ORIGINAL ARTICLE

Evaluation of Clinical Symptoms and Treatment Results of Patients with Gestational Trophoblastic Tumors Referred to the Clinic of Imam Khomeini Hospital

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ABSTRACT

Background: Gestational trophoblastic tumor is one of the diseases arising from the trophoblastic epithelium of the placenta that causes many mothers to face serious risks and complications every year; Since the gestational trophoblastic tumors have different potentials for local invasion and distant metastasis, rapid diagnosis of the tumor, followed by appropriate treatment and prevention of its severe complications, is highly important.
Methods: In this cohort study, 272 women with pathologic diagnosis of trophoblastic tumors that referred to the gynecological oncology clinic of Imam Khomeini Hospital, were selected and then they were evaluated for clinical symptoms, disease stage, and treatment results in terms of complete response to chemotherapy and the number of required chemotherapy cycles for treatment. Data were analyzed using SPSS software
Results: The most common symptoms were vaginal bleeding with 64.3% and pelvic pain with 18.4%, respectively. 62% had hydatidiform mole and abortion was observed in 22% of cases. In total, resistance to chemotherapy was observed in 24% of cases. Regarding the response to single-drug treatment in stages 1 and 2, which were low risk, the effectiveness of treatment was 66.7% in methotrexate and 83.6% in actinomycin. Resistance to single-drug chemotherapy in the methotrexate and actinomycin D groups was 16% and 33.3%, respectively. In the EMACO combination drug regimen, the therapeutic efficacy was 93.8% and in the EMAEP was 100%, and the resistance to chemotherapy in the EMACO combination drug treatment was 6.2% and in the EMAEP was very low.
Conclusion: Resistance to chemotherapy medications was observed in about a quarter of cases. Advances in targeted molecular therapy and new medications could be effective in improving therapeutic performance, especially in drug-resistant patients
Keywords: Gestational trophoblastic tumor, Clinical symptoms, Malignancy, Drug resistance

INTRODUCTION

Gestational trophoblastic tumors are a group of rare placental diseases including invasive mole, choriocarcinoma, placenta site trophoblastic tumor (PSTT), and epithelioid trophoblastic tumor (ETT). PSTT and ETT are very rare, but invasive moles and choriocarcinoma are the most common types of the disease [1]; The incidence of choriocarcinoma is between 2 to 7 per 100,000 pregnancies [2]. Gestational trophoblastic neoplasia (GTN) occurs in 60% of cases following a molar pregnancy, in 30% of cases following an abortion, and in the remaining cases following a normal pregnancy or EP[1]. In choriocarcinoma and invasive mole, HCG is high and the response to chemotherapy is appropriate, but in PSTT and ETT, HCG is lower and more resistance to chemotherapy could be observed [3]. FIGO considers only invasive moles and gestational choriocarcinoma as GTN[4]. Gestational trophoblastic tumors are classified according to the location of metastasis. In Stage I patients, the Disease is only limited to the uterus; In Stage II the metastasis extends outside the uterus but is limited to the genital structures; In Stage III, GTD metastasis develops to the lungs; In Stage IV, GTD has extended to other distant sites. FIGO has rated Stage 2-3 based on age, the type of previous pregnancy, the time interval between disease and previous pregnancy, number and location of metastasis, and the type of previous chemotherapy; Stage 1 and scores below 7 in stage 2 and stage 3 are classified as low risk and Stage 4 and scores above 7 in Stage 2 and Stage 3 are classified as high risk [4]. In low-risk cases, single-drug chemotherapy is recommended, and in high-risk cases, multi-drug chemotherapy is recommended, and Remission varies between 54-91%[3]. However, postoperative chemotherapy intervention is usually performed in cases that the surgical intervention is inappropriate or failed [5].In addition to chemotherapy, immunotherapy has been considered in cancer research. Targeting planned cell death in a variety of cancers has had significant benefits in the field of immunotherapy. The goal of chemotherapy and immunotherapy after surgery is to reduce tumor growth and metastasis[6, 7]. One of the major problems of chemotherapy is drug resistance, which makes it important to identify the level of drug resistance and the proper drug. Different and contradictory clinical results regarding treatment and drug resistance in gestational trophoblastic tumors have shown that it is important to evaluate the clinical features and response to treatment in patients with this type of cancer[8-12]. Considering that the clinic of Imam Khomeini Hospital is an important center for the diagnosis and treatment of GTN patients, we decided to collect and evaluate the treatment

results and clinical features of GTN patients with the aim of obtaining proper treatments in these patients.

MATERIALS AND METHODS

In the present research, which is a retrospective cohort study, the study population included patients with gestational trophoblastic tumors referred to the clinic of Imam Khomeini Hospital from 2008 to 2018. Before starting the study, the code of ethics(ID: IR. TUMS.IKHC.1397.239) was approved by the university research committee. Then, the records of patients with gestational trophoblastic tumors were reviewed according to the inclusion criteria.

Inclusion criteria: Increasing β-hCG titer after pregnancy, age between 20 and 74 years.

Exclusion criteria: incomplete records, multiple active cancers in individuals, interstitial pneumonia or pulmonary fibrosis, severe arrhythmias in cardiac patients in need of treatment, and other factors that affected the treatment outcomes of patients with gestational trophoblastic tumors.

After concordance with hospital officials, all records of patients with gestational trophoblastic tumors referred to the hospital through 10 years were reviewed. For this purpose, different types of tumors in patients' files were first evaluated. In this study, Placenta site trophoblastic tumor (PSTT) and Epithelioid trophoblastic tumor (ETT) cases were not evaluated due to the small sample size or incomplete file. Then, the important data were collected from the files registered in the obstetrics and gynecology clinic. Also, the files that had incomplete data were followed up by phone as much as possible. After the definitive diagnosis of GTN, all participants referred to the clinic were evaluated for physical variables using imaging. For this purpose, chest X-ray, chest CT scan, and pelvic ultrasound were used and in cases of suspected metastasis or extrauterine invasion, pelvic CT scan or MRI was applied. Study stages were performed step by step and risk assessment scores were performed according to FIGO guidelines and WHO classification (A score of 0 to 4 was considered low, 5 to 6 was moderate, and a score of 6 or higher was considered high risk). [13, 14].

The treatment regimens of 30 to 50 mg methotrexate or 1.25 mg to a maximum dose of 2 mg actinomycin for 14 days, were repeated weekly for the low- and moderate-risk groups, and for the high-risk group, the EMA / CO (etoposide, Methotrexate, actinomycin-D, cyclophosphamide) or EMA / EP (vincristine and cyclophosphamide for 8 days with cisplatin and etoposide) regimens were applied. The patients were followed up for 3 to 24 months and the mean follow-up time was 12.0 months.

Data collection: Information of the patients' file including demographic characteristics (age, race, BMI), BHCG titration at the beginning of diagnosis, duration of GTN diagnosis from the previous pregnancy, uterine mass size at the initial ultrasound, type of pregnancy before GTN, presence of Metastasis, number and location of Metastases, number of monotherapy and combination drug therapy cycles, Stage of patients, different types of GTN, successful pregnancy rate in patients' follow-up, resistance to monotherapy in LOW-RISK GTN cases, need for radiotherapy or surgery, were recorded in a predetermined form.

Data analysis: Mean, frequency and percentage were used to describe the data. The simultaneous effect of variables was investigated through logistic regression. All analyzes were performed by SPSS statistical software version 25. Statistical analysis was performed using the t-test and chi-square method. 0.5 was considered as a significant level.

RESULTS

Two hundred and seventy two people were examined in this study. The average age of the selected people was 29.19 years; 9% were under 35 years old and 91% were over 35 years old. The most common symptoms were vaginal bleeding with 64.3% and pelvic pain with 18.4%, respectively. 62.1% had a history of mole and a history of abortion was observed in 22.1% of cases. Most FIGO / WHO scores were at low risk (77.6%). β-hCG Serum levels before the treatment were less than 1000 in 25% of cases and between 1000 and 10,000 units in 36% of cases. In 79% of cases, tumor spread to surrounding tissues was seen.

Moderate and high risks were observed in terms of disease stages and risks; Several chemotherapy regimens were prescribed for all patients and the consumed diets are shown in Figure 1.A. In general, methotrexate treatment was used for 22.8% of patients, actinomycin D for 42.3%, EMA / CO regimen for 11.0%, and EMA / EP was used for 1.5% of patients. In total, resistance to treatment was observed in 24% of cases (Figure 1.A). Regarding the response to treatment in the monotherapy regimen of methotrexate, the effectiveness of treatment was 66.7% and in actinomycin was 83.6%. Resistance to single-drug chemotherapy in the methotrexate and actinomycin D groups was 16% and 33.3%, respectively (Figure 1.B).

MTX: Methotrexate; ACT: Actinomycin-D; EMACO: Etoposide, methotrexate, actinomycin-D, cyclophosphamide, and vincristine; EMA-EP: A regimen that substitutes cyclophosphamide and vincristine on day eight with cisplatin and etoposide.

Also, the therapeutic efficacy in the EMACO combination therapy regimen was 93.8% and the EMAEP regimen was 100%. Rate of drug resistance to chemotherapy was in 6.2% EMACO combination therapy and very low in EMAEP. In addition, 6.7 percent of all samples were high-risk and received EMACO. The results showed that the prevalence of clinical symptoms of the disease in different stages of the tumor was significantly different. Among the studied symptoms, AUB and pain were the most common symptoms in the first, second and third stages, respectively, and AUB and pain with nausea and amenorrhea were equally observed in the fourth stage (Table 2).

Characteristics		n	%
Age (years)	<35	24	9.0
	≥35	246	91.0
Symptoms	AUB	175	64.3
	Pain	50	18.4
	Amenorrhea	27	9.9
	Nausea	16	5.9
	Hyperemesis gravidarum	16	5.9
	Hemoptysis	9	3.3
AP outcome	*Hydatidiform*mole	196	62.1
	Abortion	59	22.1
	Term pregnancy	15	5.5
	Ectopic pregnancy	1	0.3
FIGO stage	0-4 (low risk)	211	77.6
	5-6 (intermediate risk)	25	9.1
	≥ 7 (high risk)	36	13.3
Pre-treatment β-HCG, No.(%)	< 1000	68	25.0
	1000 – 10 000	98	36.0
	10 000– 100 000	53	19.5
	> 100 000	53	19.5
Mean number of chemotherapy cycles			5.0±1.0
Invasion	NO	55	21
	YES	217	79

Figure 1. A) the relationship between chemotherapy regimens and tumor stage, B) Comparison of drug resistance in the monotherapy regimen

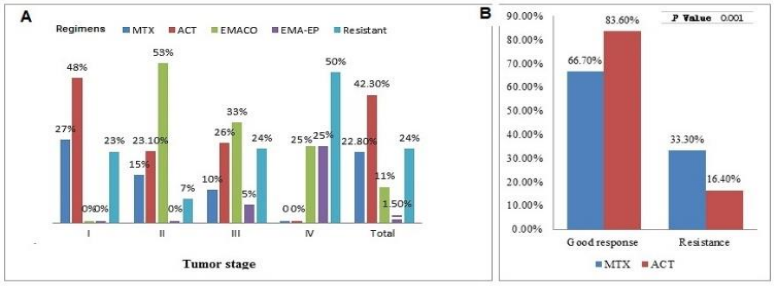

Table 2: Frequency of the prevalence of clinical symptoms based on the stage of the disease *Note.*Horizontal bars: GTN stages (1, 2, 3, & 4); Vertical bars: Number of patients (the frequency of clinical symptoms).

Stage	AUB	Pain	Amenorrhea	Nausea	P value
I	66.5%	10.6%	%	5.1%	0.025
II	69.2%	15.4%	15%	0%	0.013
III	59.6%	25%	5.3%	8.8%	0.002
IV	25%	25%	25%	25%	0.042
Total	64.3%	18.4%	9.9%	5.9%	0.011

DISCUSSION

The findings of the present study regarding the evaluation of clinical symptoms and treatment results of patients showed that most patients were older than 35 years and the most common symptom was vaginal bleeding and 62% of cases had hydatidiform moles. In 77% of cases, the FIGO / WHO score was at low risk. In addition, methotrexate treatment was used for 22.8% of patients, actinomycin D for 42.3%, EMA / CO regimen for 11.0%, and EMA / EP regimen was used for 1.5% of patients. A similar study in 2016 showed that in the initial chemotherapy the combination of MTX and folic acid was used in 36.5%, EMA in 34.9%, and EMACO in 17.5% of cases; the Remission Rate was 66.7% [15]. Another study in 2017 demonstrated that 97.4% of cases had hydatidiform mole and the most common clinical features were vaginal bleeding and amenorrhea, and in most samples the BHCG level was between 50,000 and 100,000 [16].

In our study, the response to chemotherapy in the methotrexate monotherapy group was 66.7% and in the actinomycin group was 83.6%. Resistance to single-drug chemotherapy in the methotrexate and actinomycin D groups was 16% and 92%, respectively. In total, drug resistance was observed in 24% of cases.

In another similar study, regarding the response to treatment, it was shown that the rate of complete response to methotrexate monotherapy was 81% and 75% to actinomycin as a secondary treatment. In total, 94% of patients responded to monotherapy and 6% of patients needed combination therapy or surgery. Resistance to primary methotrexate treatment was associated with high FIGO score, presence of choriocarcinoma, higher BHCG levels, and metastasis [17]. In a parallel study, it was shown that approximately 30% of patients did not respond to the initial chemotherapy regimen, also, after the changes in chemotherapy regimen, GTN patients, did not properly respond to the treatment, especially in higher stages[15].

In another study, that was performed through 30 years, the overall response to treatment was 93.7%. The response to treatment during the second 15 years was 98.1% and in the first 15 years of the study was 83.4%, and especially in stages 3 and 4, the response rate was better. Tumor recurrence rate was 2.7% in the first 15 years and 3.6% in the second 15 years of the study [18]. In a parallel study in 2018, during 3 years, 135 low-risk GTN patients after molar pregnancy were treated with actinomycin in a pulse every two weeks and it was observed that the complete and appropriate response rate was 71.1%; Also, It was concluded that there was an association between the presence of an invasion to the uterus in the ultrasound before chemotherapy, FIGO scores greater than or equal to 5, and BHCG levels above 4000IU/L and appropriate response to treatment and drug resistance to actinomycin[19].

In the present study, in most cases, β-HCG levels were between 1,000 and 10,000 units. In another study, the mean β-hCG level was 58274 [15]. The results showed that β-hCG level and pelvic ultrasound were the two main indicators in the diagnosis and monitoring of GTN patients. [20]. Follow-up and precise examination of patients with trophoblastic tumors, due to the possibility of disease recurrence, should be performed at least once every three months when testing for β-hCG levels [21]. In general, testing for β-HCG levels is an important issue in following up and identifying patients that must be noted [5, 22]. Research has shown that progress in the diagnosis and follow-up of GTN patients has a positive effect on treatment outcomes [18].

Our study also demonstrated that bleeding during pregnancy is one of the most important known symptoms in patients. In studies, it was recommended that in case of abnormal bleeding during pregnancy, GTN should be suspected and clinical-pathological examination is helpful for diagnosis, also, follow-up of this disease is necessary for the early diagnosis of GTN [16].

Treatment management is an important issue in patients because about 33% of these patients show symptoms of metastasis [23]. Responsible physicians must consider the possibility of malignant GTN in almost all patients of reproductive ages with metastatic tumors, as a simple assessment of β-hCG levels in the urine or serum of patients would be life-saving [3]. Routine chest computed tomography (CT) scans may not be effective in the management of GTN patients [24], but pelvic ultrasound and color Doppler imaging techniques could be used in cases of GTN invasion pattern or molar pregnancy [25] . Akhavan et al. Stated in their studies that despite the close relationship between the invasive pattern of tumor in the uterus during Doppler ultrasound and drug resistance, the presence of invasion pattern could be considered a new criterion for scoring tumor risk[26].

Studies have shown that targeted molecular therapies and new biologic drugs can be effective in reducing the metastasis of terboblastic tumors and have fewer complications for patients[27, 28].It is certainly important to pay more attention to this issue.

CONCLUSION

Clinical features such as age over 35 years and Symptoms such as vaginal bleeding and hydatidiform mole were highly observed in patients with gestational trophoblastic tumors and β-HCG levels showed certain amounts in these patients. Examining these factors as the prognosis of GTN after treatment management could be critical. A review of studies shows that most of the available information in this field has been obtained during the last two decades, and the continuation of studies could be effective in understanding more aspects of the disease. Survival rates and drug resistance vary between patients with low-risk and high-risk GTN diseases and need to be evaluated. In the present study, resistance to chemotherapy medications was observed in about a quarter of cases. One of the main challenges in the future is to provide effective treatment approaches for patients who are resistant to the drug. Advances in anti-angiogenesis therapy as well as targeted molecular therapies and new medications could be effective in improving therapeutic performance among these patients.

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