High risk gestational trophoblastic diseases: Diagnosis and primary management with EMACO chemotherapy

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ABSTRACT

Gestational trophoblastic disease (GTD) is characterized by abnormal proliferation of pregnancy associated trophoblastic tissue with malignant potential. GTD covers a spectrum of tumors and tumor-like conditions and may occur in a benign form as hydatiform mole or as malignancy in the form of invasive mole or choriocarcinoma. Gestational trophoblastic neoplasms are now some of the most curable of all solid tumors, with cure rates >90% even in the presence of widespread metastatic disease. An analytical prospective study of 25 patients with high risk GTN who were evaluated from a period of June 2012 to Nov 2014 at our institute and diagnosis has been described in the paper

Keywords: Gestational trophoblastic disease,chemotherapy,diagnosis

Introduction

Gestational trophoblastic disease (GTD) is characterized by abnormal proliferation of pregnancy associated trophoblastic tissue with malignant potential. GTD covers a spectrum of tumors and tumor-like conditions and may occur in a benign form as hydatiform mole or as malignancy in the form of invasive mole or choriocarcinoma. Gestational trophoblastic neoplasms are now some of the most curable of all solid tumors, with cure rates >90% even in the presence of widespread metastatic disease[1]. In patients with postpartum uterine bleeding and subinvolution, GTN should be considered along with other possible causes, such as retained products of conception or endomyometritis, primary or metastatic tumors of other organ systems, or another pregnancy occurring shortly after the first. Optimal therapy in this group of disease rests in the correct diagnosis, assessing their risk for malignant behavior using prognostic scoring systems and administering appropriate treatment. Their rarity makes it imperative that these patients are treated in special centers by experts.

Materials and methods

This is an analytical prospective study of 25 patients with high risk GTN who were evaluated from a period of June 2012 to Nov 2014 at our institute. Initialevaluation of each patient was done. This included the age and the detailed history (particularly the obstetric history including months of amenorrhoea, number of deliveries, the antecedent pregnancy, evacuation for mole and any chemotherapy administered). The investigations were sent which included CBC, RFT, LFT, and serum beta HCG level. Physical and radiological investigations (chest x-ray, ultrasonography, CT thorax, CT abdomen pelvis, MRI brain) were done. Then the FIGO 2000 staging was done for scoring and treatment. The patient having score =>7 and stage 2 or more was considered as high risk and patients with EMACO as primary management were included under the study. Those patients were also included who were already under treatment/ follow up during the period of study. During chemotherapy patients were evaluated for response in the form of β HCG level prior to each chemotherapy and partial response/ non responders and untoward effects were noted. Toxicity of chemotherapy were analysed according to WHO criteria. Follow up information were noted until year 2014 and efficacy of EMACO were seen by observing remission rate (fall in β HCG level).During each visit, patient's complaints, menstrual history, contraception were noted. If patient conceived after remission, ultrasound was done to rule out recurrent vesicular mole or any abnormality. B HCG was advised 6 weeks after delivery.

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Result

Twenty five cases of high risk GTN were studied at our institute from a period of June 2012 to November 2014 .Mean age of the patients having high risk GTN was 28.3 years. Maximum number of cases were reported in 21-30 years of age group.In our study high risk GTN was common in lower socioeconomic class group(84%)and the highest incidence was reported in multigravida patients (88%).Most common symptom was irregular vaginal bleeding (92%).Most common antecedent pregnancy was term pregnancy (44%) followed by abortion (40%) and molar pregnancy (16%).Most of the patients of high risk GTN had β-hCG level > 1 lakh(64%).Maximum number of patients of high risk risk GTN had FIGO 2000 scoring < 10.All the patients of high risk GTN were given EMACO as primary management of chemotherapy. EMACO chemotherapy showed remission in 77% , resistance in 23% of the patients and survival rate of 95%.Most common toxicity reported by EMACO chemotherapy was grade 1anaemia and grade 1febrile neutropenia followed by grade 1 oral mucositis.The number of patients who completed their one year of follow up after getting remission were 92%, out of these 2 patients had uneventful pregnancy and none had recurrent molar pregnancy. Patients coming for follow up has normal menstrual period.

Discussion

GTD is diverse group of lesions that include placental villous abnormalities characterized by hydropic changes with abnormality in proliferation and maturation of trophoblast as well as neoplastic and non neoplastic proliferation of trophoblast unaccompanied by chorionic villi. In our study,mean age of the patients was 28.32 yrs. Youngest pt. was of 20 years of age and oldest was of 42 yrs. Number of cases were highest in 21-30 yrs of age group. Our study results were comparable to study of Tertiary Hospital Sindh[2] .Maternal age is well established risk factor for GTN. Women > 35 years <20 years are at high risk[3].Most cases of GTN still occur in women under 35 years of age as most pregnant women are younger. Most common symptom was irregular vaginal bleeding which was found in 92% of the cases. The results were comparable with the study of Hyatabad medical college study[4] (Table 14). Nausea and vomiting was found in 36% of the patients. This could be because of high level of β-hCG level. Our study showed the term pregnancy as the most common antecedent pregnancy (44%). The interval from the antecedent pregnancy was < 2 months in 16% of the patients, 2-5 months in 40% of the patients and > 5 months in 44% the patients. In Tertiary Hospital Sindh study maximum patients were diagnosed between 2-5 months of duration of the antecedent pregnancy[5].Table 1 showed 64% patients who had β hCG level >1 lakh before starting the chemotherapy. Trophoblastic disease with initial levels >1 lakh are at high risk of progression to neoplasm and transformation is mainly detected by rising hCG levels. In our study, most of the patients presented in stage-III as shown in table 1.

Table 1: Stage of the disease

Stage	No. of cases(n)	%
	2	8
I	1	4
II	20	80
V	2	8

Table 2: FIGO score, Most of the patients in our study had FIGO 2000 score < 10

Scoring	no. of cases (n)	%
<10	8	32
>10	17	68

Table 3 showed lung metastasis in 88% of the cases. The lung is the most common site of metastasis in cases of GTN. In many patients pulmonary lesions remain asymptomatic .The results of our study were consistent with Berkowith & Goldstein study.Although chest X ray usually demonstrates nodular metastasis, the pattern of metastasis disease can range from atelectatic area to subtle pleural abnormalities. A CT scan often is helpful in evaluating these non specific non specific areas which occurs in around 40% of the cases[6].Out of 25 patients,

3 patients were lost to follow up, 3 patients were still in follow up and 1 patient died. Out of remaining 18 patients, 14 patients went into remission and 4 patients had resistance to EMACO chemotherapy. Figure 1 shows the graph of a patient who went into remission by EMACO chemotherapy. EMACO is the first line regimen use to treat high risk GTN as it has the best effectiveness to toxicity ratio. In our study complete remission achieved in stage I – 100%, Stage II 100%, Stage-III – 78%, stage IV – 0%. The addition of cisplatin (EMA-EP) may produce a slightly better remission rate (88%) when used as a first line therapy, but it is associated with greater hematologic toxicity[7].As second line of therapy, EMA-EP has achieved complete response rate ranging from 67 to 75%[8].Out of the four patients who were EMACO resistant, two patients were given EMA-EP regimen and other two were given BEP regimen. EMA-EP led to 100% response rate. Out of two patients who were given BEP regimen, one patient achieved remission while other is still on follow up and showing declining hCG levels. Figure 2 shows the graph of the patient who was EMACO resistant and achieved remission with BEP. The studies were comparable with J. Lurian study. In his study, out of 9 resistant EMACO patients 3 patients were given EMA-EP and 6 given BEP got remission. The authors therefore concluded that patients with persistent or recurrent GTN should be treated with drug combination employing a platinum agent and etoposide with or without bleomycin and ifosfamide [9].Combination chemotherapy is often administered 2-3 wks interval and timely administration of chemotherapy is essential. Unnecessary treatment delay and dose reduction lead to tumor resistance and treatment failure. Patients receiving combination chemotherapy should have serial hCG measurements. After the first undetectable hCG, level 2-4 additional chemotherapy course should be administered to reduce the risk of relapse[1].

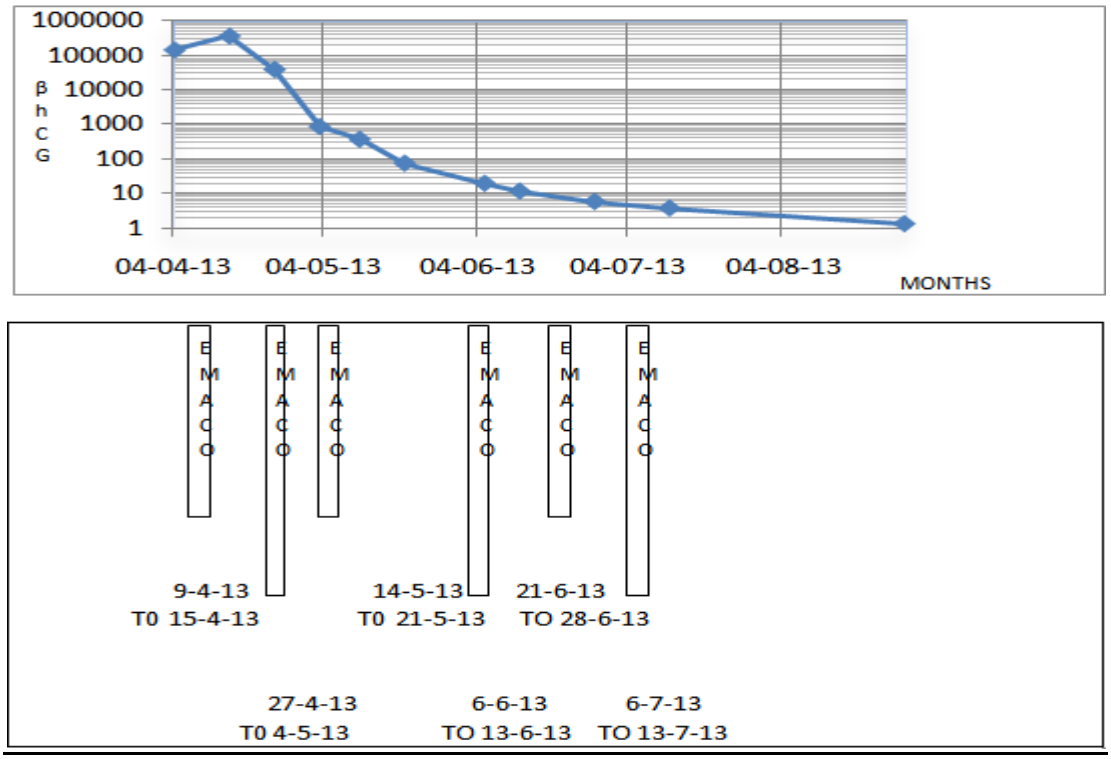

Fig 1 : Patient showed complete remission to EMACO chemotherapy

Out of 25 patients, 3 patient were lost to follow up. Out of rest 22 patients, 1 patient died in our study due to drug induced hepatotoxicity. As described in Table 3, most common toxicity by EMACO chemotherapy was anaemia and febrile neutropenia. Febrile neutropenia was seen in 11(44%) of the patients. These patients were treated with injectable antibiotics and granulocyte stimulating factors. Next common toxicities was oral

mucositis which were seen in 24% of the patients.Liver toxicity seen in 3 patients, 1 patient died due to drug induced hepatotoxicity and other 2 patients became HbsAg and HbeAg positive due to myelosuppression and repeated blood transfusion. The EMACO chemotherapy to 1 patient changed to cisplatin and Gemicitabine due to drug induced hepatotoxicity.EMACO is used as the first line regularly in high risk GTN patients as it has the best effectiveness to toxicity ratio.

Table 3: Lung metastasis in 88% cases

	Grade 1	Grade 2	Grade 3	Grade 4
Hematology				
Febrile Neutropenia	10	1	0	0
Neutropenia	8	0	0	0
Anaemia	15	5	3	1
Thrombocytopenia	2	0	0	0
Oral Mucositis	1	4	0	0
Liver Toxicity	3	0	0	0
Alopecia	2	0	0	0

On follow up,out of 14 patients which went into remission ,13 patients had completed one year follow up. After one year of completion of chemotherapy, 2 patients had uneventful pregnancy and none had recurrent molar pregnancy.During follow up period patients reported anxiety for the fear of recurrence and infertility. Patients had advised to avoid pregnancy for the first year after the completion of the chemotherapy and advised to used oral contraceptive pills during these period. Patients who received only EMACO regimen resumed regular menstrual periods within 3 months of completion of treatment while the patients who required change of chemotherapy in some other forms resumed the regular periods within 6 months.

Conclusion

Gestational trophoblastic disease is a fascinating group of pregnancy disorders characterised by abnormal proliferation of trophoblast, ranging from benign to malignant.Significant progress has been made over the past decades in the diagnosis and management of woman with GTN. GTN is a high curable disease. Low-risk disease is treated by single-agent chemotherapy while high-risk disease is treated by multi-agent chemotherapy. The preferred chemotherapy for high risk GTN is EMACO regimen and is highly effective, well tolerated and conserves fertility. Its toxicity is predictable and reversible. Proper management in the early stage strongly influences the outcome of the disease. Referral to a specialist centre is important to ensure proper monitoring and management. The presentation in advanced disease is not only because of socioeconomic problem and lack of awareness in patients but also due to lack of awareness in medical personnel. Lastly, it is well established that the diagnosis of GTN may have a significant emotional impact on the patient and her family. Therefore, it is vital that these women are followed by a multidisciplinary team, where the psychological impact of this diagnosis and its treatment can be addressed. This approach will ensure optimal, holistic care for women with GTN.

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Source of Support: Nil
Conflict of Interest: None