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Five-day infusion of fluorodeoxyuridine with high-dose oral leucovorin: a phase I study*

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Summary. Fluorodeoxyuridine (FUdR) interferes with cellular metabolism by inhibiting thymidylate synthase. Therefore, we sought to modulate its activity with leucovorin (LV) and to identify the maximally tolerated dose given as a 5-day continuous intravenous infusion in combination with oral administration of LV at a dose of 100 mg every hour for four doses immediately preceding the start of the FUdR infusion and then every 4 h for the entire duration of FUdR treatment. Patients were evaluated at six FUdR dose levels ranging from 0.1 to 0.375 mg/kg per day. Severe or life-threatening mucositis was first observed in two of six patients treated at 0.25 mg/kg daily. Further escalation of the dose to 0.3 mg/kg per day resulted in grade 2 mucositis in four of six patients and in grade 3 mucositis in two cases. A dose of 0.375 mg/kg daily resulted in grade 3 toxicity in all three patients treated. Other types of toxicities included skin rash and hand-foot syndrome, but no hematologic toxicities were observed. Stable disease was observed in 11 of 24 evaluable patients, including 3 subjects with renal cell carcinoma. Our recommended dose for phase II trials is 0.3 mg/kg FUdR per day.

Introduction

Modulation of the activity of 5-fluorouracil (5-FU) with leucovorin (LV) has been shown to increase the efficacy of the former in vitro [2, 7, 11, 14, 17, 22] and in vivo in patients with metastatic colorectal cancer [3, 4, 13, 15, 19–21, 25]. Phase I and II studies carried out at the University of Chicago in patients with head and neck cancer have shown the feasibility of giving high doses of oral LV concomitantly with a 5-day continuous infusion of 5-FU [26, 27]. When 100 mg LV was given orally every 4 h during the entire duration of the 5-FU infusion, mean total plasma levels of 2–4 μM LV were achieved. Mean plasma methyl-tetrahydrofolate levels were 1.5–2.4 μM, and no significant differences were seen between peak and trough concentrations or between concentrations measured on day 2 or day 4 of the chemotherapy. This suggested that repeated oral dosing of LV resulted in steady-state plasma concentrations of LV and its metabolites that have been shown to be sufficient to produce 5-FU modulation in vitro. In addition, we demonstrated that a significant proportion of the total reduced folate plasma concentrations was derived from the biochemically active l-stereoisomer rather than the biochemically inactive d-stereoisomer.

5-FU can be either sequentially phosphorylated and incorporated into RNA or metabolized to 5-fluorodeoxyuridine (FUdR) and, subsequently, to 5-fluoro-deoxyuridine monophosphate (5-FdUMP). 5-FdUMP binds to the enzyme thymidylate synthase and can thereby block thymidine synthesis. Only this second pathway can be modulated by LV, which forms a stable ternary complex with thymidylate synthase and 5-FdUMP. Since FUdR represents the first metabolite of 5-FU on this second pathway its investigation in combination with LV would be logical. However, clinical experience with FUdR given intravenously with LV is sparse.

Based on this background, we designed a phase I study to define the maximally tolerated dose (MTD) of FUdR given as a 5-day continuous intravenous infusion in combination with oral administration of high-dose LV every 4 h as in our previous studies.

Patients and methods

Between January 1989 and February 1990, 28 patients were registered on this protocol, which was reviewed and approved by the Institutional Review Boards at the Universtiy of Chicago and the City of Hope National Medical Center. All patients were evaluated and treated by

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physicians from two collaborating institutions. Eligible patients had histologically or cytologically documented neoplastic disease either refractory to standard therapy or for which no standard therapy existed, a performance status of 0–2 (CALGB), and a life expectancy of $\geq$8 weeks. At study entry, a total WBC count of $\geq 3.5 \times 10^3/\mu l$ and a platelet count of $\geq$ 100,000/μl were required. In addition, a serum bilirubin level of <3 mg/dl, liver function tests that were $\leq$4 times the upper normal value, and a serum creatinine level of $\leq$1.5 mg/dl or calculated creatinine clearance of $\geq 40\ cm^3/min$ were required. There were no limitations on prior therapy except that patients who had previously been treated with 5-FU and simultaneous high-dose LV were excluded. All patients signed statements of informed consent. All measurable disease was carefully documented by physical examination or appropriate radiographic studies. However, the presence of measurable disease was not a requirement for entry into this study.

Chemotherapy consisted of FUdR given as a 5-day continuous intravenous infusion. The dose of FUdR was escalated from 0.1 to 0.375 mg/kg per day in six dose levels. Four doses of 100 mg LV were given orally at 1-h intervals over the 4 h immediately preceding the FUdR infusion. LV administration then continued at oral doses of 100 mg every 4 h for the entire duration of the FUdR infusion (total, 34 doses). Cycles were repeated every 21 days. Antiemetics were given at the discretion of the attending physician. Prior to institution of therapy, placement of a venous access device was recommended. Chemotherapy cycles were repeated until documentation of tumor progression. Chemotherapy-related toxicities were assessed at least once weekly and were graded according to the NCI common toxicity criteria.

The FUdR dose was escalated after three patients had been evaluated at a given dose level, provided that no toxicity greater than grade 2 was observed. If toxicity higher than grade 2 was observed in one of three patients, a total of six subjects were treated at that dose level. Dose escalation continued until >33% of the patients (maximum, three subjects) treated at a given dose level developed toxicity equivalent to or greater than grade 3. The FUdR dose was not escalated in individual patients. Dose escalation was also stopped if two patients at any dose level developed grade 4 toxicity. At dose level 4, both of the patients seen at City of Hope National Medical Center developed grade 4 mucositis, whereas none of the four subjects treated at the University of Chicago displayed mucositis exceeding grade 2. At that time, it was decided to continue the FUdR dose escalation at the University of Chicago, whereas the three additional patients at City of Hope National Medical Center were treated at dose level 3.

Response evaluation was performed after completion of the first two cycles and at every two cycles thereafter. A complete response was defined as the complete disappearance of all detectable tumor for at least 28 consecutive days. A partial response was defined as a reduction of at least 50% of the products of the longest perpendicular diameters of the most easily measurable or largest tumor mass (indicator lesion) in the absence of both the growth of other existing lesions and the appearance of new lesions for at least 28 days. Stable disease was defined by the same criteria, except that an increase of <25% or a decrease of <50% of the size of the indicator lesion was required. Disease progression was defined as an increase of $\geq$25% of the product of perpendicular diameters of the indicator lesion or the appearance of new metastatic lesions.

Results

A total of 28 patients were registered and treated on this protocol: 7 at City of Hope National Medical Center and 21 at the University of Chicago. The pretreatment characteristics of these patients are outlined in Table 1. The median age was 61 years (range, 44–77 years). In all, 21 patients each had a performance status of 0 or 1, and 7 subjects had a performance status of 2. Patients with a variety of refractory solid tumors were treated, including 8 with renal cell carcinoma, 5 with breast cancer, and 3 each with colorectal cancer or head and neck cancer. Prior therapy included chemotherapy, biologic therapy and/or hormone therapy in 19 cases; only 2 patients with metastatic renal cell carcinoma had not undergone prior treatment.

Table 1. Patients characteristics

		Number	Percent
Patients entered		28	100
Men		12	43
Women		16	57
Age:			
Median	61 years		
Range	44–77 years		
Performance Status:			
	0	10	36
	1	11	39
	2	7	25
Primary malignancy:			
Renal cell		8	29
Breast		5	18
Colorectal		3	11
Head and neck		3	11
Melanoma		2	7
Prostate		1	4
Gastric		1	4
Lung (non-small-cell)		1	4
Leiomyosarcoma		1	4
Small bowel		1	4
Gall bladder		1	4
Unknown primary, adenocarcinoma		1	4
Prior therapy:			
Surgery		16	57
Radiotherapy		7	25
Systemic therapy		19	68
None		2	7

Toxicity

Patients were treated at six FUdR dose levels ranging from 0.1 to 0.375 mg/kg per day. All subjects were assessed for toxicity. The highest grades of toxicity observed in all patients following the first cycle of therapy are summarized in Tables 2 and 3. Mucositis was the dose-limiting toxicity of this regimen (Table 2). One patient treated at dose level 2 who developed grade 3 mucositis had received prior radiotherapy to the area that was thought to have aggravated the degree of mucositis; thus, dose escalation was continued after two additional patients at this level developed only mild mucositis. None of the three patients subsequently treated at dose level 3 developed grade 3 toxicity (level 3 a, Table 2). During dosing at level 4, differing observations were made at the two participating institutions: two patients treated at City of Hope National Medical Center developed grade 4 mucositis requiring hospitalization and intravenous hydration, whereas none of the four patients treated at the University of Chicago developed mucositis exceeding grade 2. At that time the participating physicians at the former institution felt that further dose escalation was not feasible and treated three additional patients at dose level 3 (summarized as level 3 b

Table 2. Mucositis

FUdR dose level	Patients (*n*)	Grade				
		0	1	2	3	4
1) 0.1 mg/kg daily	3	2	–	1	–	–
2) 0.15 mg/kg daily	3	1	1	–	1	–
3) 0.2 mg/kg daily (a)	3	2	–	1	–	–
(b)	3[a]	–	–	–	3	–
4) 0.25 mg/kg daily	6	1	–	3	–	2[b]
5) 0.3 mg/kg daily[c]	7	1	–	4	2	–
6) 0.375 mg/kg daily	3	–	–	–	3	–

[a] Patients on level 3b were treated at City of Hope National Medical Center after completion of level 4

[b] Both grade 4 toxicities were observed at City of Hope National Medical Center

[c] MTD

in Table 2); all three manifested grade 3 mucositis. There was no noticeable difference in the extent of prior chemotherapy or radiotherapy or in performance status between patients treated at the two institutions. At the University of Chicago, dose escalation was continued for two additional dose levels following these observations. Five of seven patients treated at level 5 tolerated this chemotherapy, although grade 2 mucositis was observed in four of these subjects and two additional patients developed grade 3 mucositis. All three patients treated at the highest FUdR dose level (0.375 mg/kg daily) developed dose-limiting grade 3 mucositis.

Hematologic and other toxicities are summarized in Table 3. Neutropenia and thrombocytopenia equivalent to or higher than grade 2 were not observed in any patient treated during this study. A maculopapular skin rash was observed in eight cases, frequently in sun-exposed areas of the neck and upper chest. Diarrhea was observed in six subjects but was severe in only one case.

Response

Four patients were not evaluable for response: three of these refused further therapy after one cycle and one patient developed grade 4 toxicity at dose level 4 and was taken off study by the treating physician. In all 24 patients were considered to be evaluable for response. Tumor shinkage of 25% was observed in one patient with renal cell cancer; this subject maintained his response for nine cycles, at which time he opted to discontinue the chemotherapy. A total of 10 additional patients had stable disease, including 2 subjects with breast cancer who were treated with 3 cycles each; 2 patients with renal cell cancer who completed 4 and 6 cycles, respectively; and 1 subject each with prostate cancer (14 cycles), colorectal carcinoma (6 cycles), small-bowel cancer (4 cycles), head and neck cancer (3 cycles), leiomyosarcoma (3 cycles), and adenocarcinoma of unknown primary (2 cycles followed by surgery).

Discussion

In the present study we have attempted to define the MTD for a 5-day continuous intravenous infusion of FUdR modulated by high-dose oral LV. The dose of oral LV used has previously been shown to result in reduced folate plasma concentrations sufficient to produce modulation of fluoropyrimidines [26, 27].

The dose-limiting toxicity of the combination was mucositis; only a few additional toxicities were observed, the most notable being a maculopapular skin rash. The recommended dose for future phase II studies is 0.3 mg/kg per day based on the University of Chicago experience, in which a total of 21 patients were treated and toxicity greater than grade 2 was not observed at daily doses of <0.3 mg/kg per day; at the City of Hope National Medical Center, only seven patients were treated, including three at dose level 3b. Thus, the greater experience took place at the University of Chicago, where a dose of 0.3 mg/kg daily resulted in mucositis in six of seven patients treated, although toxicity exceeding grade 2 was seen in only two of these subjects. Therefore, this dose resulted in only moderate degrees of mucositis in the majority of patients treated.

Mucositis resulting from a regimen that does not also induce myelosuppression may be less dangerous to the patient than a regimen resulting in simultaneous breakdown of mucosal barriers and myelosuppression. On the other hand, the complete lack of myelosuppression in this trial might enable the careful addition of a myelosuppressive drug to the combination, with the aim of achieving myelosuppression equivalent to or lower than grade 2.

Table 3. Other toxicities

Dose level	Patients (*n*)	Median WBC $\times 10^3/\mu l$ (Range)	Median platelets $\times 10^3/\mu l$ (Range)	Skin rash	Diarrhea
1) 0.1 mg/kg daily	3	6.4 (3.3–9)	199 (111–255)	2 cases (grade 2)	0
2) 0.15 mg/kg daily	3	3.7 (3.6–4.5)	265 (181–270)	0	0
3) 0.2 mg/kg daily	6	5.8 (4.4–7.9)	250 (143–515)	1 case (grade 3)	1 case (grade 2)
4) 0.25 mg/kg daily	6	5.1 (2.1–6.7)	202 (100–535)	3 cases (2 of grade 1, 1 of grade 2)	2 cases (1 of grade 1, 1 of grade 2)
5) 0.3 mg/kg daily	7	4.1 (2.9–12.7)	411 (132–560)	2 cases (grade 1)	2 cases (1 of grade 1, 1 of grade 2)
6) 0.375 mg/kg daily	3	3.9 (2.8–8.4)	93 (73–335)	0	1 case (grade 3)

The divergence of observations regarding the serverity of mucositis noted at the two participating institutions may reflect the subjectivity involved in the assessment of mucositis as a major toxicity, which relates both to the patient and his or her ability to eat in the presence of significant oral pain and to the physician and his assessment of the severity of oral lesions. This may need to be taken into account in the design of future phase I studies in which mucositis is anticipated to be a dose-limiting toxicity.

Few studies in the literature have addressed the optimal dosing for a continuous intravenous infusion of FUdR or its modulation using LV. Moore and Koike [18] found moderate toxicities at daily doses of 30 mg/kg when FUdR was given daily as an intravenous bolus for 5–7 days. Sullivan and Miller [23] used FUdR by continuous intravenous infusion for 5–10 days, initially attempting to deliver daily doses of 30 mg/kg, which resulted in intolerable toxicity. These authors documented moderate toxicities (mucositis, myelosuppression) at doses of 0.5–1 mg/kg per day. More recently, Chang et al. [1] reported on a randomized trial of intrahepatic arterial vs intravenous FUdR, both infused continuously over 14 days in patients with colorectal cancer metastatic to the liver. The daily doses used were 0.3 mg/kg for intrahepatic arterial infusion and 0.125 mg/kg for intravenous treatment; the intraarterial route resulted in an improved response rate in the liver (62% vs 17%). Toxicities consisted of chemical hepatitis, biliary sclerosis, and peptic ulcers for intrahepatic FUdR; diarrhea was the only frequent side effect observed during intravenous delivery FUdR (59% of patients), whereas mucositis occurred in only 14% of subjects. Another randomized trial was reported by Kemeny et al. [9], who compared 0.3 mg/kg per day of intrahepatic FUdR to 0.125 mg/kg per day of intravenous FUdR, each being delivered for 14 days by continuous infusion to patients with liver metastases from colorectal cancer. Responses were, again, higher in the group receiving intrahepatic chemotherapy. Toxicities were similar to those described by Chang et al. [1], with 70% of patients who received systemic chemotherapy developing diarrhea. Similar results have also been reported by the Northern California Oncology Group [6]. In all of these studies the toxicities of intrahepatic FUdR infusion were usually local (chemical hepatitis, sclerosing cholangitis), whereas systemic delivery of FUdR resulted in diarrhea as the dose-limiting toxicity and only occasional cases of mucositis.

The clinical experience of giving FUdR with simultaneous high-dose LV is even more limited [5, 8, 10, 12, 16, 24]. In a phase I study, Kemeny et al. [10] used continuous intrahepatic infusion of FUdR at a dose of 0.2–0.3 mg/kg daily for 7–14 days with intrahepatic administration of LV at 30 mg/m^2 per day in patients with intrahepatic metastases. At the higher FUdR dose, hepatic toxicity was found to be prohibitive; overall, 72% of patients responded and 18 of 25 were alive after 1 year. Marsh et al. [16] gave weekly intravenous doses of LV at 200 mg/m^2 over 4 h, followed immediately by FUdR given intravenously at 30 mg/kg over 2 h; the toxicity was moderate in degree and consisted of diarrhea, nausea, and mucositis.

Additional studies have addressed the modulation of higher doses of intravenous bolus FUdR (2,000 mg/m^2) with LV, resulting in frequently severe diarrhea [24], as well as the modulation of long-term continuous intravenous infusion of FUdR ($\geq$20 days) [12]. In addition, Hiponia et al. [5] identified nausea and diarrhea as dose-limiting toxicities in a phase I study investigating the circadian administration of LV, FUdR, and cisplatin.

This trial cannot serve to determine whether FUdR is a better drug than 5-FU in its clinical modulation by LV. It is interesting that mucositis was dose-limiting in our trial, whereas most data published on FUdR indicate that diarrhea is the dose-limiting toxicity. Thus, the toxicity spectrum described in the present study appears to resemble that seen at our institution in studies using continuous infusion of 5-FU and LV rather than the published experience with intravenously delivered FUdR.

The activity of FUdR and LV seen in this phase I study was limited. However, a persistent minor response was seen in 1 patient with renal cell carcinoma, and stable disease was observed in 10 of 24 evaluable subjects, including 2 additional patients with renal cell carcinoma. It is noteworthy that stable disease was quite durable in several of the patients treated and that this regimen could be given for up to nine cycles without undue cumulative toxicity. Phase II trials using this regimen in renal cell cancer as well as in patients with gastrointestinal or head and neck cancer may therefore be indicated. This is also supported by a report from Huben et al. [8], who observed responses in four of five evaluable patients with renal cell carcinoma who were treated with a 14-day continuous infusion of FUdR at 0.125 mg/kg per day.

Biochemical modulation of fluoropyrimidines has previously resulted in increased activity in patients with colorectal cancer and has achieved promising results in patients with head and neck cancer [26, 27]. The continued exploration of new modulators as well as the substitution of 5-FU by FUdR in carefully designed phase I and II trials may help further to advance the therapeutic options in patients with solid tumors.

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