Phase I and Pharmacokinetic Evaluation of Thiotepa in the Cerebrospinal Fluid and Plasma of Pediatric Patients: Evidence for Dose-dependent Plasma Clearance of Thiotepa

Richard L. Heideman,1 Diane E. Cole, Frank Balis, Judy Sato, Gregory H. Reaman, Roger J. Packer, Lawrence J. Singher, Lawrence J. Ettinger, Andrea Gillespie, Joseph Sam, and David G. Poplack

The Pediatric Branch, National Cancer Institute, Bethesda, Maryland 20892 [R. L. H., D. E. C., F. B., A. G., J. S., D. G. P.]; Children's Hospital of Los Angeles, Los Angeles, California 90024 [J. S.]; Children's Hospital National Medical Center, Washington, DC 20010 [G. H. R.]; Children's Hospital of Philadelphia, Philadelphia, Pennsylvania 19104 [R. J. P.]; Minneapolis Children's Medical Center, Minneapolis, Minnesota 55404 [J. S.]; and University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School, New Brunswick, New Jersey 08903 [L. J. E.]

ABSTRACT

A Phase I trial of thiotepa (TT) administered as an i.v. bolus was performed in 19 children with refractory malignancies. The starting dose was 25 mg/m² with escalations to 50, 65, and 75 mg/m². Seven additional patients were treated with 8-h infusions at 50 or 65 mg/m². The maximum tolerated bolus dose was 65 mg/m². Reversible myelosuppression was the dose-limiting toxicity.

The plasma and cerebrospinal fluid (CSF) pharmacokinetic parameters of TT and its major active metabolite tepa (TP) were also evaluated. When the bolus or infusion methods of TT administration were compared, there was little difference observed in any pharmacokinetic parameter for either TT or TP. The plasma disappearance of TT was rapid and biphasic with half-lives of 0.14 to 0.32 and 1.34 to 2.0 h. Dose-dependent pharmacokinetics was demonstrated by steadily declining plasma clearance with increasing TT dose. Clearance values declined from 28.6 liters/m²/h at the 25-mg/m² dose to 11.9 liters/m²/h at the 75-mg/m² dose.

The half-life of TP was longer than that of TT and ranged between 4.3 and 5.6 h. There was evidence of the saturation of TP production. TT and TP both exhibited excellent penetration into the CSF, producing lumbar and ventricular concentrations which were nearly identical to simultaneous plasma concentrations. In one patient with a Rickham reservoir, the CSF:plasma area under the (concentration x time) curve ratios for TT and TP were 1.01 and 0.95, respectively.

The above data indicate that TT can be safely administered to pediatric patients at doses higher than conventionally used. The favorable CSF penetration of TT and TP suggests that Phase II studies of TT be considered in patients with central nervous system tumors.

INTRODUCTION

TT² is a polyfunctional alkylating agent which has been in clinical use for more than 30 yr. It is currently used i.v. in adult oncology for the treatment of ovarian and breast cancer, as well as being administered intravesically for the treatment of bladder cancer, and intrathecally for meningeal carcinomatosis. In addition, high-dose TT has been used as preparative chemotherapy for autologous bone marrow transplantation in patients with refractory malignancies (1–5). The observation that TT displays excellent CSF penetration in the nonhuman primate following i.v. administration suggests that TT may also be of some clinical utility in the treatment of central nervous system malignancies (6).

In vivo, TT is metabolized to TP, a molecule which retains TT’s three aziridine rings and is itself a potent alkylator (Fig. 1). Although recent publications have described the human plasma pharmacokinetics of TT, only limited information regarding TP is available (1, 7–11). Similarly, little exists regarding the pharmacokinetics of these agents in human CSF (12).

In spite of its long clinical history, the optimal dose of TT has never been established in pediatric patients. Conventional doses of TT in adults range from 12.5 to 25 mg/m². However, TT is known to have a steep dose-response curve. This information, together with the knowledge that the administration of very high dose TT is feasible with autologous bone marrow transplantation, suggested that it might be possible to safely administer TT in higher than conventional doses without autologous bone marrow rescue.

The present report details the results of a Phase I study of higher than conventional dose TT in children. In addition, we describe the clinical pharmacology and pharmacokinetics of TT and its major active metabolite, TP, in human plasma and CSF.

MATERIALS AND METHODS

Patient Eligibility. Patients between 1 and 21 yr of age with malignancies refractory to conventional therapy were eligible for this trial. Prior to treatment all patients were required to have histological confirmation of their diagnosis, an Eastern Cooperative Oncology Group performance level of 3 or less, and a life expectancy of at least 8 wk.

Prior to entry, patients were required to have fully recovered from the toxic effects of antineoplastic therapy and to have adequate hepatic (bilirubin less than 2 mg/dl and serum transaminases less than 1.5 times normal) and renal function (creatinine less than 1.5 mg/dl or creatinine clearance greater than 60 ml/min/1.73 m²), as well as a normal coagulation profile, serum electrolytes, and uric acid. Patients with solid tumors (without bone marrow involvement) were also required to have adequate peripheral blood counts (a granulocyte count greater than 1,500/mm³ and a platelet count greater than 100,000/mm³) prior to treatment.

All patients or their legal guardians signed a document of informed consent consistent with federal and local institutional guidelines stating that they were aware of the investigational nature of this trial.

Study Design. Two different methods of TT administration were studied in this trial. Nineteen patients were administered a 5-min i.v. bolus dose and seven patients an 8-h continuous i.v. infusion of TT. The drug was given every 3 wk or as soon thereafter as recovery from the hematological effects of prior TT doses permitted. One dose constituted one course of therapy. The starting bolus dose of 25 mg/m² was the conventionally used dose in adults. Drug escalations to 50, 65, and 75 mg/m² were carried out once at least three patients evaluated for toxicity had been accrued at the prior dose level. Patients were allowed to escalate to the next higher dose level if they had shown some evidence of response and did not have Grade III or IV toxicity at their prior dose level. Only one escalation was allowed in an individual patient. Escalated patients were evaluated for toxicity only at their initial dose level. Patients were monitored weekly with complete blood counts, physical exams, and measurement of any palpable lesions. Bone marrow examinations, radiographic studies, and CT or magnetic resonance imaging scans, as appropriate, were obtained prior to treatment.
PHASE I AND PHARMACOKINETIC STUDY OF THIOTEPA

Fig. 1. Comparative structures of thiotepa and tepsa.

and repeated at the end of two courses of therapy to determine response to treatment. Patients who experienced objective disease progression were removed from study. Dose escalation was terminated as soon as a consistent dose-limiting toxicity was identified.

Once the bolus administration phase of the study had been completed and the dose-limiting toxicity and MTD were defined, additional patients were treated with the infusion schedule of TT. The major aim of this aspect of the study was to evaluate the pharmacokinetics of infusion doses; no attempt was made to exceed the bolus MTD. The infusion doses administered (50 and 65 mg/m²) were at or below this level.

Drug Preparation and Administration. Thiotepa was provided by Lederle Laboratories (Pearl River, NY) in 15-mg sterile glass vials containing 80 mg of NaCl and 50 mg of NaHCO₃. Vials were stored at room temperature and reconstituted with 1.5 ml of sterile distilled water prior to bolus administration. For use as an infusion, the drug was further diluted in 500 to 1000 ml of 5% dextrose in water or normal saline.

Tepa was obtained through synthesis (Dr. G. Sosnovsky, the University of Wisconsin, Milwaukee, WI). This compound was kept tightly sealed in glass vials and stored desiccated at −70°C.

Drug Assay and Sampling Times. Following bolus doses of TT, 3-ml heparinized blood samples were obtained at 15 and 30 min, and at 1, 1.5, 2, 3, 4, 6, and 8 h. In addition to the above times, patients treated with infusion doses of TT had a 15-, 30-, and 60-min post infusion sample obtained. Two patients (1 bolus and 1 infusion) also had 24-h plasma samples obtained. CSF samples were obtained by lumbar puncture at times between 2 and 8 h after TT administration in 11 patients (6 bolus, 5 infusion). In one patient with a Rickham reservoir, multiple ventricular CSF samples were obtained over 24-h period, in addition to a single lumbar sample at 1 h.

Blood samples were immediately placed on ice and then centrifuged at 400 × g to separate the plasma. Plasma and CSF were frozen at −70°C until TT and TP analysis, which typically followed within 1 wk. TT and TP were quantitated using a previously described gas chromatographic assay having a 1-ng/ml limit of detection for both agents (6).

Pharmacokinetics. The geometric mean concentration-time data for TT following bolus administration were fit to multieponential functions using MLAB, a nonlinear curve-fitting program (13). The best fit was determined by application of Akaike's information criterion (14). The half-life for each phase of elimination was calculated by dividing the terminal rate constant (15). Less than 10% of the total AUC was the result of such extrapolation. Clearance was calculated by dividing the drug dose by AUC. The steady-state volume of distribution was calculated using the area under the moment curve (16). Other pharmacokinetic parameters were calculated using model-independent methods.

RESULTS

Phase I Trial. The characteristics of the patients entered on trial are listed in Table 1. Seventeen of 19 patients receiving bolus TT and 3 of 7 patients given infusion TT were fully evaluable for toxicity. Four patients with acute lymphoblastic leukemia (2 bolus, 2 infusion) were evaluable only for nonhematological toxicity. Two patients on the infusion study were excluded from the toxicity analysis, one because of early withdrawal from study and one because of early death from progressive disease.

The bolus MTD of TT was 65 mg/m², and the dose-limiting toxicity was myelosuppression, characterized by granulocytopenia and thrombocytopenia (Table 2). The average day of granulocyte and platelet nadirs and time to recovery of an absolute granulocyte count of 1,500/mm³ and platelet count of 100,000/mm³ in 6 patients treated at the MTD were 17 and 33 days, respectively. For six patients who had multiple courses of TT, there was no significant difference between courses in either the day of nadir or grade of toxicity.

Although the numbers are small, patients who had received prior chemotherapy with nitrosoureas appeared to have more prolonged myelosuppression. The recovery times of two such patients treated at the bolus MTD were 41 and 59 days, as compared to a range of 21 to 35 days (mean, 26) in 4 non-nitrosourea-treated patients at this same dose. Similarly prolonged recoveries were evident at the other TT bolus and the 50-mg/m² infusion dose levels. Additionally, at all but the 75-mg/m² bolus dose, the only patients with Grade III and IV hematological toxicity were those that had received prior nitrosourea therapy (see Table 2).

No clinically significant alterations in hepatic or renal function, and no mucositis or neurotoxicity were noted for any TT dose or administration method studied. Nausea and vomiting

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients entered</td>
<td>26</td>
</tr>
<tr>
<td>No. fully evaluable</td>
<td>20 (3)*</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>Median 8, Range 2.5–18</td>
</tr>
<tr>
<td>Males/females</td>
<td>17/9</td>
</tr>
<tr>
<td>No. of patients with prior therapy</td>
<td>Chemotherapy alone 4, Radiotherapy alone 2, Chemotherapy and radiotherapy 20 (6)</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Ependymoma 3, Astrocytoma 3, Brain stem glioma 2, Primitive neuroectodermal tumor 1, Medulloblastoma 2 (2), Oligodendroglioma 1, Retinoblastoma 1, Acute lymphoblastic leukemia 4 (2), Ewings sarcoma 3, Wilms tumor 2 (1), Osteogenic sarcoma 1, Germ cell tumor 1, Neuroblastoma 1, Rhabdomyosarcoma 1 (1)</td>
</tr>
</tbody>
</table>

* Numbers in parentheses, number of patients treated with 8-h infusions of TT.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Hematological toxicity of thiotepa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiotepa dose/m² and method of administration</td>
<td>No. of evaluable patients</td>
</tr>
<tr>
<td>25-mg bolus</td>
<td>3</td>
</tr>
<tr>
<td>50-mg bolus</td>
<td>4</td>
</tr>
<tr>
<td>50-mg infusion</td>
<td>3</td>
</tr>
<tr>
<td>65-mg bolus*</td>
<td>6</td>
</tr>
<tr>
<td>65-mg infusion</td>
<td>0</td>
</tr>
</tbody>
</table>

* Grade III toxicity: 1,000 to 1,999 total leukocytes, 500 to 999 absolute granulocytes, 25,000 to 49,000 platelets (all per mm³), hemoglobin 5 to 7 mg/dl; Grade IV toxicity: <1,000 total leukocytes, <500 absolute granulocytes, <25,000 platelets (all per mm³), hemoglobin <5 mg/dl.

* Prior nitrosourea therapy.

* Maximally tolerated dose.

* One of 4 patients with prior nitrosourea therapy.

Downloaded from cancerres.aacjournals.org on April 13, 2017. © 1989 American Association for Cancer Research.
PHASE I AND PHARMACOKINETIC STUDY OF THIOTEPA

were uncommon (2 patients) and generally self limited, even at the highest dose evaluated.

Three of 19 patients showed some evidence of response to TT. One patient with recurrent posterior fossa ependymoblastoma who had not received prior chemotherapy showed a stable CT scan and an improved clinical exam for a period of 4 mo. Another patient with a supratentorial primitive neuroectodermal tumor treated at the 65-mg/m² bolus dose level showed a stable CT scan and clinical exam for 6 wk. A third patient with retinoblastoma metastatic to the left frontal lobe and meninges had a partial response to a 50-mg/m² bolus dose of TT which consisted of disappearance of the frontal lobe mass and clearing of abnormal CSF cytology in the face of persistent CT abnormalities in the orbits.

Plasma Pharmacokinetics. The disappearance profiles of TT from human plasma after bolus administration are shown in Fig. 2. Disappearance was best fit by a biexponential function $C(t) = Ae^{-\alpha t} + Be^{-\beta t}$ where $C$ is the concentration at time ($t$), $A$ and $B$ are the time zero intercepts, and $\alpha$ and $\beta$ are the hybrid rate constants. Table 3 lists the pharmacokinetic parameters derived after TT administration. TT was rapidly cleared from the plasma in a dose-dependent manner. As the bolus dose of TT was increased, the plasma clearance decreased from 28.6 to 11.9 liters/m²/h. The $\alpha$ and $\beta$ half-lives of TT were 0.14 to 0.32, and 1.34 to 2.1 h, respectively. The $V_{\text{dss}}$ was high, ranging from 18 to 29.6 liters/m².

When administered by infusion, TT reached steady-state concentrations by 4 h. Mean steady-state concentrations were 2.6 and 3.9 nm, respectively, for the 50- and 65-mg/m² infusion doses. Fig. 3 demonstrates the mean TT and TP concentrations at the 65-mg/m² infusion dose. As shown in this figure and in Table 3, the AUC and other pharmacokinetic parameters observed after infusion were nearly identical to those observed after bolus administration of the same dose. Similar results were noted when the 50-mg/m² infusion and bolus doses were compared (data not shown).

The pharmacokinetic parameters for TP are listed in Table 4. The mean and range values observed for parameters from either the bolus or infusion method of administration at the same TT dose are similar. The plasma disappearance of TP at each of the 4 bolus TT dose levels is shown in Fig. 4. Plasma TP concentrations rose rapidly, with peak concentrations occurring by the time of the first plasma sample (15 min after TT administration). The half-life of TP after bolus TT administration was 4.3 to 5.6 h. With the exception of the 65-mg/m² TT bolus dose, the TP:TT AUC ratios steadily diminished as the bolus dose of TT was increased. Fig. 3 and Table 4 demonstrate that, after infusion doses of TT, TP rises rapidly and then appears to approach a steady-state level in a range similar to that observed after bolus doses of TT.

CSF Pharmacokinetics. The CSF disappearance profiles of TT and TP in a patient with a Rickham reservoir following a TT dose of 75 mg/m² are demonstrated in Fig. 5. It is apparent that the single lumbar and multiple ventricular CSF TT levels in this individual are nearly identical to each other and to those in plasma at every time point examined. Although the CSF levels of TP appear to rise more slowly than those of TT, they become equivalent to those of plasma within 3 to 5 h after TT administration. The CSF:plasma AUC ratios for TT and TP in this patient were 1.02 and 0.95, respectively. CSF concentrations of TT and TP were also equivalent to plasma concentrations in 6 other patients who had single lumbar CSF samples obtained at times between 1 and 8 h after bolus doses of TT. In 5 patients treated with infusion doses of TT, single lumbar CSF TT and TP concentrations obtained at times between 4 and 7.5 h when plasma levels were at steady-state concentrations revealed the CSF:plasma ratios ranging from 0.65 to 1.4 (mean, 0.92) for TT and from 0.65 to 1.45 (mean, 0.99) for TP.

DISCUSSION

In the present study we have demonstrated that substantially higher than conventional i.v. (12.5 to 25 mg/m²) doses of TT
PHASE I AND PHARMACOKINETIC STUDY OF THIOTEPA

Table 3 Mean plasma thiotepa pharmacokinetic parameters

<table>
<thead>
<tr>
<th>Dose (mg/m²)</th>
<th>No. of patients evaluated</th>
<th>Rate constants (h⁻¹)</th>
<th>Clearance (liters/m²/h)</th>
<th>Vₚ₀* (liters/m²)</th>
<th>AUC (μM·h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>A</td>
<td>B</td>
<td>α</td>
<td>β</td>
</tr>
<tr>
<td>25 bolus</td>
<td>3</td>
<td>5.96 0.6</td>
<td>1.97 [0.32]</td>
<td>0.42 [1.66]†</td>
<td>28.6 (17–53)†</td>
</tr>
<tr>
<td>50 bolus</td>
<td>4</td>
<td>17.6 5.0</td>
<td>3.36 [0.21]</td>
<td>0.39 [1.76]‡</td>
<td>15.7 (12–20)</td>
</tr>
<tr>
<td>50 infusion</td>
<td>3</td>
<td></td>
<td>[1.2]</td>
<td>12.8 (9.7–16.4)</td>
<td>17.4 (13.4–25)</td>
</tr>
<tr>
<td>65 bolus</td>
<td>5</td>
<td>38.4 8.3</td>
<td>4.94 [0.14]</td>
<td>0.52 [1.34]§</td>
<td>15.4 (11–29)</td>
</tr>
<tr>
<td>65 infusion</td>
<td>2</td>
<td></td>
<td>[1.5]</td>
<td>13.5 (11–17)</td>
<td>18.6 (16–33)</td>
</tr>
<tr>
<td>75 bolus</td>
<td>5</td>
<td>23.1 8.6</td>
<td>2.44 [0.28]</td>
<td>0.34 [2.0]</td>
<td>11.9 (7–29)</td>
</tr>
</tbody>
</table>

* Vₚ₀ volume of distribution at steady state.
† a half-life.
‡ β half-life.
§ Numbers in parentheses, range.
| Numbers in braces, AUC normalized to TT dose of 25 mg/m².
| Terminal half-life.

Table 4 Mean plasma Tepa pharmacokinetic parameters

<table>
<thead>
<tr>
<th>Dose (mg/m²)</th>
<th>No. of patients evaluated</th>
<th>Terminal half-life (h)</th>
<th>Peak (μM)</th>
<th>AUC (μM·h)</th>
<th>AUCₚ/ₚ/AUCₚ/ₚ</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 bolus</td>
<td>3</td>
<td>4.5</td>
<td>4.2 (2–16)</td>
<td>22.3 (10–40) [22.3]</td>
<td>4.9 (1.3–11)</td>
</tr>
<tr>
<td>50 bolus</td>
<td>4</td>
<td>4.3</td>
<td>5.5 (5.7–8)</td>
<td>35.6 (22–52) [17.8]</td>
<td>2.10 (1–4.2)</td>
</tr>
<tr>
<td>50 infusion</td>
<td>3</td>
<td>4.9</td>
<td>6.1 (2.4–22)</td>
<td>45.8 (29–51) [23]</td>
<td>2.2 (1.8–10.6)</td>
</tr>
<tr>
<td>65 bolus</td>
<td>4</td>
<td>5.0</td>
<td>9.9 (6–25)</td>
<td>100 (48–225) [42.3]</td>
<td>4.6 (1.6–20)</td>
</tr>
<tr>
<td>65 infusion</td>
<td>2</td>
<td>3.7</td>
<td>3.3 (2.6–4.7)</td>
<td>34 (21–47) [17]</td>
<td>1.3 (1–1.5)</td>
</tr>
<tr>
<td>75 bolus</td>
<td>5</td>
<td>5.6</td>
<td>6 (3.3–20)</td>
<td>57 (28–124) [19]</td>
<td>1.70 (0.6–8.6)</td>
</tr>
</tbody>
</table>

* Numbers in parentheses, range.
† Numbers in brackets, AUC normalized to 25 mg/m².
| Apparent steady-state concentration.

Fig. 4. TP plasma disappearance after bolus TT administration at the four dose levels studied. Points represent the geometric mean of 3 patients at 25 mg/m² (●), 4 patients at 50 mg/m² (○), 5 patients at 65 mg/m² (△), and 5 patients at 75 mg/m² (▲).

Fig. 5. Disappearance of TT (△, ▲) and TP (○, ○) from ventricular CSF (open symbols) and plasma (closed symbols) after a 75-mg/m² bolus dose of TT in a single patient with a Rickham reservoir. Single lumbar TT (+) and TP (x) levels also shown.

can be administered to children with malignancies without the need for autologous marrow rescue. Doses up to 65 mg/m² were safely administered as an i.v. bolus dose in children every 21 days. This MTD of 65 mg/m² may also represent the bolus MTD for adult patients, as recently reported (17). TT is a potent alkylator known to have a steep dose-response curve. Our data suggest that, because of inadequate dose, previous...
The above invites a clinical reevaluation of TT in both adult and pediatric patients.

In the current study, myelosuppression was the only clinically significant toxicity. Results from other studies exploring the feasibility of high-dose TT with autologous bone marrow transplant indicate that nonhematological dose-limiting toxicity does not appear until substantially higher doses of TT (e.g., 375 to 500 mg/m² daily for 3 days) are used (18). Thus, TT may be an ideal candidate in which to investigate the ability of granulocyte or granulocyte-macrophage colony-stimulating factors to extend the MTD (19). Moreover, as TT is not associated with significant nausea and vomiting or hemorrhagic cystitis, therapy may be given in an outpatient setting without the need for extensive prehydration.

The plasma disappearance and half-lives of TT noted in this study are similar to those reported by other authors (1, 7–11). In contrast, however, we observed a clearance pattern for TT which indicates that this drug displays dose-dependent pharmacokinetics. As the bolus dose of TT was increased from 25 to 75 mg/m², a progressive decrease in the mean plasma clearance of this agent occurred. Additionally, peak TP concentration did not increase significantly with increases in TT dose, but instead plateaued at approximately the 6 μM level. This and the observation of steadily decreasing TT/TP AUC ratios with increasing bolus doses of TT suggest saturation of the metabolic transformation of TT to TP. In other studies, mean TT clearance after bolus or infusion doses of between 12 and 900 mg/m² has ranged between 11.2 and 16.7 liters/m²/h (1, 7, 10, 11). With one exception (10), none of the above reports has observed evidence of dose dependency, and in this latter instance dose dependency is not apparent when the clearance data are reanalyzed as the mean of the reported values at each dose level. Our finding of dose-dependent pharmacokinetics may be a result of the generally greater rates of drug delivery we used, 300 to 900 mg/m²/h, as compared to 2 to 420 mg/m²/h in the above noted studies. These higher rates of delivery may have produced TT concentrations which approached the Km of the unknown enzyme responsible for TT to TP conversion.

TP had a longer terminal half-life than TT (4.3 to 5.6 versus 1.2 to 2 h) and could be detected in plasma and the CSF at times up to 24 h after both bolus and infusion doses of TT at 65 and 75 mg/m². Further, as demonstrated by the TP:TT AUC ratios, TP accounts for 62 to 83% of the combined AUCs of these two alkylation species. This and the knowledge that TP is itself a potent alkylator suggest that it may contribute significantly to the clinical activity and toxicity of TT. The persistence of TP may also have important implications for the timing of bone marrow reinfusion in patients treated with high-dose TT in conjunction with autologous bone marrow transplantation.

When the infusion and bolus schedules of TT administration are compared, the total exposure to TT and TP was not significantly different, suggesting that there is no pharmacokinetic advantage for administration by infusion.

The CSF penetration of both TT and TP was excellent. In the one patient with a Rickham reservoir reported here, the CSF:plasma AUC ratios for TT and TP were 1.01 and 0.95, respectively, confirming similar observations in the nonhuman primate (6). With the exception that TP levels rise more slowly in the CSF than in plasma, the disappearance profiles of TT and TP in the CSF were virtually identical to those observed in plasma. The above suggests an advantage for the use of systemic versus regional (intrathecal, intraventricular) administration of TT as it relates to the CSF concentrations of both TT and TP.

Systemic administration of TT provides prolonged CSF exposure to TP. In contrast, when TT is administered regionally, CSF concentrations of TP are not detectable, and rapid clearance of TT results in uneven neuraxis distribution of this later drug (6).

The high degree of CSF penetration for both TT and TP after i.v. administration suggests that systemically administered TT may be a valuable agent for the treatment of central nervous system malignancies and meningeal carcinomatosis. Although multiple prior reports of TT in the treatment of these diseases have produced few responses (4, 20–24), many of these studies used regional (intraventricular or intrathecal) routes of TT administration or used systemic doses of TT which were well below the MTD described in this study. In the few instances where clinical responses have been noted, the doses used were 40 to 100 mg/m², approaching or exceeding the MTD which we have defined (23, 24). The above circumstances suggest that a Phase II evaluation of systemically administered TT, at the MTD defined in this study, be considered in patients with CNS malignancies. This suggestion is further supported by the observation that TT is an active and potent agent against intracranially and s.c. implanted human medulloblastoma cell xenografts in the athymic mouse (25). The AUC of TT produced by the MTD is well above that necessary in vitro to produce 50% inhibition of clonogenic survival of human medulloblastoma cell lines by TT alone (25) and does not take into account the contribution to efficacy that would be provided by the presence of TP. Similar in vitro studies in our own laboratory with several human leukemia and solid tumor cell lines (including medulloblastoma and glioma cell lines) show TP to be between 60 and 90% as potent as TT in its inhibition of clonogenic survival.

In summary, we have defined a pediatric MTD for TT which is considerably greater than doses conventionally administered. Further, we have demonstrated that bolus dose TT, unlike most other antineoplastic agents, shows dose-dependent pharmacokinetics, a phenomenon which leads to disproportionate increases in AUC with increases in dose. The above circumstances, as well as the excellent CSF penetration of both TT and TP, suggest that a Phase II reevaluation of TT in CNS and other solid tumors is warranted.

ACKNOWLEDGMENTS

We acknowledge Lederle Laboratories for their generous support of this study.

REFERENCES


3 Unpublished observations, manuscript in preparation.
PHASE I AND PHARMACOKINETIC STUDY OF THIOTEPA


Phase I and Pharmacokinetic Evaluation of Thiotepa in the Cerebrospinal Fluid and Plasma of Pediatric Patients: Evidence for Dose-dependent Plasma Clearance of Thiotepa


Access the most recent version of this article at: http://cancerres.aacrjournals.org/content/49/3/736

Sign up to receive free email-alerts related to this article or journal.

To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.

Downloaded from cancerres.aacrjournals.org on April 13, 2017. © 1989 American Association for Cancer Research.