

RESEARCH ARTICLE

Multicenter Analysis of Gestational Trophoblastic Neoplasia in Turkey

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Abstract

Background: To evaluate the incidence, diagnosis and management of GTN among 28 centers in Turkey. **Materials and Methods:** A retrospective study was designed to include GTN patients attending 28 centers in the 10-year period between January 2003 and May 2013. Demographical characteristics of the patients, histopathological diagnosis, the International Federation of Gynecology and Obstetrics (FIGO) anatomical and prognostic scores, use of single-agent and multi-agent chemotherapy, surgical interventions and prognosis were evaluated. **Results:** From 2003-2013, there were 1,173,235 deliveries and 456 GTN cases at the 28 centers. The incidence was calculated to be 0.38 per 1,000 deliveries. According to the evaluated data of 364 patients, the median age at diagnosis was 31 years (range, 15-59 years). A histopathological diagnosis was present for 45.1% of the patients, and invasive mole, choriocarcinoma and PSTTs were diagnosed in 22.3% (n=81), 18.1% (n=66) and 4.7% (n=17) of the patients, respectively. Regarding final prognosis, 352 (96.7%) of the patients had remission, and 7 (1.9%) had persistence, whereas the disease was mortal for 5 (1.4%) of the patients. **Conclusions:** Because of the differences between countries, it is important to provide national registration systems and special clinics for the accurate diagnosis and treatment of GTN.

Keywords: Gestational trophoblastic disease - gestational trophoblastic neoplasia - incidence - Turkey

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Introduction

Gestational trophoblastic neoplasia (GTN) is the malignant form of gestational trophoblastic disease and includes invasive mole, choriocarcinoma, placental site

trophoblastic tumors (PSTTs) and epitheloid trophoblastic tumors (ETTs) (May et al., 2011). The recent incidence of hydatidiform mole (HM) in Turkey is 0.3-16 per 1,000 pregnancies and 1.0-24.5 per 1,000 deliveries (Ozalp and Oge, 2013). Although GTN generally develops after the

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evacuation of an HM, the disease can infrequently arise in non-molar pregnancies, such as term, aborted and ectopic pregnancies (May et al., 2011). The rate of locally invasive GTN and metastatic GTN was reported to be 15% and 4%, respectively, after the evacuation of a complete HM (Berkowitz and Goldstein, 1996). Because of the curable nature of GTN, accurate diagnosis and chemotherapy with or without surgical intervention are the mainstays of management (Berkowitz and Goldstein, 2009; Manopunya and Suprasert, 2012; Oranratanaphan and Lertkachonsuk, 2014).

To date, few studies have reported the incidence of GTN in Turkey. In a study from southeast Anatolia, the incidence of invasive mole and choriocarcinoma was 0.33 and 0.83 per 1,000 deliveries, respectively, whereas the incidence of HM was high, at 10.97 per 1,000 deliveries, in this study (Harma et al., 2005). In another study from a similar part of Turkey, the incidence of choriocarcinoma was 2.35 per 1,000 deliveries (Gul et al., 1997). The incidence of invasive mole, choriocarcinoma and PSTTs was determined to be 0.16, 0.38 and 0.1 per 1,000 deliveries, respectively, in eastern Turkey (Kurdoglu et al., 2011). Due to the rarity of and geographical variations in gestational trophoblastic disease, it is important to determine the incidence and clinical features of and management strategies for both the benign and the malignant forms of the disease in different countries.

In the present multicenter study, we aimed to evaluate the diagnosis and management of GTN in Turkey. To the best of our knowledge, this is the largest study to include multiple centers in Turkey.

Materials and Methods

A Microsoft Excel spreadsheet was sent to 52 centers, including university and maternity hospitals, in Turkey, and the centers were asked to complete the form with the required data. Twenty-seven centers completed the form, and data were collected in our gynecology and obstetrics department, which served as the 28th center. The study was designed to include the GTN patients attending these centers in the 10-year period between January 2003 and May 2013. Data on the number of deliveries during the study period, age, gravida, parity, abortion, the history of molar pregnancy, the antecedent pregnancy, histopathological diagnosis, the International Federation of Gynecology and Obstetrics (FIGO) anatomical score, the FIGO prognostic score, the use of single-agent chemotherapy, the number of cycles of single-agent chemotherapy, the adverse effects of single-agent chemotherapy, the use of multi-agent chemotherapy, the number of cycles of multi-agent chemotherapy, surgical intervention and prognosis were queried in the form. After collecting the data, a statistical analysis was performed using Statistical Package for Social Sciences (SPSS) 20 software.

Results

From 2003-2013, there were 1,173,235 deliveries and 456 GTN cases at 28 centers. The incidence was

calculated to be 0.38 per 1,000 deliveries. Of the 456 patients with GTN, the data of 364 patients was available to evaluate. The incidence of GTN according to the evaluated data was 0.31 per 1,000 deliveries. The demographic characteristics of the patients are shown in Table 1. According to the patients' histories, 30% of the patients had recurrent molar pregnancies. The antecedent pregnancy was mole, miscarriage, term pregnancy or ectopic pregnancy in 54.9%, 15.1%, 16.5% and 1.1% of the patients, respectively. In 12.4% (n=45) of the patients, the type of antecedent pregnancy could not be identified. A histopathological diagnosis was present for 45.1% of the patients, and invasive mole, choriocarcinoma and PSTTs were diagnosed in 22.3% (n=81), 18.1% (n=66) and 4.7% (n=17) of the patients, respectively. According to the anatomical staging, 76.1% (n=277), 1.1% (n=4), 19.5% (n=71) and 3.3% (n=12) of the patients were in Stage I, Stage II, Stage III and Stage IV, respectively. The median FIGO prognostic score was 4 (range, 0-22). According to FIGO prognostic scoring, 10.98% (n=40) of the patients was in high-risk group while 89.02% (n=324) of the patients was in low-risk group. Single-agent chemotherapy was administered to 73.1% (n=266) of the patients. As a first-line agent, a five-day treatment regimen of methotrexate (MTX), an eight-day treatment regimen of MTX with folinic acid, weekly MTX, a biweekly regimen of actinomycin-D (ACT-D) or a five-day treatment regimen of ACT-D was used in 8.5% (n=31), 52.5% (n=191), 11.3% (n=41), 0.3% (n=1) and 0.5% (n=2) of the patients, respectively. The median number of cycles of the single-agent chemotherapy was 2 (range, 1-14). Twohundred and eighteen (60.2%) of the patients were able to complete the cycles of a single-agent chemotherapy. In total, 33 (9.7%) of patients were chemoresistant to single-agent chemotherapy and 10 (5.3%) of them received another type of single-agent chemotherapy as a second-line chemotherapy. Nausea, hematological adverse effects and allergy occurred in 20.1%, 5.8% and 1.9% of the patients, respectively. In 131 (36%) of the patients, a multi-agent chemotherapy regimen was used. EMA/CO (etoposide, methotrexate, dactinomycin/cyclophosphamide and vincristine), EMA/EP (etoposide, methotrexate, dactinomycin/etoposide and cisplatin) or other multi-agent chemotherapy regimens were used in 30.3%, 3.3% and 2.4% of the patients, respectively. EMA/CO was the first choice among multi-agent chemotherapy regimens. The median of multiagent chemotherapy cycles was 4 (range, 1-18). A second-line multi-agent chemotherapy regimen was used in 9 (2.5%) of the patients because of either adverse effects or resistance. Hysterectomy was performed in 95 (26.1%) of the patients. The number of hysterectomies performed

Table 1. Demographic Characteristics of the Patients

	Median	Range
Age (year)	31	15-59
Gravida(n)	3	0-18
Parity(n)	2	0-17
Abortion(n)	1	0-7
Recurrent molar pregnancy(n)	0	0-4

for invasive mole, choriocarcinoma and PSTT was 41, 30, 9, respectively. Other surgical interventions were also performed in 4 (1.1%) of the patients. Regarding final prognosis, 352 (96.7%) of the patients had remission, and 7 (1.9%) had persistence, whereas the disease was mortal for 5 (1.4%) of the patients.

Discussion

The chemosensitive nature of GTN is a chance especially for the cohort of the disease which is created by the reproductive aged patients. Because of the rarity of GTN, it is important to determine the incidence and features of the disease in different countries. In the present study, the incidence of GTN among 28 centers in Turkey was 0.38 per 1,000 deliveries.

The risk of developing GTN after the evacuation of a molar pregnancy was reported to be 15-20% and 1-4% for the complete and partial forms, respectively (Berkowitz and Goldstein, 1996). According to a hospital-based study from the eastern part of Turkey, the incidence of GTN was 0.6 per 1,000 deliveries, whereas the incidence of HM was calculated to be 7.3 per 1,000 deliveries. The estimated risk of GTN after the evacuation of either a complete or a partial molar pregnancy was 8.2% (Kurdoglu et al., 2011). Additionally, authors from Turkey reported an incidence of 1.16 per 1,000 deliveries for GTN in southeast Turkey, whereas the estimated risk of GTN after molar pregnancy was 10.6% in their study (Harma et al., 2005).

Treatment is related to the response to chemotherapy and close follow-up. According to FIGO anatomical and prognostic classifications, clinicians may easily administer proper treatment to patients with either low- or high-risk disease. Nonmetastatic and low-risk metastatic disease can be treated with single-agent chemotherapy, with a promising survival rate of 100%, whereas high-risk metastatic disease treated with multi-agent chemotherapy with or without surgery and radiation has a survival rate of 80-90% (Lurain, 2011). Based on data from 33 patients treated with EMA/CO in Turkey because of high-risk GTN, the response rate was 81.8%, whereas surgical intervention was performed in four patients in the chemoresistant group, and the disease was mortal for three patients (Turan et al., 2006). Based on a Cochrane Review about first-line chemotherapy in low-risk GTN, ACT-D was suggested as a single-agent chemotherapeutic that is more likely to be curative than MTX in patients with low-risk GTN (Alazzam et al., 2012). EMA/CO as a multi-agent chemotherapy for high-risk GTN is the first-line regimen worldwide (Deng et al., 2009). By the year 2001, based on a query among 55 health centers about gestational trophoblastic disease management in Turkey, MTX was the most widely used single-agent chemotherapy, whereas MAC (methotrexate, ACT-D and cyclophosphamide or chlorambucil) was the preferred multi-agent chemotherapy (Ozalp et al., 2001). In the present study, an eight-day treatment regimen of MTX and folinic acid was the most widely used regimen, covering 52.5% of the patients treated with single-agent chemotherapy, and EMA/CO was the preferred multi-agent chemotherapy regimen (31%).

Although the chemosensitivity of GTN improves the survival of patients, unfortunately, PSTTs and ETs are known as relatively chemoresistant tumors. The proper treatment of these types is hysterectomy and lymph node dissection (Pongsaranantakul and Kietpeerakool, 2009; Lurain, 2011). Nine of 17 patients with PSTTs underwent hysterectomy in our study. The remission rate of PSTTs was 100%.

The reasons for mortality from GTN are described as metastatic multidrug-resistant PSTTs and chemoresistant choriocarcinoma with non-pulmonary metastasis (Kingdon et al., 2012). The mortality rate of choriocarcinoma with chemoresistance to high-risk treatment regimens is 75% (Aydinler et al., 2012). In our study, the disease was mortal for one patient with invasive mole, two patients with choriocarcinoma and three patients with GTN were not identified histopathologically. Further studies on new treatment regimens are necessary to improve the survival rates, especially for patients with high-risk disease.

In conclusion, although GTN is rare and chemosensitive, the disease may be fatal, and the mortality rate may be reduced by accurate diagnosis and proper treatment.

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