Phase I Trial of Dipyridamole with 5-Fluorouracil and Folinic Acid

G. T. Budd, A. Jayaraj, D. Grabowski, D. Adelstein, L. Bauer, J. Boyett, R. Bukowski, S. Murthy, and J. Weick

ABSTRACT

We have performed two Phase I trials of the combination of dipyridamole, 5-fluorouracil (5-FU), and folic acid in patients with advanced refractory malignancy, based upon in vitro evidence that dipyridamole can modulate the cytotoxicity of 5-FU. In the first trial, patients were treated every 4 wk with dipyridamole (50 mg/m²) p.o. every 6 h on Days 0 to 6, beginning 24 h prior to the i.v. administration of folic acid (200 mg/m²) and escalating doses of i.v. 5-FU on Days 1 to 5. The maximum tolerated daily dose of 5-FU that could be given with this combination was 375 mg/m². Because dipyridamole is extensively bound to plasma proteins, it was hypothesized that the concentrations of free dipyridamole achieved with a dose of 50 mg/m² were inadequate to modulate the cytotoxicity of 5-FU and folic acid. Therefore, a second Phase I trial of escalating dose of p.o. dipyridamole was performed. Folic acid (200 mg/m²) and 5-FU (375 mg/m²) were given i.v. on Days 1 to 5 every 4 wk, beginning 24 h after the start of therapy with dipyridamole; dipyridamole was administered p.o. on Days 0 to 6 at doses of 75, 100, 125, 150, 175, or 200 mg/m²/day to successive cohorts of patients. Dose-limiting neutropenia, mucositis, and nausea were produced at a dose of 200 mg/m²/day; the recommended dose of dipyridamole for use in Phase II studies is 175 mg/m² p.o. every 6 h, or 700 mg/m²/day. At this dose, a mean peak plasma concentration of total dipyridamole of 16.32 µmol and a mean peak plasma concentration of free dipyridamole of 38.30 nmol were observed. Trough concentrations of free dipyridamole averaged 60% of the peak concentrations. Objective antitumor responses were seen in a number of tumor types; five of 13 patients with breast cancer treated with high-dose p.o. dipyridamole, 5-FU, and folic acid responded. High-dose p.o. dipyridamole can produce plasma concentrations of free dipyridamole within the range shown to modulate the cytotoxicity of 5-FU and other agents. Phase II trials of this combination are justified.

INTRODUCTION

Despite intensive efforts to discover new and effective anticancer drugs, the current number of clinically useful cytotoxic agents remains relatively stable at 40 to 50 (1). Great advances, however, have been made in the understanding of the mechanisms of cytotoxicity of currently available agents, making possible rational attempts to biochemically modulate the effects of cytotoxic drugs. Examples of the application of such an understanding include clinical trials of 5-FU and folic acid. 5-FU is a commonly used anticancer drug whose principle mechanism of cellular cytotoxicity results from its metabolism to FdUMP, an inhibitor of thymidylate synthase. This enzyme is responsible for the formation of dTMP, an essential precursor of DTTP, which is needed for DNA synthesis (1, 2). In vitro studies have indicated that FdUMP forms an enzymatically inactive complex with thymidylate synthase and that this inactive complex is stabilized by reduced folates at concentrations of 10 µmol or more, resulting in enhanced cytotoxicity of 5-FU (1-3). These in vitro studies have led to clinical trials of the combination of 5-FU and FA. Initial Phase II studies proved promising, and Phase III studies have indicated that the combination of 5-FU and FA produces a greater response rate in colorectal cancer than does 5-FU alone (4-6).

Another avenue of research has examined the interaction of the drug dipyridamole with the cytotoxic activity of 5-FU and other fluoropyrimidines. In vitro studies have demonstrated that DPM can inhibit intracellular nucleoside transport, thereby enhancing the cytotoxicity of 5-FU and the antifol methotrexate by inhibiting the repletion of nucleotide pools by the "salvage" of extracellular nucleosides (7, 8). This inhibition of the salvage pathway is felt to be the mechanism by which methotrexate activity is enhanced by dipyridamole in the Chinese hamster ovary system (7).

In the HCT 116 human colon cancer cell line, dipyridamole can be demonstrated to markedly inhibit the cellular uptake of physiological concentrations of the nucleosides uridine and thymidine, but this mechanism may not be the principal means by which dipyridamole augments 5-FU cytotoxicity in this system (8-10). It has been suggested that dipyridamole may block the efflux of active metabolites of 5-FU, and a marked enhancement of intracellular levels of FdUMP has been shown in colon cancer cell lines treated with dipyridamole and either 5-FU or FdUrd as compared with those treated with either fluoropyrimidine alone (10, 11).

Such biochemical modulation has resulted in significantly enhanced cytotoxicity of 5-FU and FdUrd in human colon cancer cell lines. In the HCT 116 cell line, 5-FU cytotoxicity was increased by dipyridamole in a dose-dependent manner at concentrations of dipyridamole of 5 to 5000 nmol, with clear evidence of augmentation being seen at a dipyridamole concentration of 50 nmol, and 90% of the effect being produced by a concentration of dipyridamole of 500 nmol (9). A concentration of dipyridamole of 500 nmol increased the cytotoxicity of FdUrd a median of 300-fold in 7 of 8 human colon cancer cell lines tested, an effect not reproduced in cultures of human bone marrow colony-forming units, suggesting that the addition of dipyridamole to fluoropyrimidine therapy might increase the therapeutic index (11).

Thus, the changes in intracellular pyrimidine and fluoropyrimidine metabolism associated with dipyridamole treatment suggest that an enhanced inhibition of thymidylate synthase by FdUMP is the mechanism by which dipyridamole enhances the cytotoxicity of 5-FU and related compounds. This inhibition, in turn, is optimized by the provision of reduced folates in the form of folinic acid.

These considerations constitute a rationale for the clinical investigation of the combination of 5-FU, folinic acid, and dipyridamole. We have performed two Phase I trials of this combination in patients with refractory metastatic malignancies. In the first, 5-FU dose-ranging trial, the doses of dipyridamole and folinic acid were fixed, and the maximum tolerated dose of 5-FU that could be given with these doses of folinic acid and dipyridamole was determined. The dose schedule of dipyridamole used in this first trial would be expected to pro-
duce total plasma dipyridamole levels within the concentration range used in the in vitro studies on which these clinical trials were based. However, because the toxicity of the combination of 5-FU and folinic acid was not substantially changed by the addition of dipyridamole at a total daily dose of 200 mg/m² p.o. and because dipyridamole is 91 to 99% protein bound in plasma (12–16), it was hypothesized that the concentration of free dipyridamole achieved in plasma using this dosing scheme for dipyridamole was insufficient to produce the desired effects on pyrimidine and fluoropyrimidine metabolism. Therefore, a second, dipyridamole dose-ranging study was performed. In this trial, the doses of folinic acid and 5-FU were fixed, and successive cohorts of patients were treated with progressively increasing doses of dipyridamole in order to examine the toxicity and to determine the maximum tolerated dose of p.o. dipyridamole in patients receiving 5-FU and folinic acid. This paper describes these two Phase I clinical trials.

MATERIALS AND METHODS

Patient Eligibility

The eligibility criteria for both studies were the same. These studies were open to patients with advanced malignancies which were refractory to standard therapy or for which there was no effective standard therapy. Patients were required to be of age 18 or greater and to have a performance status of 0 to 3 (Southwestern Oncology Group or Eastern Cooperative Oncology Group scale), an expected life span of at least 6 wk, a WBC count of at least 3.500/µl, a platelet count of at least 100,000/µl, a hemoglobin of at least 9.0 g/dl, a serum total bilirubin of less than 3.0 mg/dl, and either a serum creatinine less than or equal to 1.5 mg/dl or a creatinine clearance of at least 60 ml/min. A treatment-free interval of at least 3 wk from any prior major surgery, radiotherapy, or chemotherapy was required (6 wk for patients receiving mitomycin C or nitrosoureas). All patients were required to give their informed consent to participation. Pregnant patients, sexually active fertile patients practicing no form of contraception, and patients with active, symptomatic coronary artery disease were ineligible. Objectively measurable disease was not required, and no limits were placed on the extent of prior therapy; patients previously treated with 5-FU or 5-FU and folinic acid were eligible.

5-FU Dose-ranging Study

In this trial, all patients received dipyridamole p.o. at a dose of 50 mg/m²/dose, with doses being administered every 6 h for a total daily dose of 200 mg/m²/day, beginning 24 h prior to the first dose of 5-FU and continuing for 6 consecutive 24-h periods until 24 h after the last dose of 5-FU; generally, dipyridamole was begun on a Sunday and discontinued on a Saturday. Folinic acid was given at a dose of 200 mg/m²/day as a rapid i.v. infusion for 5 consecutive days, while 5-FU was given as a rapid i.v. infusion for 5 consecutive days immediately after each dose of folinic acid. Generally, folinic acid and 5-FU were administered on an outpatient basis beginning on a Monday and ending on a Friday. Consecutive cohorts of 4 or more patients were treated with increasing doses of 5-FU in a conventional Phase I study design; dose escalation was not performed in individual patients. Treatment cycles were repeated every 4 wk, provided that all acute toxicity from the previous course had resolved and disease progression had not occurred. The dose levels of 5-FU examined in this trial were 225, 300, 375, and 450 mg/m²/day. Patients underwent physical examination and had a serum chemistry profile performed every 4 wk; complete blood counts were obtained weekly. Toxicity was graded according to the National Cancer Institute common toxicity criteria.

Dipyridamole Dose-ranging Study

The dipyridamole dose-ranging study was identical in design to the 5-FU dose-ranging study, except that the dose of 5-FU was fixed at 375 mg/m²/day and the dose of p.o. dipyridamole was escalated in successive cohorts of 4 or more patients. The dose of folinic acid remained fixed at 200 mg/m²/dose. Dipyridamole was given according to the same schedule as that used in the first trial, but the doses were escalated in successive groups of patients. No dose escalation of dipyridamole was allowed in a single patient. The dose levels of dipyridamole examined were 75, 100, 125, 150, 175, and 200 mg/m²/dose, or 300, 400, 500, 600, 700, and 800 mg/m²/day. In both trials, the occurrence of Grade 3–4 toxicity of any type in ≥3 of 6 patients at a given dose level was considered unacceptable; the maximum tolerated dose was defined to be one dose level below that dose producing unacceptable toxicity.

Plasma Dipyridamole Assays

Specimen Collection. Selected patients treated as a part of the dipyridamole dose-ranging study underwent pharmacological monitoring in an attempt to determine whether concentrations of dipyridamole in the range of those used in the preclinical model systems were achievable in plasma. Plasma samples were drawn into heparinized tubes just prior to the first daily dose of dipyridamole on Day 4 (Thursday) in order to determine the "trough" concentration and again 75 min after the first daily dose of dipyridamole on Day 4 in order to determine the "peak" concentration. In some patients, plasma samples were drawn prior to any dipyridamole administration, to be used as control samples. All collected samples were transported to the laboratory on ice and centrifuged for 10 min at 2000 rpm. Plasma was transferred to plastic vials and stored at −20°C.

Assay Procedures. Plasma samples were assayed for total dipyridamole concentration using a HPLC-fluorescence method following the method of Wolfram and Bjornsson (17). The method involved extraction of the dipyridamole and internal standard, RA-433 [2,4,6-trimorpholinopyrimido(5,4-i)pyrimidine], from plasma with addition of 250 µl of 1 M Tris buffer (pH 10) to 250 µl of plasma and 3.0 ml of anhydrous ethyl acetate. The extracted samples were chromatographically separated on a Varian CN-10, 30- × 0.46-cm analytical column, with a mobile phase consisting of HPLC-grade 99.5% methanol, 0.5% glacial acetic acid, and 0.00275 M heptane sulfonic acid (Eastman Kodak Company, Rochester, NY). The flow rate was 2 ml/min. A fluorescence detector was used with the excitation wavelength at 285 nm and the emission wavelength at 510 nm. The retention times of dipyridamole and the internal standards were 2.5 min and 3.9 min, respectively. Plasma dipyridamole concentrations were calculated using peak height ratios, and the ratios from the spiked matrix standards were fitted with a linear regression equation $y = mx + b$; the daily calculated slopes ($m$) and intercept ($b$) were checked for consistency. Two different calibration standards were prepared, over the range of 5 to 100 ng/ml and 100 to 2400 ng/ml. Correlation coefficients exceeding 0.995 on each of the eight runs were obtained. Quality control samples were included in the daily run to test the accuracy of the assay method. The lower limit of the assay method was determined to be 5 ng/ml.

For the determination of the free concentration of dipyridamole in plasma samples from patients and in spiked standards, Centricon 10 microconcentration tubes (Amicon, Danver, MA) with low-absorption hydrophilic YM membrane filters were used as recommended by the manufacturer. The molecular weight cut off of these filters was 10,000. Plasma samples (0.5 ml) were transferred into individual tubes and centrifuged at 10,000 rpm for 60 min in a fixed angle rotor (Beckman). After the first centrifugation, the filtrate was removed, and the remaining plasma was centrifuged one more time, following the procedure as described above. The filtrate fractions from each sample were pooled and assayed for free dipyridamole concentration by the HPLC assay method. Standards were spiked in plasma and tested for loss due to binding to the membrane filters. Within the limitations of the sensitivity of the assay, no significant loss of compound due to binding was observed.
RESULTS

Patient Characteristics

A total of 58 patients were entered on these two trials; 21 were entered on the 5-FU dose-ranging trial and 37 on the dipyridamole dose-ranging trial. Of the 21 patients entered on the 5-FU dose-ranging study, 2 are considered evaluable. One patient withdrew from therapy prior to receiving any treatment with 5-FU or folinic acid, while the other patient received only 4 days of treatment before demonstrating marked clinical deterioration attributable to progressive malignancy; this patient died 2 days after treatment was discontinued, but did not experience significant toxicity attributable to therapy. One patient entered on the dipyridamole dose-ranging study is considered evaluable because the dose of p.o. dipyridamole actually taken was 50% of that prescribed. The clinical characteristics of the patients entered on these two studies are summarized in Table 1.

Toxicity

5-FU Dose-ranging Study. The toxicities of each dose level are presented in Table 2. While some patients complained of headache, nausea, and gastrointestinal cramping while taking p.o. dipyridamole, these side effects were tolerable to most patients. The dose-limiting toxicity of the combination proved to be myelosuppression, with significant stomatitis and diarrhea being produced in some patients. A dose of 5-FU of 450 mg/m² was associated with unacceptable toxicity, producing Grade 3-4 neutropenia (granulocyte count less than 1.0 × 10⁹/liter) in 3 of 4 patients; one of these patients died of neutropenic sepsis. In addition, this dose of 5-FU produced Grade 3 stomatitis in one patient, Grade 3 diarrhea in one patient, and Grade 4 diarrhea (necessitating hospitalization for rehydration) in one patient. The maximum tolerated dose of 5-FU, then, that could be given with folinic acid (200 mg/m²/day) for 5 consecutive days and dipyridamole (50 mg/m²) p.o. every 6 h was 375 mg/m²/day for 5 consecutive days. This is the same as the dose of 5-FU used with folinic acid (200 mg/m²) in Phase II studies that do not include dipyridamole (5).

Dipyridamole Dose-ranging Study. The toxicity experienced by patients treated as a part of the dipyridamole dose-ranging study is displayed according to dose level in Table 3. Some individual patients experienced more than one type of unacceptable toxicity. At a dose of dipyridamole of 175 mg/m² p.o. every 6 h (700 mg/m²/day), one patient experienced Grade 3 toxicity attributed to dipyridamole (headache poorly controlled by narcotic analgesics). At the next higher dose level of dipyridamole (200 mg/m² every 6 h or 800 mg/m²/day), 4 of 5 patients suffered Grade 3 or 4 toxicity. These toxic effects included neutropenia (Grade 3 in one patient and Grade 4 in another patient), mucositis (Grade 3 in 2 patients), and nausea and vomiting sufficient to require hospitalization for i.v. hydration in 2 patients. Both patients developing Grade 4 nausea did so during their second course of therapy, in the setting of progressive intraabdominal malignancy; in both cases, Grade 2 nausea had been experienced during the first course. Thus, disease progression may have played a role in the toxicity attributed to therapy in these patients. However, because Grade 3-4 toxicity had been experienced by two of the three other patients treated at a dose of 200 mg/m²², it was felt that further dose escalation was not justified. Thus, the maximum tolerated dose was determined to be the next lower dose level, i.e., 175 mg/m²/dose, or 700 mg/m²/day.

Antitumor Effects

Table 4 describes the objective antitumor responses observed in these trials. Two partial responses were produced in the 5-FU dose-ranging study, while 7 partial responses were produced in the dipyridamole dose-ranging study. No complete responses were observed. Most of the responses have been short-lived (median, 19 wk, dating from the onset of therapy), but one patient with hepatic metastases from breast cancer achieved a stable partial response which has persisted for over 1 yr.

Pharmacological Studies

The results of the pharmacological studies are summarized in Table 5. In general, higher doses of dipyridamole were associated with higher plasma concentrations of total and free dipyridamole, although considerable variation among patients treated at a given dose level was evident. Extensive binding of dipyridamole to plasma proteins was evidenced by the low proportion of free relative to total plasma concentration at all dose levels. The mean percentage of binding at the peak concentration was 99.69% (range, 99.05 to 99.96%) and at the trough concentration was 97.77% (range, 99.51 to 99.93%). Overall, mean trough free dipyridamole concentrations averaged 60% of the peak concentrations of the free drug. A statistically significant relation between plasma dipyridamole concentration and toxicity could not be demonstrated.
### Table 3 Toxicity: DPM escalation phase

<table>
<thead>
<tr>
<th>Dose (DPM/m²)</th>
<th>No. of patients</th>
<th>Neutropenia</th>
<th>Thrombopenia</th>
<th>Mucositis</th>
<th>Diarrhea</th>
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<tr>
<td>125</td>
<td>6</td>
<td>3 0 1 1 1</td>
<td>6 0 0 0</td>
<td>1 2 2 1 0</td>
<td>2 1 3 0 0</td>
</tr>
<tr>
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<td>5</td>
<td>4 0 0 0 1</td>
<td>4 1 0 0 1</td>
<td>3 1 0 1 0</td>
<td>3 1 1 0 0</td>
</tr>
<tr>
<td>175</td>
<td>7</td>
<td>2 1 3 1 0</td>
<td>6 1 0 0</td>
<td>4 0 2 1 0</td>
<td>3 3 1 0 0</td>
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<tr>
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<td>5</td>
<td>2 0 1 1 1</td>
<td>2 1 2 0</td>
<td>1 1 1 2 0</td>
<td>2 2 1 0 0</td>
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### Table 4 Characteristics of responding patients

<table>
<thead>
<tr>
<th>5-FU dose (mg/m²)</th>
<th>DPM dose (mg/m²)</th>
<th>Diagnosis</th>
<th>No. of prior regimens</th>
<th>Response</th>
<th>Duration (wk)</th>
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<td>300</td>
<td>50</td>
<td>Squamous lung</td>
<td>0</td>
<td>PR*</td>
<td>32</td>
</tr>
<tr>
<td>450</td>
<td>50</td>
<td>Breast</td>
<td>2</td>
<td>PR</td>
<td>25</td>
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<tr>
<td>375</td>
<td>75</td>
<td>Breast</td>
<td>4</td>
<td>PR</td>
<td>76</td>
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<tr>
<td>375</td>
<td>75</td>
<td>Gastric</td>
<td>0</td>
<td>PR</td>
<td>15</td>
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<tr>
<td>375</td>
<td>100</td>
<td>Breast</td>
<td>2</td>
<td>PR</td>
<td>16</td>
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<td>125</td>
<td>Breast</td>
<td>1</td>
<td>PR</td>
<td>19</td>
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<td>125</td>
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<tr>
<td>375</td>
<td>175</td>
<td>Breast</td>
<td>2</td>
<td>PR</td>
<td>15</td>
</tr>
</tbody>
</table>

* PR, partial response.

### DISCUSSION

The recommended Phase II dose-schedule of dipyridamole, 5-FU, and folinic acid is dipyridamole (175 mg/m²) p.o. every 6 h on Days 0 to 6, folinic acid (200 mg/m²) i.v. on Days 1 to 5, and 5-FU (375 mg/m²) i.v. on Days 1 to 5, with cycles repeated at 4-wk intervals. Dose-limiting neutropenia, diarrhea, and mucositis prevent further dose escalation of 5-FU, while dose-limiting gastrointestinal toxicity (predominantly nausea, vomiting, and abdominal cramping) and headache prevent further escalation of dipyridamole. This study demonstrates that high doses of p.o. dipyridamole can produce peak plasma concentrations of total and free dipyridamole equal to or greater than the steady-state concentrations reported for continuous i.v. infusion of dipyridamole at the maximum tolerated dose (16). In one such trial, a Phase I trial of dipyridamole and acivicin, a continuous 72-h i.v. infusion of dipyridamole at a dose of 7.7 mg/kg/24 h (approximately 312 mg/m²/24 h) produced a mean steady-state total plasma concentration of dipyridamole of 11.9 μmol and a mean steady-state plasma concentration of free dipyridamole of 27.8 nmol (16). This same dose-schedule of dipyridamole produced a mean serum steady-state concentration of free dipyridamole of 19 nmol when given with 5-FU and 23 nmol when given with methotrexate (18, 19). In our study, p.o. dipyridamole at a dose of 175 mg/m²/dose, or 700 mg/m²/day, produced a mean peak plasma concentration of total dipyridamole of 16.32 μmol and a mean peak free concentration of dipyridamole of 38.30 nmol. Overall, the mean trough concentration of free dipyridamole was 60% of the mean peak concentration, implying that patients were exposed to relatively high concentrations of dipyridamole throughout the day. Protein binding was high, as has been reported in other studies of dipyridamole (12-16). This binding has been reported to be primarily to α₂-acidic glycoprotein, which expresses an affinity approximately 13 times greater than albumin (15). The concentration of this acute-phase protein is highly variable, particularly in cancer patients, some of whom have been found to have elevations of this protein fraction (20, 21). This interpatient variation may account for some of the heterogeneity in the plasma free and total dipyridamole concentrations observed, as may the variability of p.o. absorption of the drug, which has been reported to range from 37 to 66% (22). Other trials attempting to modulate the activity of anticanter drugs with p.o. dipyridamole have utilized doses of 50 to 75 mg/dose (23-28). Doses in this

### Table 5 Mean plasma dipyridamole concentrations (DPM)

<table>
<thead>
<tr>
<th>DPM dose (mg/m²)</th>
<th>Trough total [DPM] (μM)</th>
<th>Trough free [DPM] (nm)</th>
<th>Peak total [DPM] (μM)</th>
<th>Peak free [DPM] (nm)</th>
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<tbody>
<tr>
<td>75</td>
<td>2.82 (single value)</td>
<td>Not done</td>
<td>4.39 (3.94-4.85)*</td>
<td>Not done</td>
</tr>
<tr>
<td>100</td>
<td>5.10 (2.46-7.92)</td>
<td>Not done</td>
<td>7.88 (4.92-12.13)</td>
<td>Not done</td>
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<tr>
<td>150</td>
<td>8.21 (3.12-13.97)</td>
<td>23.12 (8.9-43.8)</td>
<td>14.41 (13.84-17.40)</td>
<td>27.92 (24.6-59.5)</td>
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<tr>
<td>175</td>
<td>4.33 (1.21-8.90)</td>
<td>11.63 (9.3-14.1)</td>
<td>16.32 (5.17-25.4)</td>
<td>38.30 (24.6-59.5)</td>
</tr>
<tr>
<td>200</td>
<td>11.26 (2.67-22.51)</td>
<td>19.9 (11.7-40.7)</td>
<td>19.19 (9.20-26.34)</td>
<td>39.08 (18.5-58.5)</td>
</tr>
</tbody>
</table>

* Numbers in parentheses, range of DPM concentrations.
range produce mean total plasma dipyridamole concentrations of 1.86 to 3.1 μmol (23-25, 28); the corresponding plasma concentrations of the free drug are unlikely to have been adequate to modulate the cytotoxicity of the cytotoxic chemotherapeutic agent. Our trial indicates that dipyridamole can be given p.o. at a dose sufficient to produce plasma concentrations of free dipyridamole within the lower limits of the concentration range needed to modulate the cytotoxicity of 5-FU.

It is not possible to make any firm conclusions regarding the efficacy of this combination on the basis of these Phase I studies, particularly as compared with 5-FU and folinic acid alone. While in vitro studies suggest that the effects of dipyridamole on the cytotoxicity of 5FdUrd are greater in malignant cell lines than in myeloid precursors (11), it is not possible to determine from our studies whether dipyridamole changes the therapeutic index of therapy with 5-FU and folinic acid. It is disappointing that none of the 10 patients with colorectal cancer showed an objective response to therapy, but 5 of these patients had been treated previously with one or more regimens (including 2 patients previously treated with 5-FU and folinic acid) and one of these 10 patients was invaluable due to early death secondary to his malignancy. One patient with colon cancer did develop a minor response to therapy (tumor area decreased >25% but <50%). Other trials of standard dose p.o. dipyridamole, 5-FU, and folinic acid have reported objective responses in colorectal cancer patients failing 5-FU and folinic acid therapy (26, 27). Thus, while we observed no objective responses in patients with colorectal cancer, Phase II trials of high-dose p.o. dipyridamole with 5-FU and folinic acid might be considered in this tumor system. It is of interest to note that 5 of 13 patients with metastatic breast cancer responded to high-dose p.o. dipyridamole with 5-FU and folinic acid; all had been previously treated with chemotherapy. Phase II trials in this malignancy should be performed.

Dipyridamole may have effects on the cytotoxicity of drugs other than those discussed above. Dipyridamole has been reported to reduce the uptake and cytotoxicity of cytarabine in normal and malignant myeloid cells (29). By altering the cellular uptake and retention of cytotoxic drugs, dipyridamole may enhance the cytotoxicity of drugs that are not of the antimetabolite class. Agents whose activity has been reported to be enhanced by dipyridamole include mitoxantrone (30), etoposide (31, 32), doxorubicin (31, 32), vinblastine (32), and cisplatin (34). Furthermore, dipyridamole has been reported to be an inducer of Class I interferons (35) and to potentiate the inhibition of replication of human immunodeficiency virus in human monocye-macrophages by azidothymidine and dideoxycytidine (36), suggesting that this drug may become important in antiviral therapy. Most of these in vitro studies have examined the effects of dipyridamole at micromolar concentrations. Further investigations of high-dose p.o. and i.v. dipyridamole are indicated, as are further preclinical investigations. However, these studies should recognize that micromolar systemic concentrations of free dipyridamole are not achievable for prolonged periods in humans, but that concentrations in the range of 20 to 50 nmol can be achieved with tolerable toxicity.

REFERENCES


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