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CSF Drug Levels for Children with Acute Lymphoblastic Leukemia Treated by 5 g/m^2 Methotrexate

A Study from the EORTC Childrens' Leukemia Cooperative Group

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A multicenter EORTC study was conducted in children with acute lymphocytic leukemia to determine whether 5 g/m^2 of methotrexate (MTX) (24 h i.v. infusion, four cycles) is an appropriate dosage for obtaining CSF drug concentrations approaching the critical cytotoxic level of 10^{-6} M. A total of 193 cycles were analyzed for 58 patients. At the end of the 24 h infusion, the mean MTX serum level was 65.27 ± 33.11 μM; the mean CSF MTX level was 1.47 ± 1.1 μM; no significant difference in CSF MTX levels was observed between patients with (n = 20) and those without i.v. Ara-C (n = 38). The mean CSF MTX/serum MTX ratio was 0.029 ± 0.027. CSF drug concentrations greater than or equal to 10^{-6} M were achieved in 81% of the courses. The highest level was 8.4 × 10^{-6} M. Only 5% of patients failed to achieve this drug concentration in at least one cycle. No significant correlation was observed between blood and CSF MTX levels. Mean CSF MTX levels were comparable from one cycle to another.
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INTRODUCTION

METHOTREXATE (MTX) is of value in the treatment of children with acute lymphocytic leukemia (ALL) [1], however accurate determination of the optimal dose and schedule is still unclear [2]. This need is highlighted by requirements for control of CNS relapse, which remains an important problem in lymphoproliferative diseases [3]. For patients treated in the late seventies with less intensive induction therapy than presently used, a study on more than 500 children suggested thus intravenous intermediate-dose MTX (500 mg/m^2) given over 24 h provided less protection against CNS relapses than cranial irradiation [4]. In a more limited study, more intensive therapy (1500 mg/m^2) also failed to reduce the incidence of CNS relapse in increased risk patients [5]. These observations may have a pharmacological explanation as the ratio of drug levels between CSF and serum is close to 5% [6]. Consequently, co-administration of intrathecal (IT) MTX has commonly been used as a means of obtaining more consistent CSF MTX concentrations [7, 8]. Although the CSF drug levels obtained by IT MTX reached the potentially cytotoxic level of 10^{-6} M [9], this administration route does not result in uniform drug distribution throughout the entire CSF [10]. By contrast, systemic MTX administration results in homogeneous distri-

Table 1. Study population

Total number of patients	Total number of cycles administered	Males	Females	Mean age (range)	SR	MR HR
58	193	25	33	6 years (13 months to 15 years)	29	29

bution in CNS fluids [11]. In a recent pharmacokinetic study, the relationship between the MTX i.v. dose and CSF drug concentrations for two regimens (0.5 g/m^2 vs. 2.5 g/m^2) was examined [12]. Potentially cytotoxic CSF drug levels (10^{-6} M) were never obtained with 0.5 g/m^2, but were achieved in 44% of the cycles with 2.5 g/m^2. It was concluded that a dose of 5.0 g/m^2 would be adequate to obtain the desired CSF MTX concentration and limit the risk of toxicity described for higher doses (8–15 g/m^2) [13]. A multicenter cooperative pharmacokinetic study was initiated to validate this hypothesis. The results of 193 cycles of i.v. MTX at a dose of 5.0 g/m^2 are presented (58 patients).

MATERIAL AND METHODS

Pharmacokinetics were investigated during the intermediate phase of treatment, after the induction therapy described previously [14].

Table 1 describes the 58 patients (193 cycles) studied. All patients were under 18 years of age and had ALL of B or T lineage mature excluding B-cell ALL. None had any evidence of CNS involvement at the time of MTX treatment. Patients were stratified into standard risk (SR), medium risk (MR) and high risk (HR) groups according to their risk factor (RF), as used in the German BFM group [15] which provides a measure of the leukemia cell mass at diagnosis. Treatment consisted of 6-mercaptopurine started on day 1 as a single daily dose in the morning (25 mg/m^2, p.o., days 1–56). MTX was given on days 8, 22, 36 and 50 (i.e. four cycles). Intravenous MTX was given as a 24 h infusion; 1/10th of the dose (i.e. 500 mg/m^2) was given over the first hour. The other 9/10th (i.e. 4500 mg/m^2) were infused at a constant rate over 23 h. A urinary pH > 7 was required before MTX was administered. Alkalinization was obtained with sodium bicarbonate (1 meq/kg in 50 ml glucose 5% in 15 min infusion). The total hydration volume was 3 l/m^2/24 h over 72 h. On the first day, hydration was ensured by an infusion containing glucose 5%, 2/3; $NaHCO_3$ 60 meq/l, 1/3; KCl, 30 meq/l. On the second and third days, hydration and alkalinization were continued orally if no vomiting occurred. Alkalinization was maintained over the first 72 h, with diuresis > 1600 ml/m^2/24 h. Urinary pH was checked immediately after each collection of on the fresh urines, and was maintained above 7. IT MTX was given 24 h after the start of the MTX infusion, i.e. at the end of the infusion. The IT MTX doses were 6 mg if the patient was aged < 1 year, 8 mg if > 1 year < 2 years, 10 mg if > 2 years < 3 years, and 12 mg if > 3 years. Folinic acid was started 36 h after the beginning of the MTX infusion, at a dose of 15 mg/m^2 per os every 6 h. Leucovorin was stopped if the serum MTX level 72 h after the start of MTX infusion was below 2×10^{-7} M. Since January 1989, i.v. Ara-C has been added to each MTX course for HR patients ($n = 20$). Ara-C was given in two 1 g/m^2 doses 12 h and 24 h respectively after the start of the MTX infusion.

Blood (5 ml collected in a heparinized tube) and CSF (1–2 ml) were obtained 24 h after the start of the MTX infusion and immediately before IT MTX. Depending on the practice at each institution, MTX was analyzed by fluorescence polarization assay (TDX, Abbott), by the RIA kit available from ORIS Industry (France), or by an enzymatic method based on inhibition of dihydrofolate reductase [16]. These different methods all give comparable results [17].

RESULTS

Table 2 gives the means and standard deviations for MTX concentrations in serum and CSF and for the ratios between CSF and serum MTX levels. Interpatient variability was marked in all cases. Eighty-one per cent of the MTX courses exhibited CSF drug concentrations greater than or equal to 10^{-6} M. Three patients (5%) failed to achieve this critical CSF drug level in at least one cycle; the CSF MTX levels for these patients ranged between 0.46 and 0.90×10^{-6} M. The maximum CSF drug exposure encountered was 8.4×10^{-6} M.

There was no significant correlation between blood and CSF MTX levels ($r = 0.147$, $p < 0.06$) (Fig. 1). Mean CSF MTX concentrations were comparable from one cycle to the other throughout the planned four courses (Table 3).

Individual CSF MTX concentrations were analyzed as a function of patient age, a relationship was found: CSF MTX (μM) = 0.056 (years) + 1.169, $r = 0.242$ ($P < 0.09$).

No significant difference in CSF MTX levels was observed between patients with ($n = 20$) and those without i.v. Ara-C ($n = 38$): the means ($\pm$ S.D.) were respectively 1.56 ($\pm$ 0.89) 10^{-6} M and 1.49 ($\pm$ 0.96) 10^{-6} M.

Table 2. Distribution of MTX concentrations (μM) in serum and CSF after 24 h (end of infusion)

Serum MTX (mean $\pm$ S.D.)	CSF-MTX (mean $\pm$ S.D.)	Ratio $\frac{\text{CSF-MTX}}{\text{serum-MTX}}$ (mean $\pm$ S.D.)
65.27 $\pm$ 33.11	1.47 $\pm$ 1.10	0.029 $\pm$ 0.027

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Table 3. Evolution of CSF MTX (μM) from cycle to cycle

Cycle 1 (mean ± S.D.) (*n*)	Cycle 2 (mean ± S.D.) (*n*)	Cycle 3 (mean ± S.D.) (*n*)	Cycle 4 (mean ± S.D.) (*n*)
1.49 ± 1.07 (53)	1.53 ± 1.10 (51)	1.51 ± 1.31 (48)	1.37 ± 0.89 (41)

DISCUSSION

This multicenter study concerning children with ALL was designed to determine whether 5 g/m^2 of i.v. MTX is an appropriate dosage for obtaining CSF MTX concentrations approaching the critical cytotoxic level of 10^{-6} M. This dose was selected following the findings of our initial pharmacokinetic study comparing MTX doses of 0.5 and 2.5 g.m^2 in childhood ALL [12]. Borsi and Moe [18] recently reported on MTX pharmacokinetics in children with ALL given doses ranging from 0.5 to 33.6 g/m^2 by 24 h i.v. infusion, as in the present study. In their heterogeneous group of patients, all children who received 6–8 g/m^2 (66 cycles in all) achieved a CSF MTX level over 10^{-6} M. Analysis of data for 58 patients (193 cycles) given a constant MTX dose (5 g/m^2) in this study revealed that 95% of the patients exhibited at least one cycle with a CSF MTX level greater than or equal to the desired micromolar concentration. All courses considered together, 81% of them were in the expected range. The lowest CSF drug concentration was 0.46×10^{-6} M and the highest was 8.4×10^{-6} M. The results can be considered satisfactory because the lowest values are not too far from the expected 'satisfactory' levels and the highest values do not carry the risk of encephalopathy encountered with unexpectedly high CSF concentrations when doses of 8–33 g/m^2 were used [1, 13]. The mean ratio between MTX concentrations in CSF and serum was close to 3%, which is comparable to figures reported previously by others [6, 18, 19] and by ourselves [12]. This confirms the very low degree of diffusion of MTX from blood to CSF. In the present study, no significant correlation was seen between MTX concentrations in serum and CSF (Fig. 1).We previously observed such a correlation only for the lowest dose tested (0.5 g/m^2) [12]. Evans *et al.*, who used 1 g/m^2 [6], and Borsi and Moe, who gave higher doses (0.5–8 g/m^2) [18], have described a significant correlation for MTX distribution between these two compartments. This discrepancy with the present results may be due to the wider range of values covered by the latter study (serum: 10^{-6} to 10^{-3} M, CSF: 10^{-7} to 10^{-5} M) as opposed to our much narrower range (Table 2); the scattering of data points was comparable in the two studies. Under these conditions, the larger the range of values covered, the higher the probability that an underlying correlation will be seen. Borsi and Moe [18] made the interesting observation that older children had significantly higher CSF MTX concentrations when given a dose between 6 and 8 g/m^2. In the present study, individual CSF MTX concentrations were analyzed as a function of patient age. Although the relationship we found tended to confirm that CSF MTX passage is proportional to patient age, this relationship was not statistically significant ($P < 0.09$). Interestingly, coadministration of Arac-C with MTX did not modify CSF penetration of MTX. Following the report by Lankelma *et al.* [20] of a modification of CSF MTX efflux during repeated IT treatment, the behavior of CSF MTX steady-state concentrations was analyzed from one cycle to another. Mean CSF MTX levels remained stable from the first to the fourth cycle (Table 3). In a recent study [21] using a similar treatment protocol (MTX at 2.5 g/m^2), we noted an increase from cycle to cycle in CSF 5-methyl-tetrahydrofolate (5-MTHF), an active metabolite of folinic acid given for MTX rescue. Although the drug ratio in this case was favorable to MTX, this progressive CSF accumulation of 5-MTHF as opposed to constant CSF MTX concentrations may have a negative effect on the local action of the antimetabolite, and may warrant reappraisal of folinic acid rescue in terms of both dose and duration of administration, at least for the treatment of ALL by MTX.

Based on the findings of this multicenter study, 24 h i.v. infusions of MTX at a dose of 5.0 g/m^2 may be potentially effective for prophylactic CNS treatment of childhood ALL. The addition of IT MTX does not appear justified because almost all cycles demonstrated satisfactory MTX concentrations in CSF.

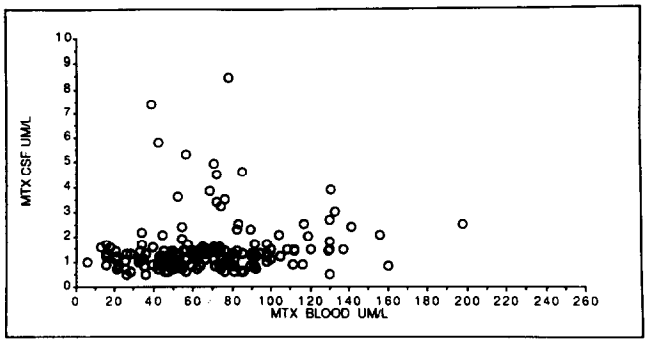

Fig. 1. Scattergram for individual serum/CSF MTX concentration points. The relationship was CSF-MTX (μM) = 0.005 MTX (μM) + 1.184, $r = 0.147$; analysis of variance: F-test = 3.56, DF = 192, $P = 0.061$.

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Early Diagnosis of Spinal Epidural Metastases Using Out-patient Computed Tomographic Myelography

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Twenty patients with known malignancies, back pain, abnormal roentgenograms of the spine, and normal neurological examinations were evaluated by outpatient computed tomographic (CT) myelography to determine the presence and extent of epidural tumor. Spinal CT following the intrathecal administration of low doses of water soluble contrast agents provided high quality diagnostic information. Three patients experienced adverse effects from this procedure which were mild and easily managed in the outpatient setting. Epidural tumor was identified in 15 of 20 (75%) patients. Patients were followed for 9–27 months following myelography. The 14 patients with epidural tumor treated with local radiation experienced pain relief and only one of these patients developed signs or symptoms of recurrent epidural tumor in the treated site. This study documents the high incidence of epidural tumor in selected patients without neurological deficits and the excellent palliative results of non-emergent, carefully planned radiation therapy. It also demonstrates that high resolution CT myelography can be performed safely in an outpatient setting in patients at high risk for epidural tumor. Outpatient myelography facilitates the early diagnosis of epidural tumor and provides needed information on the extent of the tumor for radiation treatment planning while conserving health care resources. For these reasons, outpatient CT myelography should be considered in selected patients with cancer who are at high risk for epidural metastases.
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