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Assessment of Response Rate in Patients with Gestational Trophoblastic Neoplasia: A Case Study of Healthcare Centers in Isfahan from 2011 to 2016

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ABSTRACT

Background & Objective: Gestational trophoblastic neoplastia (GTN), as one of the curable malignancies all around the world, has a higher incidence rate in developing countries. Accordingly, investigating its behavior, risk factors, and reasons of treatment failure is of prime importance in such countries.

Materials & Methods: This descriptive cross-sectional study examined the medical records of GTN cases in referral university hospitals in Isfahan from 2011 to 2016 to evaluate the risk factors affecting treatment response rate. The patients were divided into two groups of low-risk and high-risk and studied based on the International Federation of Gynecology and Obstetrics (FIGO) scoring system.

Results: Out of a total of 70 GTN patients, 59 were classified into the low-risk group and 11 into the high-risk group. 100% of the patients in the low-risk group and 90.1% of the patients in the high-risk group responded to the first and second line treatments. In the follow-up, one case of recurrence in low-risk patients and one case of mortality in high-risk patients were reported. In the high-risk metastatic group, there was one case of unusual metastasis site at the kidney and the most common site of distant metastasis was lung.

Conclusion: Response rate in the low-risk GTN patients was excellent (100%) and it was more than 90% in the high-risk GTN patients. Therefore, if GTN patients are treated in referral centers, the response rate will be favorable. Patients with brain metastases have good chances of recovery if treated timely.

Keywords: Gestational trophoblastic neoplasia (GTN), High-risk, Low-risk

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Introduction

Gestational trophoblastic neoplasia (GTN) is a term used for malignant lesions that originate from abnormal placental trophoblast proliferation. GTN includes invasive mole, choriocarcinoma (CCA), epithelioid trophoblastic tumor, and placental site trophoblastic tumor. Choriocarcinoma has a strong tendency to recur and spread throughout the body, responds completely to chemotherapy, and is a kind of cancer that can be cured even at advanced stages **(1)**.

The incidence of gestational trophoblastic disease (GTD) is about 0.6-11.5 per 1000 pregnancies, which varies across various geographical and racial regions. The incidence of GTD in Asia and Latin America is higher than that in Western countries **(2)**. The prevalence of trophoblastic diseases, especially choriocarcinoma, is higher in Iran compared to developed countries **(1)**.

The risk of drug resistance is determined based on the classification of the International Federation of Gynecology and Obstetrics (FIGO). Patients who are classified as FIGO Stage IV or get a FIGO score of up or equal to 7 are considered as high-risk patients **(3)**.

Low-risk patients whose scores are less than 7 are regarded as patients with FIGO Stage I, II, or III. They are initially treated with first-line single-agent chemotherapy including methotrexate (MTX) or Actinomycin D. Methotrexate is the preferred treatment regimen because of its ease of administration. In the case of no therapeutic response, the patient will be reassessed and his/her score will be determined again to choose second-line treatment. If the score is below 7, second-line treatment will be methotrexate or Actinomycin D (in the case of administering either methotrexate or Actinomycin D as first-line treatment, the other one will be used as second-line treatment). If the score is 7 or higher, a multidrug regimen (EMACO) will be administered **(4)**.

Due to the importance of GTN prevalence as a treatable disease, few studies **(5)** have been carried out to examine the issue in Isfahan province. This study aimed to investigate demographic and clinical characteristics and

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response rate of different chemotherapy and surgical treatment lines in GTN patients with different scores.

Materials and Methods

This descriptive cross-sectional study was carried out on all medical records of GTN patients referred to two referral centers in Isfahan, Al-Zahra University Hospitals and Shahid Beheshti University Hospital. The patients underwent chemotherapy with GTN clinical criteria, consisting of 3 or 4 times rise in plateaued BHCG or GTN pathological criteria (choriocarcinoma) in the time period between 2011 and 2016. Those patients who did not refer to the hospitals regularly or their records were incomplete were excluded.

The patients' information, including age, type of pregnancy, the gap between the diagnosis and previous pregnancy, tumor size, metastasis site, the BHCG level at the start of treatment, and type of treatment used (including surgery, chemotherapy, and radiotherapy) were gathered to determine their stages and scores.

Quantitative data were described by using means and standard deviations and qualitative data were explained by applying frequencies and percentages. All data analyses were done by SPSS 20 (SPSS Inc., Chicago, Illinois, USA).

Results

A total of patients with GTN were identified over the 5 years from 2011 to 2016. The mean ± standard deviation of the patients' age was 30±8.25 years (19-57). The majority of GTN cases occurred after molar pregnancies (86.8%). The majority of the patients had no metastases (64.3%) and 21.4% of them experienced lung metastases. Overall, 69 patients (98.6%) were cured. One patient (1.4%) did not respond to treatment and 1 patient (1.4%) experienced a recurrence seven years after the initial treatment.

59 patients (84.3%) were in the low-risk group and 11 patients (15.7%) were in the high-risk group. All patients' demographic, clinical, and treatment characteristics are presented in Table 1.

In the low-risk group, 46 patients (77.9%) were cured with first-line treatment. Thirteen patients did not respond to first-line treatment and underwent EMACO, all of whom (100%) responded to it. The disease recurred in 1 patient (1.7%).

In the high-risk group, all the patients were treated with EMACO. Except for 1 of the patients who did not respond to the treatment (9.1%), all other patients were cured (90.1%). The demographic, clinical, and treatment characteristics of the 2 patients who experienced a recurrence or did not respond to the treatment are presented in Table 2.

In the low-risk group, 45 patients (76.3%) had no metastases, all of whom were treated. Of these, 39 patients were cured with first-line treatment and 6 patients were cured with second-line treatment. Also, 14 patients (23.7%) had metastases. The most common metastasis in this group was lung metastasis (78.5%). In the metastatic group, 5 patients were cured with first-line treatment and 9 patients were cured with second-line treatment.

In the high-risk group, all the patients had metastases. The most common metastasis was lung metastasis (81.8), of which 10 patients were cured with EMACO and 1 patient did not respond to the treatment and received the EMA-EP multidrug regimen. This patient was missed in the follow-ups.

In this study, 20 patients who were in their reproductive age (15-44 years) were evaluated for pregnancy after chemotherapy. Among these people, 17 patients (85%) got pregnant after the completion of the treatment, out of which 15 patients were in the low-risk group and 2 patients were in the high-risk group.

Table 1. The GTN patients' demographic, clinical, and medical characteristics classified by considering the low-risk and high-risk groups

		Low-risk (59 patients)	High-risk (11 patients)
Age, mean ± SD (min-max)		30.63±7.41 (19-52 years)	32.82±12.09 (22-57 years)
BHCG, mean ± SD		48255±22233 (mIU/mL)	90714±104894 (mIU/mL)
Tumor size, mean ± SD		3.11±1.12 cm	4.09±0.83 cm
The gap between the diagnosis and previous pregnancy, mean ± SD		1.61±1.22 months	9.90±17.22 months
Previous pregnancy, the number of patients (%)	Molar	51 (89.5%)	8 (72.7%)
	Miscarriage	5 (8.8%)	1 (9.1%)
	Term	1 (1.8%)	2 (18.2%)
Metastasis, the number of patients (%)	None	45 (76.3%)*	0**
	Lung	11(18.6%)	5 (45.4%), 1 (9.1%)
	Renal	0	1 (9.1%)
	Liver	0	2 (18.2%)
	Brain	0	2 (18.2%)

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		Low-risk (59 patients)	High-risk (11 patients)
	Pelvic	5 (8.4%)	0
	Ovary	1 (1.7%)	0
The FIGO staging, the number of patients (%)	1	45 (76.3%)	0
	2	3 (5.1%)	3 (27.3%)
	3	11 (18.6%)	4 (36.4%)
	4		4 (36.4%)
The FIGO scoring, mean ± SD		3.03±1.75	9.27±3.03
Hysterectomy, the number of patients (%)		9 (15.3%)	2 (18.2%)
Response rate	Complete recovery	59 (100%)	10 (90.9%)
	Recurrence	1 (1.7%)	0
	Did not respond to the treatment	0	1 (9.1%)
Blood group	A	12 (20.3%)	4 (36.4%)
	B	2 (3.4%)	2 (18.2%)
	AB	1 (1.7%)	0
	O	15 (25.4%)	2 (18.2%)
Rh+, the number of patients (%)		27 (96.4%)	6 (85.7%)
Next pregnancy	Molar	0	1 (16.7%)
	Pregnant	15 (57.5%)	2 (33.3%)
	Not pregnant	2 (7.7%)	0
	Inability to get pregnant due to age	0	1 (16.7%)
	Inability to get pregnant due to hysterectomy	9(34.6%)	2(33.3%)

*In the low-risk group, 2 patients had concomitant lung and pelvic metastases and 1 patient had concomitant ovarian and lung metastases.

** In the high-risk group, 1 patient had concomitant kidney and lung metastases and 1 patient had concomitant liver and pelvic metastases. Moreover, 2 patients had concomitant lung and brain metastases.

Table 2. The demographic, clinical, and treatment characteristics of the patients who experienced a recurrence or did not respond to the treatment

	Recurrence	Did not respond to the treatment
	1 case	1 case
Age	Diagnosed at 45 years old Recurrence: 52 years old	Diagnosed at 42 years old
BHCG	2500 (mIU/mL)	100000
Tumor size	5 cm	5 cm
The gap between the diagnosis and previous pregnancy	1 month	4 years
Previous pregnancy	Molar	Term
Metastasis	Lung	Lung and Kidney
The FIGO staging	3	4
Hysterectomy	None	None
Blood group	A	A
The FIGO scoring	5	15
Treatment	Methotrexate and then EMACO since she did not respond to the first treatment	EMACO

In the high-risk patients, there was 1 case of brain metastasis and 1 case of renal metastasis. The first case was a 51-year-old woman who had a miscarriage and had her last menstrual period (LMP) two years ago. She referred to the hospital with a complaint of left hemiparesis and was admitted to the hospital with an initial diagnosis of brain tumor made based on her brain CT scan. During her hospitalization, the patient suffered from vaginal bleeding and tissue excretion. The residue of pregnancy was found in ultrasonography and the pathology indicated choriocarcinoma. Moreover, the performed tests showed high levels of BHCG over

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200,000. The patient was diagnosed with choriocarcinoma and brain and lung metastases were found in her brain radiotherapy. Then, she received 8 EMACO courses and was discharged from the hospital with a good general condition and BHCG of 0.5. During the hospitalization, the patient suffered from DVT and PTE and an IVC filter was installed for her. She received warfarin and showed a relative recovery. Additionally, chemotherapy-induced pancytopenia complication was administered by granulocyte-colony stimulating factor (G-CSF).

The second case was a 25-year-old woman who had a full-term delivery in Najafabad Hospital. Two days after the delivery, she suffered from vaginal bleeding managed by a curettage. Two days later, she had a severe headache and nausea. Brain CT scan was performed and subarachnoid hemorrhage (SAH) was reported. The patient underwent craniotomy and bleeding discharge. After the surgery, she suffered from plegia in her left hand. Brain CT scan was done again, which showed a lesion with a metastatic view. Therefore, having choriocarcinoma in mind, BHCG was examined (BHCG level=250,000). Furthermore, chest CT reported lung metastasis. The patient underwent brain radiotherapy and 10 EMACO courses and was discharged with a good general condition. Her plegia was relatively cured at the time of hospital discharge. During her hospitalization, the patient suffered from lower extremity DVT and was treated with heparin. Warfarin was prescribed to her at the time of discharge.

The third case was a 42-year-old woman who had a full-term delivery. One year after the delivery, she referred to the hospital with a complaint of hematuria and vaginal bleeding. A metastatic lesion was found in the renal examination and the BHCG level was 300,000. The patient was diagnosed with choriocarcinoma and received 25 EMACO courses; however, she did not respond to the treatment and underwent second- and third-line treatments. Unfortunately, subsequent follow-ups were not possible.

Discussion

Due to the importance of GTN, its increasing prevalence in Isfahan province, and the high response rate achieved through appropriate and timely treatment, GTN patients who referred to two University Hospitals in Isfahan were reviewed in this study.

Among these people, 70 patients had the GTN inclusion criteria according to clinical and pathological criteria, out of whom 59 patients were in the low-risk group and 11 in the high-risk group.

The patients' mean age was 30 years and 55.7% of the patients were in the age range of 20 to 30 years old. In a study conducted at Mashhad University of Medical Sciences, the patients' mean age was 27.74 years and half of the patients were younger than 30 years old **(1)**. Also, in a study carried out in one of the provinces of Turkey, the mean age of the patients was 28.6±7.3 and most of the patients were in their third decade of life **(6)**; however, reference books have mentioned that this disease mostly occurs at ages younger than 20 and older than 35 **(7)**. This difference was probably due to the mean age of the study population, which was about 30 years old. It seems that with the increasing tendency in marriage age in Iran, proper perinatal care and especially more geographic and nutritional interventional studies must be done with the aim of eliminating the obstetric complication.

In this study, 86.8% of the study population had GTN following molar pregnancies. In a similar study in India, 58.5% of the patients had GTN after molar pregnancies **(8)**. GTN occurs in 15% of complete molar cases and it is uncommon among patients who have had miscarriages or ectopic pregnancies **(9)**. This finding emphasizes the definite need for close follow-ups after molar pregnancy termination. Moreover, 15% rate of GTN progression following non-molar pregnancy termination shows the importance of awareness in reporting abnormal symptoms after delivery or miscarriage.

In this study, of the 38 patients whose blood group was available, 17 (44/7%) had blood group o and 16 (42/1%) were A. Sasaki *et al.* reported that a significant decrease in blood group A and a slight increase in blood groups O, B, and AB were observed among patients with the malignant trophoblastic disease compared to healthy pregnant women **(6)**. But in the study of Parazzini *et al.*, blood groups A and AB were associated with an increased relative risk of benign moles and persistent trophoblastic disease **(9)**. In several other studies, it was reported that this disease was more common among patients with blood group A compared to other blood groups **(1, 10)**. In a different study, most of the mothers had blood group A **(6)**. Accordingly, as WHO/FIGO showed in the last version of GTN staging and scoring protocol, all patients with different blood groups have the chance of progression to neoplasm and need equal care.

In the present study, 97.1% of the patients responded to the treatment. In a study conducted in Kermanshah province, 44 patients were studied and the results showed that 100% of the patients in the low-risk group and 91% of the patients in the high-risk group responded to the

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treatment **(11)**. Also, in a study done in India, the recovery rate was 95% **(8)**; this rate was 100% for the low-risk patients and 80% for the high-risk patients **(9)**.

In the current study, 77.9% of the low-risk patients were cured with first-line treatment and the rest were cured with second-line treatment. This finding is different from the results of the study conducted by Hussein *et al.* in which all the low-risk patients were cured with a combination of methotrexate and Actinomycin D **(8)**. In a study carried out in India, 88.5% of GTN patients after molar pregnancies were cured with methotrexate and 4.4% of them were cured with a mixture of hysterectomy and methotrexate **(4)**. In another study conducted in the UK, 72% of the low-risk patients responded to methotrexate and the rest needed second-line treatment; overall, 95% of these patients experienced complete recovery without any recurrences **(12)**. In a study performed in Mashhad, 41 patients were examined in terms of responding to first-line chemotherapy, among whom 68.4% of the patients had a good response and 10.5% of them had a poor response to first-line chemotherapy; but 21.1% of the patients did not respond to it **(1)**. This unexpected low rate of response in single agent chemotherapy could be due to the high desire to methotrexate therapy as a low-cost first-line single agent regimen.

Further studies are needed to compare different chemotherapy regimen with each other in different Iranian ethnic groups with obviously different genetic and nutritional substructure.

In the present study, 90.1% of the high-risk patients responded to EMACO treatment. In India, 91.6% of the high-risk patients were cured with EMACO treatment **(8)**. In a UK study, 86.2% of the high-risk patients responded to EMACO treatment **(13)**. Although response rate to single agent therapy was lower in our study, the similar response of high-grade GTN cases reported in other studies, emphasize the need for more genetic-based investigations.

In this study, 1 patient (1.7%) in the low-risk group had a recurrence after 7 years and 1 patient in the high-risk group (9.1%) did not respond to EMACO regimen. In a cohort study conducted in India, 41 patients with GTN recurrences were identified over 7 years. 17 patients were in the low-risk group and 24 were in the high-risk group. All the patients in the low-risk group and 22 patients in the high-risk group recovered completely. In the high-risk group, 1 person experienced a recurrence that was completely cured by second-line chemotherapy. One patient died in this group **(8)**. In a 10-year study performed in Senegal, 108 patients with GTN were identified, among whom 88 patients were in the low-risk group and 20 patients were in the high-risk group. 5 patients (5.7%) and 12 patients (60%) died in the low-risk and high-risk groups, respectively **(2)**. Also, 10 out of these 12 patients did not receive second-line chemotherapy due to their financial issues **(13)**.

Conclusion

The data indicated the patients' high response rate in both the low-risk and high-risk groups in developing countries. It is recommended that more precise risk assessments be performed and patients be referred to referral centers. Since most patients are from low socioeconomic groups, there is a great need for long-term follow-ups.

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Conflict of Interest

Authors declared no conflict of interests.

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