Evaluation of the Results of Chemotherapy in High Risk Gestational Trophoblastic Tumors with Multidrug EMA-CO Regimen + Granulocyte-Colony Stimulating Factor (G-CSF) Support

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ABSTRACT

Introduction: Among the gynecological malignancies the tumors arising from abnormal fertilization are the GTT. They are of five distinct clinicopathological characteristics, most of them are chemosensitive and curable though some of them metastasize distantly also. EMA-CO regimen provides high remission rate and prolongs survival even in high risk GTT patients, with leucopenia as common side effect. The aim of this study was to complete the treatment within the scheduled time and achieve cure.

Material and methods: This is a prospective study of 18 women of high risk gestational trophoblastic tumors evaluated over a period of 4.5 years from February 2008 to August 2012. Only the patients of high risk category were included in this study. They were evaluated for age, duration of amenorrhea, number of deliveries, abortions, the antecedent pregnancy, evacuation for vesicular mole and previous chemotherapy received. All women were put on EMA-CO regimen (EMA+CO = Etoposide, Methotrexate, Actinomycin+ Cyclophophamide and Vincristine). G-CSF 300µ SC was given on D1and D2 to prevent any delay in schedule due to leucopenia. Intrathecal methotrexate was given to patients suspected of brain metastasis and as prophylaxis in women having pulmonary metastasis.

Results: Of the 18 patients treated, 16(88.9%) achieved remission with the EMA-CO regimen. None of the chemotherapy cycles were delayed due to leucopenia, which is a major limiting side effect in earlier studies. Other toxicities of chemotherapy were evaluated.

Conclusion: In the present study a complete remission and 5 year survival of 89% has been achieved, which is comparable to the previous studies. The response of the treatment in the GTT patients in this region of the world having different demographic features is similar to those of the other parts of the world. Prophylactic use of G-CSF with EMA-CO regimen in treatment of high risk GTT patients is advocated.

Keywords: High-Risk Gestational Trophoblastic Tumors, EMA-CO Regimen

INTRODUCTION

Gestational trophoblastic tumors (GTT) is a spectrum of conditions that arise from an abnormal fertilization, they consist of five distinct clinicopathologic entities: complete hydatidiform mole (CHM), partial hydatidiform mole (PHM), invasive mole (IM), choriocarcinoma (CCA), and placental site trophoblastic tumors (PSTT). The term *Gestational Trophoblastic Tumors has* been applied to the latter three conditions. *Gestational trophoblastic tumors arise* from the trophoblastic elements; they retain the invasive tendencies of the normal placenta or metastasize and keep secreting the human chorionic gonadotropin (βhCG). Although these tumors represent less than 1% of gynecologic malignancies[1,2], it is important to understand their natural history and management because of their life-threatening potential in reproductive age females and their high curability if treated early and according to well-established guidelines. The high-risk refers [3,4,5] to those groups which are unlikely to be cured by single-agent chemotherapy and are at great risk of progressing rapidly to unresponsive tumors despite intensive multi-modal therapy. Placing a patient in an appropriate risk group is very important as it gives the best chance of tumor eradication with minimum toxicity and maximum cure.

Indications for treatment

Following a Molar Pregnancy -The early diagnosis of molar pregnancy with ultrasound has led to changes in the histologic characteristics of CHM without changing the potential for developing persistent disease. Following evacuation the diagnosis of GTT is based on: International Federation of Gynecologists and Obstetricians (FIGO) guidelines:

- A plateau in β-hCG levels over at least 3 weeks,
- A 10% or greater rise in β-hCG levels for three or more values over at least 2 weeks,
- Persistence of β-hCG levels 6 months after molar evacuation, or
- Histologic evidence of choriocarcinoma.

Following a Nonmolar Pregnancy -Patients who develop rising β-hCG titers following a nonmolar pregnancy have CCA until proven otherwise. Serum β-hCG are not routinely performed after nonmolar pregnancies (except in following ectopic), unless the women has had a previous molar pregnancy when it becomes the standard of care because of the increased risk of developing GTN. However, any woman in the reproductive age group who presents with abnormal bleeding or evidence of metastatic disease should

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undergo β-hCG screening to rule out choriocarcinoma. At this point a thorough clinical and Radiological evaluation of the patient should be carried out to determine the extent of disease. Rapid growth, widespread dissemination, and a high propensity for hemorrhage make this tumor a medical emergency. Metastases are found in the lungs (80%), vagina (30%), pelvis (20%), brain (10%), and liver (10%) and other sites (less than 5%).

International Federation of Gynecologists and Obstetricians Staging of Gestational Trophoblastic Neoplasia and World Health Organization Scoring System Based on Prognostic Factors

Stage I Disease confined to the uterus
Stage II GTN extends outside of the uterus, but is limited to the genital structures
Stage III GTN extends to the lungs, with or without genital tract involvement
Stage IV All other metastatic sites

A risk factor score should be assigned to each patient.
The stage should be followed by the sum of the risk factor score (e.g., II:4)

- The optimal management of these high-risk women depends on
  - prompt diagnosis,
  - proper treatment and
  - expertise of individuals or centers in the management of such tumors
- EMA-CO remains the preferred multi-agent chemotherapy for high-risk gestational trophoblastic tumors (GTT) and has a cure rate of 80-85% with minimum toxicity.[3,4,6,7,8]

The aim of the present study was to achieve complete cure within the scheduled time. The EMA-CO regimen, which gives very satisfactory response in GTT, together with bone marrow suppression and hematological side effects, which were the main limiting side effects and responsible for prolongation of treatment time. The addition of G-CSF prophylactically is aimed to eliminate the risk of leucopenia related delay of schedule and completion of the chemotherapy uninterrupted.

MATERIAL AND METHODS

This was a prospective study of 18 women of high risk gestational trophoblastic tumors evaluated over a period of 4.5 years from February 2008 to August 2012, at the Department of Radiotherapy, P.M.C.H, Patna, India. The patients were referred as suspected or confirmed cases of gestational trophoblastic tumors. Only the patients of high risk category were included in this study with informed consent. All the patients were given prophylactic G-CSF 300 IU/SC d1 and d2. This is not included in the EMA-CO regimen.

Initial evaluations

Once it is determined that a patient has an elevated and rising hCG level a thorough evaluation is required to determine the extent of disease including-

Blood tests to assess renal and hepatic function, peripheral blood counts, and

baseline serum hCG levels. A speculum examination should be performed to identify the presence of vaginal metastases, which may cause sudden heavy vaginal bleeding.

Radiologic evaluation should include a pelvic ultrasound, both to look for evidence of retained trophoblastic tissue and to evaluate the pelvis for local spread. Chest imaging is also required as the lungs are the most common site of metastatic disease. Pulmonary metastases can be detected by chest computed tomography (CT) in up to 40% of patients with a negative chest x-ray. However, chest CT is not mandatory, particularly if detection of overt pulmonary metastases will not alter the treatment plans. In the absence of pulmonary and vaginal involvement, brain and liver metastases are rare, and, therefore, we frequently omit further imaging of the brain.

However, magnetic resonance imaging (MRI) of the brain with contrast is mandatory in women with metastatic disease and in all patients with a pathologic diagnosis of choriocarcinoma.

It is usually not necessary to obtain histologic confirmation of the diagnosis because of the highly vascular nature of the tumor and the risk of hemorrhage.

Positron emission tomography (PET) scanning is sometimes indicated to identify sites of active disease, and confirm sites of active disease found on conventional imaging.

Chemotherapy

Chemotherapy protocol of EMA-CO regimen was as follows.

- Inj. Etoposide 100mg/m2 IV - day 1,2
- Inj. Methotrexate 100mg/m2 IV stat - day 1 and

Prognostic Factors	Score			
	0	1	2	4
Age in years	<40	>40	-	-
Antecedent pregnancy	Mole	Abortion	Term	-
Interval (months)[a]	<4	>4 but <7	>7 but <13	>13
Pretreatment serum hCG (mIU/mL)	1,000	1,000 - <10,000	10,000 - <100,000	>100,000
Largest tumor, including uterine	-	3 - <5 cm	>5 cm	-
Site of Metastases	Lung	Spleen, Kidney	GI Tract	Brain, Liver
Number of metastases	-	1- 4	5-8	>8
Prior failed chemotherapy	-	-	Single drug	2 or more drugs

GTT, gestational trophoblastic Tumors; hCG, human chorionic gonadotropin; GI, gastrointestinal. [a]Interval time (in months) between end of antecedent pregnancy and start of chemotherapy.

200mg/m2 IV infusion (12hours) - day 1
- Inj. Actinomycin-D 0.5mg/m2 IV – day 1,2
- Inj. Vincristine 1mg/m2 IV stat – day 8
- Inj. Cyclophosphamide 600mg/m2 IV stat - day 8
- Inj. GCSF 300IU/SC on day 1 and 2

- Intrathecal methotrexate was given to patients suspected of brain metastasis and as prophylaxis in women having pulmonary metastasis.
- Women with established brain metastasis were treated with radiotherapy to the brain in addition to chemotherapy.
- Chemotherapy was continued for at least 2-3 courses after the first normal βhCG.[9]

Patients were advised to delay conception for 1 year after cessation of chemotherapy to allow for uninterrupted βhCG follow-up and to permit the elimination of mature ova that may have been damaged by exposure to cytotoxic drugs.[1,2,10]

Patient characteristics

- ***Age*** - 16 women were less than 39 years of age and 2 were more than 39 years of age.
- ***Antecedent pregnancy*** - 10 women had molar pregnancy, 6 had abortion and 2 had full term deliveries.
- ***Interval between the antecedent pregnancy and start of chemotherapy*** - The interval between the antecedent pregnancy and the start of chemotherapy was less than 4 months in 2 women, 4-6 months in 3 women, 7-12 months in 4 women and more than 12 months in 9 women.
- ***Serum* βhCG *levels*** - Six women had less than one Lac IU/L of βhCG while the remaining 12 had more than that.
- ***Metastasis*** - 4 women had nonmetastatic disease while 14 presented with metastatic GTT of whom 4 had single site metastasis and 14 had multiple site metastases. 2 women had brain metastasis.
- ***Surgical intervention*** - Two women had to undergo emergency hysterectomy for bleeding during the course of treatment.
- ***Brain and liver metastasis*** - 2 women presented with brain metastasis and one woman with liver metastasis.

STATISTICAL ANALYSIS

Microsoft office 2007 was used for the analysis. Descriptive statistics like mean and percentages were used for the analysis.

RESULTS

Complete remission and 5 year disease free survival was observed in 16 out of 18 patients, this contributes to 88.9% of the 18 patients treated. As prophylactic G-CSF was incorporated with the chemotherapy schedule, in no patient the chemotherapy cycle was delayed due to leucopenia, which is a major limiting side effect in earlier studies delaying completion of treatment in scheduled time. Other toxicities of chemotherapy were evaluated and managed effectively. The toxicities observed were alopecia in all 18 patients, nausea and vomiting in 9 patients, altered liver functions in 6 patients, oral Stomatitis and mucositis upto grade II in 9 patients, anemia in 2 patients.

DISCUSSION

Newlands et al [5] observed 84% overall survival with EMA-CO in medium and high risk patients during the period of 1979 to 1984. The present study observed a complete response with 5 year survival of 89% with EMA-CO plus G-CSF regimen in only high risk patients during the period from 2008 to 2012.

Bower M et al [4] observed an overall cumulative 5 year survival rate of 86.2% in a study on a cohort of 272 high risk patients. This meta- analysis was observed in 1997. The present study, having 18 high risk patients only, having a comparable therapeutic complete response and 5 year survival of 89%.

Another good work by Bafna UD et al[11] conducting an analysis of high risk GTT patients in a third world regional cancer centre, observed a high remission rate of 87.7% in 1997. The present study also achieved a complete remission and 5 year survival in high risk GTT patients

Follow-up

- After completion of chemotherapy all the 16 women who had remission were evaluated at monthly intervals for 1 year.
- At each visit women underwent physical examination and assessment of serum β hCG levels.
- Radiological assessment was done periodically and as and when required.
- Of the 16 women who had remission, menstrual status was evaluated in 14 women only as two had hysterectomy.
- Normal menstrual function resumed 3-6 months after completion of chemotherapy.
- 12 of the 14 women had resumed normal menstrual function.
- All women of child bearing age were advised contraception for one year.

Follow-up information was obtained up to August 2013.

CONCLUSION

It is an established fact that EMA-CO regimen for the treatment if GTT is the most preferred regimen. It gives a very high complete remission rate and overall survival, but the regimen also induces neutropenia of various grades in the patients.

Use of G-CSF prophylactically enables the treatment to be completed within the scheduled time together with achieving the maximum therapeutic responses of these chemotherapeutic drugs. Thereby achieving higher cure rate.

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