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Evaluation of the Relation between Treatment Results and Predictive Factors in Metastatic and High Risk Gestational Trophoblastic Neoplasia

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Abstract

Background: High risk gestational trophoblastic neoplasia is considered a treatable malignancy due to recent advancements in chemotherapy. This report describes treatment outcomes as a predictor of prognosis in one institute.

Methods: We performed a retrospective analysis of the treatment results from 41 patients diagnosed with high risk and metastatic gestational trophoblastic neoplasia who received treatment at Mashhad University of Medical Sciences, Mashhad, Iran from January, 2008 to May, 2014.

Results: Patients had a mean age of 31.31 years. Average treatment time was 3.5 months. Within the participants; 19 patients with World Health Organization scores over 7; received methotrexate at the first line of treatment. 11 cases (26.8%) of the 19 patients with single agent chemotherapy showed resistance. The patients who were resistant to treatment received a combination chemotherapy as the second line of treatment. The response rate of the etoposide, methotrexate, actinomycin D, cyclophosphamide and oncovin chemotherapy regimen as the first line of treatment was 93.7%, which decreased to approximately 83.3% when administered as the second line of treatment. There were 76.4% of cases in remission at the one year follow-up and a successful pregnancy rate of 17.5%. A statistically significant relation existed between chemotherapy response rate with disease stage, score, site, and number of metastases (P<0.05).

Conclusion: The World Health Organization/International Federation of Gynecology and Obstetrics staging-scoring system is appropriate for gestational trophoblastic neoplasia management. The etoposide, methotrexate, actinomycin D, cyclophosphamide, and oncovin regimen showed superior efficacy. The importance of accurate patient selection for adjuvant surgery in high risk gestational trophoblastic neoplasia cannot be emphasized.

Keywords: Gestational trophoblastic disease, Drug therapy, Prognosis.

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Introduction

Gestational trophoblastic diseases (GTD) are rare diseases that originate from the trophoblastic villous of the placenta. They consist of hydatiform mole, invasive mole, choriocarcinoma and placental site trophoblastic tumors (PSTT). The last two are classified as gestational trophoblastic neoplasm.[1]

The diagnosis of GTN is based on serial β-hCG monitoring, which shows elevations or persistent levels during follow-up. Patients may show symptoms of bleeding from the metastatic site due to the vascular pattern of these tumors. Patients are categorized according to the World Health Organization/International Federation of Gynecology and Obstetrics (WHO/FIGO) staging system. The treatment varies according to the calculated score.[1,2] Metastasis can occur in approximately 15% of cases, often initially in the lungs. It is necessary to monitor patients even those currently under chemotherapy with β-hCG titrate and patient symptom for early detection of metastasis.[3,4]

Although GTN could be potentially fatal, current advances in chemotherapy and development of specialized referral treatment centers have made it a treatable malignancy with a remission rate of over 90%.[4,5]

The most common regimen for high risk GTN, with a WHO score over 7, is combined chemotherapy with etoposide, methotrexate, actinomycin D, cyclophosphamide, and oncoverin (EMA-CO).[6]

The goal of the present study was to evaluate the treatment results of metastatic and high risk GTN at one institute in Mashhad, Iran from 2008 to 2014 and predict the patient prognostic factors.

Materials and Methods

This was a retrospective study of patients with GTN who were admitted to Ghaem Hospital, affiliated with Mashhad University of Medical Sciences, Mashhad, Iran from January, 2008 to May, 2014. From 260 GTN patients, 41 had high risk GTN based on the WHO/FIGO scoring system. The study was approved by the ethics committee of Mashhad Ethic committee of Mashhad University of Medical Sciences (IR.MUMS.REC.1388.141).

The chemotherapy regimen used for the study cases consisted of methotrexate (MTX); actinomycin D (ACT); bleomycin, etoposide and cisplatin (BEP); and EMA-CO.

Response was defined as negative β-hCG results in 3 consecutive weekly titrates. If the β-hCG levels remained elevated despite treatment, the patient was considered to have chemotherapy resistance. The patient characteristic data and the treatment results were analyzed by SPSS software. *P*-values <0.05 were considered to be statistically significant.

Results

We assessed the records of 41 patients who had high risk GTN based on the WHO/FIGO scoring system. The mean age of patients was 31.31±11.07 (range: 14-53) years. Table 1 lists the patients' characteristics and metastatic sites. The number of metastatic sites was more than 3 in nine (22%) patients. Some patients underwent surgeries (Table 2).

According to the WHO/FIGO staging system, 28 (68.3%) patients had stages III and IV disease, eight (19.5%) were in stage I that progressed during follow-up, and five (12.5%) patients had stage II disease.

Methotrexate was administered to 19 patients as first line treatment in another institute before they referred to our center. Totally, these patients received 134 doses of MTX (average: 6.9 doses per person). In these patients, 11 were resistant to MTX as the first line of treatment. Two patients received ACT as the second line of treatment after resistance to MTX and both became resistant to the ACT regimen. The others received combined chemotherapy with BEP or EMA-CO (Table 3). Of 11 MTX-resistant patients, one died, one medical record was missed, and four patients became resistant to the second line of treatment. However, these four patients responded to the third line chemotherapy regimen. So at the end, all nine cases with recorded data, out of 11

Table 1. Patients' characteristics.

Mean age (years)*		31.31 ± 11.07 (14-53)
Mean interval between the end of pregnancy and treatment (months)*		3.6 ± 3.6 (1-18)
B-hCG titrate before treatment (UI/L)*		2093572 ±124330.4
Tumor size (cm)		8.1 (2.8-17)
Metastatic sites: n (%)**	34	
	Lungs	26 (63)
	Kidneys	4 (9.8)
	Spleen	1 (2.4)
	Liver	2 (4.9)
	Brain	4 (9.8)
	Vagina	13 (31.7)
	Pelvis	7 (17.1)
	Others	4 (9.8)
		(vesicle, 1 arm, 1 omentum)

*: Mean ± standard deviation

(81.8%) MTX-resistant cases which participated in the study showed response to chemotherapy switching.

The BEP regimen was used in six patients with an average of five cycles per person – first line treatment in three patients, second line in two patients after MTX, and third line in one patient after resistance to MTX and ACT.

Totally, 29 patients were treated with EMA-CO. A total of 158 cycles of EMA-CO were administered with an average of 5.44 cycles per person. This regimen was the first line treatment in 19 patients, second line in seven patients after resistance to MTX, and the third line in three patients; one had received MTX and BEP previously and the other two underwent chemotherapy with MTX and ACT.

A total of 11 (26.8%) patients were resistant to the first line chemotherapy treatment – all received MTX. The average duration of resistance to the primary chemotherapy regimen was 6.3 months. These patients all had WHO/FIGO scores above 7 and 72.7% of the patient had metastatic sign (eight cases). Of these, four patients also became resistant to the second line treatment.

Of the 19 patients treated with MTX, the average response rate for eight patients was 1.6 months (1 to 3.2 months). The response rate of this group was 42.1%. A total of 11 patients with MTX resistance received the following second line regimens: ACT (n=2), BEP (n=2), and EMA-CO (n=7). Neither of the two cases resistant to MTX had any response to ACT as second line treatment. Third line treatment for these two patients was BEP and EMA-CO.

Of the six patients who received BEP, three responded between 2.9 and 7.2 months (average: 5 months) for a response rate of 50%. One patient who received BEP as first line treatment died due to massive hemorrhage. She had choriocarcinoma and multiple pulmonary, pelvic, vesical and shoulder metastases.

The other two patients treated with BEP became resistant and received EMA-CO as third line treatment, after which they were in remission. The patient who received BEP as the third line also responded to treatment.

The response rate of EMA-CO as first line treatment was 93.7% (15 out of 19). One patient died in the first line treatment due to intensive respiratory distress and the condition of three other patients was unknown.

In the second line treatment, five out of seven (83.3%) patients responded. One patient during EMA-CO treatment became unconscious and died. The condition of one patient was unknown. The response rate of this regimen was 100% (three out of three) in the third line of treatment. Overall, without considering the response of four patients that had incomplete medical records and were missed, we noted that 23 patients out of 29 (79.3%) responded to this regimen. These patients

Table 2. Surgery type in high risk gestational trophoblastic neoplasia (GTN) patients.

Surgery	N	%
Hysterectomy	13	44.8
Hysterectomy and bilateral-salpingo- oophorectomy	5	17.2
Hysterectomy, bi-salpingo-oophorectomy, and omentectomy	1	3.4
Subtotal hysterectomy	4	13.8
Lung metastasectomy	4	13.8
Brain metastasectomy	2	6.9

were treated over 1.5 to 8.2 months. Overall, from 41 patients with metastatic or high risk GTN, the duration of treatment for 34 cured patients was 1 to 9.5 months (average: 3.5 months). The mortality rate was three (7.3%) and the condition of four (2.4%) patients remained unknown and were considered as missing data.

Between 34 cured GTN cases, five (14.7%) required second line chemotherapy and four (11.7%) responded only after switching to the third line regimen.

Table 3 summarizes the treatment results. This table shows a response rate of 91.9% (34 from 41 patients) and resistance rate of 8.1% (17 patients) for high risk GTN patients in our institute. (MTX:Methotrexate;ACT:Actinomycin D; BEP: Bleomycin, Etoposide and Cisplatin; EMA-CO: Etoposide, Methotrexate, Actinomycin D, Cyclophosphamide, and Oncovin).

Follow-up of this study showed that of the 41 high risk and metastatic GTN patients, 26 out of 34 (76.4%) cured cases remained in remission after one year follow-up, successful pregnancy was reported in seven (17.5%); 92.6% were alive after one year and 85.2% after two years.

According to the Q2 test, there was no significant relationship between the primary pathology report with treatment response (P=0.7) and resistance to first line chemotherapy (P=0.9).

There was no significant correlation between chemotherapy response rate and prior pregnancy history, past history of chemotherapy administration, age, tumor size, body mass index (BMI), interval from the last pregnancy, and serum β-hCG level. There was no statistically significant difference between the chemotherapy resistance rate to the first line regimen with age, tumor size, patient WHO score, BMI, previous pregnancy history, previous chemotherapy, and disease stage.

A statistically significant relation existed between chemotherapy response rate and disease stage according to the FIGO staging system (P=0.02), metastatic site (P=0.01), patient score according to the WHO scoring system (P=0.05), and the number of metastases (P=0.01). Table 4 shows the correlation between chemotherapy response and prognosis.

Discussion

Gestational trophoblastic neoplasia is defined as the malignancy of gestational trophoblastic tissue and is expected as a chemo sensitive neoplasm.[3,4]

In the present study, we evaluated the outcome of treatment in 41 patients with metastatic and high risk GTN to predict their prognostic factor, which could help in better management. The mean age of our high risk GTN cases was approximately 31.3 years compared to 32.5 years in a study by Feng Su.[7] The response rate of high risk patients has been reported at 80%-90%, which corresponded to our results of approximately 91.9%.[8-10]

Patients had the following overall response rates for the regimens: MTX (42.1%), BEP (50%), and EMA-CO (92%). All patients treated with MTX had also undergone surgery. The reported response rate with the EMA-CO regimen exceeded 80%. This is the current favorite regimen for high risk GTN.[11] The EMA-CO regimen is not only efficient as a first line treatment for high risk and metastatic patients, but also it brings about favorite results in patients with disease resistance to other regimens. Many studies have

Table3. Summary of treatment results.

Chemotherapy regimen*	First line	Second line	Third line	Total (n=41)	Response rate	Resistance rate
MTX	19	-	-	19 (6.9)*	8	11
ACT	-	2	-	2	0	2
BEP	3	2	1	6 (5)*	3	3
EMA-CO	19	7	3	29 (5.44)*	23	2

*Number of patients (average of chemotherapy courses which was prescribed in one patient)

considered the EMA-CO regimen to be a useful treatment for high risk and metastatic patients. Approximately 20%-25% of high risk patients who receive EMA-CO as the first line treatment do not respond and become resistant.[12] In our study, 5.3% of patients did not respond to first line EMA-CO and 14.2% did not respond to this regimen as a second line treatment. These figures were lower than other studies. Perhaps the patients in our region were more sensitive to this regimen and had a better response. We noted that 50% of patients treated with BEP responded. In a study by Lurain, the response rate to the BEP regimen was 67%.[5] The lower response rate with BEP in our study might be due to fewer patients who were treated with this regimen.

The present study revealed the statistical importance of WHO/FIGO staging and scoring system (P<0.05) in correlation with chemotherapy response rate, which was in line with prior studies.[4,10,13]

The site of metastasis is important in the WHO/FIGO staging-scoring system. In the current study,[11] (26.8%) patients were resistant to the primary chemotherapy. Most (72.7%) had metastases at the time of diagnosis. So, due to high risk of resistance in metastatic patients, close follow-up during treatment is necessary. Although the lungs are the most common site of GTN metastasis; fortunately solitary lung metastasis by itself wouldn't increase the WHO prognostic score. Recently Vree et al. refused this idea and show the independent role of lung metastasis on the recurrences and death.[14,15] The most common site of metastasis in the present study were also the lungs. Response to treatment varied according to metastatic site, which was 73% for the lungs compared to the response rate for the brain and liver, as the worst, in about 50%. Of the four patients with brain metastasis in the current study, two died and the other two responded to treatment. In addition to chemotherapy, both had brain metastatectomies. These patients were alive and in remission after two years.

Overall, 70.7% (29 out of 41) high risk patients underwent surgery as part of their treatment approach. Based on a prior study, we should consider adjuvant surgery, especially hysterectomy and pulmonary resection, as lifesaving options for high risk GTN. Expertise judgment regarding the proper time for intervention would be the main issue.[16,17] Patients older than 40 years of age had a response rate of 100% compared to younger patients (less than 40 years) who had a lower response rate (73.1%). The increased use of surgery in older patients might account for this contrast in that 88.9% of patients older than 40 and 59.4% of patients younger than 40 underwent surgery. The characteristics of patients resistant to primary chemotherapy differed from other patients. Patients resistant to treatment were younger (mean age 28 years versus 32 years), they had higher serum β-hCG levels, higher WHO score, larger tumor size, and more abortions. However, abortions were not significant. Hoekstra et al.[10] reported a significant relationship with resistance to primary treatment between patients who had previous term pregnancies in comparison with other types of pregnancies such as molar, abortion, and ectopic.

Most of our patients with choriocarcinoma (75.6%) were metastatic at the time of diagnosis. The majority of patients with invasive molar pregnancies were not metastatic at the time of diagnosis (72.7%). This finding was also reported

Table 4. Correlation between predictive factor and first line treatment response.

		Chemotherapy response rate (%)	*P*-value*	Resistance rate to first linechemotherapy (%)	*P*-value*
Age (years)					
	20-39	173	0.4	26.9	0.3
	≥40	100		11.1	
Previous pregnancy					
	Mole	100	0.8	25	0.7
	Abortion	81.5		29.6	
	Term	75		25	
Interval from last pregnancy (months)					
	<4	85.7	0.7	28.6	0.9
	4-7	100		0	
	7-12	100		100	
	≥13	50		100	
β-hCG(IU/L)					
	10^3>	66.7	0.2	0	0.7
	10^4>-10^3	88.9		22.2	
	10^5>-10^4	100		18.2	
	10^5 or above it	70.6		41.2	
Largest tumor size(cm)					
	<3	100	0.2	16.7	0.7
	3-4	83.3		25.8	
	≤5	80.6		100	
Site of metastasis					
	Lungs	73.1	0.03	26.9	0.8
	Spleen	0	-	0	-
	Kidney	75	-	0	-
	Liver	50	-	0	-
	Brain	50	0.01	25	0.4
	Vagina	61.5	0.02	23.1	0.1
Number of metastases					
	1-4	78.8	0.01	44.8	0.6
Past history of chemotherapy					
	Single agent	42.1	0.6	57.8	0.1
	Multiple agent	78.7		36.3	
WHO score					
	<7	100	0.05	0	0.1
	≤7	79.4		32.4	
FIGO stage					
	1-2	100	0.04	30.8	0.6
	3-4	75		25	

WHO: World Health Organization; FIGO: International Federation of Gynecology and Obstetrics; *P*-value <0.05 is significant.

by Bjørge et al.[11] Thus, the probability of finding metastasis in choriocarcinoma would be greater than other trophoblastic diseases. Although, in the current study, the relation between pathology and metastasis was not statistically significant.

The pregnancy rate was 17.1% (seven patients). A few retrospective studies that followed their patients for approximately one year and did not separate low and high risk GTN reported pregnancy rates of approximately 10%-27%.[7,18,19]

Lurain evaluated the relation between survival and prognostic factors, and found that a correlation existed between the site of metastasis and β-hCG.[5] There was no relation between prognostic factors and patient survival in the current study.

Conclusion

We found that the use of the WHO and FIGO systems in patients with high risk and metastatic GTN contributed to a favorable result in their treatment. We reported the superiority of the EMA-CO regimen and importance of accurate patient selection for adjuvant surgery as the most useful way to treat these patients.

Conflict of Interest

None declared.

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