J Obstet Gynecol India Vol. 57, No. 3 : May/June 2007 Pg 221-226

ORIGINAL ARTICLE

The Journal of Obstetrics and Gynecology of India

High risk gestational trophoblastic tumors

Chauhan **Anjana,** *Desai* **Ava,** *Patel* **Shilpa,** *Kapadia* **Anila,** *Garg* **Sonali,** *Dave* **Kalpana**

Department of Gynecology Oncology, Gujarat Cancer and Research Institute, Ahmedabad 380 016.

OBJECTIVE(S) : To evaluate the results of chemotherapy in high-risk gestational trophoblastic tumors.

METHOD(S) : This is a retrospective analysis of 48 cases of high-risk gestational trophoblastic tumors (WHO scoring system) evaluated for 7 years from1995 to 2002. All women received either EMA only / EMA+CO regimen as first-line chemotherapy (EMA only = etoposide, methotrexate, actinomycin; EMA+CO = etoposide, methotrexate, actinomycin+ cyclophophamide and vincristine). Intrathecal methotrexate was given to patients suspected of brain metastasis and as prophylaxis in women having pulmonary metastasis. Second line chemotherapy EMA+CO / EMA-EP / PVB (i.e.CP-cisplatin, etoposide, PVB-cisplatin,vinblastine,bleomycin) was given to women having poorer response to primary chemotherapy or showing progression of disease.

RESULTS : Only 39 women could be evaluated because nine women were lost to follow-up. Of these, 24(61.5%) achieved remission with the first line chemotherapy and an additional eight (20.5%) achieved remission with second line chemotherapy. Thus complete response rate was 32/39 (82%). Toxicities of chemotherapy were evaluated

CONCLUSION(S) : Gestational trophoblastic tumors are curable if properly scored and treated. The preferred primary chemotherapy in high-risk gestational trophoblastic tumors is EMA-CO regimen.

Key words : high-risk gestational trophoblastic tumors, EMA-CO regimen

Introduction

Gestational trophoblastic disease (GTD) is a spectrum of heterogeneous conditions which arise from the products of conception and which may threaten the health of young women if not properly treated. 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. The high-risk refers to those groups which are unlikely to be cured by a 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. Prior to the year 2000, according to the WHO scoring system based on prognostic factors, a score of ≥ 8 was considered a high-risk group requiring intensive combination chemotherapy to achieve remission [1]. But now according to new FIGO 2000 staging system, a score of ≥ 7 is considered high risk. The optimal management of these high-risk women depends on prompt diagnosis, proper treatment, and referral to individuals or centers with expertise in the management of such tumors [2].

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.

Methods

This is a retrospective analytic study of 48 women of high-risk gestational trophoblastic tumors evaluated over a period of Seven years from January 1995 to December 2002. The patients were referred as suspected or confirmed cases of gestational trophoblastic tumors

Paper received on 24/08/2006 ; accepted on 22/01/2007

Correspondence :
Dr. Anjana S Chauhan
Department of Obstetrics and Gynaecology
G/8, Sagar Apartments, Opp. Hotel Sarathi
Opp Amaltas Bunglows, Near Sandesh Press
Bodakdev Road, Ahmedabad - 380 054.
Tel. 079-268450536 Email : mailto:anjanascad1@sancharnet.in

Their initial evaluation included age, duration of amenorrhea, number of deliveries, abortions, the antecedent pregnancy, evacuation for vesicular mole and chemotherapy received. Detailed physical examination of local site (vagina and vulva) and distant sites was done for metastasis. The size and the site of the tumor were noted for scoring. Investigations such as hemogram, kidney and liver function tests, serum ?hCG, x-ray chest and ultrasonography were done. CT scan of the brain was done in patients suspected of brain metastasis. In these women CSF ?hCG was also done.

In most of the women diagnosis was confirmed by the history and serum ?hCG levels. Since this is a retrospective analytic study from 1995-2002, the Bagshawe: WHO scoring system was used. All women were scored according to the WHO scoring system based on prognostic factors (Table 1). The total score was obtained by adding the individual scores for each prognostic factor. A score of $\geq$ 8 was considered high-risk group and these patients were included in the study. Women were also grouped into metastatic and nonmetastatic gestational trophoblastic neoplasia. Nowadays new FIGO 2000 staging system is used for scoring and treatment.

Eleven patients were referred for further management after hysterectomy done elsewhere for various reasons. Two patients were referred after exploratory laparotomy done elsewhere for perforating mole. Among these, 11 women had confirmed histopathological diagnosis of choriocarcinoma. These women were grouped into high-risk metastatic or nonmetastatic gestational trophoblastic neoplasia. They received chemotherapy after proper planning.

Preferred primary chemotherapy in a high-risk gestational trophoblastic tumor was EMA-CO regimen.

Chemotherapy protocol of EMA-CO regimen was as follows.

Inj. Etoposide 100mg/m^2 IV - day 1,2

Inj. Methotrexate 100mg/m^2 IV stat - day 1

200mg/m^2 IV infusion (12hours) - day 1

Inj. Actinomycin 0.5mg/m^2 IV – day 1,2

Inj. Vincristine 1mg/m^2 IV stat – day 8

Inj. Cyclophosphamide 600mg/m^2 IV stat - day 8

EMA-only (etoposide, methothexate, actinomycin) was given in certain group of women with nonmetastatic high-risk gestational trophoblastic tumors having a score of eight or nine. EMA-EP (EP etoposide and cisplatin - 75mg/m^2 IV replacing CO on day 8) was given to patients who developed plateaued or poor response to EMA-CO regimen. Other chemotherapeutic agents like PVB (cisplatin, vinblastine, bleomycin) and BEP (bleomycin, etoposide, cisplatin) were given as second line chemotherapy. Methotrexate 10mg was given intrathecally along with CO/EP on day 8 to women suspected of brain metastasis and also as prophylaxis in cases of pulmonary metastasis, as they were at high risk of developing brain metastasis. Women with established brain metastasis were treated with radiotherapy to the brain in addition to chemotherapy.

Table 1. Bagshawe: WHO scoring system based on prognostic factors.

	Score			
Parameter	**0**	**1**	**2**	**4**
Age (years)	<39	>39		
Antecedent pregnancy	H.Mole	Abortion	Term pregnancy	
Interval between end of antecedent pregnancy and start of chemotherapy (months)	<4	4-6	7-12	>12
?hCG (IU/L)	$<10^3$	10^3-10^4	10^4 -$10^{.5}$	$>10^5$
Blood group		O or A	B or AB	
Largest tumor (cm)	<3	3-5	>5	
Site of metastasis		Spleen	GI tract	Brain
		Kidney	Liver	
Number of metastasis		1-3	4-8	>8
Prior chemotherapy			1 drug	2 drugs

Every patient's treatment response was plotted on a graph to see her response at a glance (Figure 1).

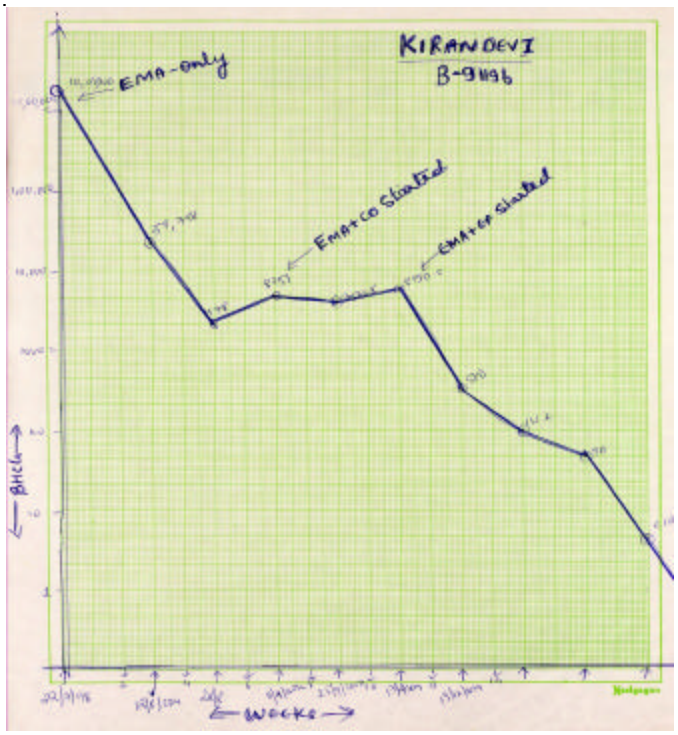

Figure 1. Response to treatment EMA-only→Secondary rise of BhCG →EMA-CO → Plateau of ??hCG →EMA-EP remission.

Prior to each cycle of chemotherapy, patients underwent a complete blood count, kidney and liver function tests, and serum ?hCG levels. Therapy was delayed if neutrophils were <3000/mm^3 and platelets <1,00,000/mm^2. Patients having hemoglobin <9g/dL were given transfusion along with chemotherapy. Toxicity of chemotherapy was evaluated and treated accordingly.

After completion of chemotherapy all patients were evaluated at 2 monthly intervals for 1 year and at gradually increasing intervals thereafter. At each visit women underwent physical examination and assessment of serum ?hCG levels. Radiological assessment was done periodically and as and when required. Menstrual status was evaluated during and after completion of chemotherapy. All women of child bearing age were advised contraception for one year. Follow-up information was obtained up to December 2002.

Results

Of the 48 women only 39 were available for evaluation as nine were lost to follow-up with incomplete treatment.

Age - Forty women were less than 39 years of age and eight were more than 39 years of age.

Antecedent pregnancy - Twenty-one women had molar pregnancy, 11 had abortion and 16 had full term deliveries.

Blood group - Sixteen women belonged to A group, 15 to B group, 14 to 0 group and 3 to AB group.

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 20 women, 4-6 months in six women, 7-12 months in four women and more than 12 months in 18 women.

Serum ?hCG levels - Sixteen women had less than one lac IU/L of ?hCG while the remaining had more than that.

Metastasis - Eleven women had nonmetastatic disease while 37 presented with metastatic GTT of whom five had single site metastasis and 32 had multiple site metastases. Three women had brain metastasis.

Surgical intervention - Two women had to undergo emergency hysterectomy for bleeding during the course of treatment.

Response - Of 39 women who could be evaluated, 33 had taken primary treatment and six were referred after prior chemotherapy taken elsewhere.

Response to primary treatment (n=33): Of the 33 women, 10 received EMA-only as they had nonmetastatic high-risk GTT having a score of eight or nine. The remaining 23 having metastatic tumor of higher score were given EMA-CO (Table 2). Of the 10 women who were given EMA-only, five (50%) achieved remission. Of the 23 women who were given EMA-CO, 19 or 82.6% achieved remission (Table 2).

Table 2. Primary treatment (n=33)

	EMA-Only n=10	EMA-CO n=23
Remission	5 (50%)	19 (82.6%)
Partial response	5	4
2nd line chemotherapy for partial response	5	4
Remission after 2nd line chemotherapy	4	-
Complete response	9/10 (90%)	19/23 (82.6%)
Persistent disease	1	3
Death	0	1

Five of the 10 women who had partial response to EMA-only were given either EMA-CO or EMA-EP (etoposide and cisplatin) as second-line chemotherapy. Remission was achieved in additional 40% (4/10) .

Four of the 23 women who did not response to EMA-CO as 1st line chemotherapy received second-line chemotherapy with either EMA-EP or PVB. But no further remission was achieved. All the four had further progression of the disease. One woman expired due to severe grade IV hematological toxicity.

Hence the preferred chemotherapy in high risk GTT remains the EMA-CO regimen.

Response of women receiving prior chemotherapy elsewhere (n=6) - Six women had received various chemotherapy agents elsewhere as shown in Table 3. They were given either EMA-CO or EMA-EP or PVB. Of these six women, four (66.67%) got remission. They all were given EMA-CO. Remission rate drops if appropriate chemotherapy is not given.

Table 3. Prior Chemotherapy taken elsewhere (n=6).

Chemotherapy received else where	Chemotherapy given by us	Number	Complete response	Persistent disease
MTX-FA,EMA	PVB	1	-	1
MTX-FA	EMA-CO	4	4	-
MTX-FA,MAC	EMA-EP	1	-	1
Total		6	4 (66.67%)	2

MTX : Methotrexate

FA : Folinic acid

EMA : Etoposide, Methotrexate, Actinomycin

MAC : Methotrexate, Actinomycin, Cyclophosphamide

PVB : Cisplatin, Vinblastine, Bleomycin

CO : Cyclophosphamide, Vincristine

EP : Etoposide, Cysplatin

Toxicity - Commonest toxicity was hematological grade I or II and was seen in 24 women. Alopecia was observed in 30 women. Liver functions were affected in six women. Stomatitis grade I or II was seen in nine women. In all these women chemotherapy was delayed till their blood reports reverted to normal. One woman had severe grade IV hematological toxicity and she eventually died.

Brain and liver metastasis - Seven women presented with either brain or liver metastasis or both. One woman with only liver metastasis achieved remission.

Response to treatment - Of the 39 women who could be evaluated, 24 (61.5%) achieved complete remission with the first line chemotherapy and additional eight (20.5%) with the second line chemotherapy. Thus complete remission was achieved by 32 (82%). Among those who were referred directly and primarily treated with chemotherapy, the remission rate achieved was 84.8% (28/33). While in those who were previously treated elsewhere and received second-line chemotherapy, the remission rate dropped to 66.67 % (4/6) (P=0.29). Hence this factor alone makes an important independent but nonsignificant difference in the response to treatment. Remission rate with EMA-CO when used both as first line and second line chemotherapy was 82.75% (24/ 29).

Follow up (n=32). All the 32 women who had remission were followed after treatment. Ten women had less than 1 year of follow-up, 12 had 1-3 years of follow-up and 10 had more than 3 years of follow-up. Of the 32 women who had remission, menstrual status was evaluated in 20 women only as five had hysterectomy and the remaining seven had inadequate follow-up. Resumeption of normal menstrual function after completion of chemotherapy may take 6-8 months and those with inadequate follow-up cannot be so evaluated. Eighteen of the 20 women had resumed normal menstrual function and four of them conceived. Three of these delivered a full term normal baby and one aborted.

Discussion

High risk GTT remains a great challenge in the field of gynecological oncology. It requires specialized skill and knowledge for management. GTD is a variety of pathologic entities, which includes both benign and malignant neoplasms ranging from hydatidiform mole to choriocarcinoma. Although the clinical management of GTD is usually medical and it can be treated without a specific histologic diagnosis, each of the pathologic entities has distinct clinical presentation, pathologic features, and behavior [2]. About 80% of the women diagnosed to have GTD, either complete mole or partial mole, will be cured after evacuation without any further treatment. Only 1-10% will be diagnosed with malignant GTD and require chemotherapy for cure. Hence it is very important that all these women are carefully followed and monitored with serum ?hCG levels.

Since GTD was found to be chemo-sensitive and chemocurable, there were many attempts to devise a staging system that would allow an accurate prediction of outcome and risk of treatment failure [6]. Bagshawe devised a scoring system that used several prognostic factors to calculate a weighted score. The World Health Organization (WHO) later modified and adopted this system for scoring. Based upon the WHO score, women were classified into three categories:

low-risk (≤ 4), middle-risk (5-7) and high-risk (≥ 8)[2,6]. Placing patient in an appropriate risk group is very important since it gives the best chance of tumor eradication with minimum toxicity and maximum cure. In September 2000, The Cancer Staging and Nomenclature Committee of the International Federation of Gynecology and Obstetric (FIGO) revised its classification system for GTD. It uses both staging / scoring system which allows precise description of the extent of the disease and of the risk factor present in trophoblastic disease [7].

A high risk group has greatest risk of developing rapidly progressive and unresponsive tumor despite intensive multimodal therapy. Over the last century, remarkable advances have been made in understanding their sensitivity to chemotherapy. Various chemotherapentic agents were used for the treatment of high risk GTT. But following the discovery of the marked activity of etoposide in GTT, this drug was incorporated in 1979 into the etoposide, methotrexate, and dactinomycin alternating with cyclophosphamide and vincristine (EMA-CO) regimen for high risk disease. This alternating combination chemotherapy regimen requires only one night of hospitalization every 2 weeks and is less toxic compared to previous longer seven drug therapy and is well-tolerated [2,5] .The optimal management of these high risk women depends on prompt diagnosis, proper treatment, and referral to individuals or centers with expertise in the management of such tumors [2].

In our series 48 women of high risk GTD were evaluated. Nine were lost to follow up with incomplete treatment, while 33 had taken primary treatment and six were referred after prior chemotherapy elsewhere. Of the 33 women, 10 were given EMA only as advised by Matusi et al [8] who reported that in high risk group EMA alone without cyclophosphamide and vincristine is effective and less toxic than EMA-CO. But as seen in our series only 50% women achieved remission with EMA alone. When the remaining 23 women were given EMA-CO, remission achieved was 82.6%. This shows that EMA-CO remains preferred chemotherapy in high risk gestational GTT (Table 1).

Six women were treated elsewhere and then referred for further management. They were given either EMA-CO or EMA-EP or PVB. Remission rate achieved was 66.67%. This factor alone makes important independent but nonsignificant difference in the response to treatment. Kohorn [7] states that previous unsuccessful chemotherapy is one of the important risk factors of independent significance in scoring system. Jones et al [9] report that high-risk GTD treated with MAC had unsatisfactory response and the preferred current treatment for this group remains EMA -CO.

In our series, 24/39 (61.5%) achieved remission with the first line chemotherapy and additional 20.5% (8/39) achieved remission with second line chemotherapy making a total complete remission of 82% (32/39) (Tables 2 and 3). Remission rate with EMA-CO when used both as first line and second line chemotherapy was 82.75% (24/29). These results are comparable with the results of Newlands et al [4], whose overall survival with EMA-CO was 84%. Bower et al [5] reported that EMA-CO is effective therapy for high risk GTT and their overall cumulative 5-year survival rate was 86.2%. Bafna et al [10] had remission rate of 87.7% in the high risk group.

The commonest toxicity was hematological and alopecia in our series. One death resulted from grade IV hematological toxicity. We had no late toxicity. Newlands et al [4] state that toxicity of the EMA-CO schedule is acceptable given the high risk nature of the disease in their series the main toxicities were anemia and leukopenia. Bower et al [5] reported that early toxicities of EMA-CO included alopecia, nausea, reversible neurotoxicity, and myelosuppression, while the late toxicities were second malignancies – acute myeloid leukemia seen in two women - which had been linked particularly to etoposide administration. Soper [2] stated that while EMA-CO regimen is generally well tolerated significant acute and chronic toxicities have been reported. Nausea and vomiting are common and virtually all women experience alopecia. Nutropenia and thrombocytopenia are the most common dose limiting toxicities. Stem cell support with granulocyte colony stimulating factor (G-CSF) has been advocated to avoid dose reduction and treatment delay during the administration of EMA-CO.

Fertility is a major issue in high risk GTT and the conservation of fertility is a challenge. Since this tumor frequently occurs among women in their twenties and thirties, most of the women desire future pregnancy after completion of chemotherapy. Newlands et al [4] report that majority of women reestablish regular menstruation within 2-6 months after completing therapy and no fetal abnormalities are recorded in subsequent pregnancies. Matsui et al [11] reported that women with GTT treated with methotrexate, actinomycin, etoposide, and combination chemotherapy may anticipate normal future reproduction. As pregnancies occurring within 6 months following remission are at risk of unfavorable outcome, a waiting period of at least 6 months after chemotherapy is suggested. Kim et al [12] reported that in their series 51.3% became pregnant within 1 year after pregnancy was permitted and 85.2% conceived within 3 years. They concluded that outcome of pregnancy after cure of GTD was not different from normal. In addition anticancer medicine used does not have harmful effects on later pregnancies. Bafna et al [10] reported four pregnancies amongst the 31 high-risk women

who had remission after treatment. Woolas et al [13] stated that maternal age is a powerful determinant of reproductive success. Women who achieved a live birth were significantly younger than those who did not. In their series of 21 successfully treated high risk women six became pregnant and delivered healthy babies. Bower et al [5] reported a total of 112 live births, including three infants with congenital abnormalities. They state that the reports of risk of congenital abnormalities in infants born to mothers treated with all forms of chemotherapy for GTT is 0.8% to 3.4%. In our series 18 of the 20 women resumed normal menstrual function and four conceived. Three women including the one who had received eight courses of EMA-CO delivered normal babies at term and one aborted.

Conclusion

In the third world countries, women come with advanced disease and are noncompliant to therapy. Hence it is very important to know that GTT is curable if properly treated. The preferred chemotherapy for high risk tumors remains EMA-CO regimen and requires expertise. It is effective, well tolerated, and conserves fertility.

References

1. Berkowitz RS, Goldstein DP. Gestational Trophoblastic Neoplasia. In: Berek JS, Hacker NF, Practical Gynecologic Oncology, 3rd edn. Baltimore. Williams & Wilkins, 1989:441-68.
2. Soper JT. Staging and evaluation of gestational trophoblastic disease. Clin Obstet Gynecol 2003;46:570-8.
3. Newlands ES, Bagshawe KD, Begent RH et al. Results with the EMA/CO (etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine) regimen in high risk gestational trophoblastic tumors, 1979 to 1989. Br J Obstet Gynaecol 1991;98:550-7.
4. Newlands ES, Bagshawe KD, Begent RH et al. Developments in chemotherapy for medium- and highrisk patients with gestational trophoblastic tumors (1979-1984). Br J Obstet Gynaecol 1986;93:63-9.
5. Bower M, Newlands ES, Holden et al. EMA/CO for high risk gestational trophoblastic tumors: results from a cohort of 272 patients. J Clin Oncol 1997;15:2636-43.
6. Schlaerth JB. Tumors of the placental trophoblast. In : Morrow CP, Curtin JP, Townsend DE. Synopsis of Gynecologic Oncology. 4th edn. New York. Churchill Livingstone, 1993:311-30.
7. Kohorn EI. The new FIGO 2000 staging and risk factor scoring system for gestational trophoblastic disease: description and critical assessment. Int J Gynecol Cancer. 2001;11:73-7.
8. Matsui H, Iitsuka Y, Suzuka K et al. Combination chemotherapy with methotrexate, etoposide, and actinomycin D for high-risk gestational trphoblastic tumors. Gynecologic Oncol 2000;78:28-31.
9. Jones WB, Cardinale C, Lewis JL Jr. Management of high-risk gestational trophoblastic disease – the Memorial Hospital experience. Int J Gynecol Cancer 1997;7:27-33.
10. Bafna UD, Ahuja VK, Umadevi K et al. Gestational trophoblastic tumors – situation analysis in a third world regional cancer center. Int J Gynecol Cancer. 1997;7:197-204.
11. Matsui H, Iitsuka Y, Suzuka K et al. Risk of abnormal pregnancy completing chemotherapy for gestational trophoblastic tumor. Gynecol Oncol 2003;88:104-7.
12. Kim JH, Park DC, Bae SN et al. Subsequent reproductive experience after treatment for gestational trophoblastic disease. Gynecol Oncol 1998;71:108-112.
13. Woolas RP, Bower M, Newlands ES et al. Influence of chemotherapy for gestational trophoblastic disease on subsequent pregnancy outcome. Br J Obstet and Gynecol 1998:105;1032-5.