thus, overall complete response rate was 96.43% (27/28).

**Conclusion:** In the present study a complete remission of 96.43% patients achieved which is comparable with other relevant studies. So, the preferred primary chemotherapy regimen in high-risk GTN is EMA-CO.

**Keywords:** Gestational trophoblastic tumors, EMA-CO chemotherapy.

**Introduction**

Gestational trophoblastic tumors are a spectrum of interrelated condition that arise from an abnormal

fertilization and which may threaten the health of young women if not properly treated, they consist of five distinct clinicopathological entities:

complete hydatidiform mole(CHM), partial hydatidiform mole (PHM), invasive mole (IM), Choriocarcinoma (CCA) and placental site trophoblastic tumor(PSTT)<sup>[1]</sup>. Invasive mole & choriocarcinoma, which make up the vast majority of these tumors, always produce substantial amounts of human chorionic gonadotropin (hCG) & are highly responsive to chemotherapy with an overall cure rate exceeding 90%, making it usually possible to achieve cure rate while preserving fertility. This success is due to the unique sensitivity of these trophoblastic neoplasms to chemotherapy & the use of hCG as tumor marker for diagnosis, monitoring treatment and follow up<sup>[2]</sup>. But the major challenge is to deal with the high-risk group. The high-risk group refers to those groups which are unlikely to be cured with single agent chemotherapy and are at greater risk of becoming refractory despite intensive multimodal therapy. Placing a patient in an appropriate risk group is very important for maximum cure with minimum toxicity<sup>[3]</sup>. According to FIGO 2000 scoring system, a prognostic score  $\geq 7$  is considered high-risk Gestational Trophoblastic Neoplasm (GTN)<sup>[3]</sup>. Rapid growth, widespread dissemination and a high propensity for hemorrhage make this tumor a medical emergency. EMA-CO remain the preferred multi agent chemotherapy for high-risk GTN and has a cure rate of 80-90% with minimum toxicity<sup>[3]</sup>. The Aim of our study was to observe the outcome of high-risk GTN in Bangladeshi perspective.

### Materials and Methods

This retrospective observational study was conducted at Radiotherapy department of Chittagong Medical College Hospital, Bangladesh over a period of 4.5 years From January 2014 to June 2018. A total of 31 patients with Confirmed cases of high-risk GTN  $\geq 7$  prognostic score were enrolled. Initial evaluation included age, duration of amenorrhea, antecedent pregnancy, Evacuation for mole, and chemotherapy received. Detailed physical examination including local and distant sites was done for scoring. Investigations such as liver function test, kidney function test, USG of

abdomen, CXR, serum beta HCG were done. In most of the cases diagnosis was confirmed by history, Serum beta HCG levels and histopathology. A prognostic score  $\geq 7$  was considered high-risk group and these patients were included in the study. Three patients were referred to Radiotherapy department after hysterectomy done elsewhere for severe per vaginal bleeding. 28 patients were referred after evacuation & curettage. Among them 21 patients had confirmed histopathological diagnosis of GTT. None of patients had brain metastasis. 8 patients presented with bilateral lung metastasis.

Chemotherapy protocol of EMA-CO regimen was given to all patients. EP/EMA was given to patients who developed poor response or become refractory to EMA-CO regimen. Other chemotherapeutic agents like TP/TE; VIP was given subsequently in patients showing poor response to EP/EMA. Prior to each cycle of chemotherapy patients underwent a complete blood count, kidney and liver function test, and serum B-hCG levels. Therapy was delayed if T-WBC counts  $< 3000/\text{mm}^3$  and platelets  $< 100000/\text{mm}^3$ . Patients having Hb  $< 10$  gm/dl were given transfusion along with chemotherapy. Toxicity was evaluated & treated accordingly.

**EMA-CO Regimen:** Every 2 weekly

Inj. Etoposide  $100\text{mg}/\text{m}^2$  IV-Day1, 2

Inj. Methotrexate  $100\text{mg}/\text{m}^2$  IV bolus- Day 1

Inj. Methotrexate  $200\text{mg}/\text{m}^2$  IV -12 hours infusion- Day1

Inj. Actinomycin D  $0.5\text{mg}$  IV-Day1, 2

Inj. Vincristine  $1\text{mg}/\text{m}^2$  IV-Day 8

Inj. Cyclophosphamide  $600\text{mg}/\text{m}^2$  IV-DAY 8

After completion of chemotherapy all patients were evaluated monthly for 3 months & then once every 3 months up to 1 year and at gradually increasing intervals thereafter. At each visit women underwent assessment of serum B-hCG level. Radiological assessment was done periodically and as needed. All women of child bearing age were advised contraception for 1 year.

**Results**

Of the 31 women only 28 were available for evaluation as 3 were lost to follow up during treatment period.

**Overall Response**

Among 28 patients, 22 achieved complete remission with EMA-CO regimen. One patient developed cerebral metastasis during the course of treatment & was treated with cranial irradiation followed by 2nd line chemotherapy with EP/EMA & subsequently died. Two patients had to undergo emergency hysterectomy for bleeding during the course of treatment & subsequently received chemotherapy with EP/EMA schedule. Among them one patient developed vaginal metastasis & received chemotherapy with changed schedule and subsequently died. Another 3 patient became refractory to EMA-CO. Two of them achieved complete remission after subsequent chemotherapy with EP/EMA & one after 3rd line chemotherapy with TP/TE.

**Table 1: Tumor Size**

Size	Patient No.
<3 CM	0
3-5 CM	11
>5 CM	20

**Table 2: Site of Metastasis**

Site	Patient No.
LUNG	8
SPLEEN, KIDNEY	0
GIT	0
LIVER, BRAIN	0

**Table 3: No. of Metastasis**

No of Metastasis	Patient No.
0	0
1-4	0
5-8	8
>8	0

**Table 4: History of Previous Chemotherapy**

Previous Chemotherapy	Patient No.
NONE	26
SINGLE AGENT	5
TWO OR MORE	0

**Table 5: Age Distribution**

Age	Patient No.
<40 Yrs	20
≥40 Yrs	11

**Table 6: History of Antecedent Pregnancy**

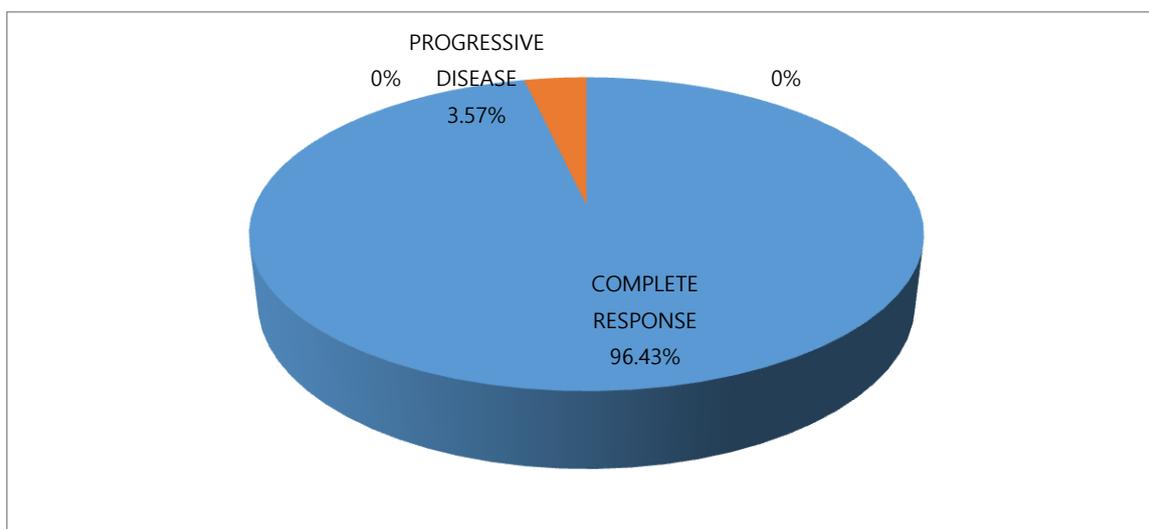
Antecedent Pregnancy	Patient No.
Hadatidiform Mole	13
Abortion	16
Term Pregnancy	2

**Table 7: Duration from Antecedent Pregnancy**

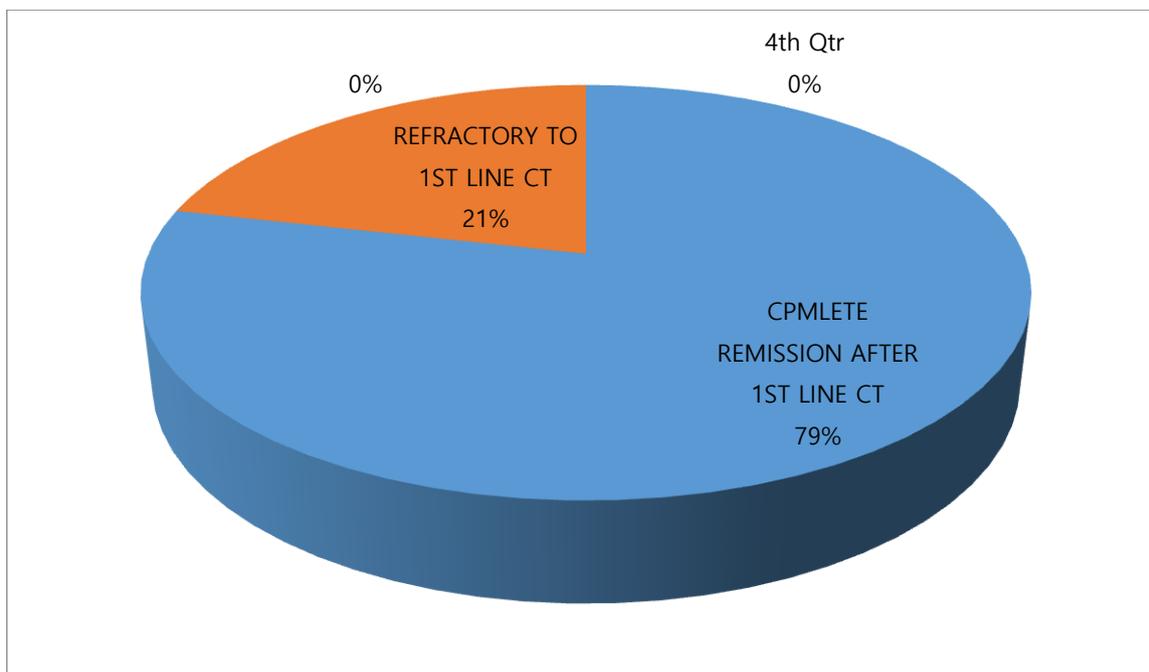
Duration	Patient No.
<4 Months	11
4-6 Months	12
7-12 Months	5
>12 Months	3

**Table 8: Pretreatment B HCG Level**

Beta HCG(IU/L)	Patient No.
<1000	0
1000-10000	2
10000-100000	11
>100000	18



**Fig 1: Overall Response**



**Fig 2: Response to 1<sup>st</sup> Line Chemotherap**

### Toxicity

Commonest toxicity was hematological grade 1 or 2 & was seen in 9 patients. Alopecia was observed in 18 patients. Neuropathy was observed in 2 patients.

### Follow up of patients

After completion of chemotherapy 28 patients were evaluated monthly for 3 months then once every 3 months up to 1 year and at gradually increasing intervals thereafter. At each visit women underwent assessment of serum beta HCG level. Radiological assessment was done periodically & as needed. All women of child bearing age were advised contraception for 1 year.

### Discussion

High-risk GTN remains a great challenge in the field of oncology. GTN is a variety of pathologic entities, which includes both benign and malignant neoplasms ranging from hydatidiform mole to choriocarcinoma. A high-risk group has greatest risk of developing rapidly progressing and unresponsive tumor despite intensive multimodal therapy. Since GTN was found to be chemosensitive and chemocurable, there were many attempts to devise a staging system that would allow an accurate prediction of outcome and risk of treatment failure<sup>[4]</sup>. In September 2000, the cancer

staging Nomenclature Committee of The International Federation of Gynecology and Obstetrics (FIGO) revised its classification system for GTN & women were classified into two categories: low risk (0-6) & high-risk ( $\geq 7$ )<sup>[5]</sup>. Histological diagnosis is not a pre-requisite according to FIGO guidelines. Nonetheless, it can be a useful predictor of the disease prognosis<sup>[6]</sup>. WHO scoring for risk stratification should be done for all cases of gestational trophoblastic neoplasia because the management differs for the low risk and high-risk groups<sup>[7]</sup>. High-risk patients are managed with combination chemotherapy EMA-CO regimen or a variant of it<sup>[8]</sup>. Pregnancy should be avoided for at least 1 year following the completion of chemotherapy and oral contraceptives are prescribed for the duration<sup>[9]</sup>. In our study among 31 patients 28 patients were referred to us after evacuation & curettage. Three patients were referred to us for further management after hysterectomy done elsewhere for p/v bleeding. Among them 21 patients had confirmed histopathological diagnosis of GTN. A total of 8 patients were presented with metastatic disease. 5 patients were treated previously with single agent chemotherapy. Chemotherapy protocol of EMA-CO regimen was given to all patients. EP/EMA was

given to patients who became refractory to EMA-CO. Other chemotherapeutic agents like TP/TE (paclitaxel, cisplatin/ paclitaxel, etoposide), VIP(Etoposide, Ifosfamide, cisplatin) was given subsequently in refractory patients. Prior to each cycle of chemotherapy patients underwent a CBC, liver & kidney function test and serum beta HCG levels. Toxicity of chemotherapy was evaluated and treated accordingly. In our study 22 patients achieved complete remission on 1st line chemotherapy with EMA-CO. One patient develops cerebral metastasis during the course of treatment & was treated with cranial irradiation followed by 2nd line chemotherapy with TP/TE. Thereafter the patient developed disease progression. Two patients had to undergo hysterectomy for p/v bleeding during the course of treatment & subsequently treated with 2nd line EP/EMA regimen. One patient achieved complete remission. Another patient subsequently developed vaginal metastasis & received chemotherapy with VIP regimen & subsequently died. Another three patients became refractory to EMA-CO. Two of them achieved complete remission after subsequent chemotherapy with EP/EMA & one patient with TP/TE regimen. Commonest toxicity was hematological & alopecia. In our series 22/28 (79%) achieved remission with the 1st line chemotherapy and additional 5/28(21%) achieved remission with second/ third line chemotherapy making a total complete remission of 96.43%(27/28). These results are comparable with the results of Newlands et al whose overall survival with EMA-CO was 84%<sup>[9]</sup>. Bower et al reported that EMA-CO is effective therapy for high-risk GTN and their overall cumulative 5-year survival rate was 82.6%<sup>[10]</sup>. Bafna et al had remission rate of 87.7% in the high-risk group<sup>[11]</sup>. Fertility is a major issue in high-risk GTN and the conservation of fertility is a challenge. Since the tumor frequently occurs among women in their twenties and thirties, most of women desired pregnancy after completion of chemotherapy. Newlands et al reported that majority of women reestablish their regular menstruation within 2-6 months after completion of therapy and no fetal abnormalities were recorded in

subsequent pregnancy. In our series 25 patient are surviving with good health, resumed normal menstrual function and 2 conceived.

### Limitations of the study

Like other studies the present study was also not flawless. Some limitations exist:

- 1) The time period was not enough to conduct a quality study.
- 2) Sample size was a major limitation in getting accurate clinical outcome.
- 3) The study was analyzed among the patients who attended CMCH only.

### Conclusion

In developing countries, women come with advanced disease and are noncompliant to therapy. GTN is curable if properly treated. The preferred chemotherapy for high-risk tumors remains EMA-CO regimen and require expertise. It is effective, well tolerated with acceptable toxicity.

### Conflict of Interest

We declare no conflict of interest.

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