Phase I and Clinical Pharmacological Study of Mercaptopurine Administered as a Prolonged Intravenous Infusion

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ABSTRACT

The bioavailability of oral mercaptopurine (MP) is poor, and plasma levels following p.o. dosing are highly variable. In an attempt to circumvent these problems, we conducted a Phase I trial and clinical pharmacological study of MP administered as a prolonged i.v. infusion. An infusion rate of 50 mg/sq m/h, which was designed to achieve therapeutic drug levels in plasma, was used in all patients. The infusion duration was escalated in 12-h increments. Thirty-eight patients were evaluated. The dose-limiting toxicity was mucositis. Other reversible toxicities were myelosuppression and hepatotoxicity. An infusion duration of 48 h was found to be safe, unassociated with dose-limiting toxicity. Objective responses were seen in five patients.

The mean plasma steady-state MP concentration achieved was 6.9 \( \mu \text{M} \) with little interpatient variability seen. Allopurinol coadministration had no effect on the plasma pharmacokinetics of i.v. MP. However, allopurinol did alter the urinary metabolite pattern, decreasing thiouric acid and increasing MP and thi oxanthine levels. The steady-state cerebrospinal fluid:plasma ratio for MP was 0.27, suggesting that this approach may be of value in the treatment of central nervous system cancer.

MP can be safely administered as a 48-h i.v. infusion at a dose rate which reliably achieves MP levels associated with optimal antileukemic activity in vitro.

INTRODUCTION

MP is one of the oldest antineoplastic agents currently in clinical use. It was introduced over 30 years ago (1) and since that time has been administered primarily by the p.o route. Despite its widespread use in the treatment of ALL, however, knowledge of the clinical pharmacology of MP has been limited. We demonstrated recently that the bioavailability of p.o. MP is low (16%) and that plasma levels following uniform dosing are highly variable (12). Peak plasma levels achieved following a p.o. dose of MP of 75 mg/sq m are usually less than 1 \( \mu \text{M} \) and remain in this concentration range for only 1 to 2 h (12). In vitro cytotoxicity data, however, suggest that MP levels in the range of 1 to 10 \( \mu \text{M} \) maintained for a minimum of 12 h are required to achieve optimal tumor cell kill (10). In efforts to overcome the low and variable bioavailability of p.o. MP and to achieve sustained plasma levels between 1 and 10 \( \mu \text{M} \), we initiated a pediatric Phase I study of MP administered as a prolonged i.v. infusion.

MATERIALS AND METHODS

Patient Eligibility. Patients were eligible for participation, provided they had a histologically proven cancer refractory to all conventional modes of therapy. Two patients with brainstem tumors did not have biopsies performed. With one exception, patients were less than 21 years of age. All patients were fully or partially ambulatory and had a life expectancy of at least 8 weeks. Patients had recovered from the toxic effects of prior therapy and had normal renal (creatinine, <1.5 mg/dl; creatinine clearance, >60 ml/min/sq m) and hepatic function (bilirubin, <2.0 mg/dl). Patients without marrow disease were required to have an absolute granulocyte count that was >1,500/cu mm and a platelet count that was >100,000/cu mm prior to each cycle of chemotherapy. Written, informed consent was obtained prior to entry onto the study. Complete blood counts, hepatic and renal function tests, and serum electrolytes were performed weekly on all patients.

Study Design and Drug Administration. MP was administered at a dose rate of 50 mg/sq m/h to all patients. The starting infusion duration of 12 h was escalated in 12-h increments until a level was reached at which consistent, dose-limiting toxicity was seen. If no toxicity was observed after 2 cycles of MP, one dose escalation was permitted. A minimum of 3 patients was entered at each dose level, at least 2 of whom were without bone marrow disease and thus evaluable for hematological toxicity. Cycles were repeated at 14- to 21-day intervals, provided there had been recovery from any toxicity from the previous dose.

MP was supplied by the National Cancer Institute as a sterile, lyophilized powder at 500 mg/vial. Each vial was initially reconstituted with 50 ml of sterile water. This was further diluted to a concentration of 1 mg/ml with either 5% dextrose in water or 5% dextrose in 0.9% NaCl solution (saline).

Forty-four patients were entered onto this study; 38 were evaluable for toxicity. Four patients were ineligible due to early death from their underlying neoplasm, and 2 registered patients were ineligible because they developed abnormal liver function tests immediately prior to the planned initiation of therapy. The 38 evaluable patients received a total of 57 cycles of MP. Three patients were treated at 2 different infusion durations. One patient who initially received a 12-h infusion was treated subsequently on the 24-h infusion schedule. Two other patients who initially received 24-h infusions were also studied at the 36-h infusion duration. All patients had received prior chemotherapy. Nineteen had received prior p.o. MP therapy. The median age was 10 years with a range of 1.1 to 36 years. Twenty-five patients were male, and 13 were female. Nineteen had ALL. Three each had ependymoma and brainstem glioma. Two each had astrocytoma, osteosarcoma, rhabdomyosarcoma,

1 To whom requests for reprints should be addressed, at Room 13C-118, Building 10, Pediatric Branch, National Cancer Institute, NIH, Bethesda, MD 20205.
2 Recipient of partial support from National Cancer Institute Grant CA05587-23.
3 The abbreviations used are: MP, mercaptopurine; CSF, cerebrospinal fluid; CNS, central nervous system; ALL, acute lymphoblastic leukemia; TG, thioguanine; TX, thioxanthine; HPLC, high-pressure liquid chromatography; TU, thiouric acid; MPR, mercaptopurine riboside; PBS, phosphate-buffered saline (6.3 mm Na2HPO4,0.8 mm KH2PO4,0.154 m NaCl, pH 7.4); f2, elimination half-life; Cmin, steady-state plasma concentration.

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MP I.V. INFUSION

Ewing’s sarcoma, and neuroblastoma; and one each had acute myeloblastic leukemia, chronic myelogenous leukemia, and Wilms’ tumor.

Responses were classified as complete, partial, or minor. In leukemic patients, a complete response was defined as the attainment of an M1 marrow (<5% blasts) in the presence of a normal peripheral blood count with no evidence of extramedullary disease in leukemic patients. In solid tumor patients, a complete response was defined as complete disappearance of all physical and laboratory evidence of disease. A partial response was defined as complete disappearance of any circulating blasts and the achievement of an M2 marrow (<25% blasts) in leukemia patients, or as >50% reduction in the size of a followable lesion with no other lesions progressing in solid tumor patients. In leukemia patients, a minor response was one in which there was at least a 50% reduction in the peripheral blast count. In solid tumor patients, a minor response was one in which physical or roentgenographic evidence of objective regression occurred but did not meet the criteria for a partial response.

Sample Collection, Analysis, and Pharmacokinetics. Five-mI plasma samples were obtained at 0.25, 0.5, 1, 2, 4, 8, and 12-h and at 12-h intervals during the MP infusion and at 0.25, 0.5, 1, 2, 3, and 3 h postinfusion. The blood samples were collected in heparinized tubes and immediately placed on ice. The plasma was separated within 1 h and stored at −20° C until the time of analysis. CSF samples were collected after steady state had been achieved in plasma (>6 h). All urine was collected during the period of drug administration and for the first 24 h postinfusion. MPR levels in plasma and CSF were measured by reverse-phase HPLC. The method of MP extraction from plasma was modified from that published previously (6) to a more rapid, but equally sensitive technique (80% recovery of drug from plasma; lower limit of detection, 10 ng/ml). One-mI plasma samples were loaded onto Waters C-18 Sep-pak cartridges after adding 10 pl of 1.0 M dithiothreitol and 20 nI of TG (20 ng/ml) (internal standard). The cartridges were rinsed with 1 ml of 35 mw acetate buffer, and the samples were eluted with a 2-ml methanol wash.

After filtration through 0.22-µm filters (Millipore), 20-µl urine aliquots were injected directly onto the system. A mobile phase of 1% acetonitrile, 0.2% acetic acid, and 98.8% water at a flow rate of 1 ml/min was utilized with UV monitoring at 342 and 313 nm. The resin was then washed 3 times with 1 ml of PBS, after which the thiol compounds absorbed to the resin were eluted with 200 µl of 20 mw mercaptoethanol in PBS. Samples (100 µl) were analyzed by anion-exchange HPLC using a Whatman Partisil-10 SAX column. This solution was then added to 2 mg of a mercurial cellulose resin (9), vortexed for 1 min, and then centrifuged on a Beckman microfuge for 30 s. The resin was then washed 3 times with 1 ml of PBS, after which the thiol compounds absorbed to the resin were eluted with 200 µl of 20 mm mercaptoethanol in PBS. Samples (100 µl) were analyzed by anion-exchange HPLC using a Whatman Partisil-10 SAX column. Samples were eluted using a 10-min linear gradient from 5 mm KH2PO4 and 10 mw KCl, pH 6.0, to 250 mw KH2PO4 and 500 mw KCl, pH 5.5, with a flow rate of 3 ml/min. The effluent was monitored at 342 and 313 nm. Amounts were normalized to 25 mg of hemoglobin (amount of hemoglobin in approximately 8 x 109 erythrocytes).

The total-body clearance of MP was calculated by dividing the drug infusion rate by the steady state MP concentration in plasma. Clearance was also determined by dividing the dose administered by the area under the plasma concentration-time curve when possible. MP renal clearance was calculated by multiplying the fraction of the administered dose of MP appearing in the urine within 24 h of completion of the infusion by the total-body clearance. The t½ was determined by log-linear regression fit of the terminal portion of the plasma concentration-time curve. The CSF:plasma ratio was calculated from simultaneous CSF and plasma samples obtained at least 6 h into the infusion.

Statistics. The statistical significance of apparent differences noted between mean values was assessed by Student’s t test for independent means.

RESULTS

Toxicity. The primary sites of toxicity were mucous membranes, bone marrow, and liver. The major and dose-limiting toxicity was mucositis. As shown in Table 1, there were no episodes of mucositis with infusion durations of 12 or 24 h. There was one moderate episode, during 7 cycles of therapy, at 36 h. With infusion durations of 48 h, there were 2 severe, one moderate, and 4 mild episodes of mucositis during 24 cycles of therapy. However, when the infusion duration was increased to 60 h, there were 6 episodes of mucositis, 3 of them severe, during 13 cycles of therapy for an incidence of 46% at this dose level. These results demonstrate the relationship between MP dose and the frequency and severity of mucositis.

Nineteen patients who did not have bone marrow disease and received 29 cycles of MP were evaluated for hematological toxicity. The results are shown in Table 2. No marrow toxicity was seen with infusions of as long as 36 h. At the 48- and 60-h infusion durations, transient, variable depression of platelet, WBC, and granulocyte counts was observed.

Hepatotoxicity was also observed in this study (Table 3). It was seen at all infusion durations and did not appear to be dose related. Hepatotoxicity was manifested primarily in the form of elevated serum transaminases rather than as cholestatic jaundice. It was usually transient and not clinically significant, with liver chemistries peaking within 3 to 5 days of completing the course of MP and returning to normal within 7 to 10 days. However, one patient developed severe jaundice with a peak bilirubin of 18.8 mg/dl that gradually resolved over a 2-week period following a 60-h MP infusion.

There was no renal (including no hematuria) or CNS toxicity. Nausea and vomiting were not seen consistently and, when observed, were mild. One patient developed a transient macular rash.

Eight patients were receiving concurrent allopurinol. Two received 60-h infusions; 3 received 48-h infusions; and one each received a 36-, 24-, and 12-h infusion. Although the number of patients treated at any one infusion duration was small, there was no evidence of more severe mucositis, myelosuppression, or hepatotoxicity in patients receiving both allopurinol and MP.

Five responses were observed in this trial. One patient with

<table>
<thead>
<tr>
<th>Table 1 Mucositis</th>
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<tr>
<td><strong>Infusion duration (h)</strong></td>
</tr>
<tr>
<td>12</td>
</tr>
<tr>
<td>24</td>
</tr>
<tr>
<td>36</td>
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<td>48</td>
</tr>
<tr>
<td>60</td>
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</table>

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neuroblastoma experienced a partial regression of tumor; 3 patients with ALL had minor responses (all of whom had received a prior conventional dose, p.o. MP), and one patient with an ependymoma had a minor response to MP therapy.

Pharmacokinetics. The plasma pharmacokinetics of MP administered as a prolonged i.v. infusion was determined in 22 patients. The mean plasma MP concentrations achieved in patients treated with infusions up to 48 h in length are illustrated in Chart 1. Steady state was achieved in plasma within 4 h; mean steady state plasma levels were 6.9 µM. There was minimal interpatient variability in plasma steady-state concentrations with only a 2-fold range between the highest and lowest values achieved. Once the drug infusion was completed, MP levels rapidly declined and were less than 1.0 µM by 2 h postinfusion. The major pharmacokinetic values for MP are shown in Table 4. The mean total-body clearance and t½ were 864 ml/min/sq m and 0.9 h, respectively. There was no evidence of time-dependent pharmacokinetics, since the duration of infusion had no effect on the Css, clearance, or t½ of MP.

As is also shown in Chart 1, steady-state MP levels in CSF were reached by 6 h into the infusion and exceeded 1.3 µM. The mean steady-state MP concentrations in plasma and CSF in the 8 patients in whom both were characterized were 6.1 and 1.7 µM, respectively, resulting in a CSF:plasma ratio of 0.27 (Table 4). Three of these patients had active meningeal leukemia at the time of study, but their MP CSF levels did not differ significantly from the 5 patients who did not.

Complete urine collections were obtained from 10 patients. The urinary elimination pattern for MP and its major metabolites is shown in Chart 2. Fifty-nine % of the dose of MP administered by i.v. infusion was recovered in the urine in the form of parent compound or metabolites (TU, TX, MPR) within 24 h of the end of the infusion. MP was the primary compound appearing in

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**Table 2**

<table>
<thead>
<tr>
<th>Infusion duration (h)</th>
<th>No. of patients</th>
<th>No. of cycles</th>
<th>Platelets&lt;sup&gt;a&lt;/sup&gt;</th>
<th>WBC&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Granulocytes&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Hemoglobin (g/dl)&lt;sup&gt;a&lt;/sup&gt;</th>
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<tbody>
<tr>
<td>12</td>
<td>2</td>
<td>2</td>
<td>137 (30-244)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>4.4 (2.8-6.1)</td>
<td>2.9 (2.0-3.7)</td>
<td>9.0 (6.8-9.1)</td>
</tr>
<tr>
<td>24</td>
<td>3</td>
<td>4</td>
<td>196 (33-211)</td>
<td>3.3 (2.4-7.4)</td>
<td>2.7 (1.1-6.3)</td>
<td>10.2 (8.2-11.0)</td>
</tr>
<tr>
<td>36</td>
<td>3</td>
<td>3</td>
<td>180 (19-267)</td>
<td>5.3 (1.9-6.6)</td>
<td>1.2 (1.0-5.1)</td>
<td>10.8 (9.1-11.3)</td>
</tr>
<tr>
<td>48</td>
<td>10</td>
<td>14</td>
<td>85 (31-330)</td>
<td>2.5 (0.5-4.6)</td>
<td>1.1 (0.18-4.2)</td>
<td>9.3 (7.7-11.8)</td>
</tr>
<tr>
<td>60</td>
<td>5</td>
<td>7</td>
<td>90 (12-234)</td>
<td>2.8 (0.7-6.2)</td>
<td>1.8 (0.4-3.1)</td>
<td>9.6 (7.5-11.4)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Median nadir (x 10<sup>9</sup>/cu mm).

<sup>b</sup> Numbers in parentheses, range.

**Table 3**

<table>
<thead>
<tr>
<th>Infusion duration (h)</th>
<th>No. of patients</th>
<th>No. of cycles</th>
<th>Bilirubin (mg/dl)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>SGOT (units/liter)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>SGPT (units/liter)&lt;sup&gt;a&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td>12</td>
<td>4</td>
<td>6</td>
<td>0.5 (0.2-2.5)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>47 (19-750)</td>
<td>70 (12-795)</td>
</tr>
<tr>
<td>24</td>
<td>6</td>
<td>8</td>
<td>1.8 (0.5-4.1)</td>
<td>57 (20-278)</td>
<td>64 (20-190)</td>
</tr>
<tr>
<td>36</td>
<td>6</td>
<td>7</td>
<td>0.6 (0.5-2.6)</td>
<td>152 (61-503)</td>
<td>151 (52-296)</td>
</tr>
<tr>
<td>48</td>
<td>17</td>
<td>24</td>
<td>0.9 (0.3-4.4)</td>
<td>57 (15-1065)</td>
<td>86 (10-670)</td>
</tr>
<tr>
<td>60</td>
<td>10</td>
<td>13</td>
<td>0.7 (0.2-18.8)</td>
<td>194 (21-605)</td>
<td>237 (25-1911)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Median peak level.

<sup>b</sup> Numbers in parentheses, range.

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**Table 4**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C&lt;sub&gt;ss&lt;/sub&gt; plasma (µM) (n = 22)</td>
<td>6.9 ± 0.4&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Clearance (ml/min/sq m)</td>
<td>864 ± 49</td>
</tr>
<tr>
<td>Half-life (h)</td>
<td>0.9 ± 0.04</td>
</tr>
<tr>
<td>C&lt;sub&gt;ss&lt;/sub&gt; CSF (µM) (n = 8)</td>
<td>1.7 ± 0.3</td>
</tr>
<tr>
<td>CSF:plasma ratio</td>
<td>0.27 ± 0.05</td>
</tr>
</tbody>
</table>

<sup>a</sup> Mean ± SE.

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**Chart 1.** Mean MP concentrations in plasma (●) and CSF (○); bars, SE.

**Chart 2.** Major drug compounds identified in urine following MP administration as an i.v. infusion; bars, SE.
urine, accounting for 30% of the dose administered. TU accounted for 25% of the dose of MP given; TX and MPR were 2 additional minor metabolites detected.

Of the 22 patients on whom pharmacokinetic data were obtained, 6 were receiving concurrent allopurinol (300 mg/sq m/day). This presented an opportunity to examine the influence of this potent inhibitor of xanthine oxidase on the disposition of MP. In contrast to the situation following p.o. MP administration (11), allopurinol coadministration had no significant (P > 0.1) effect on the plasma pharmacokinetic values of MP (CSS, clearance). These results are shown in Table 5. However, allopurinol did have an obvious effect on the urinary MP metabolite pattern (Chart 3). Of the 10 patients on whom urinary data were obtained, 4 were receiving allopurinol. In these patients, 42% of the administered dose of MP was eliminated in the urine as MP compared to 21% in patients not given allopurinol. Patients on allopurinol eliminated 13% of the administered dose of MP as TU compared to 33% in patients not on allopurinol. In addition, those on allopurinol eliminated 5% of their MP dose as TX, compared to 1% in patients not on allopurinol. Patients on allopurinol had a higher renal clearance of MP [333 ± 28 (SE) ml/min/sq m] than patients not receiving allopurinol (191 ± 26 ml/min/sq m).

MP metabolites were measured in 50 RBC samples from 9 patients during and following the i.v. infusions. None of these patients received allopurinol. The levels of thiopurine metabolites in erythrocytes increased slowly during the MP infusion and decreased much more slowly than plasma MP following completion of the infusion with a mean elimination half-life of 3.6 ± 0.4 (SE) days. The mean peak RBC thiopurine level was 870 ± 188 pmol/25 mg hemoglobin with a nearly 10-fold range. Thioguanosine triphosphate was the major intracellular metabolite after 12 h of infusion, accounting for 72 ± 2% of the total thiopurines quantified. Thioguanosine diphosphate was the metabolite found in the second largest amount with the remainder of the MP intracellular pool composed of thioguanosine monophosphate, thioxanthosine monophosphate, and TU. The time course of RBC thiopurine levels in 4 representative patients during and following MP administration is shown in Chart 4.

**DISCUSSION**

On the basis of in vitro cytotoxicity data suggesting that MP concentrations of 1 to 10 μM maintained for prolonged periods of time are required to achieve an optimal antineoplastic effect, we initiated the present Phase I study. Our goal was to administer MP at a dose rate that was calculated to result in steady state plasma concentrations of approximately 5 μM. A phase I study of MP administered as an i.v. infusion was felt to be necessary because of the very limited clinical information available on MP given in this manner (7). In this study, the infusion duration rather than the dose rate was the factor that was escalated. This approach was taken because of the known cell cycle dependence of antmitobolites (2). That is, once a biologically active concentration of MP is achieved, duration of exposure becomes an important determinant of cytotoxicity.

In the present study, infusions of 60 h in length resulted in unacceptable mucositis. Infusions of 48 h in duration, however, appeared to be well tolerated in most patients without dose-limiting mucositis or bone marrow toxicity. We therefore can recommend that Phase II studies of MP i.v. infusions at the dose rate of 50 mg/sq m/h be conducted, at least initially, at durations of not greater than 48 h. The other major toxicity seen in this study, hepatotoxicity, did not appear to be dose related.

The results of the pharmacokinetic studies indicated that this approach was successful in achieving and maintaining prolonged MP steady state concentrations exceeding 1.0 and 5.0 μM in CSF and plasma, respectively. These are concentrations of MP that are cytotoxic to leukemic cells in vitro (10). In contrast, we were unable to detect MP (<0.1 μM) in the CSF of 6 patients given conventional doses of p.o. MP (data not shown). The ability to achieve high levels of MP in the CNS is an important attribute of this mode of MP administration and may have relevance for the treatment of cancers which have a high propensity for...
metastasis to the CNS, such as ALL.

In addition, i.v. administration of MP by continuous infusion results in greater tissue exposure to drug than that which occurs with conventional, p.o. administration. For example, the mean area under the plasma concentration-time curve for a 48-h i.v. infusion was 158-fold greater than that following a standard dose (75 mg/sq m) of p.o.-administered MP (12).

A comparison of the urinary metabolite pattern seen in this study with that seen following p.o. MP administration revealed interesting differences. MP was a major urinary metabolite accounting for 42 or 21% of the administered dose of MP, depending on whether the patient did or did not receive concurrent allopurinol, when MP was given as an i.v. infusion. Following p.o. dosing, however, only 7% of the administered dose appears in the urine as MP (4). This reflects the reduced importance of metabolism and the increased importance of renal elimination in MP clearance when this compound is administered i.v.

Unlike the situation that occurs with p.o. MP dosing, allopurinol had no significant effect on the plasma pharmacokinetics of MP when administered as an i.v. infusion. These results confirm those of our earlier study of bolus i.v. MP administration (11).

Even though allopurinol had no significant effect on the disposition of MP in plasma, it did, by inhibiting xanthine oxidase, substantially alter the urinary metabolite pattern, increasing the amount of MP and TX and reducing the amount of TU appearing in the urine. Although of no consequence in patients with normal renal function, the increased amount of MP appearing in the urine of patients on allopurinol who have renal insufficiency might result in greater toxicity due to increased accumulation of MP.

MP undergoes intracellular conversion to several metabolites including MP, TG, TX, and methylated MP nucleotides (3, 10, 14). These nucleotide metabolites are responsible for the cytotoxic effects of MP and act by mechanisms that include inhibition of de novo purine synthesis and incorporation of TG nucleotides into DNA and RNA (3, 10). The measurement of these cytotoxic nucleotide metabolites within the neoplastic cells of patients undergoing MP therapy would certainly be of interest (8). However, this was not possible with current analytical methodology.

We reported previously that, when human leukemic cell lines are incubated in vitro with MP, the major intracellular metabolite formed is thioinosine monophosphate. Substantial amounts of thioanthosine monophosphate are also formed, but there is little thioguanine nucleotide present (13). In contrast, the results of the current study indicate that, in the erythrocytes of patients receiving MP as an i.v. infusion, the major intracellular metabolite is thioguanosine triphosphate. Although examination of MP metabolism in the RBC does not provide information on the antineoplastic activity of MP, it may furnish data regarding toxicity and/or compliance. For example, the observation that the half-life of erythrocyte thiopurines is 3.6 days indicates that these levels may be a useful measure of compliance and chronic MP exposure.

In summary, this study demonstrates that MP can be safely administered as an i.v. infusion for 48 h. A dose rate of 50 mg/sq m/h achieves steady state MP levels in plasma and CSF associated with optimal cytotoxicity in vitro, and these levels can be maintained for a prolonged period of time. In addition, administration of MP as an i.v. infusion results in minimal interpatient variability in plasma MP levels, an advantage not seen with conventional p.o. dosing. Phase II trials utilizing the identical dose rate and infusion duration are currently under way in both children and adults.

REFERENCES

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