Phase I Trial of 5-Fluorouracil and Dipyridamole Administered by Seventy-two-Hour Concurrent Continuous Infusion


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ABSTRACT

Forty-seven patients with advanced malignancies were treated with a concurrent 72-h continuous infusion of 5-fluorouracil (FUra) and dipyridamole. The FUra dose was escalated over the dose range of 185 to 3600 mg/m²/day for 3 days. Dipyridamole was administered in a fixed dose of 7.7 mg/kg/day for 3 days. A total of 155 courses of therapy were completed of which there were 31 paired courses of the combination and FUra alone, at the same dose of FUra and in the same patient. This was for purposes of analysis of pharmacokinetics and modulation of FUra toxicity by dipyridamole.

Stomatitis was the dose-limiting toxicity experienced by patients entered into this trial. Myelosuppression was not a serious problem. Increasing FUra plasma concentration was associated with greater leukopenia and stomatitis. Dipyridamole did not appear to modulate the systemic toxicity of FUra.

The pharmacokinetics of FUra were altered by the concurrent administration of dipyridamole. Dipyridamole promoted the total body clearance of FUra which resulted in lower mean steady-state FUra plasma concentrations when compared with courses of FUra alone administered at the same dose level. These differences were statistically significant over the course of the trial. For courses of the combination, FUra exhibited linear pharmacokinetics over the dose range studied. Total body clearance of FUra declined slightly at the higher dose levels, but the differences were not significant. For courses of FUra alone, total body clearance was significantly decreased above the dose level of 2300 mg/m²/day. At the maximal tolerated dose of FUra, 2300 mg/m²/day ×3, mean steady-state FUra plasma concentration and total body clearance were 6.6 μM and 122 liters/h/m², respectively, for courses of the combination. The corresponding pharmacokinetic parameters were 7.4 μM and 103 liters/h/m² for courses when FUra was given alone. Further evaluation of the utility of this regimen and basis of these pharmacokinetic observations appear warranted.

INTRODUCTION

The biochemical modulation of various cytotoxic drugs is an investigational approach to enhance the therapeutic efficacy of these agents. The elucidation of the complex intracellular metabolism of FUra has provided insights into biochemical mechanisms of resistance to this fluoropyrimidine and strategies to circumvent this problem through pharmacological means (1, 2). This has been the basis for combinations of FUra with methotrexate (3–5), thymidine (6–8), phosphono-N-acetyl-L-aspartic acid (9–13), and more recently leucovorin (14–16).

Dipyridamole, a nucleoside transport inhibitor, has been shown in vitro to enhance the cytotoxicity of FUra (17). One explanation for this is the inhibition of thymidine salvage by dipyridamole, as has been observed in cultured cells exposed to the combination of methotrexate and dipyridamole (18–20). However, inhibition of thymidine salvage in cells exposed to FUra and dipyridamole does not fully explain the enhanced cytotoxicity of this combination (17). Dipyridamole also alters the intracellular metabolism of FUra (21). As a direct result of nucleoside transport inhibition, intracellular levels of fluorodeoxyuridine are increased which results in increased retention of fluorodeoxyuridine monophosphate (21). This reaction ultimately leads to depletion of thymidine triphosphate pools and interferes with DNA biosynthesis, which is a prime pathway of FUra cytotoxicity. Alternative mechanisms by which dipyridamole enhances FUra cytotoxicity have been reported in detail (22). Briefly, dipyridamole blocks the efflux of ribose 1-phosphate and deoxyribose 1-phosphate donors which results in increased formation of fluorouridine and fluorodeoxyuridine from FUra, respectively. Fluorouridine is metabolized to fluorouridine triphosphate, which is incorporated into RNA, and is another pathway of FUra cytotoxicity (23).

We have developed a high dose, i.v., continuous infusion schedule of dipyridamole, which attains free plasma dipyridamole drug levels required in vitro to block nucleoside transport (24–26). In this study, we combined this high dose infusion dipyridamole regimen with a concurrent 72-h continuous infusion of FUra in a phase I trial. The goals of this study were to determine the maximal tolerated dose of FUra as a 72-h continuous infusion concurrently with dipyridamole, evaluate the ability of dipyridamole to modulate FUra toxicity, and investigate the pharmacokinetics of both drugs.

MATERIALS AND METHODS

Patient Selection

Patients with histologically documented advanced malignancies for whom no standard effective therapy was available were entered into the protocol between September 1986 and April 1988. Signed informed consent was obtained from all patients in keeping with Food and Drug Administration and institutional guidelines. All patients had Eastern Cooperative Oncology Group performance status values (PS) ≤2 (27), a life expectancy of at least 12 weeks, and received no cytotoxic chemotherapy for 4 weeks prior to entry, were free of active infection, and had adequate bone marrow (WBC ≥ 4000/mm³ and platelet count ≥ 100,000/mm³), hepatic (bilirubin ≤ 2 mg/dl, aspartate aminotransferase ≤ 3 × normal, and normal prothrombin time), renal (BUN ≤ 30 mg/dl and creatinine ≤ 2.0 mg/dl), and metabolic (normal electrolytes, calcium, and glucose; controlled diabetes was permitted) functions. Patients who had a PS ≥ 3, symptomatic coronary artery disease, central nervous system metastases, or a coagulation disorder or were taking either dipyridamole or theophylline were not eligible for the study.

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5 The abbreviations used are: FUra, 5-fluorouracil; PS, performance status; MTD, maximum tolerated dose; Cmax, mean steady-state plasma concentration.
Drug Administration and FUra Dose Escalation

Dipyridamole was administered at a fixed dose of 7.7 mg/kg/day as a 72-h continuous infusion via a controlled infusion pump through a double-lumen central venous catheter. This dose and schedule of dipyridamole is the maximal tolerated dose as determined from a prior clinical trial at our institution (26). FUra was administered in escalating doses as a concurrent 72-h continuous infusion (Table 1). The treatment cycle was repeated every 21 days. A minimum of 3 new patients were entered at each dose level. If no grade 2 mucosal or grade 3 nonmucosal toxicity occurred, the next 3 patients were entered at a FUra dose one level higher.

FUra dose was escalated one level each cycle in patients in whom the previous cycle of therapy was associated with less than grade 2 mucosal or less than grade 3 nonmucosal toxicity. Patients with grade 2 mucosal or any other grade 3 toxicity that occurred with FUra and dipyridamole received the next course with FUra alone at the same dose. This was done in order to determine whether dipyridamole modulated FUra toxicity.

The MTD of FUra was defined as that dose level at which grade 2 mucosal or grade 3 nonmucosal toxicity (other than nausea, vomiting, diarrhea, or headache which was associated with the 72-h dipyridamole infusion) occurred in greater than one-third of new patients. Once this occurred, 3 additional patients were treated at this level.

Patients with stable or responding disease and in whom all toxicity from a prior cycle had resolved continued to receive treatment with the combination. Patients with intolerable toxicity or evidence of progressive disease received no further treatment.

Drug Formulation

Dipyridamole was supplied by Boehringer Ingelheim (Ridgefield, CT) in 2-ml sterile ampules containing 10 mg of drug. The calculated 12-h dose was administered in 1 liter of normal saline. FUra was prepared in the standard fashion from ampules containing 50 mg/ml of drug. The calculated 12-h dose was administered in 500 ml of 5% dextrose in water.

Patient Follow-up and Assessment

A complete history-physical examination and laboratory evaluation including documentation of all measurable disease were done within 48 h of entry into the study. During each cycle of therapy weekly complete blood cell counts with differential and platelet count, prothrombin time, serum chemistries, and urinalysis were obtained. Disease assessment with appropriate radiological examination was undertaken at approximately 6- to 9-week intervals.

Pharmacological Evaluation and Analytical Techniques

FUra Plasma Levels. FUra plasma levels were determined for each course prior to the infusion and at the following intervals during the 72-h continuous infusion: 24, 48, and 72 h. These time points occurred midmorning to late morning during the 72-h infusion period for all patients. In 3 patients elimination kinetics of FUra were determined from plasma samples obtained at 5, 10, 20, 30, 45, 60, and 90 min after completion of the 72-h infusion. FUra was assayed by high performance liquid chromatography using a modification of the technique described by Stetson et al. (28).

Dipyridamole Assay. Dipyridamole total and free plasma levels were determined in all patients treated with the combination prior to the infusion and at 24, 48, and 72 h during the infusion period. Free dipyridamole in plasma was separated from bound dipyridamole using the Amicon CentrIFree Micropartition System (Amicon, Danvers, MA). Methodology for this procedure and high performance liquid chromatography assay for dipyridamole have been previously described in detail (24).

RESULTS

Patient Characteristics. Forty-seven patients were treated (Table 2). Patients had good performance status (45 had PS scores of 0 or 1) and the majority had received previous systemic therapy, although 11 patients had no prior treatment. Thirty patients had gastrointestinal primary malignancies of which 21 were colorectal. The remaining 17 patients had other histological types of malignancy.

FUra Dose Escalation. A total of 167 courses of therapy were initiated of which 155 were completed and evaluable. Twelve courses of therapy were initiated but un evaluable due to progressive disease (5 patients), catheter complications necessitating treatment interruption (3 patients), intolerable diarrhea (2 patients), refusal to have blood drawn (1 patient), and ineligibility for study because of an elevated aspartate aminotransferase (1 patient).

Thirty-five courses of FUra alone were administered to 21 patients. Of these, there were 32 courses of FUra alone and 32 courses of the FUra and dipyridamole combination administered at the same dose level of FUra and in the same patient. Of the paired courses, 31 were evaluable for toxicity, and 31 were evaluable for pharmacokinetic analysis. This was done to analyze modulation of FUra toxicity by dipyridamole. Three courses of FUra alone were administered without a comparable FUra and dipyridamole dose. Table 1 summarizes the dose escalation as carried out in this trial.

Toxicity. Approximately one-half of the courses administered in this trial were associated with nausea, vomiting, and headache. The majority of these episodes occurred during the 72-h infusion of dipyridamole. These toxicities were the same as we have noted in our prior dipyridamole studies (25, 26). There was little other toxicity observed over the FUra dose range of 185 to 1655 mg/m2/day. At dosages above this stomatitis and myelosuppression were more frequent manifestations of toxicity.

Table 1 Dose escalation

<table>
<thead>
<tr>
<th>Level</th>
<th>FUra (mg/m2/day x3)</th>
<th>Patients (new)</th>
<th>Cycles</th>
<th>FUra alone</th>
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<tbody>
<tr>
<td>1</td>
<td>165</td>
<td>4 (4)</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>370</td>
<td>7 (4)</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>555</td>
<td>7 (3)</td>
<td>7</td>
<td>0</td>
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<td>4</td>
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<td>8</td>
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<td>9 (3)</td>
<td>12</td>
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<tr>
<td>9</td>
<td>1655</td>
<td>10 (3)</td>
<td>17</td>
<td>7</td>
</tr>
<tr>
<td>10</td>
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<tr>
<td>13</td>
<td>3600</td>
<td>3 (0)</td>
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<td>Total</td>
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Table 2 Patient characteristics

<table>
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<th>Characteristic</th>
<th>Total patients (M:F)</th>
<th>Median age (yr) (range)</th>
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<tr>
<td></td>
<td>34:13</td>
<td>61 (39-74)</td>
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<td>Primary tumor</td>
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<td>Colorectal</td>
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<tr>
<td>Pancreas</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esophagus</td>
<td>2</td>
<td></td>
<td></td>
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<td>2</td>
<td></td>
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Grade 2 or worse stomatitis was observed in patients treated with FUra and dipyridamole combination at the higher dose levels of FUra as follows: 1840 mg/m²/day, 17% (2 of 12 courses); 2300 mg/m²/day, 25% (4 of 16); 2875 mg/m²/day, 45% (9 of 20); and 3600 mg/m²/day, 67% (2 of 3). No new patient treated with the combination 1840 mg/m²/day of FUra and dipyridamole experienced dose-limiting toxicity. Of new patients treated at the next 2 higher dose levels, 2300 and 2875 mg/m²/day FUra, 50 and 67% of patients, respectively, experienced grade 2 or worse stomatitis. There was considerable interpatient variation in the incidence of stomatitis. Stomatitis was clearly the dose-limiting toxicity observed in this trial. Table 3 summarizes the dose-limiting toxicity in new patients.

Substantial myelosuppression was infrequent. Leukopenia was more frequent than thrombocytopenia. Nadir WBC counts at the higher dose levels of FUra in evaluable patients who received the FUra and dipyridamole combination are summarized in Table 4. Only one new patient entered at the higher dose levels of FUra experienced Grade 4 leukopenia. Anemia was not a problem.

There was little hepatic or renal toxicity in this trial. Several patients experienced local skin and venous irritation from the peripheral infusion of FUra, which was circumvented by the administration of FUra via a double-lumen central venous catheter. No cerebellar symptoms or episodes of ischemic chest pain were observed.

There was one drug-related death in this trial. This patient received an initial cycle of 2875 mg/m²/day of FUra and dipyridamole, which was associated with grade 2 stomatitis. The patient developed profound myelosuppression (absolute granulocyte count, 323/mm³; platelet count, 10,000/mm³) and fever during the second course of therapy with 2875 mg/m²/day of FUra alone. This course was complicated by fatal pneumonia. Stomatitis was not a significant manifestation of toxicity in the second cycle. Postmortem examination revealed right lower lobe pneumonia and evidence of progressive disease.

Dipyridamole did not appear clearly to modulate the clinical toxicity of FUra. Twenty of the 31 paired courses of the combination and FUra alone were either not associated with stomatitis or the stomatitis incurred was the same. In 6 pairs the stomatitis was more severe for the combination and in 5 it was worse for FUra when given alone.

Although leukopenia was more pronounced in 17 of 31 paired courses of the combination versus FUra alone, there was no significant difference in the WBC nadir for courses of the combination when compared with courses of FUra alone in the same patient (P = 0.35). An analysis of the percentage change in WBC in these paired courses also failed to disclose a statistically significant difference. We did note a significant decrease in WBC nadir with increasing plasma concentration of FUra for both courses of the combination and FUra alone. Fig. 1 plots this relationship for dose levels of 1840 mg/m²/day ×3 and above (r = 0.53, P = 0.001). Prior to this level, no significant incidence of leukopenia was observed.

Increasing FUra plasma concentration was also associated with an increased incidence of dose-limiting stomatitis. Fourteen % of courses with FUra plasma concentration <4.0 μM were associated with any grade of stomatitis (1, 2, or 3). The corresponding values at higher FUra plasma concentrations were 59% at FUra plasma levels between 4.0 and 8.0 μM, 75% at levels between 8.0 and 12.0 μM, and 89% at levels >12.0 μM.

Pharmacokinetics. The mean steady-state plasma concentration during the infusion of 23 mg/kg/72 h dipyridamole were: total dipyridamole, 6.7 ± 0.29 μM (mean ± SE), and free dipyridamole, 24.1 ± 0.86 nm. The mean percentage of free dipyridamole was 0.41 ± 0.015. Ninety % of the mean steady-state plasma concentration of total dipyridamole was attained by 24 h and steady-state was maintained for the remainder of the dipyridamole infusion. The mean total body clearance for all courses of dipyridamole infusion was 4.6 ± 0.21 liters/h/m². Dipyridamole clearance varied inversely with the concentration of serum α-1-glycoprotein, (r = 0.75, P < 0.001) as reported previously (24).

Fig. 2 plots the mean steady-state FUra plasma concentration versus dose over the course of the trial. For courses of the combination and for FUra alone, the mean steady-state concentration increased linearly with dose through the dose level of 2300 mg/m²/day ×3 (r = 0.899, P < 0.001; r = 0.904, P < 0.001, respectively, by regression analysis). For courses of the combination, at doses above this level, plasma concentrations of FUra were slightly higher and corresponding total body clearance slightly lower than linearity would predict, but the differences were not significant. For courses of FUra alone, however, plasma levels at 2875 and 3600 mg/m²/day were higher than linearity would predict and the corresponding total body clearances were significantly decreased from that at 2300 mg/m²/day (P < 0.001).

A total of 31 paired courses of the combination FUra and dipyridamole versus FUra alone at the same dose level and in the same patient were studied to determine whether dipyridamole modulates FUra pharmacokinetics. Fig. 3 shows the mean
steady-state plasma concentrations and total body clearances for these paired courses. For all paired courses taken together, differences were seen at nearly all dose levels and were most pronounced at the higher levels. Table 5 gives these parameters for two FUra dose levels, 1655 mg/m²/day and 2875 mg/m²/day, in which there were 6 and 8 paired courses, respectively, available for comparison.

In 3 patients, two at dose level 2875 mg/m²/day FUra and one at 3600 mg/m²/day FUra, terminal FUra elimination kinetics were examined following cessation of the infusion for paired courses of FUra with and without dipyridamole. The mean half-life of FUra in courses of FUra and dipyridamole was compared to that of FUra alone. There was no difference in the terminal half-life of FUra in courses of FUra and dipyridamole, 15.3 min, and FUra alone, 14.6 min (P = 0.81).

At the MTD, 2300 mg/kg/day x3 FUra, mean steady-state FUra plasma concentration was 7.4 μM in courses of FUra alone and 6.6 μM in courses of the combination. FUra total body clearance at this dose level was 122 and 103 liters/h/m² for courses with and without dipyridamole, respectively. The highest mean FUra plasma concentration achieved in this trial was 20.1 μM at 3600 mg/m²/day of FUra alone.

Clinical Response. There were 2 partial responses among the 47 patients. Both remissions were observed in patients with measurable disease and colorectal carcinoma. In one patient, who received no prior treatment, there was a 50% reduction of pulmonary nodules on chest X-ray. In the second patient, who had previously received 14 months of FUra as a weekly bolus injection, there was a 50% reduction of hepatic metastases demonstrated on abdominal computed tomographic scan. The duration of both partial remissions was 4 months.

**DISCUSSION**

The dipyridamole pharmacokinetics that we observed were similar to our prior experience with this high dose continuous infusion schedule (25, 26). The steady-state dipyridamole plasma levels achieved in this trial correspond to those required in vitro to perturb nucleoside transport and FUra metabolism (17, 21). Dipyridamole appears to alter FUra clearance. When these drugs are administered concurrently as a 72-h continuous infusion, dipyridamole increases the total body clearance of FUra which results in a lower steady-state FUra plasma concentration. We demonstrated in 3 patients that dipyridamole did not affect the terminal elimination half-life of FUra.

It is not known why dipyridamole promotes the total body clearance of FUra. It is known that the rate-limiting step in the

<table>
<thead>
<tr>
<th>FUra DOSE (mg/m²/day)</th>
<th>Mean Cₘ FUra (μM)</th>
<th>FUra + dipyridamole</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1655 mg/m²/day</td>
<td>5.4 ±0.33</td>
<td>3.7 ±0.34</td>
<td>P = 0.016</td>
</tr>
<tr>
<td>2875 mg/m²/day</td>
<td>13.9 ±0.46</td>
<td>10.5 ±0.96</td>
<td>P = 0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Range Cₘ FUra (μM)</th>
<th>FUra</th>
<th>4.2–6.3</th>
<th>11.9–15.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>FUra + dipyridamole</td>
<td>2.7–4.7</td>
<td>6.2–13.8</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean total body clearance FUra (liters/h/m²)</th>
<th>FUra</th>
<th>105 ±6.3</th>
<th>67 ±2.2</th>
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<tr>
<td>FUra + dipyridamole</td>
<td>148 ±14.0</td>
<td>94 ±10.0</td>
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</tr>
<tr>
<td>P value from paired t test</td>
<td>P = 0.023</td>
<td>P = 0.018</td>
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</table>

* Mean ± SE.

Table 5 Comparison of FUra pharmacokinetic parameters in paired courses with and without dipyridamole at 2 FUra dose levels
catabolism of FUra is the reaction catalyzed by dihydouracil dehydrogenase (2, 29, 30). This enzyme has broad substrate specificity (2). It is possible that dipyridamole may interact with this enzyme in some fashion to promote the catabolism of FUra. It is reported that the concurrent administration of thymidine and FUra results in reduced FUra plasma clearance and increases steady-state FUra plasma concentration (31). Dipyridamole in vitro blocks thymidine salvage and enhances FUra cytotoxicity (18–20). Perhaps dipyridamole promotes FUra clearance by blocking the effects of thymidine on FUra metabolism. The biochemical explanation for this, however, awaits further study.

The steady-state FUra plasma concentrations achieved and the estimation of FUra total body clearance in this trial are similar to those reported by other investigators (32–35). Erhlichman et al. (32) used a 5-day continuous infusion of FUra over a dose range of 1250 to 2250 mg/m²/day. They reported a steady-state FUra plasma concentration of 7.49 µM and FUra total body clearance of 120 liters/h/m² when 2250 mg/m²/day were infused. These parameters correspond to our FUra plasma concentration and clearance of 7.4 µM and 103 liters/h/m², respectively, for FUra alone at our MTD of 2300 mg/m²/day. They also noted a linear relationship between FUra dose and plasma concentration over the dose range 1250 to 2250 mg/m²/day.

At doses above 2300 mg/m²/day FUra alone we observed nonlinear FUra pharmacokinetics. Collins et al. (36) described a nonlinear pharmacokinetic model for FUra (Fig. 3). Wagner et al. (35) cited several studies in which nonlinear FUra pharmacokinetics were observed for a variety of reasons. These include a decrease in hepatic extraction ratio (37, 38), increase in bioavailability (39, 40), and an increase in elimination half-life (30), all of which were observed with an increase in FUra dose rate. Saturable clearance mechanisms of FUra are well established.

Circadian rhythm-varying FUra plasma concentration has been reported for continuous infusion of FUra (41). The schedule of pharmacokinetic sampling used in this trial does not permit us to comment on this observation.

The frequency and severity of nausea, vomiting, and headache which were observed during the 72-h infusion of dipyridamole were similar to our prior experience with this high dose schedule. The dose-limiting FUra toxicity in this trial was stomatitis and was anticipated from prior published reports using a continuous infusion schedule (33, 42–45). Myelosuppression, which is commonly encountered with i.v. bolus FUra, was not a frequent problem. It was not insignificant, however, as one fatal toxicity occurred during the conduct of this trial. We have demonstrated that increasing FUra plasma concentration correlates with greater leukopenia and stomatitis. There was considerable interpatient variation in the incidence of myelosuppression and dose-limiting stomatitis, which has also been observed for FUra (45, 46). We could not detect modulation of FUra-induced myelosuppression or dose-limiting stomatitis by dipyridamole. It is of interest that comparable toxicity was demonstrated that increasing FUra plasma concentration correlates with greater leukopenia and stomatitis. There was considerable interpatient variation in the incidence of myelosuppression and dose-limiting stomatitis, which has also been observed for FUra (45, 46). We could not detect modulation of FUra-induced myelosuppression or dose-limiting stomatitis by dipyridamole. It is of interest that comparable toxicity was encountered in courses of the combination versus FUra alone despite approximately 21% lower mean FUra plasma concentration. A detailed pharmacodynamic analysis of FUra plasma concentrations and toxicity is being developed and will be reported separately (47).

In summary, the MTD of FUra as administered in this trial is 2300 mg/m²/day ×3 in combination with dipyridamole at 7.7 mg/kg/day ×3. Dipyridamole modulates the clearance of FUra. It promotes the total body clearance of FUra which results in lower steady-state FUra plasma concentration. Dipyridamole does not clearly modulate the systemic toxicity of FUra. Preclinical data indicate that dipyridamole enhances FUra cytotoxicity. Since tumor cells may be more susceptible to disruption of nucleoside transport than normal cells, the enhanced cytotoxicity of dipyridamole may be selective. Therefore, further evaluation of FUra-dipyridamole combination therapy appears warranted.

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24. Willson, J. K. V., Fischer, P. H., Remick, S. C., Tutsch, K. D., Grem, J. L., 
22. Oken, M. M., Creech, R. H., Tormey, D. C., Horton, J., Davis, T. E., 
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