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Pharmacokinetics of Methotrexate in Children with Acute Lymphocytic Leukemia

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Key Words
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Abstract
Plasma methotrexate (MTX) levels were measured in 10 children (age 3–12 years) who received a total of 43 infusions of MTX. The total dose (1,000 mg/m^2) was administered as a bolus of 200 mg/m^2 with 24-hour infusions of 800 mg/m^2. The clearance was fast at 158 ± 81 ml/min/m^2 and the elimination half-life ($t_{1/2\beta}$) 3.0 ± 0.7 h (mean ± SD). The inter- and intrapatient variations in the steady state were wide, up to 6 times, suggesting the need for dose adjustment during infusion. The patients were at low risk for toxicity with a predicted MTX concentration at 39 h (5 half-lives) postinfusion of 0.28 ± 0.10 μmol/l (mean ± SD). None of them required leucovorin rescue 72 h postinfusion. An additional assessment of the MTX level may be useful as a guide to the duration of leucovorin rescue, which may be more or less than the routine 72 h postinfusion. The time suggested for this assessment was 48 h postinfusion. The mean ± SD concentration at this time was 0.23 ± 0.12 μmol/l and it correlated (r = 0.841) with the level measured 36 h postinfusion (n = 10). The value of this level needs to be investigated on a larger number of infusions.

Introduction

Methotrexate (MTX) is the only anticancer drug included in the routine therapeutic drug monitoring program [1]. The measured concentrations can be used to predict the decline in MTX level and as a guide to leucovorin dosages. High-risk patients can then be discovered early and the chances for MTX toxicity are minimized [1, 2]. The intermediate dose of methotrexate (ID-MTX) is now widely accepted as an effective treatment in acute lym-

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phocytic leukemia (ALL) patients. The range of this dose, which has been tested clinically, is between 500 to 1,500 mg/m^2 [3, 4]. The variations in steady state are substantial, which may result in some of the patients being exposed to lower MTX concentrations compared to the others [5, 6]. Evans et al. [7, 8] identified the presence of a relationship between the plasma concentration of MTX and the risk of relapse in ALL patients. Those patients who had an MTX concentration well above 16 µmol/l remained in remission for a longer period than those with a lower value.

In the present study we investigate the pharmacokinetics of MTX in a group of ALL patients treated with ID-MTX infusions. Furthermore, since the appropriate time for MTX measurements is different between centers, assessment of the proper time for the drug monitoring seemed important.

Materials and Methods

A total of 10 ALL patients (age 3–12 years) were included in this study. They were newly diagnosed, except 1 who had been treated because of a relapse. The chemotherapy protocol used was that of the pediatric oncology group which consisted of three phases. The induction phase consisted of prednisone (40 mg/m^2/day p.o.) for 28 days, vincristine (1.5 mg/m^2 i.v.) maximally 2 mg on days 1, 8, 15 and 22 and *L*-asparaginase (10^4IU/m^2 i.m.) on days 2, 4, 6, 8, 10 and 12. When complete remission was achieved the patient received six successive cycles of ID-MTX and cytosine arabinoside every 3–4 weeks to consolidate the therapy. During maintenance therapy the patient received 6-mercaptopurine (75 mg/m^2/day p.o.) and MTX (20 mg/m^2/week p.o.) for up to 3 years from diagnosis. Pulses of prednisone, vincristine and triple intrathecal therapy (hydrocortisone, MTX and cytosine arabinoside) were maintained between cycles and during maintenance therapy. The standard renal, hepatic and hematological function tests were carried out 1 day before starting each course.

Prehydration and urine alkalinization with normal saline and sodium bicarbonate were carried out 6 h before MTX infusion and continued for 48 h post infusion. The patients also received either promethazine or metoclopramide as an antiemetic. MTX (Lederle, 50 mg/vial) was infused at a dose of 1,000 mg/m^2 divided into bolus and 24-hour infusion. The bolus dose of 200 mg/m^2 i.v. was followed by 800 mg/m^2 infused over 24 h. The infusion pump used was the 'Lifecare' model 3 (Abbott/Shaw). Cytosine arabinoside (1 g/m^2) was infused over 24 h, started 12 h after MTX infusion using a separate external intravenous line. The leucovorin rescue was initiated 36 h post-MTX infusion. The dose and duration for standard risk patients consisted of 30 mg/m^2 every 6 h beginning at the 36th hour, then 3 mg/m^2 every 6 h up to 72 h postinfusion.

Blood samples were collected routinely just before stopping infusion (24 h) and during elimination (36 or 42 h) postinfusion. An additional two samples were collected in 10 courses within the time interval of 48–72 h postinfusion. The samples were analyzed for MTX by fluorescence polarization immunoassay using TDX machines.

The total body clearance (TBC), elimination half lives ($t_{1/2}$) and the predicted concentration were calculated using the following relationships [9]:

$TBC = K_o$ (mg/min/m^2)/C_{ss} (mg/l), $K_d = (\ln Cp_1 - \ln Cp_2)/(t_2 - t_1)$, $t_{1/2} = 0.693/K_d$, $\log Cp_2 = -K_d\, t/2.3 + \log Cp_1$, where K_o = infusion rate, C_{ss} = steady state MTX concentration, K_d = elimination rate constant, Cp_1 and Cp_2 = MTX concentrations, t_1 and t_2 = sampling times for Cp_1 and Cp_2, respectively, and $t = t_2 - t_1$.

Results

The pharmacokinetic parameters reported were taken from 43 ID-MTX infusions. The remaining infusions were ignored because of the missed 24-hour samples. All patients had normal liver, renal and hematological functions before starting each cycle. The mean ± SD steady state MTX concentration was 9.1 ± 3.2 µmol/l (range 2.3–15.3) (fig. 1). This corresponded to a total body clearance of 158 ± 81 ml/min/m^2 (range 79–502). The inter- and intrapatient variations in the steady state were relatively high, reaching up to 6 times. The distribution of MTX concentrations at 24, 36 and 42 h postinfusion are shown in figure 1. The line connecting the means of these concentrations is linear (r = 0.951). The elimina-

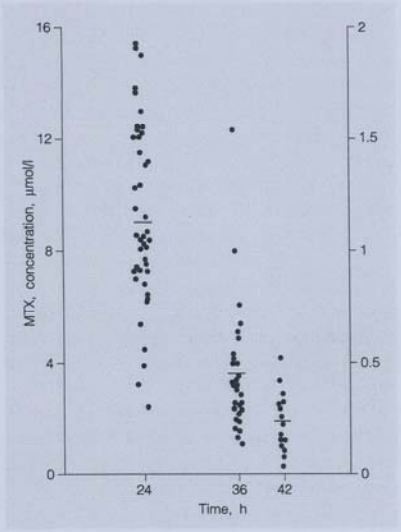

Fig. 1. Distribution of plasma concentrations of MTX at 24, 36 and 42 h postinfusion in 10 ALL patients receiving a total of 43 courses. The dose consisted of 200 mg/m^2 as bolus followed by 800 mg/m^2 as a 24-hour infusion. The line connecting the means of these concentrations is linear ($r = 0.951$). The right ordinate (Y_2) is for the 36- and 42-hour MTX levels.

Table 1. Individual patient characteristics and their MTX pharmacokinetics parameters (mean ± SD), steady state (C_{ss}), clearance (CL) and elimination half-life ($t_{½}\beta$)

Patient	Sex	Age years	n	C_{ss} µmol/l	CL ml/min	$T_{½}\beta$ h	Duration months
1	m	3.5	3	5.7 ± 2.1	243 ± 116	4.7 ± 0.78	R
2	m	9	3	9.0 ± 1.5	137 ± 24	2.9 ± 0.39	41
3	m	3	5	9.1 ± 3.1	147 ± 53	2.8 ± 0.47	35
4	m	3	5	13.8 ± 1.5	89 ± 10	2.7 ± 0.60	31
5	m	3.5	4	9.0 ± 2.2	141 ± 30	2.9 ± 0.49	36
6	m	6	3	7.4 ± 3.3	194 ± 104	2.9 ± 0.81	42
7	m	4	2	8.7 ± 3.9	155 ± 69	3.7 ± 0.76	41
8	f	8.5	6	10.7 ± 4.1	137 ± 75	3.1 ± 0.50	16
9	m	5	6	7.6 ± 1.1	164 ± 24	2.6 ± 0.35	12
10	f	12	6	7.7 ± 2.9	201 ± 14	3.0 ± 0.86	7

The patients are still in remission for the duration indicated except patient 1 who relapsed (R) after 30 months. n = Number of infusion.

tion half-life ($t_{1/2}\beta$) was about 3.0 ± 0.7 h (range: 2.1–5.3). The concentration of MTX at the time corresponding to 5 half-lives after the end of infusion was predicted for all infusions, being 39 h, and it corresponded to a concentration of 0.28 ± 0.10 μmol/l (mean ± SD). Neither the age nor the number of infusions had any influence on the clearance of MTX (table 1).

The patients were monitored during hospitalization for possible renal, liver, oral, dermal and hematological toxicities. The follow-up continued as they returned for the pulse therapy and for the next cycle. Generally, toxicity was mild, where most of the patients were discharged within the first 72 h without complications. Stomatitis was the main adverse effect discovered after discharge in about 30% of the patients. Neutropenia was the next common finding and in a few cycles the subsequent course was delayed for a week or more.

The two samples collected at 48–72 h postinfusion appeared as a terminal elimination phase with a half-life of 13.9 ± 8.1 h (fig. 2). In almost all the courses the level dropped to less than 0.05 μmol/l within the interval 48–72 h postinfusion. A good correlation (r = 0.841) was found between the concentrations of MTX measured at 36 and 48 h postinfusion.

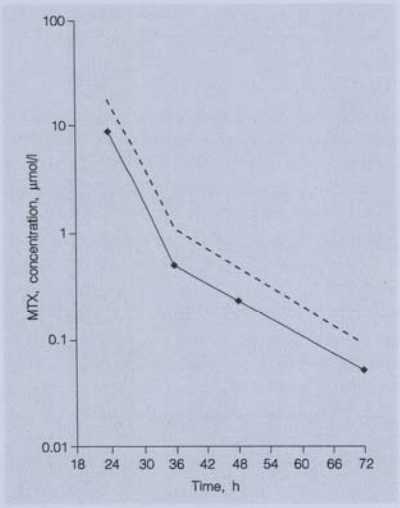

Fig. 2. Plasma concentration-time profile of MTX in ALL patients following 10 ID-MTX infusions each consisted of bolus injection of 200 mg/m² and 24-hour infusions of 800 mg/m². – – – = 2 SD above the mean (——) for 10 infusions. The correlation (r) between the concentration at 36 and 48 h postinfusion is 0.841.

Discussion

The clearance of MTX in this group of patients was fast compared to that reported in previous studies. The mean was 158 ml/min/m² as compared to a value between 74 and 104 ml/min/m² in similar groups of patients [6, 7, 10, 11]. The fast clearance was associated with a steady state plasma concentration of less than 16 μmol/l (range: 2.3–15.3) during all the courses. The 16 μmol/l value was used by Evans et al. [7] as a cutoff, below which the risk of relapse in ALL patients significantly increased. Although they used the same dosage regimen, about 45% of their patients had a level above 16 μmol/l. According to these findings, it seemed that our patients had cleared the drug faster than those in the other studies. The reason is not clear, although the age of the patients was slightly less than that reported in those studies. In children, an increase in the clearance of MTX is apparent with a decrease in age [12]. Cytosine arabinoside and MTX sequentially overlapped for a synergistic effect which is the only known interaction between the two drugs [13].

A higher dosage of MTX is used to achieve an adequate MTX concentration at the sites

of action. It has been shown that extracellular MTX concentrations in excess of 5 μmol/l are required for active intracellular transport [14]. This should correspond to a plasma level greater than 10 μmol/l, provided that MTX is 50% bound to plasma protein and only the free fraction is available for diffusion. This raises the point that some of the patients did not achieve adequate MTX concentration by using fixed ID-MTX. It is this group of patients who may need titration of their dose early on during the infusion in order to get more than 10 μmol/l. This notion is supported by the fact that the patients were able to tolerate these doses without complications. The mild toxicity has also been reported by other investigators using similar protocols [7, 8]. Adjusting the dose during infusion may not be difficult in practice, since the ID-MTX steady-state relationship is linear [4]. It had been done for research purposes where the new infusion rate was selected during the initial 5 h of a 24-hour infusion [15]. This seems necessary for all infusions because variations within patients may be as high as 4 times.

Despite extensive studies on the pharmacokinetics of MTX, the appropriate time for MTX measurements is still unknown. Most investigators rely on a single MTX measurement during elimination to detect high risk patients [2, 16]. The sample is taken at 42 h postinfusion for the 24-hour ID-MTX infusion protocol [2]. This study suggested 39 h postinfusion to insure sampling during the first elimination phase, and the level should be more than 0.5 μmol/l. During this interval, it is expected that the concentration of MTX should point to any defect in its clearance. However, it is quite possible that the alteration in MTX elimination occurs only during the terminal phase [2, 17]. In this case leucovorin administration should be maintained for more than the recommended 72 h after infusion. On the other hand, some of the patients may stop taking MTX (i.e. < 0.05 μmol/l) early around the 48th hour postinfusion as was the case in this study. To identify these groups, we may need an additional MTX level, suggested to be 48 h postinfusion. The MTX level at this time is 0.23 ± (SD) 0.11 μmol/l, which is similar to that reported by others [14]. There is a good correlation (r = 0.841) between the concentration measured at 36 and 48 h postinfusion. The value of this relationship in predicting the elimination of MTX needs to be established in a larger number of infusions.

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