Management of Gestational Trophoblastic Neoplasms in Our Clinic

KLİNİĞİMİZDE GESTASYONEL TROFOBLASTİK NEOPLAZİLERİN YÖNETİMİ

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Abstract

Objective: Aim of this study was to examine treatment strategies and prognosis of Gestational Trophoblastic Neoplasms (GTN).

Material and Methods: Suction curettage was applied to 112 patients having the diagnosis of GTN and curettage material was sent for cytopathologic examination. Hysterectomy was done to older patients without child desire. Single agent chemotherapy was applied to the patients with persistant disease or nonmetastatic choriocarcinoma and combined chemotherapy in high risk patients and cases unresponsive to single agent chemotherapy.

Results: Complete mole was detected in 71 (63.3%) patients, partial mole in 15 (13.2%), invasive mole 22 (20%) and choriocarcinoma in 4 (3.5%) patients. Incidence of GTN was 0.73%. Molar pregnancy rate was 0.58%. Gestational choriocarcinoma rate was found as 0.02%. Suction curettage was applied to all patients. After curretage hCG levels turned to normal in 6 weeks in 76.7% of patients. 20% of patients developed persistant disease after the evacuation of molar pregnancy. Single agent chemoteraphy was applied to 11 (50%) patients with persistence. Hysterectomy was applied to 9 (40.9%) patients over the age of 40 years without child desire. Both hysterectomy and chemotherapy were applied to 2 patients. 2 patients in invasive mole group who didn't enter remission with single agent chemoteraphy and 1 patient with choriocarcinoma were treated with MAC regimen. EMA-CO regimen was given to 3 patients with choriocarcinoma and other choriocarcinoma patient who didn't enter remission with MAC regimen. Hormon levels turned to normal in 9 weeks (4-13) after chemotherapy. All cases in invasive mole group entered remission in 10 weeks. Cases with choriocarcinoma entered remission in 12-13 weeks.

Discussion: The optimal management of gestational trophoblastic neoplasms depends on prompt diagnosis, correct stratification of the risk category and appropriate treatment using various modalities such as chemotherapy and surgery.

Key Words: Gestational trophoblastic neoplasms, therapy, drug therapy

Özet

Amaç: Gestasyonel trofoblastik neoplazilerde (GTN) tedavi yöntemleri ve prognozun incelenmesi.

Gereç ve Yöntemler: GTN tanısı alan 112 hastaya suction küretaj uygulandı. Küretaj materyali sitopatolojik incelemeye gönderildi. Çocuk isteği olmayan ileri yaştaki hastalara histerektomi uygulandı. Metastaz yapmamış koryokarsinomlarda veya persistan hastalığı olanlarda tek ajanlı kemoterapi, tek ajanlı kemoterapiye cevap vermeyen veya yüksek riskli hastalarda kombine kemoterapi uygulandı.

Bulgular: Yetmiş bir (%63.3) hastada komplet, 15 (%13.2) hastada parsiyel, 22 (%20) hastada invaziv mol ve 4 (%3.5) hastada koryokarsinom tespit edildi. GTN insidansı %0.73, molar gebelik oranı %0.58 ve gestasyonel koryokarsinom oranı %0.02 idi. Bütün hastalara suction küretaj uygulandı. Hastaların %76.7'sinde hCG seviyeleri 6 hafta içinde normale döndü. Hastaların %20'sinde küretaj sonrası persistan hastalık gelişti. Persistans gelişen hastaların 11'ine (%50) tek ajanlı kemoterapi uygulandı. Çocuk isteği olmayan yaşı 40'ın üzerinde 9 hastaya (%40.9) histerektomi uygulandı. 2 hastaya da hem histerektomi hem kemoterapi verildi. Koryokarsinom olan bir hastaya ve tek ajanlı kemoterapiye cevap vermeyen 2 hastaya MAC protokolü uygulandı. Koryokarsinomlu 3 hastaya ve MAC protokolüne cevap vermeyen 1 hastaya EMA-CO rejimi uygulandı. Kemoterapi sonrası hormon seviyeleri ortalama 9 haftada (4-13) normale döndü. İnvaziv mol grubundaki tüm hastalar 10 haftada, koryokarsinomlu vakalar 12-13 haftada remisyona girdi.

Sonuç: Gestasyonel trofoblastik neoplazilerde ideal yönetim kesin tanıya, risk kategorisinin doğru olarak belirlenmesine ve uygun tedavinin (kemoterapi veya cerrahi) verilmesine bağlıdır.

Anahtar Kelimeler: Gestasyonel trofoblastik neoplaziler, tedavi, kemoterapi

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Trophoblasts are main cells forming placenta. Tumors originating from these cells are called gestational trophoblastic neoplasms (GTN).[1] GTN is divided into 4 groups by histopathologic examination: Complete-partial

mole, invazive mole, placental site trophoblastic tumor and choriocarcinoma.[2]

Mole hydatidiform has a low malignant potential. 15% of the patients with molar pregnancy develop locally invasive trophoblastic tumor and 4% metastatic tumor.[3] The choice of treatment of molar pregnancy is suction evacuation. Hysterectomy can also be done if patient has no child desire.

Another form of GTN is invasive mole. It's usually located in uterus but can make metastasis in 40% of cases. Also it may turn to choriocarcinoma in 15% of the cases if not treated properly. Invasion is detected by hormonal follow up.[1-3]

Choriocarcinoma is most malignant form of GTN and usually develops after invasive mole. Rarely it may develop directly as choriocarcinoma. Choriocarcinoma metastase easily and early. Sometimes patients admitted with signs of metastasis. Choriocarcinoma can be treated 80% with chemotherapy.[2]

Aim of this study was to examine treatment strategies and prognosis of GTN.

Material and Methods

One hundred and twelve patients having the diagnosis of GTN were evaluated between 01.1998-31.12.2002 retrospectively. Systemic and pelvic examinations were done to the all patients. Their obstetric history was obtained. Age of the patients and their partners, cause of admission, gestational age, gravida, parity, previous molar pregnancy or previous treatments for this, time, type and outcome of last pregnancy were asked. Serum beta-hCG levels were measured, anteroposterior chest X-ray was taken, hematologic tests, liver, renal, thyroid function tests were determined and abdominal-pelvic ultrasonography were applied to all of them. Cases with choriocarcinoma or persistant disease were evaluated by brain, lung and abdominal computed tomography. Written informed consent was obtained from the subjects.

Suction curettage was applied to the patients and curettage material was sent for cytopathologic examination. Patients were divided into four groups according to the classification of WHO as hydatidiform mole, invasive mole, choriocarcinoma and placental site trophoblastic tumor. All patients were followed postcuratively by beta-hCG levels. During hormonal follow-up, when beta-hCG level was persisted above the normal level after 8 weeks or rising plateau forming beta-hCG values were accepted as persistant disease.

Patients with choriocarcinoma were divided into 3 groups: Non-metastatic disease, low risk and high risk metastatic disease. Pretreatment hCG levels higher than 100.000 IU/day or 40.000 IU/mL, brain or liver metastasis, previous unsuccessful chemotherapy or more than 4 months after last pregnancy were accepted as high risk or bad prognosis metastatic disease. The others without these criteria were accepted as low risk or good prognosis group.[4]

Hysterectomy was done to older patients without child desire. Single agent chemotherapy was applied to the patients with persistant disease or nonmetastatic choriocarcinoma. Methotrexate + folinic acid (MTX-FA) was used as single agent chemotherapy. Complete blood count was done before chemotherapy was given. WBC less than 2500/mm^3, neutrophiles less than 1500/mm^3 and trombosite less than 100.000 and increase of AST and ALT above 50/U were accepted as toxicity criterias. Minimum 1 log fall in hCG levels was accepted as enough response to the chemotherapy. After 2 courses treatment with MTX-FA, if there wasn't enough response combined chemotherapy regimens were applied.

MAC and EMA-CO protocols were used for combined chemotherapy. MAC protocol was applied to the patients who didn't respond to single agent chemotherapy or to the patients having low risk metastatic disease. Patients with high risk metastatic disease, EMA-CO protocol was preferred. In order to decrease the risk of relapse, combined chemotherapy was applied until the hCG levels turned to the normal levels for 3 times consecutively.

Patients with persistant disease, metastatic disease or choriocarcinoma were examined with

pelvic examination and ultrasonography on a monthly basis. Chest X-ray or CT of these patients was done every 6-12 months.

Oral contraceptives were given to patients during hormonal follow up. Patients who concieved during follow up were taken antenatal follow up.

Statistical evaluation of results was done by SPSS for windows 8.0 programme. Data were summarised as mean ± SD and as percentages. For the cases where parametric conditions were satisfied, Analysis of Variance (ANOVA) was utilized for the comparison of 2 or more groups; and Kruskal-Wallis variance analysis was utilized where these conditions were not satisfied. The dual comparisons of significant variables from this test were performed via post hoc Bonferroni-modified Mann-Whitney U Test. For the cases where parametric conditions were satisfied, paired T and; for the cases where parametric conditions weren't satisfied, Wilcoxon Test were applied for the measurements marked by repetititon. The comparisons of categorical data, ki-square test were utilized. Level of significance was taken as $p< 0.05$.

Results

112 patients with GTN were admitted to our clinic during a 5-year period. Complete mole was detected in 71 (63.3%) patients, partial mole in 15 (13.2%), invasive mole 22 (20%) and choriocarcinoma in 4 (3.5%) patients. Incidence of GTN was 0.73%. Molar pregnancy rate was 0.58%. Gestational choriocarcinoma rate was found as 0.02%.

Age of the patients and their partners, mean gestational age, mean parity, uterine enlargement, pre-treatment beta-hCG levels and theca-lutein cysts were seen in Table 1.

Molar pregnancy was the first pregnancy in 26.7% of patients. Last pregnancy was terminated by term birth in 45.5% of cases and abortus in 33%. Two choriocarcinoma was developed after complete molar pregnancy and 2 after term delivery.

Most frequent symptom of GTN was vaginal bleeding (81.2%). Abdominal pain (8.9%), vesicles dropped out from vagina (2.2%), hyperemesis gravidarum (14.2%), signs of preeclampsia (8%) and hyperthyroidism (6.2%) were found.

Pretreatment hCG levels were below 100.000 mIU/mL in 50% of patients, between 100 000-500 000 in 35.7% of cases and above 500 000 in 14.3% of cases. Pretreatment hCG levels were below 100.000 mIU/mL in all patients with partial mole. 49.2% of complete moles, 81.8% of invasive moles and all patients with choriocarcinoma, this level was above 100.000 mIU/mL. Pretreatment hCG level above 500.000 mIU/mL in 40.9% of invasive moles but only 11.2% in complete moles.

Theca-lutein cysts were reported in 25 (22.3%) of cases. hCG level above 100.000 mIU/mL in 92% of these cases. 36% of theca-lutein cysts were found in complete mole, 56% in invasive mole and 8% in choriocarcinoma group.

Metastasis was seen in choriocarcinoma patients, lung metastasis in 2 cases, vaginal metastasis in 1 case and liver metastasis in 1 case. Partial hepatectomy was done the patient with liver metastasis due to intra abdominal bleeding. The other

Table 1. Clinical and laboratory findings in gestational trophoblastic diseases.

Type of GTD	Number of cases	Age (year)		Partner age (year)		Multiparity (%)		hCG over 100 000 IU/ml (%)		Theca-lutein cysts (%)		Excessive uterine enlargement (%)	
Complete	71 (63.3%)	25.6 ± 6.3	NS	27.7 ± 6.4	NS	22 (30.9%)	NS	35 (49.2%)	S	9 (12.6%)	S	32 (45%)	S
Partial	15 (13.2%)	29.8 ± 10.5	NS	33.3 ± 9.0	NS	5 (33.3%)	NS	0	NS	0	NS	0	NS
Invasive	22 (20%)	39.6 ± 9.1	S	42.1 ± 9.1	S	19 (86.3%)	S	17 (81.8%)	S	14 (63.6%)	S	9 (40%)	S
Chorioca	4 (3.5%)	30 ± 1.7	NS	31.6 ± 2.8	NS	1 (25%)	NS	4 (100%)	S	2 (50%)	S	1 (25%)	NS
Total GTD	112	28.8 ± 9		31.6 ± 9.3		47 (41.9%)		56 (50%)		25 (22.3%)		42 (37.5%)	

S: Significantly different from the other groups ($p<0.05$)
NS: Not significantly different from the other groups ($p> 0.05$)

patients were entered complete remission with combined chemotherapy.

Suction curettage was applied to all patients. After curretage hCG levels turned to normal in 6 weeks in 76.7% of patients. During hormonal follow-up, if beta-hCG level was not falling or rising-plateau forming values were accepted as persistant disease (22 cases). 20% of patients developed persistant disease after the evacuation of molar pregnancy. Single agent chemoteraphy was applied to 11 (50%) patients with persistence. Hysterectomy was applied to 9 (40.9%) patients over the age of 40 years without child desire. Both hysterectomy and chemotherapy were applied to 2 patients. 2 patients in invasive mole group who didn't enter remission with single agent chemoteraphy and 1 patient with choriocarcinoma were treated with MAC regimen. EMA-CO regimen was given to 3 patients with choriocarcinoma and other choriocarcinoma patient who didn't enter remission with MAC regimen. Hormon levels turned to normal in 9 weeks (4-13) after chemotherapy. All cases in invasive mole group entered remission in 10 weeks. Cases with choriocarcinoma entered remission in 12-13 weeks.

Patients were given oral contraceptives during hormonal follow up. Patients followed at least 2 years after treatment. 12 (10.7%) patients became pregnant during this time. 9 of them terminated with term birth, 3 of them with abortus.

Discussion

GTN is a spectrum of tumours with a wide range of biologic behaviour and potential for metastases. Over the last four decades, GTN has developed from one of the most fatal malignancies to one of the most curable, with the advent of effective chemotherapy. Besides chemotherapy, other factors have played a key role in the good prognosis for this disease. These include the development of a very sensitive tumour marker, human chorionic gonadotropin (hCG), for diagnosis and assessment of treatment response; identification of prognostic factors that have been put into a scoring system to individualize treatment; and finally the judicious use of surgery and radiotherapy in addition to chemotherapy for selected patients.

Incidence of molar pregnancy differs in different populations. Incidence is 0.6-2/1000 pregnancy. Incidence of gestational choriocarcinoma is 2.4/100,000.[5] In this study incidence of GTN was 7.3/1000. Molar pregnancy rate was 5.8/1000 and gestational choriocarcinoma rate was found as 2/10,000. When compared with literature, GTN incidence was higher. This is probably due to that this hospital is a reference center in this region.

GTN is mostly seen below the 20 years of age and after 35 years. Invasive mole incidence is higher after 35 years. There is no risk increase with the maternal age in partial mole group.[6] 21.4% of patients were over 40 years in this study. Partial mole was seen in similiar rates in all age groups in reproductive period. 11.2% of patients in complete mole group and 77.2% of patients in invasive mole group was above the age of 35. Maternal age over 35 years was accepted risk factor for invasive mole development.

Choriocarcinoma may develop after any type of pregnancy. 70% of it develops after complete mole, 20% after abortus or tubal pregnancy and 10% after term pregnancy.[7] In this study, there were 4 choriocarcinoma; 2 developed after mole hydatidiform and 2 after term pregnancy.

GTN is diagnosed and treated at early weeks like 6-10 weeks.[8] 75% of cases were under 12 weeks at the time of diagnosis in this study. Mean gestational age was 10.5 weeks. Delay in diagnosis was due to low sociocultural status of patients and insufficient antenatal follow up. Hyperemesis gravidarum, preeclampsia and hyperthyroidism were found more frequently in advanced gestational weeks. But there was no significant difference in terms of persistancy between early and late gestational weeks.

Beta hCG is the most important marker in diagnosis and follow up of GTN. HCG levels are found to be higher than 100.000 mIU/mL in complete mole with excessive uterine enlargement.[9] In this study excessive uterine enlargement were detected in 45% of complete moles and hCG levels

higher than 100.000 in all of them. Hormon levels were higher than 100.000 mIU/mL in 81.8% of invasive moles and all of the choriocarcinoma cases. An important relation was found between hCG levels over 100,000 mIU/mL and persistence of disease. So patients with high hCG levels must be followed carefully for persistence.

Early metastasis to vagina, lung and late metastasis to liver and brain are seen in metastatic GTN.[1-3] In this study metastasis were seen in choriocarcinoma patients; lung metastasis in 2 cases, vaginal metastasis in 1 case and hepatic metastasis in 1 case.

The choice of treatment of molar pregnancy is suction evacuation, followed by sharp curettage. Suction evacuation can be performed for uterus of any size. Hysterectomy may be necessary to eradicate a focus of resistant disease in the uterus. For older women (40 years and above) hysterectomy with the mole in situ is the treatment of choice especially if the patient wants to be sterilized.[10] The ovaries need not be removed even though theca lutein cysts are present. There is also some evidence that hysterectomy may decrease the risk of post molar malignant sequelae. Bahar and colleagues[11] found it to be 10% in those with hysterectomy as compared to 33% in those without. In a much larger series, the risk of malignant sequelae decreased to 3.5% after evacuation with hysterectomy compared to the 20% anticipated with evacuation with a D&C;[12] however it should be emphasized that hysterectomy does not negate the necessity for close follow up with hCG monitoring after evacuation of the mole.

The first treatment in persistant GTN is single agent chemotherapy. Methotrexate ve actinomycin D are most frequently used agents for single agent chemotherapy.[13] But today methotrexate-folinic acid is the first line treatment in single agent chemotherapy. Systemic toxicity is very low when methotrexate combined with folinic acid. Cure rate is 80-90% with this regimen.[14] Also hysterectomy can be done in older cases without child desire. In this study, 10 cases with invasive mole hysterectomy were applied (52.6%). Complete cure was observed in 8 cases with hysterectomy. 11 cases together with 2 patients whose hCG levels was not fall after hysterectomy were given MTX-FA. Complete cure was seen with single treatment in 9 patients. Cure rate was 81.8%.

For the cases, which don't give response to single agent chemotherapy or with high risk metastatic disease, combined chemotherapy are applied. Most frequently used combined regimens are MAC and EMA-CO. Remission rate with MAC is 49%.[15] It's not enough for primary treatment of high risk patients. EMA-CO has 76-94% complete remission rate if used as a primary treatment in high risk patients. EMA-CO regimen is generally well-tolerated.[16,17] In order to decrease the risk of relapse, combined chemotherapy must be applied until the hCG levels turned out to be normal for 3 times consecutively.

In this study suction curettage was primary treatment in molar pregnancy. After curretage hCG levels turned to normal in 6 weeks in 76% of patients. Patients with persistant disease (19 cases), single agent chemoteraphy was applied to 9 and hysterectomy was applied to 8 patients. Both hysterectomy and chemotherapy were applied to 2 patients. 2 patients in invasive mole group who didn't enter remission with single agent chemoteraphy were given MAC regimen and entered remission in 10 weeks. All cases with choriocarcinoma were entered remission with EMA-CO regimen in 12-13 weeks.

The impact of long-term chemotherapy on fertility and fetal malformations has been a major concern. Several studies have been reassuring. In the longest follow up published from a single centre, Song et al reported on the outcome of 265 patients given chemotherapy between 1959 through 1980. By the end of 1985, 205 patients had become pregnant, with a total of 355 pregnancies.[18] The rates of fetal wastage, malformations, twin pregnancies, and neonatal and infant deaths did not deviate from normal. Berkowitz et al summarized the post-chemotherapy fertility from five different centres; 77.5% of the patients had live births and only 2% had fetal abnormalities.[19]

In a study of Lan et al 22 patients becoming pregnant after chemotherapy in a year was examined. They found 9.1% GTN, 27.1% fetal loss, and 40.9% term healty pregnancy.[20] In this study, patients were followed minimum 2 years. In 12 (10.7%) patients pregnancy was seen. 9 (75%) of these pregancies ended with term labour and 3 (25%) with abortuses.

The optimal management of gestational trophoblastic neoplasms depends on prompt diagnosis, correct stratification of the risk category and appropriate treatment using various modalities such as chemotherapy and surgery. As it is an uncommon disease, it is best that all patients be referred to experts in referral centres familiar with their management. It is this expertise that has converted an almost uniformly fatal disease into a very curable one.

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