Cancer Chemother Pharmacol (2004) 54: 34–38
DOI 10.1007/s00280-004-0781-6

ORIGINAL ARTICLE

Yoshiyuki Kagawa · Rika Mukohara · Hiroki Hori
Hajime Kawasaki · Yoshihiro Komada · Michio Kojima

Fever as a risk factor causing delayed elimination of methotrexate in pediatric patients receiving high doses of cancer chemotherapy

Received: 11 September 2003 / Accepted: 14 January 2004 / Published online: 13 March 2004

Abstract *Purpose*: Delayed elimination of methotrexate (MTX) has been reported to be caused by a number of factors. In order to identify these causes, we retrospectively investigated the risk factors for delayed elimination in pediatric patients who received high doses of MTX. *Subjects and methods*: The study included 69 courses of therapy involving 22 patients who received more than 1000 mg/m^2 of MTX. Plasma MTX concentrations 48 h (C48) and 72 h (C72) after infusion were used as indices of MTX elimination. *Results*: Neither C48 nor C72 was directly proportional to the dose of MTX infused. Both C48 and C72 were significantly higher in patients who developed fever of above 38°C within a 10-day period (i.e., from 7 days before to 3 days after infusion) than in patients with no fever. Subgroup analysis revealed that C72 was significantly higher in patients who either developed fever and received antipyretics or developed fever but did not receive antipyretics than in patients who did not develop fever and did not receive antipyretics. Changes in the serum creatinine concentrations before and after MTX infusion revealed that renal function was significantly decreased in patients who developed fever compared to patients without fever. *Conclusions*: The present results suggest that the development of fever is one of the main risk factors for the delayed elimination of MTX.

Keywords Methotrexate · Risk factor · Fever · Delayed elimination · High-dose MTX therapy

Y. Kagawa (✉) · R. Mukohara · M. Kojima
Department of Hospital Pharmacy,
Mie University School of Medicine,
2-174 Edobashi Tsu-city,
514-8507 Mie, Japan
E-mail: y-kagawa@clin.medic.mie-u.ac.jp
Tel.: +81-59-2321111 ext. 5335
Fax: +81-59-2321201

H. Hori · H. Kawasaki · Y. Komada
Department of Pediatrics,
Mie University School of Medicine,
2-174 Edobashi Tsu-city,
514-8507 Mie, Japan

Introduction

Methotrexate (MTX) is a competitive enzyme inhibitor of cellular dihydrofolate reductase that blocks the synthesis of nucleic acids and proteins [10]. It is widely used as an antineoplastic drug in the treatment of lymphocytic leukemias, lymphomas and a variety of solid tumors. To facilitate the eradication of cancer without unacceptable toxicity, therapeutic drug monitoring (TDM) of MTX is thought to be essential [5]. High-dose administration of MTX in combination with rescue therapy using leucovorin is well established as a treatment for childhood acute lymphocytic leukemia (ALL) and osteosarcoma [7]. The treatment schedule for rescue therapy using leucovorin is based on plasma MTX concentrations. However, plasma MTX concentrations exceeding 10^{-6} *M* 48 h or 10^{-7} *M* 72 h or more after infusion place patients at risk of toxicity [1]. Both MTX and its metabolites are excreted by an active process in the renal tubules. This active transport mechanism may be inhibited by nonsteroidal antiinflammatory drugs (NSAIDs), including ibuprofen and ketoprofen, which could increase the toxicity of MTX [9]. These interactions are, however, still a matter of controversy among researchers [4].

We monitored plasma MTX concentrations after high-dose cancer chemotherapy in pediatric patients and encountered several cases in which the elimination of MTX was delayed. NSAIDs were first believed to cause this delay. However, some patients who did not receive antipyretics showed delayed elimination. To determine the causes of these conflicting findings, we retrospectively explored the factors behind the delayed elimination of MTX.

Materials and methods

This study was designed to investigate retrospectively all children receiving high doses of MTX (above 1000 mg/m^2) in Mie University Hospital over a 2-year period. The study included 69 courses of therapy involving 22 patients (1.3 to 21 years old). The plasma

concentrations of MTX 48 h (C48) and 72 h (C72) after infusion were measured in all courses using a fluorescence polarization immunoassay method (TDx; Abbot Diagnosis, Chicago, Ill.). The characteristics of the patients are listed in Table 1. All the patients had normal renal function before MTX infusion and no history of chronic renal failure. None of the patients had renal metastasis derived from primary carcinoma. The infusion time of MTX ranged between 4 and 24 h. All the patients received intravenous fluids for hydration and alkalization of urine using intravenous sodium bicarbonate to avoid nephrotoxicity.

C48, C72, and the elimination rate constant from 48 to 72 h were used as indices for the delayed elimination of MTX. Toxicity threshold concentrations that placed the patients at risk of MTX-related toxicity were regarded to be 10^{-6} *M* at 48 h and 10^{-7} *M* at 72 h [7]. We monitored both C48 and C72 after high-dose MTX administration as much as possible. If C72 exceeded 10^{-7} *M*, we continued to monitor plasma MTX concentrations every 24 h until the concentration dropped below 10^{-7} *M*. C48, C72, the elimination rate constant from 48 to 72 h after infusion, urine pH and urine output in patients who developed fever above 38°C were compared with those in patients with no fever. C48, C72, the elimination rate constant, urine pH and urine output in patients who received antipyretics were also compared with those in patients who did not receive antipyretics. The elimination rate constant was calculated according to a one-compartment model. Patients who developed fever were then divided into two subgroups based on whether they had received antipyretics or not.

We also determined whether the following factors affected MTX disposition or not: age, sex, diagnosis (difference in disease), number of infusion cycles, infusion time of MTX, fluid intake for hydration, presence of diarrhea and concomitant use of antibiotics. Fever was defined as an increase in body temperature to above 38°C during a 10-day period (i.e., from 7 days before to 3 days after MTX infusion). Use of antipyretics was recognized if the patients took antipyretics during the 10-day period. The relationships between the plasma MTX concentrations and the day of fever onset, antipyretic administration or the type of antipyretic were investigated.

We further investigated the influence of fever and antipyretics on renal function in patients who received high doses of MTX. Renal and hepatic function were monitored twice or three times weekly during the high-dose MTX therapy. Changes in the mean serum creatinine (SCr) and blood urea nitrogen (BUN) concentrations from 3 days to 1 day before MTX infusion and from the day of infusion to 2 days after infusion were estimated and compared among patients who developed fever and those who did not, and between those who received antipyretics and those who did not.

Data analysis

We carried out a logarithmic conversion of the plasma concentrations of MTX to acquire a normal distribution of the data. The data are presented as means ± SD. Scheffé's *F*-test was used for statistical analysis with the aid of the computer program StatView 5.0 (Abacus Concepts, Berkeley, Calif.). *P* values < 0.05 were considered significant.

Table 1 Patient characteristics

No. of patients	20
Male/female	10/10
No. of courses	69
Age (years)	
Median	8
Range	1.3–21
Diagnosis	
Acute lymphocytic leukemia	12
Osteosarcoma	3
Non-Hodgkin's lymphoma	4
Anaplastic large cell lymphoma	1
MTX dose (g/m^2)	
Median	3.0
Range	1.0–12.0

Results

Relationship between plasma MTX concentrations and doses administered

Either C48 or C72 exceeded the corresponding threshold concentration of MTX toxicity (i.e., 10^{-6} or 10^{-7} *M*, respectively) in 28 of 69 courses (in 15 of 22 patients), whereas both C48 and C72 did so in 10 of 69 courses (in 9 of 22 patients). The relationship between the plasma concentration and dose infused, based on body surface area, was determined. C48 (Fig. 1) and C72 (Fig. 2) did not directly change in proportion to the dose infused. Neither C48 nor C72 was correlated with MTX dose based on body weight (data not shown).

Influence of fever and antipyretics on MTX elimination

The influence of fever and administration of antipyretics on the elimination of MTX was investigated. Table 2 lists the number of courses in which the patient developed fever or received antipyretics with or without a delayed decrease in plasma MTX concentration. As shown in Table 3, both C48 and C72 were significantly higher in patients who developed fever during MTX therapy than in patients who did not. Figure 3 also

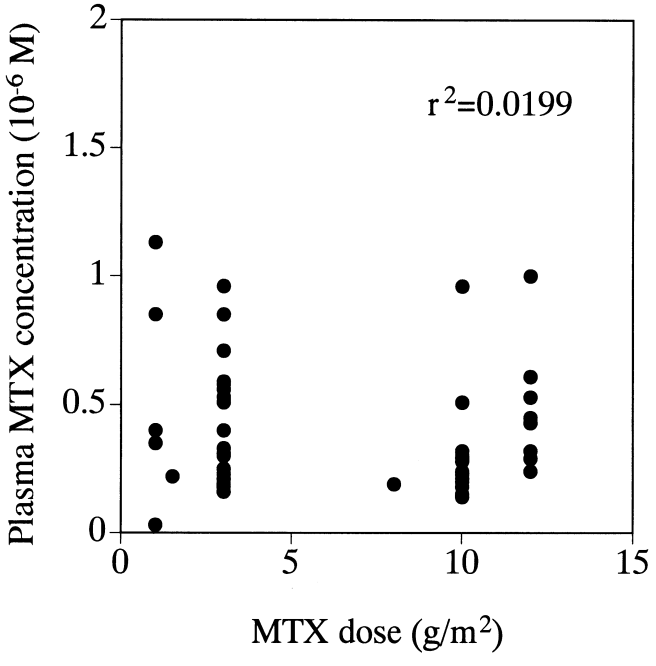

Fig. 1 Relationship between MTX dose and plasma concentration 48 h after infusion. Plasma concentrations of MTX were measured using a fluorescence polarization immunoassay method

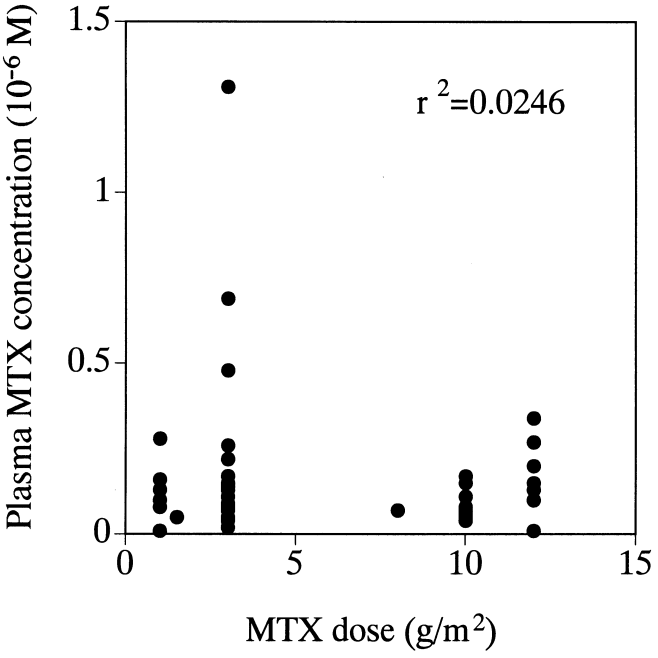

Fig. 2 Relationship between MTX dose and plasma concentration 72 h after infusion. Plasma concentrations of MTX were measured using a fluorescence polarization immunoassay method

Table 2 Number of courses in which the patient developed fever or received antipyretics with or without elevated plasma MTX concentration

No. of courses	Fever	
	Yes	No
Total	21	48
With antipyretics	13	2
With C48 10^{-6} *M* or more	1	0
With C72 10^{-7} *M* or more	11	0
Without antipyretics	8	46
With C48 10^{-6} *M* or more	3	3
With C72 10^{-7} *M* or more	6	11

presents a scatter plot of patients with fever versus those without fever 48 and 72 h after administration of MTX. There was no significant relationship between the plasma MTX concentration and the day of fever onset (data not shown). As shown in Table 3, neither C48 nor C72 was significantly higher in patients who received antipyretics than in those who did not. In patients who either developed fever or received antipyretics, the mean elimination rate constant (Kel) for the period 48 to 72 h after MTX administration was not significantly different from that of the corresponding control group.

The effects of antipyretics administered during MTX therapy on C48 and C72 are shown in Table 4. No significant differences in C48 and C72 were seen among three types of antipyretics. Regardless of whether antipyretics were received or not, only the C72 values of patients who developed fever were significantly higher than those of patients who did not (Table 5). No significant differences were seen among other subgroups divided on the basis of the development of fever and receipt of antipyretics.

As shown in Table 6, the SCr concentrations observed after infusion of MTX were significantly increased in patients who developed fever compared with levels before administration, although the BUN concentrations did not change from before to after MTX treatment. Neither the SCr nor BUN concentration changed significantly from before to after infusion of MTX regardless of whether the patients received antipyretics or not. Baseline SCr values did not differ between the groups with and without fever, or between those with and without antipyretics.

Influence of other factors on MTX elimination

Age, sex, diagnosis (difference in disease), repeated cycles of chemotherapy, infusion time of MTX, fluid intake, presence of diarrhea and concomitant use of antibiotics did not influence C48 or C72 (data not shown).

Discussion

The threshold MTX concentrations for toxicity are thought to be 10^{-6} *M* and 10^{-7} M at 48 and 72 h, respectively, after infusion [2]. When the plasma MTX concentration exceeds the threshold concentration, the risk of developing ulcerations of the gastrointestinal mucosae, erythroderma, aplastic anemia, interstitial pneumonia, hepatitis, renal impairment etc., increases significantly [8]. The present study demonstrated that fever is an important factor in the delayed elimination of MTX used in high-dose therapy for pediatric patients. We did not find any significant relationship between the plasma MTX concentration and the day of fever onset, although the study population might have been too small to detect a significant difference. Regardless of the day of onset within the 10-day period, the development of fever significantly elevated the plasma MTX concentration. This finding indicates that the delayed elimination was not caused by renal failure secondary to the destruction of tumor cells, because the fever brought about a delay in the clearance of MTX even before the infusion of MTX. Not all of the causes of the fevers were identified. However, in 8 of 21 courses of therapy the fever started on the first day MTX was administered, indicating that it was caused by tumor destruction or related to the administration of MTX.

The concomitant use of antipyretics did not significantly affect, although it tended to delay, the elimination of MTX. Thyss et al. have reported that the concomitant use of ketoprofen with high-dose MTX therapy increases the risk of severe MTX toxicity [6]. Since

Table 3 Influence of fever and antipyretics on the plasma concentrations of MTX, elimination rate constant, urine pH and urine output. The data presented are medians (range)

		No. of courses	C48 (10^{-6} *M*)	C72 (10^{-6} *M*)	Kel (h^{-1})[a]	Urine pH	Urine output (ml/kg body weight)
Fever	No	48	0.29 (0.03–1.42)	0.07 (0.01–0.78)	0.0598 (0.0194–0.1350)	7.67 (6.50–8.17)	88.0 (35.8–133.1)
	Yes	21	0.59 (0.09–155.50)*	0.20 (0.02–43.51)*	0.0563 (0.0076–0.0916)	7.83 (7.00–8.33)	90.2 (47.5–126.8)
			$P=0.0024$	$P=0.0007$	$P=0.16$	$P=0.20$	$P=0.57$
Antipyretics	No	54	0.30 (0.03–40.50)	0.07 (0.01–11.30)	0.0595 (0.0076–0.1350)	7.67 (6.50–8.17)	93.9 (35.8–133.1)
	Yes	15	0.53 (0.09–155.50)	0.16 (0.01–43.51)	0.0539 (0.0244–0.0783)	7.83 (7.00–8.33)	67.7 (47.5–126.8)
			$P=0.15$	$P=0.21$	$P=0.25$	$P=0.090$	$P=0.075$

*$P<0.05$ vs corresponding group, statistical comparisons were made using Scheffé's *F*-test
[a]Elimination rate constant from 48 to 72 h after infusion of MTX

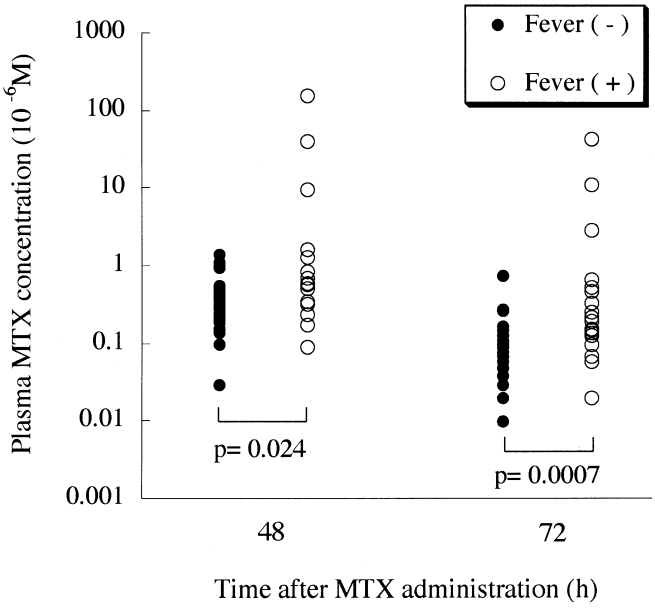

Fig. 3 Plasma MTX concentrations 48 and 72 h after administration in patients with and without fever

NSAIDs inhibit the synthesis of prostaglandins and reduce the renal perfusion rate, it is thought that they may reduce MTX clearance. However, developing fever was the only risk factor identified in the present study. Furthermore, the subgroup analysis revealed a significant increase in C72 in patients who developed fever but did not receive antipyretics when compared with those who neither developed fever nor received antipyretics. This result suggests that developing fever and receiving NSAIDs are independent risk factors for the delayed elimination of MTX.

Table 5 Influence of the combination of fever and antipyretics on the plasma concentration of MTX. The data presented are medians (range)

Fever	antipyretics	No. of courses	C48 (10^{-6} *M*)	C72 (10^{-6} *M*)
No	No	43	0.29 (0.03–1.42)	0.07 (0.01–0.78)
	Yes	2	0.28 (0.23–0.32)	0.05 (0.01–0.08)
Yes	No	8	0.59 (0.18–40.50)	0.18 (0.02–11.30)*
	Yes	13	0.61 (0.09–155.50)	0.22 (0.02–43.51)**

*$P=0.009$,
**$P=0.0037$, vs the C72 values without fever; Scheffé's *F*-test

The elimination rate constants for MTX from 48 to 72 h after infusion were not significantly different between the patients who developed fever and those who did not. This indicates that the period from 0 to 48 h after infusion is important when investigating the cause of delayed elimination of MTX. Increased permeability of vessels has been reported in some febrile conditions [3]. Increased vessel permeability of the arteries caused by fever may lead to an increase in the distribution of MTX. An increase in the distribution of the drug may cause the retention of MTX in the interstitial fluid and reduce elimination during the initial period. The reason why fever causes this delayed elimination of MTX is now under investigation.

The concentration of SCr, an indicator of renal function, in patients who developed fever during the 10-day period increased significantly after infusion of MTX when compared with levels before the 10-day period.

Table 4 Types of antipyretics administered. The data presented are medians (range). No significant difference was seen among three types of antipyretics

	Sulpyrine	Mefenamic acid	Diclofenac
No. of patients	7	5	3
Administration route	Injection	Oral suspension	Suppository
C48 (10^{-6} *M*)	0.61 (0.09–155.50)	0.62 (0.33–1.13)	0.32 (0.23–0.85)
C72 (10^{-6} *M*)	0.25 (0.02–43.51)	0.22 (0.07–1.31)	0.08 (0.01–0.26)

Table 6 Influence of fever and antipyretics on indicators of renal function. Changes in indicators were calculated by subtracting the pretherapy (baseline) concentration from the posttherapy concentration. In 23 of 69 courses either pre- or posttherapy concentrations were not recorded and a comparison was not made. The data presented are medians (range)

		No. of courses	Serum creatinine (mg/dl)		Serum BUN (mg/dl)	
			Baseline	Change	Baseline	Change
Fever	No	32	0.60 (0.40 to 0.80)	0.00 (−0.20 to 0.30)	9.0 (2.0 to 18.0)	−1.0 (−11.0 to 11.0)
	Yes	14	0.60 (0.30 to 0.90)	0.10 (−0.10 to 1.90) $P = 0.015$	9.0 (2.0 to 17.0)	2.0 (−8.0 to 7.0) $P = 0.60$
Antipyretics	No	36	0.60 (0.40 to 0.80)	0.00 (−0.20 to 1.00)	9.00 (2.0 to 18.0)	−1.0 (−11.0 to 11.0)
	Yes	10	0.60 (0.30 to 0.90)	0.10 (−0.10 to 1.90) $P = 0.16$	8.5 (2.0–17.0)	0 (−8.0 to 7.0) $P = 0.76$

Statistical analysis was performed with Scheffé's *F*-test

This indicates that the delayed elimination of MTX with development of fever significantly affects indicators of renal function. We did not find any other causes, e.g. antipyretics or hydration, besides higher plasma MTX concentrations, for the development of renal dysfunction. Although urine output tended to be lower in patients receiving antipyretics than those not receiving antipyretics, as shown in Table 3, no significant difference in renal function was found, as shown in Table 6. Fluid intake for hydration did not influence renal function after administration of MTX (data not shown).

One patient whose C48 and C72 values were 155.50×10^{-6} and 43.51×10^{-6} *M*, respectively, developed nephrotoxicity which was manifested as an increase in SCr concentration of 2.1 mg/dl (0.5 to 2.4 mg/dl). Another patient whose C48 and C72 values were 40.50×10^{-6} and 1.61×10^{-6} *M*, respectively, also developed nephrotoxicity which was manifested as an increase in SCr concentration of 1.0 mg/dl (0.6 to 1.6 mg/dl). Of 69 courses of therapy, 3 were associated with nephrotoxicity with an increase in SCr concentration exceeding 0.5 mg/dl. All of these patients had developed a fever.

In conclusion, the present results suggest that the development of fever is a factor in the delayed elimination of MTX in pediatric cancer patients receiving high-dose therapy. The delayed elimination of MTX due to fever may cause renal dysfunction.

References

1. Bleyer WA (1983) A comprehensive guide to the therapeutic use of methotrexate in bladder cancer. In: Bleyer WA (ed) Pharmanual. PharmaLibri, New Jersey, p.51
2. Bleyer WA (1989) New vistas for leucovorin in cancer therapy. Cancer 63:995
3. Geimonen E, Neff S, Raymond T, Kocer SS, Gavrilovskaya IN, Mackow ER (2002) Pathogenic and nonpathogenic hantaviruses differentially regulate endothelial cell responses. Proc Natl Acad Sci U S A 99:13837
4. Herrick AL, Grennan DM, Aarons L (1999) Lack of interaction between methotrexate and penicillins. Rheumatology 38:284
5. Seidel H, Andersen A, Kvaloy JT, Nygaard R, Moe PJ, Jacobsen G, Lindqvist B, Slordal L (2000) Variability in methotrexate serum and cerebrospinal fluid pharmacokinetics in children with acute lymphocytic leukemia: relation to assay methodology and physiological variables. Leuk Res 24:193
6. Thyss A, Milano G, Kubar J, Namer M (1986) Clinical and pharmacokinetic evidence of a life-threatening interaction between methotrexate and ketoprofen. Lancet 8475:256
7. Treon SP, Chabner BA (1996) Concepts in use of high-dose methotrexate therapy. Clin Chem 42:1322
8. Troche G, Sacquin P, Achkar A, Korach JM, Laaban JP, Gajdos P (1991) Severe methotrexate poisoning (in French). Presse Med 20:1724
9. Uwai Y, Saito H, Inui K (2000) Interaction between methotrexate and nonsteroidal anti-inflammatory drugs in organic anion transporter. Eur J Pharmacol 409:31
10. Waltham MC, Holland JW, Robinson SC, Winzor DJ, Nixon PF (1988) Direct experimental evidence for competitive inhibition of dihydrofolate reductase by methotrexate. Biochem Pharmacol 37:535