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Case Series

Gestational trophoblastic neoplasia: management and outcomes with EMACO regimen

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ABSTRACT

Gestational trophoblastic neoplasia (GTN) is a rare and malignant condition arising from the maternal placental tissue. It is a highly chemo sensitive tumor, EMACO (etoposide/methotrexate/dactinomycin alternating with cyclophosphamide and vincristine) is the most common multiagent chemotherapy used for patients with high risk. An audit was conducted for patients with gestational trophoblastic disease (GTD) receiving EMACO regimen during the past five years at a tertiary care referral centre. Records were analysed for efficacy, toxicity and outcomes with EMACO regimen. Total of eight patients received EMACO during the study period. Median age at presentation was 25 years. All patients, except one gave a history of an antecedental molar pregnancy. The mean duration of development of GTN from the index pregnancy was 3.4 months. FIGO stage I, II and III were seen in one, three and four patients respectively. The average quantitative human chorionic gonadotrophin (hCG) prior to starting EMACO was 157,705 IU/L (6149-629,442 IU/L). The mean number of EMACO cycles for achieving normal hCG levels was 4 (2-6). All but one patient also received two additional cycles of consolidation chemotherapy. Grade 3/4 neutropenia was seen in seven patients. Hepatotoxicity was seen in one patient. At a median follow up of 36 months (18-50 months), all but one patient was alive, and four patients have successfully conceived, while three delivered healthy babies after receiving EMACO regimen. EMACO is a highly effective regimen with manageable toxicity, good patient compliance and fertility preservation. EMACO administration requires experienced multidisciplinary team approach which can help to adequately monitor response, manage toxicity, provide supportive care and detect early relapses.

Keywords: EMACO, GTN, High risk, Low-risk relapse, Fertility preservation

INTRODUCTION

Gestational trophoblastic disease (GTD) consists of a group of tumors that arise from the abnormal proliferation of the trophoblasts of the placenta. GTD includes a spectrum of conditions ranging from benign conditions like hydatiform mole to malignant conditions like invasive mole, choriocarcinoma or the rare placental site trophoblastic tumor and epithelioid trophoblastic tumor. When GTD is associated with malignant conditions, it is called GTN.[1] GTN is a rare disease with an incidence that varies from 1 in 1000 pregnancies in the west to 2 in 1000 pregnancies in Asia.[2] Pathologically, invasive mole is characterized by the chorionic villi with trophoblastic proliferation that invades into the myometrium of the uterus or to adjacent structures. GTN results from aberrant fertilization.[3] Though GTN can happen after any

pregnancy, it occurs most commonly following a molar pregnancy. Around 15%-20% cases of complete mole progress to GTN.[1,3] Other etiologies related to development of GTN includes extremes of reproductive age including maternal age >40 years and teenage pregnancy, blood group A, Asian population and dietary deficiency of vitamin A.[2,4] Majority of the patients present with abnormal uterine bleeding, haemoptysis can be seen in patients with lung metastases, excessively raised serum levels of hCG could lead to hyperthyroidism or hyperemesis.[5]

Diagnostic workup of GTN includes radiological investigations to rule out metastatic disease including ultrasound pelvis, contrast enhanced computed tomography (CECT) chest/ abdomen/pelvis with or without magnetic resonance imaging (MRI) brain. Other investigations include routine haematology, biochemistry including renal functions, liver functions, thyroid profile and serum hCG levels.[4,5] Staging for GTN is based on a combination of FIGO staging and FIGO prognostic risk assessment.[6,7] FIGO staging for GTN is based on the tumor extent; whether the tumor is confined to the uterus (Stage I); has spread to the other genital structures (Stage II); has metastasized to lungs (Stage III) or other non-pulmonary distant organs (Stage IV).[6] FIGO prognostic risk categorization is done into low risk or high risk categories based on individual patient characteristics including age, antecedent pregnancy, interval from index pregnancy, pretreatment hCG, largest tumor size, site and number of metastases, and previous unsuccessful chemotherapy regimens.[7,8] If the sum of individual scores is <7, it is categorized into low risk and if the sum of individual scores is ≥7, it is categorized into high risk. This categorization is important as high risk patients are usually refractory to single agent chemotherapy and should be considered for multi-agent chemotherapy while low risk patients can be treated by single agent chemotherapy.[8-10]

GTN is considered to be a highly chemo-sensitive tumor. Hence chemotherapy is the mainstay of treatment for GTN. The recommended multiagent chemotherapy for high risk disease is EMACO which is associated with a complete remission rate of nearly 95%.[10] Most common single agent chemotherapy used for low risk disease is single agent methotrexate or single agent dactinomycin.[11] Surgery is limited to patients with chemo-refractory disease not responding to single agent or multiagent chemotherapy.[12] The current cure rates for these tumors are over 90%, even in the presence of metastatic disease. This is because of their inherent chemosensitivity; use of hCG as an effective tumor marker for diagnosis, monitoring of therapy, and follow up; and availability of prognostic markers which help to individualize treatment using various available modalities including chemotherapy, surgery and radiation.[13]

Due to rarity of the GTN coupled with multidisciplinary management required at centres with experience of treating GTN, published data from India on this disease is limited. Further EMACO being a multiagent chemotherapy is associated with significant toxicity, the tolerance and compliance to which is specific to the regional population.[14] With the current gaps in literature, we present here eight cases of GTN treated with EMACO regimen along with the efficacy, toxicities and outcomes.

CASE SERIES

Patient characteristics and evaluation

Patients of GTN who presented at a tertiary care referral centre in North India for treatment during the period from 2019-2023 were retrospectively analysed. Only those patients who received EMACO regimen as primary treatment or after failure of previous single agent chemotherapy were included for analysis. Total of eight patients had received EMACO regimen during the study period. All patients were referred to the oncology department after initial assessment and management at the obstetrics and gynaecological department of our institute.

Diagnostic workup

As part of initial assessment all patients gave a detailed history and underwent physical examination including pelvic examination, pelvic ultrasound, chest X ray, CECT abdomen and pelvis, quantitative hCG assay, complete blood count, renal function tests, liver function tests, thyroid profile including T3/T4/TSH. Patients in whom CXR was suggestive of any metastases underwent CECT chest. Patients with proven lung metastases underwent MRI brain to rule out brain metastases. Initial workup was followed by FIGO stage grouping and prognostic score assessment as per the WHO classification.

Treatment details

Patients with high risk GTN with a prognostic score of ≥7 or FIGO stage IV were considered for multiagent chemotherapy.[10] Patients with low risk GTN but with either poor response to single agent chemotherapy (hCG level plateaus with <10% change after 3 cycles) or initial good response to single agent chemotherapy followed by hCG level plateau or rapid rise in hCG levels (>1000) were considered for multiagent chemotherapy.[9]

Chemotherapy regimen

Multiagent chemotherapy used in our patients was EMACO regimen.[4]

Injection etoposide 100 mg/m^2/day iv on day 1, 2, injection dactinomycin 0.5 mg iv push on day 1, 2, injection methotrexate 300 mg/m^2 iv infusion over 12 hours on day 1. Tablet leucovorin 15 mg PO every 12 hours repeated 4 times, started 24 hours after the methotrexate infusion. Injection cyclophosphamide 600 mg/m^2 iv on day 8 and injection vincristine 0.8 mg/m^2 (maximum of 2 mg) IV on day 8.

The above cycle was repeated once every 2 weeks. Patients were not routinely administered primary GCSF prophylaxis but patients who developed febrile neutropenia were administered secondary prophylaxis with GCSF 50 mcg/kg body weight subcutaneously on day 4 or day 10 onwards for 2-3 days of a 2-weekly cycle.[4]

Response evaluation

History, physical examination and quantitative hCG levels were used for response assessment. hCG levels were monitored every 2 weeks during chemotherapy. Patients whose hCG levels became normal after chemotherapy were advised 2-3 additional cycles of consolidation chemotherapy with same regimen.[13] Patients with poor response, plateau of hCG levels or progressive disease were considered for second line chemotherapy for refractory disease and may be given options of surgical resection.[12]

Follow up

Patient follow up after treatment included routine history, physical examination and hCG assays every 1 month for 1 year. Radiological workup was not performed routinely until the patient was symptomatic. Patients were strictly advised to avoid conceiving for 1 year after cessation of last chemotherapy cycle and to use contraception, preferably oral contraceptives.[4,5]

Clinical profile and patient characteristics

Clinical profile of the patients is detailed in Table 1. Median age of the patients at presentation was 25 years. All patients, except one gave a history of an antecedental molar pregnancy diagnosed on histopathology while one patient had a history of antecedental normal term pregnancy. The mean duration of development of GTN from the index pregnancy in this group was 3.4 months. The average quantitative hCG prior to starting EMACO regimen was 157,705 IU/L (6149-629,442 IU/L). The radiological diagnostic workup was performed as per the institutional protocol listed in methodology. FIGO stage I, II and III were seen in one, three and four patients respectively. Lungs were the only site of metastatic disease seen in our patients (Table 2).

Treatment details

Four patients with a previous category of low risk disease, had received prior single agent chemotherapy with methotrexate and were subsequently treated with EMACO in view of poor response or progressive disease on single agent chemotherapy. One patient who was 35 years of age and had completed her family, underwent hysterectomy after the diagnosis of molar pregnancy. All eight patients were treated with EMACO regimen as per the standard schedule and dosing. The mean number of EMACO cycles received in this study group for achieving normal hCG levels was 4 (2-6). All but one patient also received 2 additional cycles of EMACO as consolidation therapy after achieving a normal hCG level (Table 3).

Toxicity

Neutropenia was the most common toxicity reported in this study group (Table 3). All patients, except one, developed grade 3/4 neutropenia following EMACO regimen. Two patients also developed febrile neutropenia followed by sepsis and one patient developed bacterial vaginosis. Grade 2 thrombocytopenia was seen in two patients. All these toxicities were managed conservatively. Liver functions including SGOT, SGPT and serum alkaline phosphatase were deranged in one patient after first cycle of chemotherapy and had to be managed with 25% reduction in dose of etoposide and vincristine.

Outcomes

All patients responded to EMACO regimen as assessed with normal serum hCG levels. With a median follow up of 36 months (18-50 months), all but one patient was alive and disease free. One patient died after sudden massive bleeding per vagina, 6 months after treatment with EMACO regimen. Four patients conceived after receiving EMACO regimen and three, successfully delivered healthy babies.

Table 1: Characteristics of patients treated with EMACO regimen.

Characteristics	Category	N
Age (in years)	<20	1
	20-30	5
	>30	2
Mean age (in years)	26.5	
Residence	Rural	3
	Urban	5
Parity	Nulliparous	4
	Multiparous	4
Symptoms	Bleeding PV	7
	Abdominal pain	4
Duration of symptoms	<2 weeks	3
	>2 weeks	5
Radiology	USG abdomen and pelvis	8
	CXR	8
	CECT chest	5
	CECT abdomen	5
	MRI brain	2
FIGO stage	I	1
	II	3
	III	4
Hysterectomy		1

EMACO: etoposide/methotrexate/dactinomycin alternating with cyclophosphamide and vincristine, USG: Ultrasonography, CXR: Chest X ray, CECT: Contrast enhanced computed tomography and MRI: Magnetic resonance imaging.

Table 2: Prognostic score for GTN patients.

Patient no.	Age (in years)	Antecedental pregnancy	Interval from index pregnancy (months)	Pre-treatment hCG (IU/L)	Largest tumor size (cm)	Site of metastases	No. of metastases	Previous failed chemotherapy	Stage: risk score
1	26	Hydatiform mole	4	200000	3-5	Lungs	3	Prophylactic MTX	III: 7
2	35	Hydatiform mole	3	155084	>5	Lungs	2	Hysterectomy prophylactic MTX	III: 7
3	20	Hydatiform mole	3	150020	>5	Lungs	7	-	III: 8
4	29	Term pregnancy	4	629442	>5	Lungs	6	-	III: 9
5	22	Hydatiform mole	4	53621	>5	-	-	Single drug (MTX)	II: 7
6	24	Hydatiform mole	2	6149	<3	-	-	Single drug (MTX)	I: 3
7	24	Hydatiform mole	4	58600	<3	-	-	Single drug (MTX)	II: 5
8	32	Hydatiform mole	3	8722	3-5	-	-	Single drug (MTX) Single drug dactinomycin	II:4

Table 3: Outcomes and toxicity with EMACO regimen.

Patient no.	Age (in years)	Stage: risk score	Number of cycles for remission	Number of cycles for consolidation	Toxicity	Outcomes
1	26	III: 7	EMACO×5	2	Neutropenia (Grade 3) bacterial vaginosis	Disease free, Conceived through assisted reproductive techniques
2	35	III: 7	EMACO×4	2	Neutropenia (Grade 4)	Disease free, Underwent hysterectomy as part of treatment
3	20	III: 8	EMACO×4	2	Neutropenia (Grade 4) with sepsis Thrombocytopenia (Grade 2)	Died
4	29	III: 9	EMACO×6	2	Neutropenia (Grade 4) with sepsis Thrombocytopenia (Grade 2)	Disease free, One healthy baby delivered post treatment
5	22	II: 7	EMACO×4	0	---	Disease free, One healthy baby delivered post treatment
6	24	I: 3	EMACO×4	2	Neutropenia (Grade 4)	Disease free, Does not wish to conceive
7	24	II: 5	EMACO×2	2	Neutropenia (Grade 4)	Disease free, One healthy baby delivered post treatment
8	32	II:4	EMACO×4	2	Neutropenia (Grade 4) Deranged SGOT (2 times), Deranged SGPT (4 times), Deranged ALP (2 times)	Disease free, Does not wish to conceive

EMACO: etoposide/methotrexate/dactinomycin alternating with cyclophosphamide and vincristine, SGOT: Serum glutamic-oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase and ALP: Alkaline phosphatase.

DISCUSSION

This analysis on patients with GTN, demonstrated the excellent response, manageable toxicity and fertility preservation in patients receiving EMACO regimen. The mean age of patients in our study was 26.5 years, which is similar to the mean age of 26.8 years and 26.58 years observed by Lu et al and Jain et al respectively in high risk GTN patients.[15,16] As per Lurain et al and Oranratanaphan et al bleeding per vagina is the most common symptom at presentation and the same was seen in our patients.[1,17] Hydatiform mole is considered to be the strongest risk factor associated with GTN and according to Hou et al and Schmitt et al about 10-15% patients develop GTN following hydatiform mole.[18,19] This strong association between molar pregnancy and GTN, was similar to what was seen in our study, where seven out of eight patients developed GTN following a molar pregnancy. Hence it is important to diligently follow patients of molar pregnancy with serial hCG levels to facilitate early diagnosis and treatment.[4] If hCG levels plateau, remain elevated or begin to rise following a molar pregnancy, the patient should be treated on lines of GTN.[4,5]

As per Cochrane systematic review, prophylactic administration of single agent, single dose of chemotherapy with either methotrexate or dactinomycin, at the time of or immediately following evacuation of the molar pregnancy, remains controversial.[20] Prophylactic administration of methotrexate in high risk molar pregnancy, where the risk of development of post-molar GTN is much greater than normal or where adequate follow-up with hCG is not possible, is associated with a reduction in the development of post-molar GTN by 3-8%.[20] The poor benefit of prophylactic chemotherapy in preventing progression to GTN was similar to what was seen in our study, where two patients who had received single dose of prophylactic methotrexate after high risk molar pregnancy, with high hCG assays >100,000 developed GTN.

The response rate for single agent methotrexate in low-risk patients as reported by Growdon et al and Taylor et al varies from 75-80%.[21,22] Four patients in our analysis were initially diagnosed as low risk disease and received single agent methotrexate, however they progressed on single agent therapy and were subsequently treated with multiagent EMACO regimen. Higher pre-treatment hCG levels and higher risk score (5-6) is usually associated with failure to single agent chemotherapy for low-risk patients.[21] This is similar to our study where two patients of low risk GTN with high-risk score progressed on single agent chemotherapy. Of the four patients who progressed from low risk to high risk GTN, one of the patients was also treated with single agent dactinomycin after failure on single agent methotrexate but had to be subsequently shifted to multiagent EMACO regimen in view of poor response to dactinomycin. A systematic review by Alazzam et al has shown, superior efficacy of dactinomycin over methotrexate for low-risk disease but methotrexate is usually preferred due to its favourable toxicity profile.[23]

EMACO is the preferred regimen for high-risk patients in view of its superior efficacy, good tolerance and fertility preservation in this young population. The toxicity is well manged, self-limiting and reversible.[10] The average number of EMACO cycles required for remission in our study were 4 (2-6). This is similar to that reported in other studies where a mean of 5.4 cycles (Lu et al) a median number of 3-5 cycles (Lybol et al) and a mean of 6 cycles (Jareemit et al) of EMACO were required for remission in high risk GTN patients.[15,24,25] As per the guidelines, after the hCG level has returned to normal, consolidation with 2-3 more cycles of chemotherapy will decrease the chance of recurrence.[4,5] All except one patient received 2 cycles of consolidation chemotherapy in our analysis, however, one patient did not consent for consolidation therapy.

GTN is a very chemo-sensitive tumor and when treated appropriately, EMACO regimen is associated with a response rate of 75-90%.[10,25] Cyriac et al reported an overall survival of 71% while Turan et al reported a survival rate of 90.9% with EMACO for high risk GTN.[26,27] This corresponds to our study where all patients except one, were disease free and alive at a median follow up of 36 months (18-50 months). Inspite, of the multi agent chemotherapy used, these young patients with GTN retain their fertility. Patients usually resume their menstrual period within 3-6 months after completing EMACO regimen, depending on the age.[28,29] In a study by Chauhan et al 60% patients resumed normal menstrual function and 12/65 women became pregnant after receiving EMACO while in another study by Wong et al 100% patients with high-risk GTN resumed their menstrual function and 33% became pregnant.[30,31] This is representative of our study where 4/8 women became pregnant and three of these have delivered healthy babies after receiving EMACO. However, women are advised to avoid conceiving for one year post chemotherapy to allow for uninterrupted follow up with hCG for one year and to eliminate the mature ova that have been exposed to chemotherapy.[5,32]

Haematological toxicity is well reported with EMACO regimen.[10,25] In our study, though EMACO was well tolerated and all patients completed it with good compliance, but it was associated with significant toxicity. In a study from Rwanda 72% (13/18) patients developed grade 3/4 neutropenia following EMACO regimen while in another study from India 6/17 patients developed febrile neutropenia following EMACO regimen.[14,33] In our study, 7/8 patients developed grade 3-4 neutropenia, and 2/8 patients developed febrile neutropenia with EMACO regimen. The greater haematological toxicity seen in our patients, may be secondary to poor baseline characteristics including anemia and nutritional deficiencies.[34] Hepatic toxicity with use of EMACO has not been extensively reported in literature, self-recovery of LFT was seen in one patient who developed mild to moderate derangement of liver function tests.

Surgery can also be used to remove limited metastatic sites or chemo-refractory disease in uterus, lungs, etc. Besides, surgery can also be used for large masses, excessive haemorrhage, perforation, and in those with completed family.[12,35] In a study by Mirji et al 9.7% patients of GTN required surgical intervention particularly for controlling haemorrhage and treating chemo-resistant disease while in the study by Tejas et al 12% patients required surgery for chemo-refractory disease specifically, confined to uterus and lungs.[36,37] Hysterectomy is also an option for select patients who have completed their family, postoperative chemotherapy and hCG monitoring will still be needed, similar to patients managed exclusively with chemotherapy.[4,5] In our study, one patient with 35 years of age and having completed family, preferred to undergo hysterectomy after the diagnosis of GTN. Radiation has a very limited role in the management of GTN, usually for management of brain metastases using whole brain radiotherapy and/or stereotactic radiotherapy.[38]

Around 25-30% patients may have initial poor response with EMACO or recur on long term follow up.[35] hCG is considered as a tumor marker for GTN, used both to assess response to treatment during chemotherapy and for early diagnosis of relapse during follow up.[4,35] According to a study by Raudina et al Asian people are known to show more chemo refractory disease, secondary to certain biological factors, non-compliance to treatment and follow up.[28,39] Jareemet et al reported that factors associated with refractory or recurrent disease include age >40 years, hCG levels at start of treatment >100,000, interval of >4 months from the index pregnancy, metastatic disease in more than 2 organs, metastatic sites like liver and brain or FIGO risk score >13.[22,25] Babaier et al suggest that treatment delays or dose reductions should be avoided to prevent chemotherapy resistance and treatment failure. In our study, one patient died of sudden acute vaginal bleeding, while having known to be in remission.[35] She had high baseline hCG levels >1,00,000, though metastases were limited to lungs but were extensive, seven in number. These patients can be successfully salvaged through a variety of second line chemotherapy regimens used for incomplete responses or relapse, including platinum-based chemotherapy, EMA-EP (etoposide, methotrexate, actinomycin D-etoposide, cisplatin), paclitaxel and etoposide alternating with paclitaxel and cisplatin (TE/TP) or newer checkpoint immunotherapies like pembrolizumab.[35,40]

In resource limited settings like ours, it is important to educate the health delivery team dealing with maternal care in the rural areas to correctly identify the signs and symptoms of GTD and to promptly refer these patients to referral centres for appropriate management which requires a multidisciplinary, experienced team including gynaecologists, radiologists, oncologists, psychologists and reproductive specialists.[14,41] Early diagnosis and close monitoring after treatment is the key to successful outcomes as this can save lives in this highly curable disease.[42] Treatment for GTN in these young women in the reproductive age group is associated with a psychological and emotional distress and includes mood disorders, fatigue, anxiety, concerns about future fertility, sexual and marital disorders.[29,43] In a survey by Carnelli et al on 37 women treated for GTN, patient's illness perception of GTN impacted their anxiety and infertility related stress.[43] This needs to be addressed as part of comprehensive disease management to maintain a good quality of life in these young long term survivors.[44]

Limitations of this study include that this is a retrospective study with a small patient number. However, given the rarity of this disease, it is difficult to conduct prospective randomized controlled trials. Nevertheless, this study demonstrated the efficacy and toxicity of the EMACO regimen in the Indian cohort who generally have a poor nutritional build and baseline characteristics.

Future research should focus on development of a risk prediction tool to correctly identify patients needing single agent chemotherapy, multiagent chemotherapy or more aggressive regimens to help individualize treatment. This may require better understanding of the prognostic and predictive factors. All GTN tumors, generally exhibit PDL1 positivity, hence use of immunotherapy for these targets is being explored.[35]

CONCLUSION

GTN is a disease of the young reproductive women. Management involves timely diagnosis and referral to appropriate centre for a multidisciplinary approach. Multiagent chemotherapy with EMACO is associated with cure rates >90%, with manageable toxicity and fertility preservation. Administration of EMACO requires close monitoring for toxicities, simultaneous response assessment using serum hCG levels and appropriate supportive care. Identification of newer targets like PDL1 for patients with GTN and treatment with immunotherapy may further reduce chemotherapy induced toxicity and improve outcomes.

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