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A phase I trial of 5-fluorouracil, leucovorin, and dipyridamole given by concurrent 120-h continuous infusions*

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Summary. A phase I trial of 5-fluorouracil (FUra) and leucovorin (LV) given with and without dipyridamole (DP) by concurrent 120-h continuous infusion was performed in 27 patients with advanced solid malignancies, 8 of whom had previously received FUra. The LV and DP doses were fixed at 500 mg/m^2 daily and 7.7 mg/kg daily, respectively, whereas the FUra dose was escalated. Level 3 (450 mg/m^2 FUra daily) represented the maximum tolerated dose for both FUra/LV + DP and FUra/LV. Dose-limiting stomatitis ($\geq$ grade 3 or grade 2 occurring during the infusion) was encountered in 75% of the first courses given at level 4 (600 mg/m^2 daily). Stomatitis was observed in 44/78 (56%) courses. Diarrhea was infrequent and mild. DP infusions were complicated by mild to moderate headache, which was controlled with narcotic analgesics, and mild to moderate nausea/vomiting. FUra-related toxicity was not enhanced by DP administration. Limited pharmacokinetic sampling at levels 3 and 4 revealed mean steady-state FUra concentrations of around 1.0 μM with infusions of FUra/LV + DP. Among three paired courses given with and without DP, no statistically significant difference was found in the total body clearance of FUra ($P = 0.44$). One partial response was seen in a patient with metastatic gastric carcinoma. For phase II trials, we recommend that concurrent 120-h continuous infusions of FUra (450 mg/m^2 daily) and LV (500 mg/m^2 daily) be given with and without DP (7.7 mg/kg daily) every 21 days.

Introduction

The antimetabolite 5-fluorouracil (FUra) exhibits activity against a wide spectrum of solid tumors. Due to the low objective response rates obtained in clinical trials of FUra, considerable attention has been devoted to pharmacological strategies designed to enhance its action [10, 20]. One important mechanism of its action involves inhibition of the enzyme thymidylate synthase (TS) secondary to covalent binding with the FUra metabolite 5-fluorodeoxyuridine monophosphate (FdUMP). Subsequent depletion of thymidine triphosphate results in inhibition of DNA synthesis [10, 20]. The extent of the FUra-induced inhibition of TS is associated with the concentration of reduced folates [3, 13]. Leucovorin (LV) enhances the cytotoxicity of FUra by increasing the cellular pools of reduced folate [10].

The nucleoside transport inhibitor dipyridamole (DP) has also been shown in vitro to augment the cytotoxicity of FUra against a human colon-cancer cell line [11]. Grem and co-workers [12] have shown that DP increases FdUMP levels secondary to a blockade of fluorodeoxyuridine efflux from cells. DP also inhibits cellular uptake of the nucleosides thymidine and uridine [11]. Nucleoside salvage has been shown to be a mechanism of resistance to antimetabolites in some models [9, 25].

In vitro work with DP strongly suggests a dose-dependent enhancement of FUra toxicity. Although optimal effects were observed at a concentration of 0.5 μM free DP, modulation occurred at 50 nM free DP [11, 25]. Following oral administration of DP, plasma levels of free drug lie in the range of 5–10 nM [19]. In our previous studies, continuous infusion (CI) of DP resulted in steady-state plasma levels of free DP amounting to 25–50 nM [27, 28].

The present phase I FUra dose-escalation trial was undertaken to examine the feasibility of concurrent administration of the modulators LV and DP, which enhance FUra cytotoxicity via separate mechanisms. Prior investigations using FUra in the presence and absence of DP suggest that a CI schedule of >24 h would be most effective [4, 8, 17, 21]. Preclinical and clinical studies on LV given as a CI

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have also demonstrated improved FUra cytotoxicity [6, 7, 14, 16]. Due to an increase in the duration of FUra infusions to ≥120 h in many clinical regimens, a 120-h CI schedule for the concurrent administration of LV, DP, and FUra was chosen for the present study. The doses of LV and DP were fixed at 500 mg/m^2 daily and 7.7 mg/kg daily, respectively. These doses have previously been shown to give plasma concentrations that are capable of modulating FUra or methotrexate toxicity [7, 21]. The dose of FUra was escalated to determine an appropriate phase II dose for the combination. The phase II dose for a 120-h CI of FUra and LV in the absence of DP was also determined.

Patients and methods

Patient selection. Individuals with advanced malignancy for whom no standard effective therapy was available, who gave informed consent according to institutional and Food and Drug Administration guidelines, and who displayed adequate bone marrow (WBC, ≥4,000/mm^3; platelet count, ≥100,000/mm^3), renal (creatinine clearance, ≥45 ml/min), hepatic (aspartate aminotransferase level <3 times the normal value; bilirubin level, ≤1.5 mg/dl), and metabolic (calcium, ≤11.5 mg/dl; sodium, ≥130 and ≤150 mEq/l; normal glucose or controlled diabetes mellitus) function were eligible. Individuals who had an Eastern Cooperative Oncology Group (ECOG) performance status of >2 and a life expectancy of <12 weeks, who had received chemotherapy or radiotherapy within 4 weeks prior to the present trial (6 weeks for nitrosoureas and mitomycin), who had symptomatic coronary artery disease, or who were taking DP, theophylline, allopurinol, quinidine, methadone, aspirin, probenecid, propranolol, or other beta-blockers were ineligible. In addition, individuals presenting with central nervous system metastases and evidence of either abnormalities in coagulation or ingestion of anticoagulants were excluded from the study.

Drug administration and FUra dose escalation. DP was given at a fixed dose of 7.7 mg/kg daily (the maximum tolerated dose in our prior phase I study on DP [27]) as a 120-h CI by a controlled-infusion pump through a double-lumen central venous catheter. FUra and LV were concurrently given as a 120-h CI by a controlled-infusion pump through a separate lumen of the central venus catheter. The LV dose was fixed at 500 mg/m^2 daily in accordance with past work using a prolonged CI of LV [7]. The daily FUra dose was escalated as follows: level 1, 225 mg/m^2 level 2, 375 mg/m^2; level 3, 450 mg/m^2; and level 4, 600 mg/m^2. The starting FUra dose (level 1) was considered to be safe on the basis of prior trials [2, 21]. The treatment cycle was repeated every 21 days or when toxicity encountered during the preceding cycle had resolved.

FUra dose escalation was undertaken after three patients had been followed for one complete cycle as long as toxicity was limited to ≤ grade 1 diarrhea and ≤ grade 2 hematologic, mucosal, hepatic, or other toxicity apart from acute side effects that were attributable to the DP infusion (nausea, vomiting, or headache). Uncontrollable toxicity, i.e., ≥ grade 3 nausea, vomiting, and headache, or ≥ grade 2 cardiovascular complications related to DP administration that occurred during the treatment resulted in termination of the infusions, with treatment being resumed if clinically appropriate at a 25% decrease in the DP dose after resolution of the toxicity. When grade 2 mucositis was observed during the drug infusions, the treatment was discontinued.

Patients entered at level 1 only were advanced to the next level if their unacceptable toxicity, defined as grade 2 stomatitis occurring during the 5-day infusion, ≥ grade 3 stomatitis occurring beyond the infusion period, ≥ grade 2 diarrhea, and other hematologic and nonhematologic toxicities of ≥ grade 3, with the exception of nausea, vomiting, and headache occurring during the DP infusion. If the preceding cycle was associated with unacceptable toxicity as defined above, DP was withheld, but the doses of FUra and LV were kept constant. This strategy enabled the assessment as to whether DP modulated FUra/LV toxicity. If the subsequent course resulted in acceptable toxicity, treatment with DP was resumed with the combination of FUra + LV at the prior dose level.

The maximum tolerated dose (MTD) was based on a "best of five" schema according to unacceptable versus acceptable toxicity. When unacceptable toxicity occurred in ≤2 of 5 patients, dose escalation was continued. The occurrence of unacceptable toxicity in ≥3 of 5 subjects designated the preceding dose as the MTD. Moreover, if any grade 4 toxicity developed in more than one-third of the patients at a given level, the preceding dose was considered to be the MTD; additional subjects were entered at the next lowest level to define better the incidence of dose-limiting toxicity.

Two MTD determinations were made during this trial. Initially the MTD was determined for the three-drug combination FUra/LV + DP. Once this had been accomplished, new patients were entered starting at level 4 (FUra dose 450 mg/m^2 daily) to determine the MTD (according to the above-mentioned criteria) for FUra/LV given as a 120-h CI. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria.

All patients showing no obvious evidence of progressive disease received two courses and were then evaluated for disease response. Patients with stable disease received another two courses (total, four courses) and were again evaluated. Only patients showing evidence of disease response received more than four courses.

Drug formulation. DP was supplied by Boehringer Ingelheim in liquid form in ampules containing 10 mg DP/2 ml. Each 12-h dose was diluted into 1 l normal saline and given through a micropore filter into a central venous catheter. Each 24-h dose of FUra, which was commercially obtained as a sterile liquid (500 mg FUra/10 ml in one ampule), was diluted into a 500-cm^3 diluent by (diluent: normal saline, 0.45 *N* saline in 5% dextrose, or 5% dextrose and water) and given through a central venous catheter. Each 24-h dose of LV, which was supplied by the Division of Cancer Treatment, National Cancer Institute, in 10-ml vials containing 50 mg LV and 45 mg sodium chloride that had been reconstituted in 5 ml sterile water, was diluted into the same diluent bag used for the daily FUra dose and the two drugs were infused together [24].

Patient follow-up and assessment. Patients were examined prior to treatment and at 3-week intervals thereafter. Hematologic and metabolic parameters were followed weekly. Tumor response was assessed radiographically or clinically at ≤6-week intervals.

Pharmacokinetics. FUra plasma levels were determined for selected courses given with and without DP at levels 3 and 4 during the trial. Plasma samples were obtained prior to the infusions and at mid-to-late morning daily (at approximately 24, 48, 72, and 96 h into the infusion) during the 120-h treatment. FUra was assayed by high-performance liquid chromatography using a modification of the technique described by Stetson and colleagues [23].

Results

A total of 27 patients received 78 courses during the trial; 2 courses were unevaluable due to a catheter complication (1 case) and to an unexplained change in mental status (1 case). The patients' characteristics are listed in Table 1. The majority of subjects showed a good ECOG performance status of 0–1, had gastrointestinal malignancies, and had undergone prior therapy, including eight patients who had previously received FUra.

Table 1. Patients' characteristics

Age (years):	
Median	61
Range	21–74
Sex (M:F)	21:6
Initial performance status (ECOG):	
0	6
1	18
2	3
Prior therapy:	
None	13 (48%)
Chemotherapy and/or radiotherapy	14 (52%)
FUra	8 (30%)
Diagnosis (malignancy):	
Colorectal	10
Pancreatic	6
Lung:	
Non-small-cell	2
Small-cell	1
Gastric:	
Adenocarcinoma	2
Sarcoma	1
Gallbladder	1
Breast	1
Renal	1
Ovarian	1
Thyroid	1

Toxicity

Stomatitis was the dose-limiting toxicity encountered during the trial (see Table 2). Level 3 (FUra dose, 450 mg/m^2 daily) was considered to be the MTD for the three-drug combination FUra/LV + DP after unacceptable toxicity involving one course marked by grade 4 stomatitis and two courses marked by grade 3 stomatitis had occurred during three of four of the first courses given at level 4 (FUra dose, 600 mg/m^2 daily). At level 3, acceptable toxicity occurred during six of eight of the first courses given (two courses marked by grade 3 stomatitis, four courses complicated by grade 2 stomatitis and two courses during which no stomatitis was observed). Level 3 was designated the MTD for the two-drug combination FUra/LV due to the occurrence of unacceptable toxicity during three of four of the first courses given at level 4. Toxicity encountered during the five first courses of FUra/LV given at level 3 consisted of two courses during which no stomatitis occurred, one course marked by grade 2 stomatitis, and two courses marked by unacceptable stomatitis (the latter two infusions were stopped early due to grade 2 and grade 3 toxicity, respectively).

Toxicity encountered during the infusions secondary to DP was similar to that observed in past phase I trials [21, 27, 28]. Headache was the main DP-associated toxicity. Table 3 details the incidence of headache and nausea/vomiting. The majority of patients receiving the DP infusion developed a mild headache that started on day 1 or 2 and persisted until the end of the infusion. The headache was generally controlled by narcotic analgesics. Nausea/vomiting was also a frequent complaint during DP administration. It was mild to moderate in nature, could be controlled with antiemetics, and did not persist beyond day 5.

The stomatitis noted during the trial started as early as day 3 of the infusion and as late as day 11. The duration of the stomatitis ranged from 2 to 21 days (see Table 5). In general, patients complained of a painful mouth on days 6–8, which lasted for 7–10 days. The incidence and severity of the stomatitis increased with the FUra dose as shown in Table 2. A comparison of the occurrence of stomatitis between courses given with DP and those given without DP revealed no appreciable difference (see Table 2). Six patients received consecutive courses given with and without DP, with three being treated at level 2; one, at level 3; and two, at level 4. The grade of stomatitis (grade 2 or 3) observed was the same for each consecutive course. An interesting finding was the more rapid onset of stomatitis during treatment with the two-drug combination FUra + LV as compared with FUra/LV + DP. In all, 20 (45%) of

Table 2. Incidence of stomatitis and diarrhea

FUra level	Number of courses	Number of courses resulting in								
		Stomatitis of grade					Diarrhea of grade			
		0	1	2	3	4	0	1	2	3
1:										
+LV+DP	8 (3)	6 (2)	1 (1)	1	0	0	8 (3)	0	0	0
+LV	4	2	0	2*	0	0	4	0	0	0
2:										
+LV+DP	15 (3)	7 (0)	4 (1)	4 (2)	0	0	14 (3)	0	0	1
+LV	8	2	1	5 (3)	0	0	8	0	0	0
3:										
+LV+DP	17 (8)	10 (2)	0 (0)	5 (4)	2 (2)	0	16 (7)	1 (1)	0	0
+LV	16 (5)	7 (2)	0 (0)	8 (2)***	1 (1)	0	16 (5)	0	0	0
4:										
+LV+DP	4 (4)	0 (0)	1 (1)	0 (0)	2 (2)*	1 (1)	4 (4)	0	0	0
+LV	6 (4)	0 (0)	1 (1)	1 (1)*	4 (2)	0 (0)	5 (5)	0	1	0

Figures in parentheses signify the numbers of first-treatment courses during which the corresponding toxicities were encountered. *, Each course in which the infusion was stopped early due to grade 2 stomatitis

Table 3. Predominant toxicity encountered during the infusion

FUra level	Number of courses	Number of courses resulting in							
		Nausea/vomiting of grade				Headache of grade			
		0	1	2	3	0	1	2	3
1:									
+LV+DP	8	2	2	3	1	2	1	5	0
+LV	4	4	0	0	0	4	0	0	0
2:									
+LV+DP	15	4	1	10	0	5	2	8	1
+LV	8	7	1	0	0	8	0	0	0
3:									
+LV+DP	17	4	5	8	0	4	2	11	0
+LV	16	11	5	0	0	15	0	1	0
4:									
+LV+DP	4	0	1	3	0	2	0	2	0
+LV	6	3	1	2	0	6	0	0	0

Table 4. Summary of FUra pharmacokinetics determined in 12 patients

FUra dose level (mg/m^2 daily)	Number of courses	c_{ss} (μM)	c_{TB} (l h^{-1} m^{-2})
3 (450) + LV + DP	12	0.8±0.2	193± 36
3 (450) + LV	2	1.0	142
4 (600) + LV + DP	4	1.1±0.5	224±135
4 (600) + LV	2	1.8	107

Data represent mean values ± SD

Table 5. Day of onset and last day of stomatitis in a total of 44 courses given at levels 1–4 that resulted in grades 1–4 stomatitis toxicity

	Courses (n)	Median day of onset of stomatitis (range)	Median last day of stomatitis (range)	Median duration of stomatitis in days (range)
FUra/LV+DP	20	6 (3–11)	12 (8–26)	8 (2–21)
FUra/LV	24	5 (4–9)	15 (8–23)	9 (4–19)

44 courses given with DP were marked by the occurrence of ≥ grade 1 stomatitis; during 1 of these courses (level 4), grade 2 stomatitis developed during the infusion. Overall, 22 (65%) of 34 courses of FUra/LV given without DP were complicated by the occurrence of ≥ grade 1 stomatitis; during 10 of these courses, grade 2 stomatitis developed during the infusion (median infusion duration prior to discontinuation due to grade 2 stomatitis, 96 h; range, 77–116 h). The stomatitis observed during these 10 courses did not progress beyond grade 2. There was no complaint of abdominal cramping, and diarrhea was infrequent, with only one course (level 2) being complicated by grade 3 diarrhea (see Table 2).

During seven courses involving all dose levels (FUra/LV/DP, n = 2; FUra/LV, n = 5), skin toxicity was noted (grade 1–2). These episodes consisted of complaints of pain and erythema involving the foreskin and scrotum in men, the vulva in women, and rectal excoriations in both sexes. One patient developed a generalized pruritic rash during the sixth course. No palmar-plantar erythrodyesthesia syndrome was seen during the study, and no significant hematologic, hepatic, or renal toxicity was encountered.

Suspected FUra-related neurotoxicity was encountered in two patients: one case involved subtle changes in mental status and the other probably involved cerebellar toxicity, which has only rarely been reported during CI of FUra [15]. In a patient with lung cancer, subtle changes in mental status were noted during course 3 of the drug infusions (level 3, FUra/LV+DP); these changes did not resolve on discontinuation of the infusions at 50 h. The patient's mental status never returned to the baseline level, and clinical evaluation suggested tumor progression. The second case involved a patient presenting with ovarian cancer and no prior exposure to FUra who developed classic symptoms and signs of FUra-induced cerebellar toxicity (grade 3) on day 4 of course 1 (level 4, FUra/LV). The infusion was discontinued at 91 h, and the symptoms gradually subsided over 7 days. The patient received no further FUra therapy.

All patients on study were required to have a indwelling double-lumen central venous catheter. At course 3, a subclavian-vein thrombus that was presumably related to the central venous catheter was detected in one subject after problems arose in obtaining the proper infusion rate due to resistance from the catheter. No other patient showed symptomatic evidence of catheter-related thrombosis. No treatment-related death occurred during this study.

Only one treatment course was delayed by 1 week due to persistent toxicity (stomatitis beyond day 21) in a patient treated at level 4 (course 1, FUra/LV + DP). Two other patients had persistent stomatitis beyond day 21 but were taken off study due to progressive disease.

FUra pharmacokinetics

Limited pharmacokinetic sampling was done at levels 3 and 4. As observed in our prior phase I trial of FUra and DP, there was a trend toward an increased in the total body clearance (c_{TB}) of FUra when it was given together with DP [6] (see Table 4). The mean steady-state concentrations

(c_{ss}) of FUra were around 1 μM during treatment with FUra/LV + DP (level 3, 0.77 μM; level 4, 1.1 μM). Data on three paired courses (course 1 of FUra/LV + DP, course 2 of FUra/LV, 1 patient at level 3, and 2 patients at level 4) were available for pharmacokinetic analysis. Two of the paired courses showed no change in c_{ss} or c_{TB} from FUra/LV + DP to FUra/LV, whereas the values obtained for a paired course at level 4 differed widely (FUra/LV + DP: $c_{ss} = 0.89$ μM, $c_{TB} = 216$ l h^{-1} m^{-2}; FUra/LV: $c_{ss} = 1.98$ μM, $c_{TB} = 98$ l h^{-1} m^{-2}). Overall, no statistically significant difference in c_{TB} ($P = 0.44$) was found between the three courses given with DP and the three courses given without DP.

Clinical response

A patient with gastric cancer who had not previously been treated showed a partial response to FUra/LV that lasted for 24 weeks. A woman who had undergone extensive treatment including FUra, for breast cancer exhibited a mixed response to six courses of FUra/LV + DP; marked resolution of cutaneous metastases were noted, but the patient experienced progressive pelvic pain due to a documented metastasis.

Discussion

The initial objective of the present study was to test whether clinical evidence (enhanced normal tissue toxicity) exists for DP-induced enhancement of FUra/LV cytotoxicity. A trial conducted by Remick et al. [21] involved 31 paired courses of a 72 h CI of FUra given with and without concurrent CI of DP; no apparent modulation of FUra toxicity by DP was observed. The current trial also failed to show any enhancement of FUra/LV toxicity by DP. The MTDs for FUra/LV given with DP and without DP were identical. As a phase I study, this trial was not designed to evaluate the effect of DP on the antitumor activity of FUra/LV. However, both in vitro studies and a prior phase I trial have demonstrated enhancement of methotrexate cytotoxicity by DP [11, 25, 28], and the data of Weber [26] have shown that tumor cells appear to rely more heavily on nucleoside salvage than does normal tissue.

Although the previous phase I trial of FUra + DP conducted by Remick et al. [21] did not reveal any DP-induced change in FUra toxicity, it did demonstrate an alteration in FUra pharmacokinetics by DP. That trial found that DP increased the total body clearance of FUra, which resulted in lower steady-state FUra plasma concentrations. These significant differences in FUra pharmacokinetics were most pronounced at the higher doses used. The current trial showed a trend toward an increase in the total body clearance of FUra following DP administration.

The toxicity encountered during the present trial was similar to that observed in previous studies using various combinations of the three drugs. DP-associated toxicity occurring during the infusion (primarily headache) was easily controlled and dissipated rapidly on the completion of the infusion. The plasma level of DP maintained on this schedule was higher than that previously obtained following oral dosing of DP [19]; however, DP toxicity was very similar to that previously observed for oral DP regimens. Schmoll et al. [22] gave oral DP (50–75 mg, 3 × daily) with bolus infusions of FUra/LV; they could not give a higher DP dose due to complaints by the patients of severe headache. Allen et al. [1] mentioned the occurrence of headache and lightheadedness during their trial of oral DP (75 mg, 3 × daily) and bolus FUra/LV but did not describe it as being a major toxicity.

The observation of FUra/LV-associated toxicity, principally stomatitis, was consistent with the results of previous studies on the two-drug combination, especially when FUra or LV were given by CI [7]. As found for other infusional schedules of FUra/LV [5], diarrhea was not commonly seen during the present trial. A comparison of the toxicities encountered in our trial and those observed in two others using different schedules of FUra/LV + DP also discloses a fairly consistent degree of FUra-related toxicity [1, 22]. The observation that only 9% (4/44) of the courses given with DP were marked by unacceptable toxicity (grade 2 stomatitis occurring during the infusion or >grade 2 stomatitis developing thereafter) as compared with 41% (14/34) of the courses given without DP suggests that FUra/LV is more toxic. Concurrent administration of DP may change the onset or duration of the stomatitis. As shown in Table 5, no significant difference was found between courses given with DP and those given without DP. Possible explanations for the observed difference in toxicity might be the effect of DP on FUra clearance, resulting in decreased relative toxicity, or an effect of DP on LV. Another reason for this discrepancy might involve differences in the selection of patients during the initial part of the study for determination of the MTD for the combination FUra/LV + DP and the selection of those entered during the final phase for determination of the MTD for FUra/LV.

This trial confirms the finding of earlier phase I studies that prolonged DP infusions, which produce levels of free DP amounting to 25–50 nM, are tolerable. Although these levels of free DP are significantly lower than the optimal concentrations used to modulate FUra cytotoxicity in vitro, they have been associated with augmentation of methotrexate toxicity in the clinical setting [28]. The current prolonged DP infusion schedule does not enhance the toxicity of FUra/LV. Alterations in clinical activity can be tested in phase II/III trials in patients with FUra-sensitive malignancies only by comparing the results obtained for CI of FUra/LV + DP with those obtained for CI of FUra/LV. As a recent randomized trial has demonstrated an improved response rate for FUra/LV + methotrexate as compared with FUra/LV [18], it would be interesting to explore the use of DP with this combination [18]. DP has been shown to increase methotrexate toxicity both in vitro and in vivo [25, 28].

The current trial indicates that DP can safely be given with chemotherapy, that a more extended CI (120 h) of DP is easily tolerable, and that the combination of FUra/LV, and DP can safely be given by CI. The dose and schedule recommended for phase II trials on the basis of the present

phase I study involve a concurrent 120-h CI of FUra (450 mg/m^2 daily) and LV (500 mg/m^2 daily) given with and without DP (7.7 mg/kg daily) every 21 days.

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