Gynecologic Oncology 117 (2010) 477–480

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Weekly methotrexate (50 mg/m^2) without dose escalation as a primary regimen for low-risk gestational trophoblastic neoplasia

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ARTICLE INFO

Article history:
Received 7 January 2010
Available online 29 March 2010

Keywords:
Methotrexate
Low-risk
Gestational trophoblastic neoplasia
Single-agent chemotherapy

ABSTRACT

Objectives. The aim of this study was to compare the efficacy and toxicity of an 8-day methotrexate–folinic acid regimen and a weekly methotrexate regimen (50 mg/m^2 without dose escalation) for low-risk gestational trophoblastic neoplasia (GTN) according to the revised FIGO 2000 scoring system in a single institution.

Methods. Between January 1997 and June 2007, 107 patients with low-risk GTN were treated with an 8-day methotrexate–folinic acid regimen (MTX–FA group; $n=59$) or a weekly methotrexate regimen (50 mg/m^2 without dose escalation) (MTX group; $n=48$). The primary remission rate, change of chemotherapy because of drug resistance or toxicity, and relapse rate were compared.

Results. All 107 patients with low-risk GTN were cured. The primary remission rates were 69.5% and 70.8% for the MTX–FA and MTX groups, respectively ($P>0.99$). The commonly reported toxic effects in the MTX–FA and MTX groups, respectively, were as follows: hepatotoxicity (31/59 and 9/48), neutropenia (7/59 and 4/48), stomatitis (3/59 and 2/48), alopecia (2/59 and 2/48), and thrombocytopenia (2/59 and 0/48). Drug toxicity necessitating changes in chemotherapy were reported to be 13.6% (8/59) in the MTX–FA group and 2.1% (1/48) in the MTX group ($P<0.05$). The overall duration of treatment was 8.6 weeks in the MTX–FA group and 6.4 weeks in the MTX group ($P<0.001$).

Conclusions. The weekly methotrexate regimen was as effective as the 8-day methotrexate–folinic acid regimen for low-risk GTN. The weekly methotrexate regimen was less toxic, better tolerated, and more convenient for patients compared to the 8-day methotrexate–folinic acid regimen.

Introduction

Gestational trophoblastic neoplasia (GTN) is a rare tumor resulting from abnormal growth of trophoblasts. GTN is extremely responsive to chemotherapy and is recognized as the most curable gynecologic malignancy [1].

The choice of a chemotherapeutic regimen is based upon the characteristics of the presenting GTN. Patients are stratified into low- and high-risk GTN by combining the International Federation of Obstetrics and Gynecology (FIGO) stage with the World Health Organization (WHO) prognostic scoring system (the revised FIGO 2000 scoring system). Low-risk GTN is defined by FIGO stages I–III with a WHO score ≤ 6, and high-risk is defined by FIGO stage IV or any FIGO stage with a WHO score ≥ 7 [2]. Single-agent therapy is indicated for low-risk GTN, while multi-agent chemotherapies are used for high-risk GTN.

Since Li et al. [3] first reported the successful use of methotrexate (MTX) to treat choriocarcinoma in 1956, most patients with low-risk GTN may be successfully treated with single-agent MTX therapy. Many single-agent MTX protocols are distinguished based on the association with folinic acid, dose, and frequency within each treatment course.

The most commonly used MTX regimen in Europe, and possibly the rest of the world, excluding North America, is an 8-day alternating intramuscular MTX and folinic acid regimen repeated every 14–16 days [4,5]. In North America, many centers use the weekly low-dose MTX protocol, which was first tested and reported by the Gynecologic Oncology Group (GOG) [6]. This parenteral regimen is initiated at 30 mg/m^2 per week and the dose is escalated by 5 mg/m^2 at 3-week intervals to 50 mg/m^2. However, there is as yet no consensus on a single best regimen.

The aim of this study was to compare the efficacy and toxicity of an 8-day MTX–folinic acid regimen and a weekly MTX regimen (50 mg/m^2 without dose escalation) for low-risk GTN according to the revised FIGO 2000 scoring system.

Materials and methods

We retrospectively reviewed the records of all 166 patients with GTN who had been treated in the Department of Obstetrics and Gynecology of Chonnam National University Hospital (CNUH) between January 1997 and June 2007.

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doi:10.1016/j.ygyno.2010.02.029

All patients met the 2000 FIGO classification [7], as follows: (1) plateau of hCG lasting for 4 measurements over a period of ≥3 weeks (i.e., days 1, 7, 14, and 21); (2) an increase in hCG of ≥3 weekly consecutive measurements, over a period of ≥2 weeks (i.e., days 1, 7, and 14); (3) hCG level remaining elevated for ≥6 months; and (4) histologic diagnosis of choriocarcinoma.

Before the start of chemotherapy, all patients underwent a complete physical and pelvic examination, including a complete blood cell count, urinalysis, and liver and renal function tests. All patients with evidence of persistence had a chest x-ray. If the chest-ray was negative, a chest CT scan was performed. If the chest CT scan demonstrated evidence of pulmonary disease, the patient was considered to have stage III disease even if the chest x-ray was normal. We routinely performed brain MRI and abdominopelvic CT scan for the detection of metastases. Upon reviewing the medical records of patients with GTN, all patients were restaged according to the 2000 revised FIGO scoring system [7]. Those with risk scores ≤6 were classified as having low-risk GTN.

The final study population of 107 patients was identified after the exclusion of 32 patients who were diagnosed with high-risk GTN according to the 2000 revised FIGO scoring system [7] and 29 patients who received another chemotherapeutic regimen. Between January 1997 and July 2002 all patients received an 8-day MTX–folinic acid regimen, and between August 2002 and June 2007, patients were treated with a weekly intramuscular MTX protocol (50 mg/m^2 without dose escalation). Fifty-nine patients were received intramuscular MTX (50 mg on alternate days [1,3,5,7]) with folinic acid (7.5 mg orally on alternate days [2,4,6,8]) repeated after a 7-day treatment window (MTX–FA group) and 48 patients were treated with weekly intramuscular MTX (50 mg/m^2 without dose escalation [MTX group]). Serum hCG levels were measured weekly to monitor the response. After the first negative human chorionic gonadotropin level (<5 mIU/mL), the patients received additional two chemotherapy courses for consolidation of treatment. Remission was declared if a patient's hCG level was undetectable for 1 year.

A complete blood cell count, along with renal and liver functions, was also measured before starting the chemotherapy. Complete blood cell counts with platelet counts, as well as renal and hepatic function tests, were then measured every 1 week during the follow-up period. The criteria for hematologic and hepatic toxicity were those of the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI) [8]. All side effects were noted. Patients were routinely asked about the development of adverse events and their response was noted in their records. Second-line chemotherapy was used in the case of resistance or grade 3 or 4 toxicity. A second-line chemotherapy protocol (dactinomycin [1.25 mg/m^2 intravenously every 2 weeks]) or combination chemotherapy (etoposide, MTX, dactinomycin, cyclophosphamide, and vincristine [EMA-CO]) were used, depending on the presenting WHO score when the response to MTX alone was unsatisfactory. The primary remission rate, change in chemotherapy because of drug resistance or toxicity, and relapse rate were compared. The study protocol was evaluated and approved by the Institutional Review Board at CNUH.

Statistical analysis

Statistical comparison was carried out by a Mann–Whitney *U* test or Fisher exact test. Statistical analyses were performed using SPSS software (version 17.0; SPSS Inc., Chicago, IL, USA). All *P* values reported are two-sided, and *P* values <0.05 were considered statistically significant.

Results

All 107 patients with low-risk GTN were divided into 2 groups (8-day MTX–folinic acid regimen [MTX–FA group, $n=59$] and weekly MTX at 50 mg/m^2 without dose escalation [MTX group, $n=48$]). The patient characteristics are detailed in Table 1. The two groups were matched with respect to age, antecedent pregnancy, interval months from index pregnancy, pre-treatment serum hCG level, largest tumor size, FIGO score, and presence of pulmonary metastases. The mean ages ± SD of the patients were 33.8 ± 8.6 and 35.3 ± 9.4 years in the MTX–FA and MTX groups, respectively ($P=0.366$). The mean FIGO scores ± SD were 2.35 ± 1.59 and 2.52 ± 1.49 in the MTX–FA and the MTX groups, respectively ($P=0.556$). The median serum hCG levels were 4400 and 3300 mIU/mL in the MTX–FA and the MTX groups, respectively, with ranges of 67–670,000 and 85–590,000 mIU/mL, respectively ($P=0.082$). None of these characteristics were significantly different between the two groups.

The remission rates of the 107 patients with low-risk GTN initially treated with first-line chemotherapy are shown in Table 2. There were 75 patients (70.1%) who responded to first-line chemotherapy (41 [69.5%] in the MTX group and 34 [70.8%] in the MTX–FA group; $P>0.99$). Twenty-three (21.5%) of 107 patients required a change in chemotherapy because of drug resistance. Additional 9 patients (8.4%) required a change in chemotherapy because of drug toxicity. The change rates in chemotherapy due to drug resistance were reported to be 16.9% in the MTX–FA group and 27.1% in the MTX group. In addition, drug toxicity necessitating a change in chemotherapy was significantly more frequent in the MTX–FA than in the MTX group ($P=0.04$).

With respect to age, antecedent pregnancy, interval months from index pregnancy, largest tumor size, and pulmonary metastases, there were no differences between those who were successfully treated and those who failed first-line chemotherapy. The median pre-treatment serum hCG level was 3160 mIU/mL in the group of patients who were

Table 1
Patient characteristics.

	MTX–FA group ($n=59$)	MTX group ($n=48$)	*P* value
Age (years)			0.862
<40	45	35	
≥40	14	13	
Antecedent pregnancy			0.651
Molar	50	42	
Abortion	8	6	
Term	1	0	
Interval month from index pregnancy			0.670
<4	55	45	
4≤7	1	2	
7≤13	1	0	
≥13	2	1	
Pretreatment serum hCG (mIU/mL)			0.286
$<10^3$	16	10	
$10^3 \le 10^4$	29	20	
$10^4 \le 10^5$	13	14	
$\ge 10^5$	1	4	
Largest tumor size (cm)			0.975
<3	50	41	
3≤5	6	5	
≥5	3	2	
FIGO score			0.966
0	7	3	
1	11	8	
2	15	15	
3	17	14	
4	2	2	
5	3	3	
6	4	3	
Pulmonary metastasis			0.851
Yes	28	21	
No	31	27	