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Is Not It the Time to Change the Treatment of Intermediate-Risk Patients Suffering From Gestational Trophoblastic Neoplasia?

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Abstract

Objectives: The present study attempted to provide a clear view of gestational trophoblastic neoplasia (GTN) with the focus on resistance to treatment approaches in Iran.

Materials and Methods: This retrospective cohort study reviewed the medical records of 272 patients with the definitive diagnosis of GTN referring to Imam Khomeini hospital in Tehran during 2007-2017.

Results: The mean age of participants was 29.19 ± 7.46 years. The abnormal uterine bleeding (AUB) was the most common clinical manifestation in 64.3% of patients. Regarding the risk scoring condition according to the World Health Organization criteria, 77.6%, 9.1%, and 13.3% were categorized as low-, intermediate-, and high-risk cases. Single therapy with methotrexate was used in 22.8% of patients and actinomycin-D was planned for 42.3% whereas 11.0% and 1.5% were considered for treatment with the EMA-CO (Etoposide, methotrexate, actinomycin D, cyclophosphamide, vincristine) and EMA-EP (Etoposide methotrexate and actinomycin-D/etoposide and cisplatin) regimens, respectively. Good response to methotrexate was 66.7% but it was 83.6% in the ACT group (P = 0.001). The resistance to single-agent chemotherapy in low- and intermediate-risk groups was 16% and 92%, respectively. In addition, 20.2% of patients in stage one had tumor invasion pattern in the uterus in pretreatment Doppler ultrasonography, but 52% and 30% had resistance to chemotherapy treatment in invasive and noninvasive groups, respectively (P = 0.008).

Conclusions: In general, due to the high resistance of the intermediate-risk subgroup to a single therapy, a combination therapy may be more useful to treat this disorder. The close association between tumor invasion pattern in the uterus in Doppler ultrasonography and drug resistance can be considered as a new criterion for tumor risk scoring.

Keywords: GTN, Intermediate risk, Chemotherapy resistance

Introduction

Gestational trophoblastic disorders include proliferative disorders that originate from the placental trophoblastic tissue with two none-neoplastic (hydatidiform moles) and neoplastic (gestational trophoblastic neoplasia or GTN) patterns (1). GTN consists of three entities including choriocarcinoma, epithelioid trophoblastic tumor, and placental site trophoblastic tumor (2). In addition, GTN may follow term or preterm pregnancy, molar pregnancy, abortion, or ectopic pregnancy (3). This tumor can be manifested by uterine bleeding or extrauterine hemorrhages (4,5).

Following the molar evacuation, serial serum human chorionic gonadotropin (hCG) levels are measured weekly until it becomes undetectable. Further, postmolar GTN is diagnosed by the International Federation of Gynecology and Obstetrics (FIGO) criteria as follows (6):

- Weekly hCG levels plateau over a three-week period;
- An increase of >10% in the hCG level in a two-week duration;
- Existence of β-HCG six months or more after molar evacuation;
- Existence of histological diagnosis of choriocarcinoma.

The diagnosis of GTN after a nonmolar pregnancy is evaluated with serum hCG and ultrasound after patients become symptomatic.

For patients with GTN, both a stage and a risk score are assigned before treatment. The staging and scoring system can predict the possibility of resistance to single-agent chemotherapy with methotrexate (MTX) and actinomycin D. One of the main issues in the management of GTN is to investigate the main causes of resistance to common therapeutic regimens. Some previous studies emphasized the importance of the earlier identification of chemotherapy resistance in patients (7,10). Although prognosis in GTN was shown to be excellent, chemotherapy resistance was considered as a challenging matter in the treatment of GTN patients (11).

Considering the above-mentioned explanation, the present study attempted to provide a clear view of GTN

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in ten years in our center with respect to chemotherapy resistance in GTN subgroups.

Materials and Methods

The protocol of this retrospective cohort study was approved by at Research and Ethical Committees at Tehran University of Medical Sciences (ethical code: IR.TUMS.IKHC.REC.1397.239). Then, the medical records of all patients with the definitive diagnosis of GTN were retrospectively reviewed, who referred to the Department of Gynecology and Oncology of Vali-Asr, Imam Khomeini hospital of Tehran between June 2007 and December 2017. According to Chapman-Davis et al (12), with a 95% confidence interval and 5% error, the minimum sample size was 256. There were 355 medical records of GTN patients who referred to our hospital in 10 years. All these medical records were studied as our sample size. In this study, only the cases suffering from an invasive mole or gestational choriocarcinoma were assessed and thus other types of malignancies including placental site trophoblastic tumor and epithelioid trophoblastic tumor were not included because of the small sample size or information unavailability. The baseline characteristics including age, the antecedent pregnancy, clinical manifestations, and the level of pre-treatment serum β-hCG, as well as the results of imaging, the site of metastasis, the types of cycles of chemotherapy, and the outcome of surgical management were extracted from the recorded files at the obstetrics and gynecology clinic. In addition, those with incomplete data were collected by telephone follow-ups. After the definitive diagnosis of GTN, all participants referring to the clinic were physically examined and assessed by imaging tools such as chest x-ray, chest CT scan, and pelvic ultrasonography. Further, abdominopelvic CT scan or magnetic resonance imaging was indicated in cases suspected to metastasis or extra-uterine invasion. Then, the patients were staged by the FIGO guidelines (13,14). Furthermore, the World Health Organization (WHO) risk classification rule was employed to determine the risk level as the low (score 0 to 4), intermediate (score 5 to 6), and high (score ≥ 7) risk. The patients were finally treated based on the clinical decision of the physician as medical therapy with methotrexate 30 to 50 mg/m^2 intramuscular weekly or actinomycin-D 1.25 mg/m^2 to a maximum 2 mg single dose repeated every 14 days for low- and intermediate-risk group. Additionally, EMA/CO (i.e., Etoposide, methotrexate, actinomycin-D, cyclophosphamide, and vincristine) or EMA/EP (a regimen that substitutes cyclophosphamide and vincristine on day 8 with cisplatin and etoposide) chemotherapy regimens for the high-risk group. The patients were followed-up for 3 to 24 months with a mean follow-up time of 12.0 months.

For statistical analysis, the results were reported as mean ± standard deviation (SD) for quantitative variables and presented by absolute frequencies and percentages for categorical variables. Then, they were compared using the chi-square or Fisher exact tests. The quantitative variables were also compared with the *t* test or Mann-Whitney U test. Finally, SPSS, version 16.0 for windows (SPSS Inc., Chicago, IL) was used for data analysis. The *P* values of 0.05 or less were considered statistically significant.

Results

Overall, 272 patients were qualified and enrolled in our study. The underlying characteristics of patients are summarized in Table 1. The average age of the participants was 29.19 ± 7.46 years ranging from 14 to 53 years and 39.3% of them were primigravid cases. The most common clinical feature included abnormal uterine bleeding

Table 1. Baseline Characteristics of Study Population

Variables	
Mean age (year), Mean ± SD	**29.19 ± 7.46**
Gravid, No.(%)	
1	107 (39.3)
2	81 (29.8)
3	50 (18.4)
More	34 (12.5)
Clinical manifestations, No.(%)	
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)
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)
Antecedent pregnancy, No.(%)	
Complete mole	158 (58.0)
Partial mole	38 (14.1)
Abortion	59 (22.1)
Term pregnancy	15 (5.5)
Ectopic pregnancy	1 (0.3)
FIGO stage, No.(%)	
I	198 (72.8)
II	13 (4.8)
III	57 (21.0)
IV	4 (1.4)
FIGO/WHO score, No.(%)	
0-4 (low risk)	211 (77.6)
5-6 (intermediate risk)	25 (9.1)
≥ 7 (high risk)	36 (13.3)
Mean number of chemotherapy cycles	5.0 ± 1.0
Type of surgery, No.(%)	
Evacuation	47 (17.3)
Hysterectomy	19 (7.0)
Evacuation and hysterectomy	3 (1.1)
None	203 (74.6)

AUB: Abnormal uterine bleeding; hCG: Human chorionic gonadotropin; FIGO: International Federation of Gynecology and Obstetrics; WHO: World health organization.

(AUB) in 64.3% of patients, followed by pelvic pain and amenorrhea in 18.4% and 9.9% of cases, respectively. Regarding antecedent pregnancy, the complete and partial moles were observed in 58% and 14.1%, respectively, and abortion was found in 22.1%. The pre-treatment serum β-hCG level was less than 1000 in 25.0% while the level of higher than 100 000 was detected in 19.5% of the patients. In addition, 72.8%, 4.8%, 21%, and 1.4% of patients were in stages 1, 2, 3, and 4, respectively. As regards the risk scoring condition according to the WHO criteria, 77.6%, 9.1%, and13.3% of cases were categorized as low, intermediate, and high risk, respectively.

Regarding the patient's stages and risks, several chemotherapy regimens were prescribed for all patients (Table 2). Single therapy with methotrexate was used in 22.8% of all patients and actinomycin-D was planned for 42.3% whereas 11.0% and 1.5% were considered for treatment with the EMA/CO and EMA/EP regimens, respectively. Good response to methotrexate was 66.7% but it was 83.6% ($P = 0.001$) in the ACT group (Table 3). The resistance to single-agent chemotherapy in low- and intermediate-risk groups was 16% and 92%, respectively. Similarly, resistance to the first-line multi-agent drug in the high-risk group was 8%. Further, 20.2% of patients in stage 1 had a tumor invasion pattern in the uterus in pretreatment Doppler ultrasonography but 52% and 30% of them had resistance to chemotherapy treatment in invasive and noninvasive groups, respectively ($P < 0.008$). For controlling severe vaginal bleeding, evacuation, hysterectomy, as well as hysterectomy and evacuation were scheduled for 17.3%, 7.0%, and 1.1%, respectively. However, the non-surgical approach was considered in 74.6% of patients.

There was a significant difference in the prevalence of clinical symptoms in different tumor stages, indicating that the AUB was the prominent symptom in stages I and II, pain in stage III, along with nausea and amenorrhea in stage IV (Figure 1). The mean number of cycles for chemotherapy did not vary in different stages (stage I: 14.50 ± 3.54, stage III: 8.40 ± 4.45, stage IV: 8.33 ± 2.52, $P = 0.204$).

Table 3. Comparing Resistance to Single Agent Drug in Low-Risk Patients

Drug Response	MTX	ACT	*P* Value
Good response	66.7%	83.6%	0.001
Resistance	33.3%	16.4%	0.001

Note. MTX: Methotrexate; ACT: Actinomycin-D.

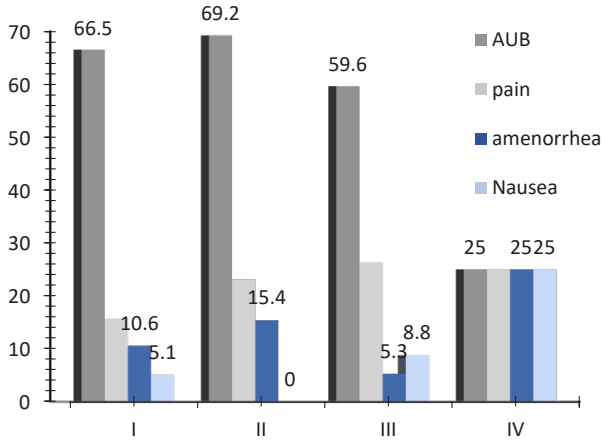

Figure 1. The Frequency of Clinical Symptoms According to Tumor Stage. *Note.* Horizontal bars: GTN stages (1, 2, 3, & 4); Vertical bars: Number of patients (the frequency of clinical symptoms).

Discussion

GTN affects the women of reproductive age and it is treated by different types of chemotherapy regimens. It can influence future fertility or early menopause of women (15). The main risk factors related to GTN progression include previous molar pregnancy, within the age of 40 years and above, and Asian and American ancestry (16). Unfortunately, no comprehensive view is available with respect to epidemiological aspects, clinical features, and treatment outcomes of patients suffering from gestational trophoblastic tumors in our country. The current study attempted to present a clear view of such neoplasia among our population. In our study, the average age of the participants was 29 years ranging from 14 to 53 years, which is near those of the other studies like Melamed et al (17) and Mayun et al (18) demonstrating a mean age of 24.5 and 25.7, respectively. In our study, complete and partial moles, along with abortion were the most frequent gestational events related to the tumors. Approximately, GTN occurs following molar pregnancy, abortion or ectopic pregnancy, and term or preterm delivery in 50%, 25%, and 25% of patients, respectively (19, 20). In our study, complete and partial moles were

Table 2. Chemotherapy Regimens and Stage

Tumor stage	MTX	ACT	EMACO	EMA-EP	Resistant
I	54 (27%)	97 (48%)	0 (0%)	0 (0%)	47 (23%)
II	2 (15%)	3 (23.1%)	7 (53%)	0 (0%)	1 (7%)
III	6 (10%)	15 (26%)	19 (33%)	3 (5%)	14 (24%)
IV	0 (0.0)	0 (0%)	1 (25%)	1 (25%)	2 (50%)
Total	62 (22.8%)	115 (42.3%)	27 (11%)	4 (1.5%)	64 (24%)

Note. 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.

revealed in 58% and 14.1% of our subjects, respectively. In addition, the most prevalent clinical symptoms included AUB (64.3%) and pelvic pain (18.4%). The most common symptom in the study by Suprasert et al (21) was the AUB (40% of patient). It shows that attention to changing the statue of menstruation bleeding is important. The first manifestation in metastatic GTN patients can be bleeding from vital organs such as lung, liver, brain, gastrointestinal tract, and vagina (22,23) but it is less common.

In our survey, about one-third of the patients with gestational trophoblastic tumors faced with raised pre-treatment serum β-hCG level (higher than 10 000) and only 19.5% experienced an increase in the β-hCG higher than 100 000. The raising serum β-hCG level can be an important diagnostic finding in patients suffering from gestational trophoblastic tumors. However, very high levels of this serum biomarker are unpredictable so that in our study only one-fifth of the patients demonstrated a rate higher than 100 000.

In our study, good response to methotrexate and ACT in low-risk GTN was 66.7% and 83.6%, respectively, and overall, the primary remission to single-agent drugs was achieved in 77.6% of cases. In the study by Li et al, complete response to ACT in low-risk GTN was 71.1% (24), which is similar to our results. The most commonly used agents for low-risk GTN were methotrexate and actinomycin-D. At the New England Trophoblastic Disease Center, methotrexate is a first-line drug because of its lower side effect compared to actinomycin-D (25). In a randomized trial of the Gynecologic Oncology Study Group (26), Act-D had a higher complete response rate compared to the MTX in the low-risk GTN (70% versus 53%, $P = 0.01$). However, single-agent chemotherapy can be very useful for treating low-risk patients, but as it is well shown, the response to the biweekly actinomycin-D regimen is significantly higher than weekly intramuscular methotrexate. In addition, physicians prefer more to prescribe actinomycin-D than methotrexate in our center. Further, among low- (score 0-4) and intermediate-risk (score 5-6) subgroups, resistance to single-agent chemotherapy was 16% and 92%, respectively. Thus, the intermediate-risk group probably needs multi-agent chemotherapy drugs. According to Mousavi et al, the resistance to single-agent chemotherapy in the intermediate-risk patients was 14 times higher than the low-risk patients (27), which is very close to our finding. Furthermore, Li et al noted that a FIGO score ≥5 is an important factor showing resistance to the ACT (24). Perhaps, a combination therapy can be considered for the patients stratified as the intermediate-risk subgroups, but this suggestion requires more studies in further trials.

More importantly, the invasive pattern of the uterus tumor in stage 1 demonstrated by the Doppler ultrasonography was associated with resistance to therapeutic regimens. Agarwal et al concluded that the uterine artery pulsatility index in Doppler sonography was a good prognostic factor for resistance to MTX (28). Additionally, Li et al showed that the existing invasive uterine lesions were a significant factor in resistance to the ACT (24). Likewise, Akhavan et al found that ultrasonography can be a good diagnostic test for the invasive mole and our finding shows that it can be a good prognostic test for the drug response (29). This novel finding should be more assessed in future studies, but the authors recommended that all patients suspected to gestational trophoblastic tumors should be evaluated with respect to invasive behavior. Moreover, the presence of an invasion pattern can be considered as a new criterion for tumor risk scoring. Our finding reveals that combination therapy is an appropriate treatment for the intermediate-risk subgroup of GTN and Doppler ultrasonography is a good devise to predict chemotherapy resistance although this issue needs further investigation.

The retrospective nature of this study was its main limitation because some file information was incomplete or different physicians visited patients and some of them acted arbitrarily.

Conclusions

The patients suffering from low-risk GTN responded well to both single therapy with methotrexate or actinomycin-D, but the latter medication was more preferred. Thus, a combination therapy may be more useful for treating this disorder because of the high resistance of the intermediate-risk subgroup to single therapy. Finally, the presence of the invasion pattern can be considered as a new criterion for tumor risk scoring due to a close association between the invasive pattern of the tumor in the uterus in the Doppler ultrasonography and drug resistance.

Conflict of Interests

Authors declare that they have no conflict of interests.

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