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Effect of Dose and Repeat Intravenous 24 hr Infusions of Methotrexate on Cerebrospinal Fluid Availability in Children with Hematological Malignancies

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Abstract—*This pharmacokinetic study examined the relationship between methotrexate (MTX) dose and drug concentrations in blood and cerebrospinal fluid (CSF) during repeated* 24 hr *infusions. Two regimens were used: an intermediate dose (ID) of* 0.5 g/m^2 (7 *patients*, 23 *cycles) and a high dose (HD) of* 2.5 g/m^2 (8 *patients*, 39 *cycles*).

Inter-patient variability in the drug concentration was apparent in serum and CSF for both doses. The dispersion was particularly wide in CSF for HD MTX. Considering median values, serum and CSF MTX were linked to dose escalation. Individual CSF/serum drug ratios were not modified by the dose (1.1% *for ID MTX versus* 1.4% *for HD MTX*). *A potentially cytotoxic drug level in CSF* (10^{-6} M) *was never obtained for ID MTX cycles, but was achieved in* 44% *of HD MTX cycles: for HD MTX, this corresponded to* 88% *of patients* (7/8). *Total body clearance did not modify the degree of CSF MTX passage. A positive, significant correlation* ($r = 0.62$, $P < 0.05$) *was observed for ID MTX between individual serum and CSF MTX; no such relationship was seen with HD MTX. Individual cycle-to-cycle variations in the MTX concentration were particularly marked in CSF and for HD MTX, without strict concordance with blood levels.*

INTRODUCTION

CNS INVOLVEMENT in acute lymphatic leukemia (ALL) and non-Hodgkin's lymphoma (NHL) is a complication with a high rate of morbidity and mortality [1]. Chemoprophylaxis by methotrexate (MTX) is an alternative to cranial irradiation in children with ALL [2], especially since radiotherapy is known to promote leukoencephalopathy in children administered intravenous (i.v.) [3] or intrathecal (i.t.) MTX [4]. Radiotherapy, however, allows precise determination of the cranial dose delivered; it is harder to obtain uniform, cytotoxic drug concentrations in CSF with i.v. or i.t. MTX. Because i.v. MTX administration is hampered by poor CSF penetration [5–7], i.v. MTX treatment at conventional doses is ineffective for the control of CNS involvement [8]. Co-administration of i.t. MTX has been proposed as a means of obtaining more consistent CSF MTX concentrations [9], but the resultant overexposure is not uniform, and does not guarantee adequate drug distribution throughout the entire CSF space [10].

The use of a sufficiently high dose of i.v. MTX has been suggested as a means to obtain potentially cytotoxic CSF drug levels (10^{-6} M or more) [11]. Recent data [12] have reported achievement of remission for meningeal leukemia with high dose i.v. MTX. Evans *et al.* have established a concentration–effect relation for high dose MTX in childhood ALL [13]. This pharmacokinetic study more thoroughly examines the relationship between the MTX dose (0.5 g/m^2 vs. 2.5 g/m^2) and consecutive individual drug levels in serum and CSF. The effect of repeat treatment on these pharmacokinetic parameters has been analysed.

MATERIALS AND METHODS

Table 1 describes the 15 patients (14 ALL, 1 lymphoblastic T lymphoma) studied; none had any evidence of CNS involvement at the time of MTX treatment. For all patients and all cycles, MTX

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Table 1. Study population

Patient	Age	Sex	Type of cancer	Treatment protocol	No. of cycles
1	10	M	ALL	0.5 g/m²(a)	4
2	6½	F	ALL	0.5 g/m²(a)	3
3	10½	F	ALL	0.5 g/m²(a)	2
4	4½	M	ALL	0.5 g/m²(a)	4
5	3½	M	ALL	0.5 g/m²(a)	4
6	3½	M	ALL	0.5 g/m²(a)	3
7	5	F	ALL	0.5 g/m²(a)	3
8	9	F	ALL	2.5 g/m²(b)	1
9	4½	M	ALL	2.5 g/m²(b)	4
10	13	M	NHL	2.5 g/m²(c)	8
11	19	M	ALL	2.5 g/m²(b)	3
12	5	F	ALL	2.5 g/m²(b)	4
13	11½	F	ALL	2.5 g/m²(b)	4
14	8	F	ALL	2.5 g/m²(b)	5
15	4	M	ALL	2.5 g/m²(d)	10

M, Male; F, female; ALL, acute lymphocytic leukemia; NHL, non-Hodgkin's lymphoma.

(a), (b) Sequence interval therapy of BFM protocol from CLCG EORTC group including ID or HD MTX plus age-dependent IT MTX (see Materials and Methods). (a) Protocol 58 831: 0.5 g/m²/2 weeks × 4. (b) Protocol 58 832: 2.5 g/m²: 2 weeks × 4; (c) Protocol of Wollner *et al.* (*Cancer* 1979, **44**, 1990) modified: protocol of the French Society for Pediatric Oncology. HD MTX (2.5 g/m²), *idem* (b) on days 10, 24, 32, 47, 60 and during consolidation until a total of 10 HD MTX. (d): (b) plus, at the end of consolidation phase, HD MTX: 2.5 g/m²/2 weeks × 4 and every 3 months × 4 until 12 HD MTX total.

(Ledertrexate, Lederle, France) was administered i.v. as follows: 10% of the dose in 1 hr and 90% in 23 hr. Forced diuresis providing 3 l./m²/24 hr of 5% glucose in water with $NaHCO_3$ 60 meq/l and KCl 20 meq/l was started 12 hr before MTX administration; this infusion was continued for 48 hr afterwards. Urinary pH was monitored and maintained at ≥ 7, if necessary with supplementary $NaHCO_3$. Leucovorin rescue (30 mg/m²) was given both i.v. (6 hr after the end of MTX infusion) and per os (15 mg/m², 7 times every 6 hr). Two different MTX doses were tested: an intermediate dose (ID) of 0.5 g/m² (7 patients, 23 cycles) and a high dose (HD) of 2.5 g/m² (8 patients, 39 cycles). Details are given in Table 1. A total of 62 cycles were analysed. CSF (1–2 ml) was obtained 8 hr after the start of treatment and immediately before i.t. administration of MTX (6–12 mg depending on patient age). A blood sample was obtained systematically at the same time as lumbar puncture. Various authors [9, 10, 14] who have used prolonged i.v. MTX infusions have reported obtaining stable CSF drug levels from 2–4 hr until the end of infusion; CSF samples obtained 8 hr after the start of treatment can thus be considered representative of the drug level reached in CSF during infusion. After 24 hr infusion, a blood sample was also taken to

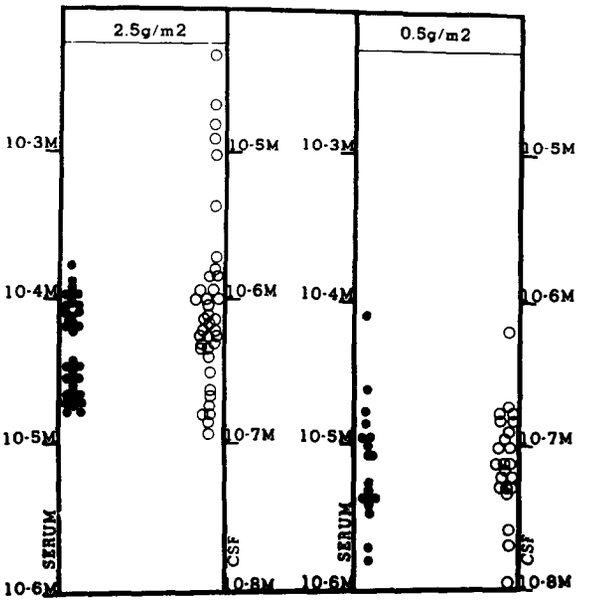

Fig. 1. Respective MTX concentrations in CSF and serum as a function of dosage.

determine total body clearance, using the formula:

$$Cl\ (ml/min/m^2) = \frac{Ko(mg.min/m^2}{C_{SS}(mg/ml)} \text{ where}$$

K_0 = i.v. MTX infusion rate and

C_{SS} = blood MTX after 24 hr i.v. infusion.

Evans *et al.* [9] have reported obtaining comparable MTX blood levels after 24 hr infusions with or without i.t. MTX (12 mg/m²), and C_{SS} was therefore not significantly influenced by MTX efflux from CSF due to the i.t. push. A sensitive and specific immunoenzymatic method [15] was used for MTX assays.

RESULTS

Figure 1 shows the respective distributions of MTX levels for coupled samples of CSF and serum at the two drug doses. Interpatient variability is apparent in both serum and CSF and both doses. Variation was particularly wide in CSF for HD MTX. Table 2 provides a synthesis of results. On the basis of median values, serum and CSF MTX were globally linked to dose escalation; however, CSF MTX tended to increase out of proportion to the dose. Individual drug ratios between CSF and serum were comparable for ID MTX (1.1%) and HD MTX (1.4%). As concerns achievement of an adequate, potentially cytotoxic drug level in CSF (10^{-6} M), none of the ID MTX cycles reached this threshold whereas 44% (17/39) of HD MTX cycles did.

In this last group, MTX clearance values for cycles with CSF MTX ≥ 10^{-6} M were not statistically different from those with CSF MTX < 10^{-6} M; median and extreme values (ml/min/m²) were, respectively: 69 (18–384) and 55 (25–192). As concerns the association between

Table 2. Serum and CSF MTX levels

	MTX serum*	MTX CSF	CSF/serum	Percentage of cycles with CSF MTX $\geq 10^{-6}$ M
ID MTX	7.1×10^{-6} M†	8×10^{-8} M	1.1%	
0.5 g/m²	1.6×10^{-6}–8.8×10^{-5} M (18 cycles, 6 patients)	1×10^{-8}–1×10^{-6} M (23 cycles, 7 patients)	0.1–6.9% (18 cycles, 6 patients)	[0%] (0/26)
	$P < 0.01$	$P < 0.005$	NS	
HD MTX	3.5×10^{-5} M	6.0×10^{-7} M	1.4%	44%
2.5 g/m²	1.1×10^{-5}–1.7×10^{-4} M (39 cycles, 9 patients)	3×10^{-8}–4.8×10^{-5} M (39 cycles, 9 patients)	0.1–60% (39 cycles, 9 patients)	(17/39)

*Sample obtained 8 hr after the start of treatment, at the same time as puncture.
†Median value, extremes (number of cycles, number of patients).
Statistical evaluation by the Mann and Whitney test.

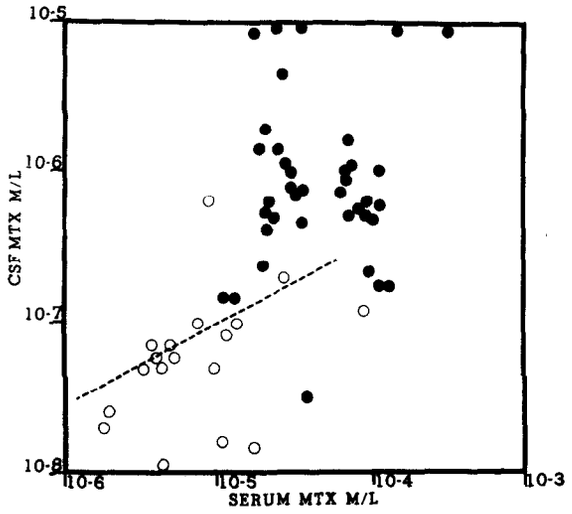

Fig. 2. Relationship between concomitant MTX levels in CSF and serum for all cycles and all patients. Black points: MTX 2.5 g/m², no correlation. Open circles: MTX 0.5 g/m², regression line y = a + bx, r = 0.62, P < 0.05, a = −0.57, b = 0.52 *with* y = *log MTX* × 10^{-6} M *in CSF and* x = *log MTX* × 10^{-8} M *in serum.*

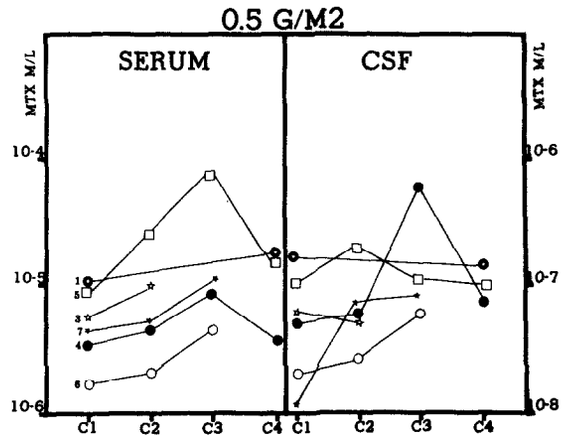

Fig. 3. Individual profile of MTX levels: evolution from cycle to cycle for a dose of 0.5 g/m². *Figures indicate patients referenced in Table* 1.

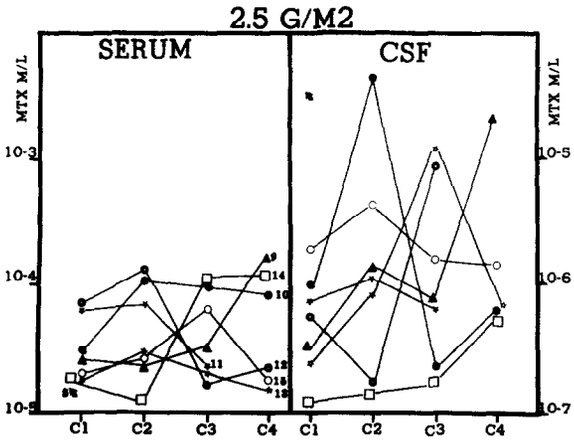

Fig. 4. Individual profile of MTX levels from cycle to cycle for a dose of 2.5 g/m². *Figures indicate patients referenced in Table* 1. *For patients* 10, 14, 15 *only the first* 4 *cycles are represented.*

serum and CSF drug concentrations at 8 hr, a positive and significant correlation ($r = 0.62$, $P < 0.05$) was noted for ID MTX. No such correlation was observed for HD MTX (Fig. 2). Serial drug levels in CSF and serum during the treatment course are shown in Figs 3 and 4. Intra-individual variations with time were more marked in CSF than in serum. Cycle-to-cycle modification in serum MTX were not closely associated with parallel variations in CSF. The most striking changes concerned CSF MTX during HD MTX: for 7/8 patients (88%), a potentially cytotoxic level (10^{-6} M) was obtained in at least one cycle per patient.

DISCUSSION

This study was performed to obtain additional knowledge about MTX CSF passage as a function of a sufficiently wide i.v. dose range (0.5 vs. 2.5 g/m²) and duration of therapy. This information is potentially useful because chemotherapeutic control of CNS involvement by MTX in ALL and lymphoma patients may depend on obtaining an adequate cytotoxic level of around 10^{-6} M [11].

Because intermediate dose MTX (500–1500 mg/m^2) rarely succeeds in obtaining such levels in the CNS [16, 17], adjuvant use of i.t. MTX has been suggested. Although the resultant increase in the drug concentration is significant [9, 16, 17], this exposure may not be uniform because, following i.t. administration of MTX, distribution throughout the different CSF compartments is variable and thus unsatisfactory [10]. Moreover, human error in setting the i.t. MTX dose can have severe neurologic consequences [18]. By contrast, systemic MTX results in homogeneous diffusion throughout the CSF [3], a pharmacological prerequisite for rational prophylactic or curative chemotherapeutic meningeal therapy. The problem lies in poor drug penetration of the CSF. We agree with previous workers who have reported CSF/serum MTX ratios of around 1% during steady state i.v. infusions [16]. The present data confirm the wide interpatient variability of CSF MTX during i.v. infusion [9, 14, 16,17]; in addition, these findings indicate that this variability is amplified by the dose increase (Fig. 1). However, considering median values, serum and CSF MTX both rise as a function of the dose (Table 2). We agree with Evans *et al.* [9], who demonstrated a good correlation between individual MTX levels in CSF and blood. These authors found an r value of 0.63 for 24 hr infusion of 1000 mg/m^2: we obtained a comparable value ($r = 0.62$) with 500 mg/m^2. The CSF MTX concentration of a patient during infusion thus appears to be relatively well predicted by the corresponding level in blood. Unfortunately, this relationship is not maintained at higher doses: no correlation has been found between individual serum and CSF MTX during HD MTX (Fig. 2). As a corollary, the degree of individual CSF drug passage was not linked to total body clearance of MTX.

MTX efflux from CSF is governed by both passive and active transport mechanisms [19]. The unpredictably high levels observed for CSF MTX might be due to saturation of active transport from CSF. Considering individual variations in serum and CSF drug concentrations from cycle to cycle, a lack of stability was apparent, particularly in CSF during HD MTX. Lankelma *et al.* [20] have described a modification in individual kinetics of CSF MTX efflux during repeated i.t. treatment. The possibility that CSF drug permeability may be time-dependent could partially explain our observations. Repeat folinic acid administration following MTX treatment may eventually lead to CSF accumulation of folinic acid and/or its metabolites and thus compete with MTX antitumor effect. Such a point merits further investigation. All cycles considered together, none of the ID MTX cycles but 44% of the HD MTX reached the potentially cytotoxic CSF level of 10^{-6} M. This concentration threshold must be considered with caution because it has been established *in vitro* from adult and not pediatric ALL cell lines [11]; furthermore this study did not deal with the duration of exposure to MTX.

Treatment follow-up revealed that 88% of patients (7/8) receiving HD MTX had at least one cycle with a "satisfactory" CSF MTX level. From a pharmacokinetics standpoint, we thus feel that 24 hr i.v. infusions of HD MTX (2.5 g/m^2 or more) may be potentially effective for curative or prophylactic treatment of CNS involvement or hematological malignancies in children. They do not obligatorily require adjuvant i.t. MTX. However the blood levels obtained with these MTX doses cannot be considered indicative of individual drug passage into CSF.

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