“Concentration × Time” Methotrexate Via a Subcutaneous Reservoir: A Less Toxic Regimen for Intraventricular Chemotherapy of Central Nervous System Neoplasms


Neurotoxicity associated with intrathecal methotrexate therapy has been shown to correlate with elevated concentrations of the drug in the cerebrospinal fluid as well as with the total cumulative dosage. In our study 19 patients with meningeal leukemia were randomized to receive courses of intraventricular methotrexate via an Ommaya reservoir consisting of either single injections of 12 mg/sq m/dose or a low-dose “concentration × time” (C × T) schedule of 1 mg every 12 hr for 3 days. There were no significant differences between the two treatment groups in the rate of remission induction, the number of relapses, or the durations of remission. The mean (± 1 SD) cumulative methotrexate dose was 66 ± 41 mg/sq m in the C × T group and 173 ± 64 mg/sq m in the 12 mg/sq m/dose group (p < 0.005). Neurologic toxicity occurred in one of the eight patients in the C × T group and in seven of ten patients in the 12 mg/sq m/dose group (p < 0.05). These observations suggest that the C × T dosage schedule is less neurotoxic and equally effective in the treatment of central nervous system leukemia.

Neurotoxicity associated with intrathecal methotrexate has been correlated with the total amount of methotrexate administered and with elevated concentrations of the drug in the central nervous system. In an attempt to improve intrathecal therapy, we devised a “concentration × time” (C × T) regimen that reduced peak methotrexate concentrations in the cerebrospinal fluid and that delivered less total antifolate than conventional dosage regimens. Patients with meningeal leukemia were randomized to receive via a subcutaneous reservoir either courses of low-dose C × T therapy or single injections of 12 mg/sq m. After the first 19 patients were treated, a significantly lower incidence of neurotoxicity was noted in the C × T group and is described in this report.

MATERIALS AND METHODS

Nineteen children with acute lymphocytic leukemia were entered into study between August 1, 1973 and December 31, 1975. The results were analyzed as of September 1, 1976. Meningeal leu-
leukemia was diagnosed when the cerebrospinal fluid white cell count was elevated and cytocentrifuge analysis revealed leukemia cells. If the white cell count was not elevated, two consecutive lumbar punctures demonstrating lymphoblasts on cytocentrifugation were required. After parental informed consent was obtained, an Ommaya reservoir (2.5 cm diameter, standard burr-hole design) was inserted above the right forehead with the tip of the cannula in the frontal horn of the right lateral ventricle. The patient was then randomized to receive via the reservoir one of two treatment regimens (Fig. 1):

- **12 mg/sq m/dose.** This regimen involved single injections of methotrexate, 12 mg/sq m, in 6 ml Elliott's B solution, with a maximum dose of 15 mg. Injections were repeated twice weekly until remission was induced as defined below. Consolidation therapy commenced immediately and comprised six doses at weekly intervals. Maintenance therapy consisted of single injections administered monthly for 2 yr or until relapse, whichever occurred earlier.

- **C × T therapy.** A "course" of C × T therapy consisted of six injections of methotrexate, 1 mg, in 1 ml Elliott’s B solution at 12-hr intervals. This schedule was selected because it provided a relatively constant methotrexate concentration between $5 \times 10^{-7}$ and $2 \times 10^{-6}$ M in lumbar cerebrospinal fluid (Fig. 2). A lumbar cerebrospinal fluid sample was obtained 12 hr after the first dose. If the methotrexate concentration in the sample was not $5 \pm 2 \times 10^{-7}$ M, the dose was adjusted accordingly. C × T courses were repeated every 7–10 days until remission induction, then every 2 wk for three courses (consolidation therapy). Maintenance therapy con-
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sisted of C × T courses administered monthly for 2 yr or until relapse, whichever occurred earlier.

Ventricular sampling and injection via the reservoir were conducted according to the following protocol: The patient was placed in the left lateral decubitus position and the reservoir chamber was pumped six times to insure adequate mixing of ventricular and reservoir fluid. The skin over the chamber was shaved and isolated with sterile drapes. The reservoir site was then swabbed sequentially with 3% hexachlorophene, a dry sponge, and 10% povidone-iodine solution. After the iodine dried, a 25-gauge scalp-vein needle was inserted through the skin into the reservoir chamber and a volume of fluid equal to that to be injected was removed (maximum 6 ml). The drug was injected slowly, the tubing of the needle was flushed with Elliott's B solution, and the needle was removed. The injection site was then covered with a spot adhesive bandage to which povidone-iodine ointment had been applied. The reservoir was again pumped six times.

Central nervous system (CNS) remission induction was defined as the disappearance of leukemia cells from both ventricular and lumbar cerebrospinal fluid, as determined by cytocentrifugation analysis. Cytocentrifuge examinations were then performed monthly on ventricular fluid and every 3 mo on lumbar fluid. Relapse was defined as the recurrence of leukemia cells in the cerebrospinal fluid. If the total white cell count was not elevated, two consecutive cytocentrifuge specimens containing lymphoblasts were required for the diagnosis of relapse. None of the patients received CNS radiotherapy while on this study.

Two types of drug-induced neurotoxicity were recognized, an acute syndrome and a delayed encephalopathy. The acute toxic syndrome was characterized by headache, meningismus, fever, cerebrospinal fluid pleocytosis, and increased intracranial pressure occurring within hours after a methotrexate injection and persisting for 2-4 days. Encephalopathy was characterized primarily by signs or symptoms of brain dysfunction: dementia, obtundation, seizures, paresis, and focal neurologic deficits. In evaluating neurotoxic reactions attributable to intraventricular methotrexate rather than to the disease itself, only those reactions occurring during CNS remission were included. Severity of neurotoxic reactions was classified according to the criteria of Duttera et al.

Nine patients died of progressive systemic leukemia during clinical CNS remission and while on this study. Two of these patients, both in the 12 mg/sq m/dose group, did not have postmortem examinations of the brain and meninges. For purposes of statistical analysis these patients were censored from analysis (i.e., considered lost to follow-up) at the time of death.

RESULTS

Patients

Nine patients received C × T methotrexate therapy and ten were treated with 12 mg/sq m/dose. In two C × T patients the 12-hr lumbar cerebrospinal fluid methotrexate level fell outside the desired range of 5 (± 2) × 10⁻¹⁷ M. C × T dosage in these patients was adjusted to 1.5 and 0.75 mg every 12 hr. The treatment groups were comparable (as determined by Student's t test and χ² analyses) with respect to the following parameters: age, sex, concurrent hematologic relapse, number of leukemic cells in the cerebrospinal fluid at diagnosis, prior CNS leukemia, prior CNS therapy, the type of prior CNS therapy and the number of patients who subsequently died while in CNS remission. (Table 1).

Efficacy

All patients achieved meningeal remission except one C × T patient. Clinical or autopsy evidence for CNS relapse was found in three C × T patients at 157, 186, and 240 days and in three 12 mg/sq m/dose patients at 87, 192, and 639 days (Fig. 3). Of those patients remaining in remission, the median (range) remission duration was 345 (67–1178) days for the C × T group and 324 (35–689) days for the 12 mg/sq m/dose group. There were no significant differ-
Table 1. Comparison of C × T and 12 mg/sq m/Dose Patients

<table>
<thead>
<tr>
<th>Data Compared</th>
<th>C × T</th>
<th>12 mg/sq m/Dose</th>
<th>p*</th>
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<tbody>
<tr>
<td>Patients entered</td>
<td>9</td>
<td>10</td>
<td>—</td>
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<tr>
<td>Prognostic factors</td>
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<td></td>
<td></td>
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<tr>
<td>Age (yr)†</td>
<td>9 (5-20)</td>
<td>10 (5-19)</td>
<td>NS</td>
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<tr>
<td>Male patients</td>
<td>6</td>
<td>7</td>
<td>NS</td>
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<tr>
<td>Patients with concurrent hematologic relapse</td>
<td>2</td>
<td>3</td>
<td>NS</td>
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<tr>
<td>Patients with prior CNS leukemia</td>
<td>5</td>
<td>5</td>
<td>NS</td>
</tr>
<tr>
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<td>7</td>
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<td>NS</td>
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<tr>
<td>Patients with prior intrathecal methotrexate</td>
<td>5</td>
<td>7</td>
<td>NS</td>
</tr>
<tr>
<td>Patients with prior intrathecal cytosine</td>
<td>4</td>
<td>4</td>
<td>NS</td>
</tr>
<tr>
<td>arabinoside</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with prior cranial x ray, 2400 R</td>
<td>5</td>
<td>7</td>
<td>NS</td>
</tr>
<tr>
<td>Cerebrospinal fluid blast cells at diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(/μl)†</td>
<td>129 (2–1800)</td>
<td>111 (2–2500)</td>
<td>NS</td>
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<tr>
<td>Efficacy</td>
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<tr>
<td>Remission inductions</td>
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<td>10</td>
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<td>1</td>
<td>NS</td>
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<tr>
<td>Meningeal leukemia at autopsy/autopsies performed</td>
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<td>2/4</td>
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<td>Cumulative methotrexate dosage</td>
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<tr>
<td>During remission induction (mg/sq m)‡</td>
<td>8 ± 3</td>
<td>22 ± 11</td>
<td>&lt;0.005</td>
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<tr>
<td>Total (mg/sq m)</td>
<td>66 ± 41</td>
<td>173 ± 64</td>
<td>&lt;0.005</td>
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<td>Toxicity</td>
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<td></td>
<td></td>
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<tr>
<td>Patients with neurotoxicity</td>
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<td>7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Complications related to reservoir</td>
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<td>1</td>
<td>NS</td>
</tr>
</tbody>
</table>

* x2 or unpaired t test, NS, not significant.
† Medians (ranges in parentheses).
‡ Values are means ± 1 SD.

ences between the two groups in the relapse rate, the duration of remission, or the time on study (Table 1).

The mean (± 1 SD) cumulative methotrexate dosage was 66 ± 41 mg/sq m for the C × T group and 173 ± 64 mg/sq m for the 12 mg/sq m/dose group (p < 0.005). The mean (range) amount of methotrexate required for remission induction was 8 (6-12) mg in the C × T group and 22 (12-36) mg in the 12 mg/sq m/dose group (p < 0.05). Five (63%) of the eight patients achieving remission in the C × T group did so after one course of therapy (6 mg methotrexate). In the 12 mg/sq m/dose group half of the patients required two or more doses (≥ 24 mg/sq m methotrexate).

Toxicity

Neurologic toxicity during remission occurred in one of eight patients in the C × T group and in seven of ten patients in the 12 mg/sq m/dose group (p < 0.05). The one patient in the C × T group was a 12-yr-old girl who sustained a single grand mal seizure 6 days after completing her third C × T maintenance course. Of the seven patients with neurotoxic reactions in the 12 mg/sq m/dose group, two had the acute toxic syndrome, four developed encephalopathy, and one had both. The five encephalopathic reactions in this group are described below.
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60 CxT

0 - 0

2mg/m²

5: METHOTREXATE

Fig. 3. Life table analysis of CNS remission with C × T therapy and in patients treated with
12 mg/sq m/dose.

Case 1
This 7-yr-old girl developed progressive dementia beginning 6 mo after the onset of therapy.
The dementia slowly subsided after discontinuation of methotrexate. This patient has been re-
ported elsewhere.7

Case 2
At the end of CNS consolidation this 9-yr-old boy developed dementia and palsies of cranial
and cervical nerves. There was no improvement in his neurologic status despite discontinuation
of methotrexate and treatment with folate and citrovorum factor.

Case 3
In this 15-yr-old boy dementia began during consolidation and progressed gradually over the
ensuing 9 mo of his life. Areas of white matter necrosis were observed at autopsy, with a con-
centration of the lesions in the centrum ovale and periventricular tissues. There was no evidence
for meningeal leukemia.

Case 4
Severe intracranial hypertension began after the third consolidation dose in this 12-yr-old boy.
Cerebrospinal fluid examination, brain scan, radionuclide cisternogram, and computerized axial
tomogram showed no abnormalities other than diffuse cerebral edema. Thirty to fifty ml of cere-
brospinal fluid were withdrawn from the reservoir once or twice daily to help reduce the increased
intracranial pressure.

Case 5
This 5-yr-old boy was unable to walk for 7 days after one of his monthly maintenance injections.
Subsequent injections were given at half dosage. The gait abnormality did not recur.

Two of the neurotoxic reactions in the 12 mg/sq m/dose group were life
threatening, one was severe, three were moderate, and one was mild. The one
reaction in the C × T group was judged to be mild.

The neurotoxic and nontoxic patients were also compared separately for
factors that may have predisposed to neurotoxicity. Cranial irradiation prior to entry onto this study had been administered to four of the six patients with the acute toxic syndrome and to five of the ten nontoxic patients. There were also no significant differences between the toxic and nontoxic patients in the total amounts of intrathecal methotrexate administered prior to treatment on this study.

Complications related to the reservoir were encountered in two patients (Table I). One C × T patient sustained a Staphylococcus epidermidis meningitis and a 12 mg/sq m/dose patient developed a subdural hematoma on the side of the reservoir. The latter occurred in association with severe thrombocytopenia and head trauma and probably was unrelated to the presence of the reservoir.

This study was closed to patient entry on January 1, 1976, when it became apparent that the incidence of neurotoxicity was significantly greater with single injections of 12 mg/sq m/dose than in the C × T group. Patients on study at that time were continued without therapy modification provided that there was no evidence of encephalopathy.

DISCUSSION

Design of the C × T regimen was based in part on the cytokinetics of human leukemia cells. The cell cycle time and the S-phase duration have been estimated at 3 days and 1 day, respectively, although these intervals may be longer for blast cells residing in the CNS. The minimal cytocidal extracellular methotrexate concentration, estimated from studies in vitro, is approximately $5 \times 10^{-7} \text{M}$. Six injections of 1 mg given every 12 hr provides this concentration for 72 hr, whereas a single injection of 12 mg/sq m provides this level for less than 32 hr (Fig. 1). The theoretical advantages of this C × T regimen include a reduction in the total amount of methotrexate required for a single treatment course (from 12 to 6 mg) and for consolidation therapy (from 72 to 18 mg), elimination of the high peak cerebrospinal fluid methotrexate level thought to be one of the causes of neurotoxicity, and prolongation of cytocidal antifolate concentrations to encompass the S phase of the cell cycle.

Our experience thus far with the C × T schedule indicates that it is as effective against established meningeal leukemia as conventional dose therapy. It requires significantly less drug, reducing by one-half to two-thirds the total methotrexate used in the conventional dose regimen. It is also significantly less neurotoxic, with only one toxic reaction, a single seizure, in nine patients treated thus far. One disadvantage is that it requires more visits to the hospital for the additional reservoir injections. We are exploring the possibility of halving the number of injections by administering two doses with one injection. This objective may be accomplished by flushing the first dose out of the reservoir and leaving the second dose in the reservoir chamber. The second dose is then self-administered by the patient 12 hr later by pumping the reservoir.

In this study the more conventional dosage schedule was excessively neurotoxic, and this arm of the randomization was discontinued. The more toxic schedule involved single intraventricular injections of 12 mg/sq m twice weekly until remission induction, weekly for 6 wk (consolidation therapy), and monthly thereafter for 2 yr (maintenance therapy).
The only published study of intralumbar methotrexate given at the same
costality was that of Duttera et al. who administered 15 mg/sq m to 31 chil-
dren, 15 of whom did not receive other CNS therapies. Of the 15, 4 developed
moderate neurotoxicity and 6 had severe toxicity. Sullivan et al. studied main-
tenance intralumbar methotrexate, 12 mg/sq m every 8 wk, in 26 children. The
schedule differed from ours, however, in that there was no consolidation
therapy between remission induction and maintenance therapy. Nausea, vomit-
ing, headache, and local signs of meningeal irritation were noted in 17 chil-
dren, and in all but two symptoms were graded severe. Therapy was interrupted
or discontinued in 4 children. Based on these comparisons, it appeared that
similar dosage schedules were equally or somewhat more neurotoxic when
given intraventricularly than when given by lumbar puncture. That most of the
neurotoxic reactions occurred during consolidation or later in maintenance
suggests that the frequency of administration may also have contributed to the
neurotoxicity. Less frequent injections, or lower doses (e.g., 6.25 mg/sq m used
by others), are probably less neurotoxic. These modifications may also
jeopardize efficacy, however, and ideally would require another controlled trial
for clinical comparison.

Although the biochemical basis for the adverse effect of methotrexate on the
brain remains unknown, prior cranial irradiation may predispose the patient
to methotrexate encephalopathy. It cannot account for the neurotoxicity ob-
erved in this study in that the frequency of prior radiotherapy was similar in
the two treatment groups as well as in toxic versus nontoxic patient groups,
or were there any significant differences between the two treatment groups in
other factors known to be correlated with intraventricular methotrexate neuro-
toxicity. In general, toxic patients had higher ventricular methotrexate concen-
trations than nontoxic patients within the same treatment group, an observa-
tion consistent with our previous findings on analysis of lumbar antifolate levels.

This study also supports the conclusion of Shapiro et al. that the Ommaya
reservoir can be a safe and effective therapeutic modality. Only 1 patient of the
19 in this study had a significant complication definitely related to the reservoir.
Our patients and their families unanimously preferred the reservoir to lumbar
punctures and regarded the surgery (2-3 days hospitalization) and costs as ac-
ceptable. The need for optimal neurosurgical expertise must be emphasized,
however. We specifically recommend the use of intraoperative fluoroscopy for
insertion of the cannula, a frontal approach into the lateral ventricle in the
nondominant hemisphere, and the use of the 25-gauge scalp-vein needles and a
strictly sterile technique for sampling and injection.

This study showed that compared to a regimen of 12 mg/sq m/dose, 1 mg of
methotrexate every 12 hr for six doses is equally effective and significantly less
neurotoxic. We believe that this concentration \times time approach should be con-
tinued and that it is worthy of study in CNS neoplasms other than meningeal
leukemia.

Three patients have had CNS relapse since this manuscript was submitted
for publication. Two of the three relapses occurred in patients treated with
single injections of 12 mg/sq m, one at 612 days after entry on study and the
other at 944 days after starting (180 days after stopping) intraventricular chemotherapy. The third relapse occurred in a C × T patient 1444 days after entry and 396 days after stopping maintenance therapy. Maintenance intraventricular chemotherapy was discontinued at 2 yr as scheduled in two other patients, one C × T patient and one 12 mg/sq m/dose patient who continue in remission 282 and 324 days, respectively, after termination of therapy. No additional neurotoxicity has been observed. These events do not alter the conclusions discussed in the manuscript.

REFERENCES


"Concentration x time" methotrexate via a subcutaneous reservoir: a less toxic regimen for intraventricular chemotherapy of central nervous system neoplasms

WA Bleyer, DG Poplack and RM Simon