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Gestational trophoblastic neoplasia: A 6 year retrospective study

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Abstract

Aims and Objectives: To study the clinical presentations of gestational trophoblastic neoplasia and its response to chemotherapy. **Materials and Methods:** This is a retrospective study of 28 women of gestational trophoblastic neoplasia evaluated over a period of 6 years from January 2004 to December 2009. Patients were evaluated on the basis of their age, number of deliveries, history of abortion or molar pregnancy, and the treatment received. All patients were scored on the basis of WHO scoring system. Patients with low risk (score </=6) received single agent chemotherapy with methotrexate or actinomycin D. Patients with high risk (score >/=7) received multiple agent chemotherapy with EMACO regimen. After completion of chemotherapy patients were followed for a minimum of 2 years. The response to treatment was evaluated during follow-up by clinical examination, beta hCG levels and imaging as and when required. **Results:** Out of 28 women only 27 could be evaluated, because 1 patient was lost to follow-up. Out of 27 patients, 18 patients (66.67%) achieved complete remission with the first-line chemotherapy and additional 25.92% (7/27) achieved complete remission with second line chemotherapy resulting in complete remission of 92.5% (25/27). **Conclusion:** Gestational trophoblastic neoplasia is curable if patient is properly evaluated and scored. It shows good response to chemotherapy.

Key words: Actinomycin-D, choriocarcinoma, chemotherapy, EMACO regimen, gestational trophoblastic neoplasia, Methotrexate

Introduction

Gestational trophoblastic disease (GTD) defines a heterogeneous group of interrelated lesions arising from the trophoblastic epithelium of the placenta. All forms of GTD are characterized by a distinct tumor marker, the beta hCG. There are several histologically distinct types of GTD: hydatiform mole (complete or partial), persistent/invasive gestational trophoblastic neoplasia (GTN), choriocarcinoma and placental site trophoblastic tumors. The majority of women with this disease will be cured by single agent chemotherapy. But the major challenge is to deal with the high-risk group.

Chemotherapy is highly effective in most patients with GTN. Cure rates of 100% in low-risk cases and 80% to 90% in high-risk cases are reported from a number of treatment centers.[1] Methotrexate (MTX) and actinomycin-D (ACT-D), used sequentially, are the most widely used single agents for low-risk GTN.[2,3] Multiple-agent chemotherapy should be used primarily in all patients with prognostic FIGO scores of seven or greater. The most widely used regimen includes etoposide, MTX, ACT-D, cyclophosphamide and vincristine (EMA/CO) with cure rates ranging from 70% to 90%.[4]

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Materials and Methods

This is a retrospective analytic study of 28 women of GTN evaluated over a period of 6 years from January 2004 to December 2009. Being a cancer institute most of the patients were referred from other hospitals as diagnosed case of GTN. We do have an ethical committee in our institute, but for retrospective study its permission is not mandatory, therefore ethics committee approval was not obtained.

Case records of patients were studied and evaluated on the basis of their age, number of deliveries, history of abortion or molar pregnancy, the treatment received, and response to the treatment during follow up. The statistics were obtained from the case records and were calculated by simple percentage method. Detailed physical examination of local site was done. Investigations such as hemogram, kidney and liver function tests, serum beta hCG, x-ray chest, and ultrasonography were done. CT scan of the brain was done in patients with lung mets and suspected of brain metastasis.

All patients were scored on the basis of WHO scoring system [Table 1]. The decision of treatment was taken at the tumor board meeting after consulting medical oncologists and radiation oncologists.

Patients with low risk (score </=6) received single agent chemotherapy with MTX or ACT-D. In single agent chemotherapy beta hCG was evaluated weekly after completion of first cycle of chemotherapy. Remission was considered to be achieved when the hCG level was undetectable for three consecutive weeks. The patient was

followed with monthly hCG levels for 12 months. The decision of treatment was taken in tumor board meeting and the specific drugs to be used was decided by the medical oncologist.

- Treatment protocol for low risk
- MTX 1 mg/kg IM/IV on days 1,3,5,7
- Folinic acid 0.1mg/kg PO on days 2, 4, 6, 8
- ACT-D 12 mcg/kg IV push for 5 days.

Patients with high risk (score >/=7) received multiple agent chemotherapy with EMACO regimen. Beta hCG was evaluated after completion of each cycle. Treatment was continued until the hCG level became undetectable and remained undetectable for three consecutive weeks. Two courses of the remission regimen were administered after the patient achieved remission. After completion of chemotherapy, patients with high-risk disease were followed for 24 months. During follow up, effective contraception was advised for all patients for 2 years.

- Treatment protocol for high risk cases:
  - EMACO Regimen
  - Day 1
    Actinomycin D 0.5 mg i.v. bolus
    Etoposide 100 mg/m^2 iv. in 500 ml normal saline over 30 min
    Methotrexate 100 mg/m^2 i.v. push slowly
    Methotrexate 200 mg/m^2 i.v. in 500 ml 5% dextrose over 12 hr
  - Day 2
    Actinomycin D 0.5 mg i.v. bolus
    Etoposide 100 mg/m^2 i.v. in 500 ml N saline over 30 min
    Folinic acid 15 mg i.m. 12-hourly × 4 doses starting 30 hr after commencing
    Methotrexate
  - Day 8
    Vincristine 1 mg/m^2 i.v. bolus (max. 2mg)
    Cyclophosphamide 600 mg/m^2 i.v. in 500 ml N saline over 30 min.

During follow up patients were evaluated by physical examination, serum beta hCG levels and ultrasound (whenever needed). Patients were asked about their menstrual cycle status during treatment and follow up. Follow-up information was obtained up to December 2011.

Results

Total numbers of cases of GTN reported during Jan 2004 to Dec 2009 were 30. Files of 28 patients were retrieved, out of which 1 patient defaulted and was lost to follow up without taking any treatment. One patient could not complete treatment due to grade III mucositis after first cycle of EMACO and was subsequently lost to follow up. The case records of all these 28 patients were studied and analyzed. Various prognostic factors of high-risk patients are summarized in Table 2.

Presenting complaints

Being a Cancer Institute all patients came as diagnosed cases of GTN. Twenty-six patients had history of either amenorrhea followed by bleeding per vaginally or abortion followed by irregular bleeding per vaginally. Two patients had post menopausal bleeding per vaginum.

Four patients had received MTX after suction and evacuation. Seven patients had undergone total abdominal hysterectomy for different reasons, out of which two patients had received MTX.

Histopathology

There were 13 cases of hydatiform mole, out of which 9 were complete mole and 4 were incomplete mole. Eleven cases of choriocarcinoma and four cases of invasive mole were reported.

Table 1: World health organization scoring system based on prognostic factors

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

GTN=Gestational trophoblastic neoplasms, hCG=Human chorionic gonadotropin, GI=Gastrointestinal. [a]Interval time (in months) between end of antecedent pregnancy and start of chemotherapy

Table 2: Various prognostic factors of high risk cases (*N*=20)

	Age		Antecedent pregnancy			Beta hCG Level (IU/ml)			Metastasis (*n*=4)			Treatment failure (*n*=6)
	<40 yr	>40 yr	Molar	Abortion	Term	>1000<10,000	>10,000<100,000	>100,000	Lung	Brain	Vagina	
No. of Pt	12	8	4	6	10	10	4	6	4	2	1	5

Treatment given

For all cases, WHO scoring was done, eight cases were scored below six and rest were above seven. Treatment plan was discussed in tumor board meeting along with medical oncologists and radiation oncologists.

In the low-risk group, five patients received MTX and three patients received ACT-D. Among high-risk patients, 17 received EMACO regimen. One patient presented in a comatose state because of brain mets [Figure 1]. This patient, after stabilization, received 10 fractions of Cranial RT with a dose of 300 cGy each, followed by EMACO regimen.

One patient expired as she presented in unconscious state with advanced stage and metastases in multiple sites like brain, lung and vagina [Figure 2].

Surgical intervention

Two patients had to undergo hysterectomy after two to three cycles of chemotherapy because of persistent bleeding per vagina and MRI showing mass lesion inside the uterus. Out of these two patients one was found to be invasive mole on histopathological examination.

Response

The low-risk patients treated with MTX achieved complete remission after one cycle (four doses). Those who were treated with ACT-D achieved complete remission after three cycles.

All high risk patients treated with EMACO responded well to treatment. Ten women achieved remission after three cycles and six patients achieved remission after six cycles. The mean time taken to achieve a remission in low-risk patients was 6.25 ± 2.4 weeks (ranging from 3 weeks to 8 weeks) and for high-risk cases was 11.25 ± 3.5 weeks (ranging from 6 weeks to 20 weeks).

One patient with WHO score more than seven was started with EMACO regimen; the patient was responding well to treatment, but discontinued the treatment and was lost to follow-up after third cycle. The patient came back again after 4 years with complaints of pain in chest and neck. Her beta hCG level was >1000 IU/ml and had pulmonary mets in the right lower zone. She was again started with EMACO regimen and complete remission was achieved after six cycles. Two more cycles of EMACO were given as a part of remission regimen to all high-risk cases after achieving remission. She is doing well at present.

Side effects and complications

During treatment mainly hematological side effects like anemia, neutropenia, thrombocytopenia were encountered. Six patients required blood transfusion. Granulocyte colony stimulating factor was advocated to avoid treatment delay during the administration of EMA-CO. Some patients had complaints of nausea and vomiting during chemotherapy and were treated symptomatically. Alopecia was seen in all patients treated with EMACO regimen.

Only 1 patient suffered from grade 3 mucositis after first cycle of EMACO regimen and discontinued treatment after that. Details of side effects of chemotherapy are summarized in Table 3.

Response of women who were referred after treatment failure

Six cases were referred after treatment failure. Four women had suction evacuation followed by MTX cycles and two women had hysterectomy followed by MTX. Five patients were scored as high risk and treated with EMACO regimen. Complete remission was achieved after three cycles followed by two more cycles of EMACO regimen as a part of remission regimen [Table 4]. Among the referred cases one patient had hysterectomy followed by seven cycles of MTX. She had a normal follow up for 3 years till 2009 then she had rise in beta hCG (23.42 IU/ml) with a cannon ball appearance on the chest X-ray. She was treated with one cycle of ACT-D. On follow up, her beta hCG was normal, so one more cycle of ACT-D was given in view of low risk.

Follow up: (*n* = 25)

Among the 26 cases treated, 4 patients had follow-up for less than 1 year, 10 patients followed up for up to 2 years,

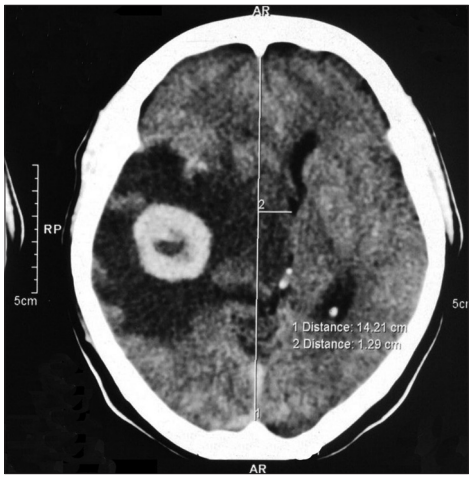

Figure 1: CT-scan brain showing brain metastases

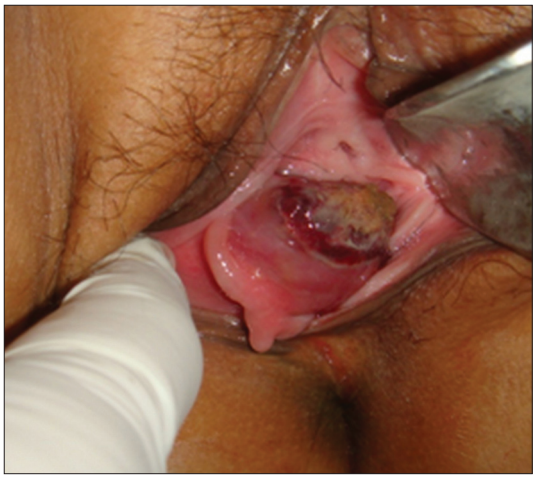

Figure 2: Vaginal metastases

11 patients followed up for more than 2 years and 1 patient lost to follow up after 1 cycle of chemotherapy, the mean duration of follow up being 29.12 ± 15.9 months. The patients were evaluated with the serum beta hCG levels, ultrasound (if indicated) and menstrual cycle of all patients were enquired. Nine patients had hysterectomy done during their treatment procedure and two patients had already attained menopause before they suffered from GTN.

One patient presented with irregular bleeding per vaginum after 6 years. On investigation she had a local recurrence (all other investigations were normal). She was hysterectomized in a private hospital, after which she had normal beta hCG level on follow up.

One patient underwent hysterectomy after 2 years on follow up due to the persistent residual mass in uterus with normal beta hCG levels. She had a normal follow-up after hysterectomy.

Resumption of normal menstrual function after completion of chemotherapy may take 6 to 8 months. Two patients had attained early menopause at the age of 40 and 42 years respectively and 8 patients had resumed their normal menstrual function approximately 6 to 8 months after chemotherapy. The patients with inadequate follow-up could not be evaluated. Newlands *et al*.[5] reported that majority of women reestablish regular menstruation within 2-6 months after completing therapy.

Out of 28 patients, 26 patients received treatment, out of which 25 patients achieved complete remission. Only two patients had local recurrence after 2 years and 6 years of remission, respectively, which was successfully treated with hysterectomy. Hence, the overall survival in GTN patients was 89.3% (25/28).

Discussion

GTN comprises a group of tumors like persistent trophoblastic tumor, invasive mole, choriocarcinoma, etc., These tumors represent less than 1% of gynecologic malignancies and have high curability if treated early and according to well-established guidelines.[6]

Table 3: Side effects and complications of chemotherapy

Side effect	No. of patients (%)
Anaemia	18 (66.67)
Neutropenia (Grade I)	06 (22)
Nausea and Vomiting	20 (74)
Mucositis (Grade III)	01 (3.7)
Alopecia	17 (63)

Before the advent of chemotherapy, metastatic choriocarcinoma carried mortality close to 100%. Chemotherapy is highly effective in most patients with GTN, but the role of other modalities such as surgery and radiation therapy should not be overlooked. The best results are achieved when patients are treated under the auspices of a multidisciplinary team.

In our institute, the incidence of GTN was found to be 1.08% (30 cases of GTN out of 2777 cases of gynecological malignancies over a period of 6 years.) Out of 30 cases, files of 28 patients were retrieved. One patient was lost to follow up without taking any treatment.

Maternal age is considered as one of the high-risk factor for GTN.[7] In this study, 8 out of 27 (29.6%) patients were aged above 40 years and all were scored as high-risk GTN. All low risk cases were aged below 40 years. Thirteen (48%) patients were diagnosed as hydatiform mole, 10 (37%) patient had choriocarcinoma, and 4 (14.8%) patients had invasive mole.

As our center is a regional cancer center of north-east region, all cases were referred after being diagnosed as GTN. All patients had suction and evacuation done as primary procedure. Seven patients were referred after hysterectomy. Only six patients had received prior chemotherapy, rest of the patients took primary chemotherapy at our center. One patient died without receiving any treatment as she came at very advanced stage with multiple metastases.

Twenty patients received primary chemotherapy at our center. Seven patients were scored as low-risk patient, out of which five (25%) received MTX, two (10%) received ACT-D as first line of chemotherapy. Thirteen (65%) patients were diagnosed to be of high risk and received EMACO regimen as first-line therapy. Out of these 13 patients, 5 (38.46%) patients achieved remission after three cycles of EMACO and 6 (46.15%) patients achieved remission after six cycles of EMACO.

In our case study, 18/27 (66.67%) achieved remission with the first-line chemotherapy and additional 25.92% (7/27) achieved remission with second-line chemotherapy making a total complete remission of 92.5% (25/27). Remission rate in high-risk cases was 89.47% (17/19), this can be compared to with the results of Bafna *et al*.[8] who had remission rate of 87.7% in the high-risk group. Bower *et al*.[9] reported that EMA-CO is effective therapy for high-risk GTT and their overall cumulative 5-year survival rate was 86.2%. In a study performed by Bolis *et al*. showed a 32-month survival of 88%, in patients with high risk.[10]

Table 4: Referred from outside after treatment failure (*n*=6)

Treatment received	Number of patients	Treatment given at our centre	Results	
			Complete remission	Persistent disease
DandE f/b MTX-FA	4	EMACO	4	-
TAH f/b	2	EMACO	1	-
MTX-FA		ACT-D	1	-

Most of the complications faced during treatment were mild and not life threatening. Most common complaint was nausea and vomiting, seen in 74% of patient and treated symptomatically. Sixty-seven% patient suffered from anemia, out of which only 33% patients required blood transfusion. Grade I neutropenia was seen in 22% of patients and was treated with GCSF. One patient suffered from grade III mucositis and discontinued the treatment after that. Soper[11] stated that EMA-CO regimen was generally well tolerated, but few acute and chronic toxicities had been reported, such as nausea and vomiting were the most common side effects experienced by all women. Bower *et al*.[9] reported that early toxicities of EMA-CO included alopecia, nausea, reversible neurotoxicity, and myelosuppression, while the late toxicities were second malignancies – two women developed acute myeloid leukemia, two cervical malignancy, and one gastric adenocarcinoma after EMA/CO. Acute myeloid leukemia had been linked particularly to etoposide administration. In our study no case of second malignancy was seen.

Conclusion

GTD represents one of the modern success stories in oncology with very little mortality because it responds very well to the medical (chemotherapy) and surgical (suction evacuation) line of management with beta hCG playing the main role not only in the pre treatment evaluation but also as a excellent prognostic marker for follow-up. The preferred chemotherapy for high risk tumors remains EMA-CO regimen. Even in the presence of disseminated disease, most of the cases are amenable to treatment with almost 100% survival.

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