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ORIGINAL ARTICLE

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Pharmacokinetics and toxicity of high-dose intravenous methotrexate in the treatment of leptomeningeal carcinomatosis

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Abstract *Purpose*: To evaluate the pharmacokinetics and toxicity of high-dose intravenous (i.v.) methotrexate (MTX) with leucovorin in patients with meningeal carcinomatosis. *Methods*: Of 16 eligible patients entered on this study, 13 with meningeal carcinomatosis from breast cancer, lung cancer, or osteosarcoma were treated with MTX at loading doses of 200–1500 mg/m^2, followed by a 23-h infusion of 800–6000 mg/m^2. Three patients without meningeal disease were also treated and the cerebrospinal fluid (CSF) MTX concentrations were compared in patients with and without central nervous system (CNS) disease. *Results*: Patients without CNS disease had lower CSF MTX concentrations relative to the plasma MTX levels than those with CNS disease, who all had CSF MTX concentrations above the target cytotoxic concentration (1 μM). The CSF MTX concentrations correlated better with the free and the total plasma MTX concentrations than with the doses. The mean half-life of CSF MTX was 8.7 ± 3.4 h. The mean plasma clearance of MTX was not significantly different in patients with CNS disease (84 ± 41 ml/min per m^2) versus without CNS disease (59 ± 38 ml/min per m^2). All toxicities were grade 2 or less except grade 3 hematologic toxicity. No patient had an objective response in the CSF. *Conclusion*: This trial demonstrates that potentially cytotoxic CSF MTX concentrations (> 1 μM) are delivered safely by i.v. infusion, a less invasive and better distributed CSF therapy compared with intrathecal MTX. Because of the excellent pharmacokinetics and toxicity, high-dose i.v. MTX should be evaluated at a loading dose of 700 mg/m^2 and a 23-h infusion of 2800 mg/m^2 with leucovorin in less heavily pretreated patients with carcinomatous meningitis.

Key words Methotrexate · Leptomeningeal carcinomatosis

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Introduction

Meningeal carcinomatosis, defined as diffuse or multifocal leptomeningeal metastasis from solid tumors, is most commonly associated with disseminated breast or lung cancer [18, 22]. The most common therapy consists of intrathecal or intraventricular administration of methotrexate (MTX) as a single agent and radiation therapy to symptomatic sites. The best responses to this treatment have been achieved in patients with breast cancer, with several studies showing a greater than 50% response rate and a median survival after diagnosis of approximately 2 to 6 months [22, 23]. Most patients die of disseminated disease, but nearly all have progression of neurologic involvement at the time of death [22].

The use of intravenous (i.v.) MTX for the treatment of meningeal malignancy has been evaluated sparingly in the past and principally in patients with hematopoietic malignancies. High-dose i.v. MTX combined with leucovorin rescue has been examined for the treatment of non-Hodgkin's lymphoma involving the central nervous system (CNS) and meninges [20] as well as in the treatment of leukemic meningitis in pediatric acute lymphocytic leukemia [1]. The safety of this approach in these patient populations has been well documented. In one study in patients with extensive small-cell lung cancer without established carcinomatous meningitis, the use of high-dose i.v. bolus MTX was compared with low-dose i.v. MTX and no difference was found in the rate of

CNS relapse [10]. One recent study [8] of high-dose i.v. MTX in patients with non-leukemic leptomeningeal cancer did suggest improved cytologic clearing of the CSF and improved survival with this therapy compared with a non-randomized patient population treated with intrathecal MTX, but half of the patients treated with i.v. MTX had lymphoma, which would be expected to respond better than solid tumors.

The theoretical advantage of i.v. versus intrathecal therapy for meningeal carcinomatosis would be the achievement of cytotoxic drug levels in all parts of the CNS. In contrast, intrathecal therapy diffuses through the cerebrospinal fluid (CSF) counter to bulk flow and thus is less likely to distribute evenly throughout the CNS. Slow excretion of MTX from the CSF would allow for prolonged exposure to cytotoxic levels of MTX (1 μM) [13] while peripheral leucovorin rescue could prevent potential bone marrow and gastrointestinal toxicities of prolonged exposure to MTX due to slow egress from the CSF [5, 15, 19].

Balis et al. [1] have utilized a regimen of high-dose i.v. MTX with leucovorin rescue in children with meningeal disease from acute lymphoblastic leukemia as a means of achieving and maintaining a therapeutic MTX concentration throughout the CNS without the need for concomitant administration of intrathecal MTX. The MTX was administered as a 1-h loading dose at 6 g/m^2 followed by a 23-h i.v. infusion at 1.2 g/m^2. The loading dose followed by a continuous infusion produced steady-state concentrations (C_{ss}) of MTX in both the plasma and the CSF from 6 h into the infusion until the end of the infusion [16]. All 20 patients responded to the regimen (80% complete, 20% partial). Toxicities consisted of liver function test abnormalities, neutropenia, and mucositis, all of which were transient and resolved completely. The mean CSF level of MTX obtained at steady-state (36 μM) was well above the reported cytotoxic concentration of MTX (1 μM) [24].

In the dose-escalation study reported here, intermediate to high-dose i.v. MTX with leucovorin rescue was administered to adults with meningeal carcinomatosis from solid tumors. The total dose of MTX was divided into a 1-h loading dose (20%) and a 23-h continuous infusion (80%). It was anticipated that the initial dose of MTX could be administered safely as repeated weekly doses and that the higher doses in the escalation scheme would provide concentrations of MTX in the CSF in excess of 1 μM at steady-state, even if the ratio of CSF to plasma MTX were no higher than reported in patients without meningeal disease [6]. MTX levels in the CSF and plasma were followed to analyze the pharmacokinetics in this patient population. The primary objective of the study was to evaluate the tolerance of the subjects to this treatment. Secondary objectives were to evaluate the feasibility of treating patients with repeated weekly courses and to describe the response to this schedule of high-dose i.v. MTX in patients with meningeal carcinomatosis.

Materials and methods

Patient eligibility

Patients were eligible for this study if they had cytologically proven meningeal carcinomatosis. A brain CT scan was required prior to study entry. Patients with recurrent or progressive intracranial metastases or active systemic disease were not excluded from the study. However, if parenchymal CNS metastases or spinal cord compression were present, radiation therapy to those lesions was required before patients were eligible for the study. Patients with incapacitating neurologic deficits attributable to parenchymal brain metastases were ineligible.

Three patients with metastatic malignancies without meningeal carcinomatosis who were felt to have disease which might be responsive to high-dose MTX were treated at the lower dose levels as a control group; their CSF and plasma MTX concentrations were also measured.

Adequate liver function (serum bilirubin less than or equal to 1.5 mg/dl and transaminases not exceeding three times the upper limit of normal) and renal function (creatinine clearance greater than 50 ml/min) were required, as was adequate hematologic function (white blood cell count greater than 3000/μl and platelet count greater than 100,000/μl). Patients with a Karnofsky performance status of less than 50% or a life expectancy of less than 1 month were ineligible.

Patients with "third-space" fluid collections such as ascites or pleural effusion were ineligible, unless those fluid collections could be drained completely prior to treatment with MTX. Prior systemic treatment with MTX was allowed. Concomitant chemotherapy and radiotherapy were prohibited.

All patients entered on this study voluntarily signed a consent form meeting institutional and federal guidelines. This study was approved by the Institutional Review Board of the City of Hope National Medical Center.

Study design and treatment plan

Lumbar puncture was performed prior to each treatment for evaluation of CSF cytology. Treatment was administered in the hospital. Patients received i.v. fluids containing sodium bicarbonate to achieve alkaline diuresis prior to the administration of MTX. At the initial dose level, i.v. MTX was administered as a 1-h loading dose of 200 mg/m^2 followed by a 23-h continuous infusion of 800 mg/m^2. Each cycle consisted of the loading dose and continuous infusion of MTX followed by a minimum of 1 week of observation. The treatment interval (1–2 weeks) depended on recovery from toxicities. Our a priori assumption was that this dose could be safely repeated at weekly intervals, but was unlikely to produce MTX concentrations in the CSF above the known cytotoxic concentration of MTX in vitro (1 μM). Dose escalations in cohorts of patients were planned as approximate doublings of the total dose (loading and continuous infusion) to a maximum of 15 g/m^2. The maximum dose estimate was based on the intention to achieve a range of concentrations in the CSF (1–7 μM) above the cytotoxic concentration of MTX, calculated assuming linear pharmacokinetics and a range of two standard deviations (SD) from the CSF concentrations (mean $\pm$ SD, 0.27 $\pm$ 0.1 μM) reported for patients who had received a total dose of 1 g/m^2 of MTX administered in an identical manner [6]. Table 1 indicates the dose levels actually administered. The MTX dose was not escalated in individual patients.

In the initial four patients (dose level 1A), i.v. leucovorin was started 12 h after the completion of the MTX infusion at a dose of 50 mg/m^2 as an i.v. bolus followed by 25 mg/m^2 every 6 h for four doses, then 12 mg/m^2 every 6 h until the serum MTX level was less than 10^{-7} M. After grade 3 hematologic toxicity was observed following subsequent cycles in two patients at dose level 1A, the dose of leucovorin was increased and the delay between completion of the MTX infusion and the first dose of leucovorin was reduced to 6 h in all patients (dose levels 1B–4). Serum MTX concentra-

Table 1 Dose levels

	Level 1A	Level 1B	Level 2	Level 3	Level 4
MTX loading dose (mg/m^2)	200	200	400	700	1500
MTX infusion (mg/m^2 over 23 h)	800	800	1600	2800	6000
Leucovorin first dose (mg/m^2)	50	200	200	400	400
Leucovorin doses two through five (mg/m^2)	25	100	100	200	200
Leucovorin subsequent doses (mg/m^2)	12	50	50	100	100

tions were obtained daily and leucovorin rescue was continued until the MTX concentration was less than 10^{-7} *M*.

Evaluation of toxicity and efficacy

Treatment was continued until disease progression or the occurrence of any grade 4 toxicity. If lesser toxicities occurred, treatment was delayed for not longer than 28 days until patients once again met all eligibility criteria. Toxicities were graded according to the NCI Common Toxicity Scale. Complete blood counts, platelet counts, and blood chemistry profiles were obtained weekly. Lumbar puncture for cytology was obtained prior to each treatment.

Patients must have completed at least one cycle of protocol therapy to be evaluable for toxicity. To be evaluable for response, patients must have completed four doses of MTX, have had progressive disease, or have been unable to continue therapy on protocol because of toxicity. A response was defined as two sequential negative CSF cytologies obtained at least 1 week apart in addition to an improved neurologic status.

Pharmacokinetic analysis

Pretreatment CSF was obtained during the lumbar puncture performed to determine CSF cytology. Pretreatment plasma was obtained at the same time. Plasma and CSF were then obtained between hour 18 and 24 of the MTX infusion. Previous studies had indicated that plasma and CSF concentrations reach steady-state by 6 h when MTX is administered as a loading dose followed by a continuous infusion [16]. In five patients with positive CSF cytology and one patient found to have negative cytology upon review, additional CSF and plasma samples were obtained 24 and 48 h after the end of the MTX infusion.

Total MTX concentrations in the plasma and CSF were determined against an aqueous standard by HPLC with UV detection at 303 nm of samples (both controls and unknowns) extracted with trichloroacetic acid (TCA) as previously described [17]. To determine the concentration of free MTX in plasma, 99.9% protein-free ultrafiltrates were obtained by centrifuging fresh plasma samples for 20 min at 1500 *g* in Amicon Centrifree micropartition devices (#4104, 1-ml capacity) in a Sorvall SS34 fixed-angle rotor centrifuge. No more than 200 µl of ultrafiltrate was obtained from each 1-ml sample. The MTX concentrations in the ultrafiltrates were determined by the same HPLC method used for the TCA extracts. Controls to determine the recovery of MTX in the TCA extracts were processed in the same manner as unknown samples after spiking individual pretreatment plasma and CSF samples with 5 µ*M* MTX. The mean ± SD recovery from plasma was 62 ± 6% ($n = 8$), which was used to correct the total plasma MTX concentrations. The CSF concentrations were not corrected because the recovery from CSF was quantitative (109 ± 7%, $n = 9$). To obtain within-day ($n = 10$) and between-day (triplicate analyses on each of 3 days) coefficients of variation (CV), a pooled plasma TCA extract, a pooled plasma ultrafiltrate, and a pooled CSF TCA extract were analyzed multiple times as indicated. All CV were less than 5%.

Plasma clearances (CL_p) were calculated for individual patients using the equation CL_p = (dose rate of MTX)/(C_{ss} of total plasma MTX). The half-life ($t_{1/2}$) of MTX in the CSF was estimated in a subset of the patients from the slope of $t_{1/2}$(MTX) versus time using the C_{ss} obtained near the end of the infusion and one or two daily samples after the end of the infusion. (In one patient, the MTX was not detectable at 48 h; in one patient, no sample was obtained at 48 h.)

Statistical analysis

Analyses of correlations between the MTX concentration in the CSF and the MTX dose, its total concentration in plasma, and its free concentration in plasma used logarithmic scales. For repeated measurements, a generalized estimating equation method was used to allow for the dependence of multiple observations from the same patient [14]. (Analyses using ordinary linear models of the mean values from each patient gave similar results.)

Results

Patient characteristics

Of 16 eligible patients entered on this study, 13 had positive CSF cytologies and 3 were known to have negative CSF cytologies prior to study entry and served as controls for the ratio of CSF to plasma MTX concentration in patients with an intact blood-brain barrier. One additional patient with small-cell lung cancer was enrolled in the treatment group with positive cytology but was found to be ineligible when the initial CSF cytology was reviewed and determined to be negative; this patient was included in the analysis of pharmacokinetic data.

Of the 13 patients with carcinomatous meningitis, 9 had breast cancer, 2 had small-cell lung cancer, and 2 had adenocarcinoma of the lung. Of the 3 eligible patients with negative CSF cytologies, 2 had breast cancer and 1 had osteosarcoma. The demographic features of the eligible patients are shown in Table 2.

Of the 16 eligible patients, 15 had received prior systemic chemotherapy (1 as neoadjuvant treatment, 3 as adjuvant therapy, 6 for metastatic disease, and 5 as both adjuvant and metastatic therapy), and 10 had received prior radiation therapy. None of the patients had received prior intrathecal therapy. Seven of the breast cancer patients with positive CSF cytology had previously received MTX, but not high-dose MTX: 4 as adjuvant therapy, 2 for metastatic disease, and 1 for both adjuvant treatment and for metastatic disease. Five of these previously-treated patients were considered refractory to MTX; 3 developed progressive disease while receiving a MTX-containing regimen; 1 progressed within 3 months and another within 11 months of stopping MTX-containing therapy. The patients with lung cancer or osteosarcoma had not previously been treated with MTX.

Toxicity

The toxicity assessment included the one ineligible patient who was evaluable for toxicity. Only one patient

Table 2 Patient characteristics

	Positive CSF cytology	Negative CSF cytology
No. of patients entered	13	3
Age (years)		
Median	57	54
Range	30–67	51–58
Karnofsky performance status		
Median	60	80
Range	50–90	60–90
Sex		
F	9 (69%)	2 (67%)
M	4 (31%)	1 (33%)
Primary Site		
Breast	9	2
Lung (small-cell)	2	0
Lung (adenocarcinoma)	2	0
Osteosarcoma	0	1
Sites of metastasis (no. of patients, percentage)		
Bone	7 (54%)	1 (33%)
Lung	3 (23%)	2 (67%)
Soft tissue	2 (15%)	1 (33%)
Adrenal gland	2 (15%)	0
Lymph nodes	1 (8%)	1 (33%)
Liver	1 (8%)	0
Parenchymal brain	1 (8%)	0

(with negative CSF cytology) developed grade 3 toxicity (grade 3 neutropenia and thrombocytopenia at dose level 2) on the first cycle of therapy. All other toxicities were grade 2 or less. There was no neurotoxicity attributable to protocol treatment. No delayed or cumulative toxicity occurred.

Extent of treatment and response to therapy

The number of cycles administered to each cohort of eligible patients is listed in Table 3. The median number of treatment cycles was two (five patients received one cycle, 4 received two cycles, 3 received three cycles, and 1 each received: four cycles, five cycles, seven cycles, and ten cycles.

Grade 3 leukopenia occurred with later cycles in two patients treated at dose level 1A. Therefore, the decision was made to start the leucovorin at 6 h rather than at 12 h after the MTX, and to increase the leucovorin dose at that level and thereafter even though later cycles were not considered in the determination of dose-limiting toxicity. Two more patients were treated with the same dose of MTX and the higher doses of leucovorin (dose level 1B) in order to expand the entire cohort receiving that dose of MTX to a total of six patients. Subsequently, the dose escalation of MTX resumed. The three patients treated at dose level 2 include the ineligible patient who was evaluable for toxicity.

Table 3 Number of cycles of high-dose MTX

	Dose level					Total
	1A	1B	2	3	4	
Patients with positive CSF cytology						
Eligible patients	4	2	2	3	2	13
Cycles	12	4	2	12	10	40
Patients with negative CSF Cytology						
Eligible patients		2	1			3
Cycles		6	2			8

Because the CSF to plasma MTX ratios were higher than in patients without meningeal disease, we found that the C_{ss} of MTX in the CSF were consistently greater than concentrations reported to be cytotoxic to MTX-sensitive neoplastic cells in vitro [24]. After this pharmacologic result was achieved, dose escalation was stopped at a level which did not produce dose-limiting toxicities. In the 16 evaluable patients, there were no objective responses, defined as two sequential negative CSF cytologies with an improvement in the neurologic status.

Pharmacokinetics

The CL_p of MTX was highly variable, ranging from 26 to 184 ml/min per m^2 (Table 4). In patients with CNS disease the mean ± SD was 84 ± 41 ml/min per m^2 ($n = 11$). Although the mean was lower in the limited number of patients without CNS disease, the difference was not significant.

Although there was a correlation between the CSF MTX C_{ss} and the doses of MTX (Fig. 1), the CSF MTX C_{ss} were better correlated with both the total (Fig. 2) and the free (Fig. 3) plasma MTX C_{ss}. The patients without CNS disease had the lowest CSF MTX concentrations when adjusted for either the total or the free plasma concentrations. The difference was highly significant: the probability that the three patients with negative cytology would, by chance, have the three lowest or highest adjusted levels was 0.0017. From these data, a model for the CSF MTX concentration as a function of the free plasma concentration and CNS disease (no = 0, yes = 1) is:

$$\ln(\text{CSF } C_{ss}) = -2.7 + 1.2 \cdot \ln(\text{free plasma } C_{ss}) + 0.94 \cdot (\text{CNS}) + \varepsilon$$

where the residual SD of ε is 0.25. Variation of $2 \times$ SD on a log scale implies that it is not uncommon for C_{ss} CSF to vary from 0.6 to 1.6 times the values predicted from the C_{ss} free. The dose, the total plasma C_{ss}, and the free plasma C_{ss} were highly colinear. Neither the dose nor the total plasma C_{ss} added significant information to a model that included the free concentration.

In the patients with CNS disease, the $t_{1/2}$ of MTX in the CSF ranged from 4.6 to 12.5 h, and the mean ± SD was 8.7 ± 3.4 h (Table 4).

Table 4 Pharmacokinetic parameters (for patients in whom data was collected on multiple treatment cycles, the mean steady-state data is shown)

	Dose level	Plasma			CSF		CSF/plasma total[f]
		C_{ss} total (μM)[a]	C_{ss} free (μM)[b]	CL_p (ml/min/m^2)[c]	C_{ss} CSF (μM)[d]	$t_{1/2}$ CSF (h)[e]	
CNS disease	1	14.7		87	7.9		0.537
	1	6.9		184	2.2		0.317
	1	13.7		93	5.3		0.386
	1	12.8	3.5	100	1.2		0.092
	1	15.2	9.0	84	1.9	12.5	0.127
	1	27.0	8.2	47	2.1	4.6	0.080
	2	46.8	22.0	55	11.2	7.8	0.240
	2	48.7		52	3.1	11.9	0.064
	3					6.8	
	3	55.3	25.7	81	9.2		0.167
	3	43.2	20.4	103	5.9		0.144
	4	290.0	103.6	34	59.7		0.207
Mean ± SD				84 ± 41		8.7 ± 3.4	0.215 ± 0.147
No CNS disease	1	12.6	5.2	101	0.5		0.039
	2	51.4	20.7	50	2.7	9.1	0.053
	2	98.8	20.6	26	3.0		0.030
Mean ± SD				59 ± 38			0.041 ± 0.011

[a] Total plasma MTX concentration at steady-state, obtained between 12 and 24 h
[b] Ultrafilterable plasma MTX concentration at steady-state
[c] Plasma clearance (dose rate/C_{ss} total)
[d] CSF concentration at steady-state
[e] Postinfusion half-life in CSF
[f] C_{ss} CSF/C_{ss} total plasma

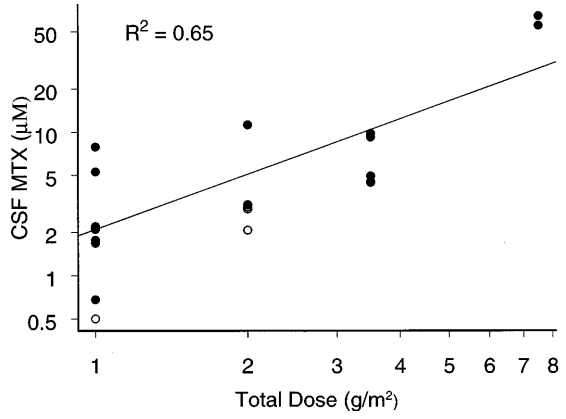

Fig. 1 Association between MTX concentration in CSF and the total MTX dose (sum of the loading dose and the infusion dose). Data were obtained from 11 patients with meningeal carcinomatosis (●) and 3 patients without (○), each treated on one or more occasions. The line indicates the regression on the data from the patients with meningeal carcinomatosis. A generalized estimating equation was used for multiple observations from the same patient

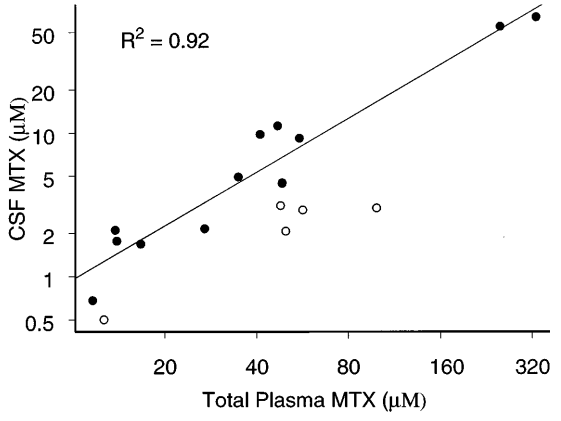

Fig. 2 Association between MTX concentration in CSF and total MTX in plasma. Data were obtained from 7 patients with meningeal carcinomatosis (●) and 3 patients without (○), each treated on one or more occasions. The line indicates the regression on the data from the patients with meningeal carcinomatosis. A generalized estimating equation was used for multiple observations from the same patient

Discussion

The results of this study demonstrate that high-dose MTX administered over 24 h with early high-dose i.v. leucovorin rescue is a well-tolerated regimen which results in high CSF MTX levels in patients with meningeal carcinomatosis. Toxicities were mild, all grade 2 or less, except in one patient who developed grade 3 leukopenia, neutropenia, and thrombocytopenia at dose level 2. Of note is that no significant neurologic toxicity developed, and no cumulative toxicity was observed. The study was closed at a dose which did not produce dose-limiting toxicities because all of the CSF MTX concentrations in patients with meningeal carcinomatosis were above the minimum target value of 1 μM. No patient cleared his/her CSF cytology after high-dose i.v. MTX therapy. However, five of the nine patients with breast cancer were refractory to standard MTX therapy. A high level of MTX resistance in this patient population is the most likely explanation for the lack of response in this study despite achieving high levels of MTX in the CSF.

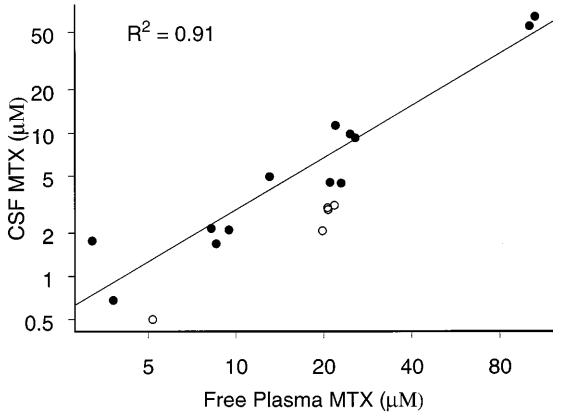

Fig. 3 Association between MTX concentration in CSF and free MTX in plasma. Data were obtained from 7 patients with meningeal carcinomatosis (●) and 3 patients without (○), each treated on one or more occasions. The line indicates the regression on the data from the patients with meningeal carcinomatosis. A generalized estimating equation was used for multiple observations from the same patient

Because the levels of MTX achieved in the CSF were > 1 μM, i.v. MTX administered in this manner might be of benefit in less heavily pretreated patients. I.v. administration of MTX provides more uniform drug exposure, avoids the need for lumbar punctures, and offers a therapeutic approach for patients in whom repeated CSF access is a problem, thus allowing less-invasive administration of a potentially effective therapy [1, 8, 19].

Shapiro et al. [19] have demonstrated a lack of consistent CSF distribution of intrathecal MTX administered via lumbar puncture. Peak ventricular MTX CSF levels obtained via Ommaya reservoir following lumbar administration of identical doses of intrathecal MTX resulted in interpatient variability of greater than an order of magnitude. The CSF MTX concentrations in the patients treated with lumbar puncture fell to subtherapeutic levels (< 1 μM) within 24 h. However, when the MTX was administered i.v. over 24 h, potentially therapeutic MTX concentrations were sustained longer throughout the CSF. The i.v. administration of high-dose MTX may offer improved CSF distribution and more prolonged therapeutic MTX levels compared to administration via lumbar puncture.

Several agents have been used to treat meningeal carcinomatosis, including thiotepa, MTX, cytarabine (ara-C), and a depot formulation of ara-C (DepoCyt). Most often the drugs have been administered intrathecally or intraventricularly. These agents have shown some activity, although the response is much lower than in the treatment of meningeal metastasis of leukemias or lymphomas. Intrathecal thiotepa has been compared to intrathecal MTX therapy in the treatment of meningeal carcinomatosis, including patients with lymphoma [9]. Conversion of the CSF cytology to negative occurred in approximately one-third of patients on each treatment arm. However, 75% of patients developed neurologic progression within 8 weeks of initiating therapy. The authors concluded that the efficacy and toxicities of intrathecal MTX and thiotepa are similar, but neither reverses neurologic deficits. The combination of intrathecal MTX and ara-C has been compared with intrathecal MTX alone in patients with meningeal carcinomatosis [12]. The conclusion of the study was that the addition of ara-C does not improve the outcome. DepoCyt releases ara-C slowly, permitting sustained cytotoxic levels in the CSF without frequent dosing [4, 7]. In one study a greater efficacy at a similar level of toxicity was found with intrathecal DepoCyt than with intrathecal MTX in the treatment of patients with meningeal carcinomatosis [4].

As discussed above, i.v. administration of drugs which can penetrate into the CSF is an attractive alternative to intrathecal or intraventricular administration. The lipophilic drug thiotepa distributes into the CSF well [11], but lacks significant activity against solid tumors. Glantz et al. [8] have recently reported a nonrandomized comparison of the response rates and survival durations of patients with meningeal carcinomatosis treated with conventional intrathecal MTX, or with high-dose i.v. MTX (8 gm/m^2 over 4 h). One-half of the patients treated with i.v. MTX had lymphoma and only one had breast cancer, while only one-third of the patients treated with intrathecal MTX had lymphoma. Prior systemic chemotherapy received by these patients, including prior MTX therapy, was not discussed. In another recent report, high-dose i.v. MTX improved survival in patients with primary cerebral lymphomas, reflecting the chemosensitivity of lymphoma to this agent [2]. The patients treated on the trial reported here were heavily pretreated with both chemotherapy and radiation therapy and many had systemic disease considered refractory to MTX. In the study by Glantz et al. [8], cytologic response was defined by clearing of CSF tumor cells 1 month after initiation of treatment. In the study reported here, six patients had a negative cytology on at least one occasion, but none met the study requirement for response of two sequential negative CSF cytologies. The different patient populations, particularly the lack of patients with lymphoma in the current study, and the different response criteria preclude direct comparison of the results of the current study with the results of the previous studies.

It is possible that the high doses of leucovorin used in this trial decreased the tumor response to MTX by rescuing malignant cells. The doses of leucovorin were selected to decrease hematologic toxicity. At the time the study was initiated, hematopoietic growth factors were not available for routine clinical use and it would be difficult to integrate growth factor support into the weekly chemotherapy as administered in this trial. Early in this trial, the dose of leucovorin was increased to allow subsequent courses of MTX to be administered without unacceptable delays. While the administration of weekly doses of MTX was feasible using the higher dose of leucovorin, the dose of leucovorin required was not systematically studied. The optimal amount of

leucovorin to be used in combination with high-dose MTX therapy needs to be explored in further studies to find the minimum dose required to allow for retreatment at the desired interval.

The ratio of CSF MTX concentration to total plasma MTX concentration (0.22 ± 0.15) in our patients with CNS disease was higher than expected from the ratio reported in patients without CNS disease (0.023 ± 0.04) [6], and was higher than the ratio (0.04 ± 0.01) in the limited number of patients on our study with solid tumors, but not CNS disease. Two studies of the CSF to plasma MTX ratio after high-dose i.v. MTX administered as a loading dose followed by a 23-h infusion to children with meningeal leukemia produced different results [1, 16]. In one study, 11 children with overt meningeal leukemia were found to have a mean ratio of 0.157, which was significantly higher than the mean ratio of 0.013 in 49 children who never had evidence of CNS leukemia [16]. The mean ratio during the initial infusion administered to four patients with meningeal leukemia at diagnosis was even higher (0.472). Another study of the treatment of meningeal leukemia with the same high-dose MTX regimen included 13 patients in whom CSF MTX was determined; the mean CSF to plasma MTX ratio in that group of patients was 0.03 [1]. Thus it is not clear whether or not there is a difference between meningeal carcinomatosis and meningeal leukemia with regard to effects on the ratio of CSF to plasma MTX obtained during prolonged continuous i.v. administration of the drug.

The CL_p in this study was similar to the data from children without CNS disease reported by Evans et al. [6] (98 ± 51 ml/min per m^2, $n = 29$), both in regard to the mean and the variability. Although the range was large, the mean and median $t_{1/2}$ in CSF were similar to the value of 7.1 h reported by Ettinger et al. [5] in patients with acute lymphocytic leukemia with and without overt CNS disease. From examination of their data at 24 and 48 h after the MTX was administered, there did not appear to be a difference in the $t_{1/2}$ with and without CNS disease, even though the concentrations in patients with overt CNS disease were tenfold higher. The graphical data presented by Glantz et al. [8] indicate a similar $t_{1/2}$ in the CNS in patients treated with high-dose i.v. MTX, all of whom had overt CNS lymphoma or carcinoma. The $t_{1/2}$ which we observed were somewhat shorter than the range of 12 to 18 h reported by Bleyer et al. [3]. Although limited, our data do not support the conclusion that elevated concentrations of MTX in the CSF of patients with meningeal carcinomatosis were due to slow clearance from either the plasma or the CSF. The most likely explanation is a decreased blood/CSF barrier for MTX in these patients. This alteration may be due to the presence of new, permeable blood vessels in the tumors, or to a breakdown in the barrier between meningeal capillaries and the CSF induced by tumor growth over the leptomeninges [21]. Whatever the mechanism that permits increased distribution of MTX into the CSF in patients with carcinomatous meningitis, it is clear that cytotoxic concentrations of MTX can be obtained safely by prolonged i.v. infusion.

A concentration of 1 μM is a frequent pharmacologic target for MTX because the limited data available suggest that this concentration is cytocidal against MTX-sensitive tumors [24]. Glantz et al. [8] maintained concentrations of MTX >1 μM in the CSF for >48 h in the average subject by i.v. administration of a high dose (8000 mg/m^2) over a short interval (4 h). Since the MTX was administered at a uniform rate over 4 h, neither the serum nor the CSF were likely to have reached steady-state when the mean peak concentrations of MTX (858 μM and 17.1 μM, respectively) were determined.

The same duration of CSF MTX above the 1 μM threshold can be obtained with a lower total dose of i.v. MTX by administering a loading dose and prolonging the infusion to 24 h. Given a $t_{1/2}$ in the CSF of approximately 8 h, a concentration of MTX in the CSF >8 μM at the end of the infusion should maintain concentrations >1 μM for the subsequent 24 h; i.e. >1 μM for a total of 48 h. In the current study, the log-log regression of the CSF C_{ss} versus the dose (Fig. 1) predicts a mean CSF C_{ss} of 12 μM at dose level 3, satisfying this goal in the average patient. However, the lower limit of the 95% confidence interval at this dose is 6.5 μM. Because there is a better correlation of the CSF C_{ss} with the free plasma C_{ss} than with the dose, an alternative strategy to maintain MTX above 1 μM in the CSF for a minimum of 48 h would be to obtain a plasma sample after the first 6 h of the MTX infusion and increase the dose rate, if necessary, to achieve a minimum free plasma MTX concentration of 25 μM, which is highly correlated with a CSF concentration of 8 μM.

Administering MTX at 700 mg/m^2 over 1 h followed by 2800 mg/m^2 over 23 h is expected to produce the same duration of CSF MTX >1 μM in the average subject as reported by Glantz et al. [8]. On that basis, this dose, with a dose adjustment at 6 h (if rapid determination of MTX concentrations is available), is recommended as appropriate for further study in patients with meningeal carcinomatosis whose primary disease is less likely to be resistant to MTX.

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