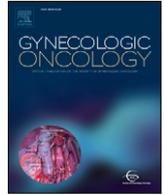


Comparison of 5-day MTX and 5-day ETP treatment results and early predictors of drug resistance to 5-day MTX in patients with post-molar low-risk gestational trophoblastic neoplasia

メタデータ	言語: jpn 出版者: 公開日: 2019-02-08 キーワード (Ja): キーワード (En): 作成者: 木崎, 尚子 メールアドレス: 所属:
URL	https://doi.org/10.20780/00032087



Comparison of 5-day MTX and 5-day ETP treatment results and early predictors of drug resistance to 5-day MTX in patients with post-molar low-risk gestational trophoblastic neoplasia

Shoko Kizaki ^a, Kazunori Hashimoto ^a, Hideo Matsui ^{a,*}, Hirokazu Usui ^b, Makio Shozu ^b

^a Department of Obstetrics & Gynecology, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan

^b Department of Reproductive Medicine, Chiba University Graduate School of Medicine, 1-8-1 Inohana, Chuo-ku, Chiba 260-8670, Japan

HIGHLIGHTS

- More than 35% of patients required a change in chemotherapy from 5-day IM MTX.
- High pre-treatment hCG levels and FIGO scores were drug resistance factors of MTX.
- A <30% decrease in hCG may be an early indicator of drug resistance.

ARTICLE INFO

Article history:

Received 22 June 2015

Received in revised form 21 August 2015

Accepted 5 October 2015

Available online 9 October 2015

Keywords:

Low-risk gestational trophoblastic neoplasia

Drug resistance

Chemotherapy

ABSTRACT

Objective. To determine the primary remission rates and predictors of drug resistance in patients with post-molar low-risk gestational trophoblastic neoplasia (GTN) who were treated with a 5-day intramuscular methotrexate (5-day IM MTX) or a 5-day drip infusion etoposide (5-day DIV ETP) regimen.

Methods. Between 1980 and 2014, 166 consecutive patients with low-risk post-molar GTN were initially treated with a 5-day IM MTX or a 5-day DIV ETP regimen. The primary remission rates, changes in chemotherapy due to drug resistance or toxicity, and relapse rates were compared. Furthermore, we analyzed the factors that influenced the development of resistance to MTX.

Results. Primary remission rates were significantly higher among the ETP-treated patients than among the MTX-treated patients. Among the 42 patients who required a change in chemotherapy, 23 patients (22.6%) and 4 patients (6.3%) were diagnosed as being resistant to MTX and ETP, respectively. Maternal age and the presence of metastasis did not significantly influence the development of MTX resistance, although higher FIGO scores and pre-treatment human chorionic gonadotropin (hCG) levels of $>5 \times 10^4$ mIU/mL were significantly more common among patients who developed MTX resistance. Moreover, a <30% decrease in hCG after the first cycles of MTX chemotherapy was significantly associated with the development of MTX resistance.

Conclusions. All patients with low-risk GTN eventually achieved complete remission, although several patients developed drug resistance to the first-line chemotherapy. A <30% decrease in hCG during the first chemotherapy cycle may be an early indicator of drug resistance after commencing a 5-day MTX regimen.

© 2015 Elsevier Inc. All rights reserved.

1. Introduction

Gestational trophoblastic neoplasia (GTN) is extremely responsive to chemotherapy, and almost all patients with low-risk GTN can achieve remission. The most common and effective chemotherapy regimens for patients with low-risk GTN are 5-day intramuscular methotrexate (5-day IM MTX), 8-day alternating intramuscular MTX and folinic acid

(MTX-FA), 5-day intravenous actinomycin-D (5-day Act-D), and 5-day drip infusion etoposide (5-day DIV ETP) [1–4]. The most popular first-line treatment for patients with low-risk GTN is a MTX regimen with or without folinic acid rescue, due to its favorable safety and toxicity profiles, such as the reduced risk of alopecia, ovarian dysfunction, and second malignancies. However, approximately one-quarter of patients with low-risk GTN who are treated with MTX have to change their chemotherapy regimen due to the development of drug resistance or intolerable toxicity [1–4]. Although almost all primary treatment failures in these cases are successfully salvaged with another single-agent or combination chemotherapy, the change to a second-line chemotherapy

* Corresponding author at: Department of Obstetrics & Gynecology, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo, Japan.

E-mail address: matsui.hideo@twmu.ac.jp (H. Matsui).

regimen undoubtedly increases the total treatment duration and may reduce the patient's quality of life. Moreover, salvage treatment with a combination chemotherapy that contains ETP causes alopecia, is associated with an earlier onset of menopause, and may slightly increase the risk of developing secondary malignancies [5].

In this study, we retrospectively compared the primary remission and relapse rates among patients with low-risk GTN who were treated with 5-day IM MTX or 5-day DIV ETP. Furthermore, we analyzed the risk factors for developing drug resistance in low-risk GTN patients who were treated with a 5-day IM MTX regimen.

2. Patients and methods

Between 1980 and 2014, 268 patients with post-molar FIGO stages I–III GTN (scores of <7) were treated at Chiba University (1980–2009) and Tokyo Women's University (2010–2014). The design for this retrospective study was reviewed and approved by our institutional ethics review board. The pre-treatment evaluation of each patient included a complete history and physical examination, complete blood count, renal and liver function tests, serum human chorionic gonadotropin (hCG) levels, pelvic ultrasonography, and chest radiography and/or lung computed tomography. Serum hCG levels were evaluated before each chemotherapy cycle and twice per week during the chemotherapy cycle. We excluded 102 patients from this analysis due to combined planned hysterectomy and chemotherapy (72 patients), initial treatment with several kinds of combination chemotherapy (13 patients), and other non-MTX/non-ETP single-agent regimens (MTX-FA: 12 patients, 5-day Act-D: 5 patients). The remaining 166 patients (61.9%) were started on 5-day IM MTX (102 patients) or 5-day DIV ETP (64 patients) (Table 1).

Because there is no international consensus definition for drug resistance to first-line chemotherapy for GTN, patients were defined as developing drug resistance if they had a <50% decrease in their hCG levels for ≥ 2 consecutive cycles of chemotherapy, or if they experienced an increase in hCG levels for 1 week. Drug toxicity profiles were classified according to the Common Terminology Criteria for Adverse Events (version 4.0) [6]. Cases with at least grade 3 stomatitis, at least a grade 2 increase in aspartate aminotransferase levels, or at least grade 1 skin rash (macules, papules) were diagnosed as having drug toxicity, and their chemotherapy regimen was changed. Primary remission was defined as three consecutive weekly hCG levels that were within the normal range using the same chemotherapy regimen.

All data are reported as mean \pm standard deviation, median (range), or number (%). Continuous data were examined for skewness (a measure of symmetry) and kurtosis (whether data are peaked or flat, compared to a normal distribution) using JMP Pro software (version 11.2.0; SAS, Inc., Japan, Tokyo). Pre-treatment hCG levels did not fit a Gaussian

distribution, and were analyzed using the Mann–Whitney U test for inter-group comparisons. Proportional data were analyzed using Fisher's exact test. Differences with a p-value of <0.05 were considered statistically significant.

3. Results

The characteristics of the 166 patients with low-risk GTN who were treated with 5-day IM MTX or 5-day DIV ETP are shown in Table 1. The patients' ages were 32.4 ± 7.4 years and 29.4 ± 7.1 years, respectively ($p = 0.01$). Metastatic disease was present in 32 patients (31.4%) in the MTX group (one vaginal wall and 31 lung metastases) and in 25 patients (39.1%) in the ETP group (one vaginal wall and lung metastases and 24 lung metastases) ($p = 0.37$). All of these metastatic tumors were <3 cm and the numbers of lung metastases were ≤ 4 , except for those in one patient. That patient had 8 lung metastatic foci and developed drug resistance to 5-day DIV ETP. The MTX and ETP groups' FIGO scores were 2.1 ± 1.2 and 2.4 ± 1.5 , respectively ($p = 0.12$), although significantly more patients in the ETP group had a score of ≥ 5 ($p = 0.02$). The MTX and ETP groups' median pre-treatment hCG levels were 4000 mIU/mL and 7500 mIU/mL, respectively ($p = 0.12$). Pre-treatment hCG levels of $> 10^5$ mIU/mL were observed in six patients (5.9%) who were treated with MTX and in 9 patients (14.1%) who were treated with ETP ($p = 0.07$).

The primary remission and relapse rates for patients who were treated with 5-day IM MTX or 5-day DIV ETP are shown in Table 2. The primary remission rates for patients who were treated with MTX (64.7%) and ETP (90.6%) were significantly different ($p < 0.0001$). Thirty-six patients (35.3%) who were treated with MTX required a change in regimen due to developing drug resistance ($n = 23$) and drug toxicities ($n = 13$). The drug toxicities for MTX were severe stomatitis (\geq grade 3: 4 patients), deteriorating aspartate aminotransferase levels (\geq grade 2: 5 patients), and skin rash (\geq grade 1: 4 patients); grades 3–4 leukocytopenia, thrombocytopenia, and anemia were not observed in this series. In contrast, only 6 patients who were treated with ETP required a change in regimen due to the development of drug resistance (4 patients) and drug toxicities (2 patients). The drug toxicities for ETP were skin rash (grade 1) and deteriorating aspartate aminotransferase levels (grade 2). When we compared the MTX and ETP groups, we observed significant differences in the frequencies of drug resistance (22.6% vs. 6.3%, $p = 0.006$) and drug toxicity (12.7% vs. 3.1%, $p = 0.04$).

After primary remission was achieved using 5-day IM MTX, 2 patients relapsed at 4 months and 5 months, after their last chemotherapy cycle. These 2 relapsed patients were successfully re-treated with ETP-containing combination chemotherapy [7]. Another patient who was initially treated with 5-day DIV ETP also relapsed. After 7 cycles of 5-day DIV ETP, she developed drug resistance and the regimen was changed to a combined ETP and Act-D regimen to achieve remission. However, she relapsed at 5 months after the last chemotherapy cycle. This patient was also successfully re-treated with ETP-containing combination chemotherapy [7].

Among the 102 patients with low-risk GTN who were treated with 5-day IM MTX, 23 patients had to change the initial chemotherapy regimen due to the development of drug resistance. Therefore, we compared the factors that might influence the development of drug

Table 1

The characteristics of 166 patients with low-risk gestational trophoblastic neoplasia who were treated with 5-day methotrexate and 5-day etoposide.

	MTX (n = 102)	ETP (n = 64)	P-value
Age, years (mean \pm SD)	32.4 \pm 7.4	29.4 \pm 7.1	0.01
FIGO stage, n			
I	70	39	
II	1	0	
III	31	25	NS
FIGO score (mean \pm SD)	2.1 \pm 1.2	2.4 \pm 1.5	NS
<5	98	55	
≥ 5	4	9	0.02
Median pre-treatment hCG, mIU/mL (range)	4000 (1.4–640,000)	7500 (7.2–1,875,200)	NS
hCG > 10^5 mIU/mL, n (%)	6(5.9)	9(14.1)	NS
hCG > 10^4 mIU/mL, n (%)	37(36.3)	27(42.1)	NS

MTX: methotrexate, ETP: etoposide, SD: standard deviation, FIGO: International Federation of Gynecology and Obstetrics, hCG: human chorionic gonadotropin, NS: no significant difference.

Table 2

Primary remission rates, drug resistant rates, and relapse rates.

	5-day MTX (n = 102)	5-day ETP (n = 64)	P-value
Primary remission	66 (64.7%)	58 (90.6%)	<0.0001
Regimen change due to:			
Drug resistance	23 (22.6%)	4 (6.3%)	0.006
Drug toxicity	13 (12.7%)	2 (3.1%)	0.04
Relapse	2 (2.0%)	1 (1.6%)	NS

MTX: methotrexate, ETP: etoposide, NS: no significant difference.

resistance between the drug resistant group (n = 23) and the non-drug resistant group (n = 79; primary remission: 66 patients; drug toxicity: 13 patients) (Table 3). We did not observe any significant differences between the two groups in maternal age (p = 0.21) and the presence of metastases (p = 0.74). In contrast, the median pre-treatment hCG levels in the drug resistant group (16,000 mIU/mL, 85.8–256,000 mIU/mL) were significantly higher than those in the non-drug resistant group (2000 mIU/mL, 1.4–640,000 mIU/mL) (p = 0.0004). Although we only identified a small number of cases with elevated pre-treatment hCG levels, a pre-treatment hCG level of $\geq 10^5$ mIU/mL did not significantly influence the development of drug resistance (p = 0.09). The FIGO scores in the drug resistant group (2.8 ± 1.3) were significantly higher than those in the non-drug resistant group (1.8 ± 1.1) (p = 0.0006).

After commencing the 5-day IM MTX regimen, weekly serum hCG decreases were calculated during the first and second chemotherapy cycles. In the first cycle, the hCG percentage decrease in the drug resistant group (21.9 ± 24.8%) was significantly lower than that in the non-drug resistant group (38.3 ± 14.6%) (p < 0.0001). During the second chemotherapy cycle, the frequency of hCG decreases was also significantly lower in the drug resistant group (p = 0.0012). Moreover, among the 23 patients with drug resistance, 17 patients (73.9%) were diagnosed as being drug resistant within 5 cycles (median: 3 cycles, range: 1–5 cycles), and the remaining 6 patients were diagnosed as being drug resistant at a later time (median: 8 cycles, range: 6–9 cycles). The frequencies of hCG decreases in the early drug resistant group (17.4 ± 27.1%) were significantly lower (p = 0.0005) than those in the late drug resistant group (34.8 ± 9.2%) and the non-drug resistant group (38.3 ± 14.6%) (data not shown).

The drug resistant group had a significantly higher median number of chemotherapy cycles that was needed to achieve remission (8.8 cycles, 4–19 cycles), compared to the non-drug resistant group (4.7 cycles, 2–9 cycles) (p < 0.0001).

4. Discussion

The cure rates for low-risk GTN have approached 100%, even in the presence of metastasis, higher pre-treatment hCG levels, and higher FIGO scores (5–6 points) with effective chemotherapy regimen. Although there is no clear international consensus regarding what is the best single-agent therapy for low-risk GTN [8–9], a MTX regimen with or without folic acid rescue is preferred, due to its favorable safety and toxicity profiles, such as the reduced risk of alopecia, ovarian

dysfunction, and second malignancies [5]. Nevertheless, 11–31% of patients with low-risk GTN who are treated with MTX (with or without folic acid rescue) required a change in their chemotherapy regimen, due to the development of drug resistance and/or intolerable toxicity. These patients require second-line single-agent or ETP-containing combination chemotherapy, and are typically successfully salvaged after this treatment [1–4]. However, this change in regimen undoubtedly increases the total duration and cost of treatment, and potentially reduces the patient's quality of life [10]. Therefore, it would be useful to identify patients with low-risk GTN who will develop drug resistance to MTX.

In their study of a 5-day IM MTX regimen for patients with low-risk GTN, Soper et al. [11] reported that primary remission was achieved in 60% (31/52) of their patients, although 21 patients required second-line chemotherapy due to the development of drug resistance (10 patients) and drug toxicity (11 patients). They also found that high pre-treatment hCG levels (>10,000 mIU/mL) were associated with the development of drug resistance. Lurain et al. [4] have also reported a primary remission rate of 89.3% (226/253), with 27 patients (10.7%) developing resistance to MTX. In this context, the factors that are associated with the development of MTX resistance are pretreatment hCG levels of >50,000 mIU/mL, non-molar antecedent pregnancy, and a clinicopathological diagnosis of choriocarcinoma. We have also previously reported that the 5-day IM MTX regimen for patients with low-risk GTN provides a primary remission rate of 73.6% (89/121), although 7 (5.8%) and 25 (20.7%) patients required second-line chemotherapy due to drug resistance and drug toxicities, respectively [3]. However, cases with a transient deterioration in aspartate aminotransferase levels were over-judged as drug toxicities during that period (1974–1979).

In the present study, the antecedent pregnancy was hydatidiform mole, the FIGO scores were ≤ 6 (median: 2, range: 0–6), and we excluded patients who underwent combined planned hysterectomy and chemotherapy. Among the remaining patients, the primary remission rate for 5-day IM MTX was 64.7% (66/102), and 23 patients (22.6%) had to change their chemotherapy regimen due to drug resistance. Compared to the 5-day DIV ETP regimen, the MTX primary remission rate was significantly lower and the MTX drug resistance rate was significantly higher. Nevertheless, ETP treatment can increase the risk of secondary malignant tumors [5], and so ETP is currently considered unattractive as a first-line therapy.

We also analyzed the factors that influenced the development of drug resistance in patients who were treated with 5-day IM MTX. Our findings indicated that maternal age, the presence of metastasis, and pre-treatment hCG levels of $> 10^5$ mIU/mL did not influence the development of drug resistance. However, these findings conflict with those of previous reports [12–15]. Although we only included a small number of cases with high pre-treatment hCG levels, the median pre-treatment hCG levels and frequency of pre-treatment hCG levels of $\geq 5 \times 10^4$ mIU/mL were significantly higher in the drug resistant group. The FIGO scores were also significantly higher in the drug resistant group, which is similar to the findings of other reports [16], although the differences in the FIGO scores between the drug resistant and non-drug resistant groups were small for the predictors of developing drug resistance. The drug resistant group also exhibited a significantly lower frequency of weekly hCG decreases, as well as a higher frequency of <30% decreases in hCG. The definite values for weekly hCG decreases in predicting drug resistance were not estimated in this series, although an approximately < 30% decrease in hCG during the first cycle may be a predictor of drug resistance to 5-day IM MTX. Although we only identified a small number of cases that were resistant to ETP, the frequency of hCG decreases during the first cycle was lower among the patients who were resistant to ETP (17.6 ± 9.5%) than among the patients who were not ETP resistant (31.4 ± 15.6%). In addition, multiple lung metastases and high FIGO scores were common in the drug resistant group (data not shown).

In conclusion, the primary remission and drug resistant rates for the 5-day IM MTX regimen were significantly poorer than the rates for 5-

Table 3
Risk factors for developing drug resistance.

	5-day MTX		P-value
	Drug resistant (n = 23)	Non-drug resistant (n = 79)	
Age, years	34.1 ± 7.2	31.9 ± 7.4	NS
Metastatic GTN	6 (26.1)	26 (32.9)	NS
Median pre-treatment hCG, mIU/mL (range)	16,000 (85.8–256,000)	2000 (1.4–640,000)	0.0004
$\geq 10^5$ mIU/mL, n (%)	3 (13.0)	3 (3.8)	
$< 10^5$ mIU/mL, n (%)	20 (87.0)	76 (96.2)	NS
$\geq 5 \times 10^4$ mIU/mL, n (%)	6 (26.1)	4 (5.1)	
$< 5 \times 10^4$ mIU/mL, n (%)	17 (73.9)	75 (94.9)	0.003
FIGO score	2.8 ± 1.3	1.8 ± 1.1	0.0006
Weekly hCG decreases, %			
First cycle	21.9 ± 24.8	38.3 ± 14.6	<0.0001
<30% decrease	14 (60.9)	19 (24.0)	0.0012
Second cycle	21.3 ± 20.4	33.9 ± 2.0	0.0012
Median chemotherapy cycles (range)	8.8 (4–19)	4.7 (2–9)	<0.0001

MTX: methotrexate, GTN: etoposide, SD: standard deviation, FIGO: International Federation of Gynecology and Obstetrics, hCG: human chorionic gonadotropin, NS: no significant difference.

day EIV ETP, although the first-line use of MTX regimen is recommended, due to the possibility of harmful toxicities with ETP regimen. Therefore, early prediction for developing MTX resistance may help improve the management of patients with low-risk GTN. In this study, high pre-treatment hCG levels, pre-treatment hCG levels of $\geq 5 \times 10^4$ mIU/mL, high FIGO scores, and poor weekly hCG decreases during the first and second chemotherapy courses influenced the development of MTX resistance. An approximately $< 30\%$ decrease in hCG during the first chemotherapy cycle may be an early indicator of drug resistance after beginning a 5-day MTX regimen.

Conflicts of interest

None.

References

- [1] I.A. McNeish, S. Strickland, L. Holden, G.J. Rustin, M. Fokkett, M.J. Seckl, et al., Low-risk persistent gestational trophoblastic disease: outcome after initial treatment with low-dose methotrexate and folic acid from 1992 to 2000, *J. Clin. Oncol.* 20 (2002) 1838–1844.
- [2] J.P. Roberts, J.R. Lurain, Treatment of low-risk metastatic gestational trophoblastic tumors with single-agent chemotherapy, *Am. J. Obstet. Gynecol.* 174 (1996) 1917–1924.
- [3] H. Matsui, Y. Iitsuka, K. Seki, Sekiya S. Comparison of chemotherapies with methotrexate, VP-16 and actinomycin-D in low-risk gestational trophoblastic disease. Remission rates and drug toxicities, *Gynecol. Obstet. Investig.* 46 (1998) 5–8.
- [4] J.R. Lurain, E.P. Elfstrand, Single-agent methotrexate chemotherapy for the treatment of nonmetastatic trophoblastic tumors, *Am. J. Obstet. Gynecol.* 172 (1995) 574–579.
- [5] G.J. Rustin, E.S. Newlands, J.M. Lutz, L. Holden, K.D. Bagshawe, J.G. Hiscox, et al., Combination but not single-agent methotrexate chemotherapy for gestational trophoblastic tumors increase the incidence of second tumors, *J. Clin. Oncol.* 14 (1996) 2769–2773.
- [6] Cancer Therapy Evaluation Program (CTEP). Common Terminology Criteria for Adverse Events (CTCAE) v4.0. http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40
- [7] H. Matsui, K. Suzuka, Y. Iitsuka, K. Seki, S. Sekiya, Combination chemotherapy with methotrexate, etoposide, and actinomycin D for high-risk gestational trophoblastic tumors, *Gynecol. Oncol.* 78 (2000) 28–31.
- [8] R.J. Osborne, V. Filiaci, J.C. Schink, R.S. Mannel, A.A. Secord, J.L. Kelley, et al., Phase III trial of weekly methotrexate or pulsed dactinomycin for low-risk gestational trophoblastic neoplasia: a Gynecologic Oncology Group Study, *J. Clin. Oncol.* 29 (2011) 825–831.
- [9] C. Aghajanian, Treatment of low-risk gestational neoplasia, *J. Clin. Oncol.* 29 (2011) 786–788.
- [10] H. Matsui, K. Suzuka, K. Yamazawa, N. Tanaka, A. Mitsuhashi, K. Seki, et al., Relapse rate of patients with low-risk gestational trophoblastic tumor initially treated with single-agent chemotherapy, *Gynecol. Oncol.* 96 (2005) 616–620.
- [11] J.T. Soper, D.L. Clarke-Pearson, A. Berchuck, G. Rodriguez, C.B. Hammond, 5-day methotrexate for women with metastatic gestational trophoblastic disease, *Gynecol. Oncol.* 54 (1994) 76–79.
- [12] R.S. Berkowitz, D.P. Goldstein, M.R. Bernstein, Ten years' experience with methotrexate and folic acid as primary therapy for gestational trophoblastic disease, *Gynecol. Oncol.* 23 (1986) 111–118.
- [13] E.B. Smith, J.C. Weed, L. Tyrey, C.B. Hammond, Treatment of nonmetastatic gestational trophoblastic disease: results of methotrexate alone versus methotrexate-folic acid, *Am. J. Obstet. Gynecol.* 144 (1982) 88–92.
- [14] L.C. Wong, Y.C. Choo, H.K. Ma, Methotrexate with citrovorum rescue in gestational trophoblastic disease, *Am. J. Obstet. Gynecol.* 152 (1985) 59–62.
- [15] S. McGrath, D. Short, R. Harvey, P. Schmid, P.M. Savage, M.J. Seckl, The management and outcome of women with post-hydatidiform mole 'low-risk' gestational trophoblastic neoplasia, but hCG levels in excess of 100 000 IU I(–1), *Brit. J. Cancer.* 102 (2010) 810–814.
- [16] E. Chapman-Davis, A.V. Hoekstra, A.W. Rademaker, J.C. Shink, J.R. Lurain, Treatment of nonmetastatic and metastatic low-risk gestational trophoblastic neoplasia: factors associated with resistance to single-agent methotrexate chemotherapy, *Gynecol. Oncol.* 125 (2012) 572–575.