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ORIGINAL ARTICLE

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Phase I study of 5-day continuous infusion fluorodeoxyuridine and high-dose folinic acid with oral hydroxyurea

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Abstract Fluorodeoxyuridine (FUdR), the deoxynucleoside metabolite of 5-fluorouracil (5-FU), can be converted in a single step to fluorodeoxyuridine monophosphate (FdUMP), which binds covalently to thymidylate synthase (TS). Ribonucleotide reductase, an obligatory enzyme in the synthesis of deoxynucleotides, can be inhibited by hydroxyurea. Recognizing the well-established synergism between 5-FU and folinic acid (leucovorin), we hypothesized that the simultaneous administration of FUdR, leucovorin, and hydroxyurea might afford more effective inhibition of TS. Thirty-six patients with neoplastic disease considered refractory to standard therapy were entered into this phase I protocol. Treatment was administered on days 1 through 5 of a 28-day cycle and consisted of folinic acid (500 mg m^{-2} day^{-1}) and FUdR at escalating doses of 0.1, 0.15, or 0.2 mg kg^{-1} day^{-1} both administered by continuous i.v. infusion, and hydroxyurea given p.o. once per day at doses ranging from 0 to 2500 mg in 500-mg increments. The hydroxyurea and FUdR levels were escalated in a sequential fashion. The majority of patients had refractory breast or lung cancer. Dose-limiting toxicities were mucositis and diarrhea at the maximally tolerated dose of 0.15 mg/kg FUdR and 2000 mg hydroxyurea per day in conjunction with high-dose folinic acid. Hematological toxicity was minor. Of the 18 patients in whom response could be evaluated, none had evidence of objective disease regression. Mucositis and diarrhea are the dose-limiting toxicities when continuous infusions of FUdR and high-dose folinic acid are combined with oral hydroxyurea, effects that are consistent with the observed toxicities for FUdR when administered alone or in combination with leucovorin.

Key words Fluorodeoxyuridine · Folinic acid · Hydroxyurea

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Introduction

The enhancement of 5-fluorouracil (5-FU) cytotoxicity by folinic acid (leucovorin) is well documented, and clinical trials have shown improved response rates in patients with metastatic colorectal cancer treated with this combination [4, 7, 9, 10]. Fluorodeoxyuridine (FUdR), the deoxynucleoside metabolite of 5-FU, can be converted in a single step to fluorodeoxyuridine monophosphate (FdUMP), which binds covalently to thymidylate synthase (TS), forming a ternary complex [3, 8, 13]. Deoxyuridine monophosphate (dUMP), the substrate for TS, accumulates behind the block. The elevated dUMP competes with FdUMP for binding to newly synthesized TS and to free TS that is released by dissociation of the ternary complex. An obligatory enzyme in the de novo synthesis of dUMP and other deoxynucleotides is ribonucleotide reductase, which can by inhibited by hydroxyurea. This suggests the possibility that the simultaneous administration of FUdR, leucovorin, and hydroxyurea might allow more effective inhibition of TS [12]. However, there have been few studies directed at evaluation of this combination of agents [5, 15, 16]. Hence, we embarked upon a phase I investigation to define the maximally tolerated dosage of continuous infusion FUdR and oral hydroxyurea in conjunction with a fixed dose of leucovorin.

Materials and methods

Thirty-six patients were entered onto this protocol which had been reviewed and approved by the City of Hope National Medical Center Institutional Review Board. Eligible patients included those with histological or cytological documentation of neoplastic disease considered refractory to standard therapy or for whom no standard therapy existed. Patients were required to have a Karnofsky performance status of at least 60%, an estimated survival of at least 2 months, a leukocyte count of more than 4000/μl, and a platelet count of more than 150,000/μl. Total serum bilirubin, transaminases, and alkaline phosphatase were all required to be less than four times the institutional upper limit of normal, and the serum creatinine less than 2.0 mg/dl or creatinine clearance more than 40 ml/min. Patients who possessed measurable lesions were required to have baseline determinations performed with appropriate radiographic studies within 4 weeks of entry into the trial; pleural effusions, ascites, and bone metastases were not considered measurable. There were no limitations on the extent of exposure to prior radiotherapy or on the types and number of previously administered chemotherapeutic agents except that patients who had received the combination of 5-FU and high-dose folinic acid were not eligible. All prior therapy had to be completed at least 4 weeks before study entry. Patient exclusion criteria included pregnancy or the presence of concomitant non-malignant disease that was either poorly controlled by therapy or of such severity that it was considered potentially unsafe for the patient to participate in the trial. All participants provided written, voluntary informed consent before therapy was initiated.

Treatment was administered on days 1 through 5 of a 28-day cycle of chemotherapy. Folinic acid (500 mg m^{-2} day^{-1}) was administered as a 24 h i.v. infusion; 4 h after its initiation, FUdR was also delivered by continuous infusion at 0.1, 0.15, or 0.2 mg kg^{-1} day^{-1}. Hydroxyurea was administered p.o. once per day. The dose of hydroxyurea ranged from 0 to 2500 mg in increments of 500 mg/day. Patients were monitored weekly with complete blood counts; prior to each cycle, all baseline laboratory and radiographic studies were repeated. Treatment could be delayed by up to 7 days to allow recovery to defined levels of hematopoietic or gastrointestinal function. Therapy was given until objective evidence of disease progression was documented, and toxicity was graded according to the NCI common toxicity guidelines. Antiemetics were administered at the discretion of the treating physician.

The initial dose of FUdR was chosen because it was close to the maximally tolerated dose (MTD) achieved when combined with oral leucovorin in prior institutional experience [16]. The modulatory agent, hydroxyurea, was then added and escalated to MTD. Finally, an attempt was made to further escalate the dose of FUdR. If no grade 3 or 4 toxicity was manifest within a cohort of 3 patients, the hydroxyurea dose was escalated to the next dose level in the subsequent 3 patients while the FUdR dose was held at level 1. If any toxicity greater than grade 2 was observed at a dose level, the cohort was expanded to 6 patients. Dose escalation continued as long as there were two or fewer grade 3 toxicities in a cohort of 6. The MTD was defined as that followed by the occurrence of more than two grade 3 toxicities in such an expanded cohort or any grade 4 toxicity. Once the MTD of hydroxyurea was defined, the FUdR dose was escalated with the hydroxyurea dose held constant at the MTD −1 level (one dose level below that of the MTD). The study was terminated when 6 patients had been treated at the MTD-1 level for both hydroxyurea and FUdR with less than two grade 3 and no grade 4 toxicities observed.

Patients who completed at least one cycle of therapy were considered evaluable for toxicity; those with measurable disease who completed at least two cycles of treatment were considered evaluable for response. A complete response was defined as the disappearance of all detectable tumor on two separate measurements (either radiographic or by clinical exam) at least 28 days apart. Partial response was considered a 50% or greater reduction of the sum of the products of the longest perpendicular diameters of all measurable lesions and the appearance of no new lesions, both conditions persisting on two separate measurements (either radiographic or by clinical exam) at least 28 days apart. Stable disease was defined by similar criteria except that indicator lesions decreased or increased by less than or equal to 25%. Progressive disease was defined as an increase in the product of perpendicular diameters of the indicator lesion(s) by more than 25% or the appearance of new lesions.

Table 1 Mucositis

FUdR dose (mg kg^{-1} day^{-1})	Hydroxyurea dose (mg/dose)	Patients (*n*)	Grade 0	1	2	3
0.1	0	7[a]	2	2	2	1
0.1	500	3	1	–	2	–
0.1	1000	3	1	1	1	–
0.1	1500	5[b]	1	–	3	1
0.1	2000	3	–	4	2	1
0.1	2500	1	–	–	–	–
0.15	2000	7[b]	–	2	3	2
0.2	2000	1[a]	–	–	–	–

[a] One inevaluable patient excluded
[b] Two inevaluable patients excluded

Results

Thirty-six patients were registered and treated on this phase I protocol. The median age of the 23 women and 13 men was 52 years (range 30–79). Twenty-six (72%) had a performance status of 80 or better; ten (38%) had a KPS of 60–70. Among the variety of underlying tumor types in the patients treated, the majority had refractory breast (22%) or lung (19%) cancers. Six patients had gastrointestinal tract primaries, 3 had cancer of the head and neck, 3 had adenocarcinomas of undefined primary site, and 2 patients had gynecological malignancies. Prior therapy consisted of chemotherapy in 94% (including previous 5-FU exposure in 9 patients), radiation treatment in 64% or hormonal therapy in 22%; no patients had prior biologic therapy. Eighteen patients received only a single course of treatment; eleven received 2 cycles; and 6 others received from 3 to 7 courses of therapy. A single patient, with an underlying pancreatic islet cell tumor, received 17 cycles of therapy.

Toxicity

The first cohort of patients was treated with folinic acid and FUdR alone to ensure that the schedule would be tolerable before the potential toxicity of hydroxyurea was added to the regimen. A total of 8 patients were treated at this level with grade 3 toxicity (mucositis/leukopenia) observed in 2; 1 patient was inevaluable due to early death from disease progression. Thereafter, accrued patients received all three drugs in the regimen. Two additional patients were inevaluable during the hydroxyurea escalation phase, 1 due to early death from disease progression and the other because of acute cholecystitis requiring surgery shortly after chemotherapy. Hydroxyurea was eventually escalated to a level of 2,500 mg/day; the first patient so treated developed grade 4

Table 2 Other toxicities

FUdR dose (mg kg^{-1} day^{-1})	Hydroxyurea dose (mg/dose)	Patients (n)	Diarrhea		Leukopenia		Thrombocytopenia		CNS	Skin rash
			Grade 2–3	Grade 4	Grade 2–3	Grade 4	Grade 2–3	Grade 4	Grade 2–3	Grade 2–3
0.1	0	7[a]	1		1					
0.1	500	3								
0.1	1000	3	1							
0.1	1500	5[b]	1		1					
0.1	2000	3								
0.1	2500	1		1	1			1		1
0.15	2000	7[a]			2				1	1
0.2	2000	1[a]								

[a] One inevaluable patient excluded
[b] Two inevaluable patients excluded

mucositis and diarrhea. During the FUdR dose escalation phase, 2 patients were considered inevaluable because they were lost to follow-up. One registered patient was ineligible due to an elevated baseline bilirubin. When grade 4 mucositis was observed in a patient at the 0.2-mg/kg FUdR dose level, the MTD of the study was established as 0.15 mg/kg FUdR and 2000 mg hydroxyurea per day in conjunction with high-dose folinic acid (Table 1).

Toxicities, other than mucositis, are summarized in Table 2. There was minor hematological toxicity with five episodes of grade 2 or 3, but no grade 4, leukopenia observed. While no grade 2 or 3 platelet toxicities occurred, there was a single instance of grade 4 thrombocytopenia. Four patients suffered diarrhea of grade 2 or worse, with one episode of grade 4 diarrhea, concomitant with grade 4 mucositis, necessitating parenteral fluid support. On the other hand, 1 patient had constipation of sufficient degree to warrant designation as a grade 3 toxicity. Grade 2 or 3 skin rash, manifested as a generalized, occasionally pruritic, maculopapular eruption, occurred in 2 patients. Nausea and vomiting consequent on the therapy was no worse than grade 2 in any patient, and there were no episodes of neutropenic sepsis.

Response

Of the 18 patients who received more than 1 cycle of therapy and were eligible for response evaluation, none had evidence of objective disease regression. Disease was stable for more than 28 days in 5 patients, in 3 of whom the disease eventually progressed during therapy. One patient with breast cancer, who had previously received 5-FU, had progressive disease after 7 cycles of therapy; a patient with renal cell carcinoma progressed after 4 cycles; and a patient with small-cell lung cancer progressed after 3 cycles. Two patients refused further therapy despite stable disease; 1 after 4 cycles of treatment for adenocarcinoma of unknown primary and the other after 17 courses for pancreatic islet cell carcinoma who had previously been treated with streptozotocin and 5-FU.

Discussion

The results of this study indicate that mucositis and diarrhea are the dose-limiting toxicities when continuous infusions of FUdR and high-dose folinic acid are combined with oral hydroxyurea. These effects are consistent with the observed toxicities of FUdR when it is administered alone or in combination with leucovorin. [1, 6, 11, 14] We had anticipated that the addition of hydroxyurea, an agent with known myelosuppressive potential, would lead to the observation of more neutropenia in our patients, but this was not the case. The FUdR dose found to be tolerable in this study was much smaller than the dose that is tolerable when this agent is used alone, but similar to that described by Creaven et al., who defined the MTD of FUdR as 0.125 mg kg^{-1} day^{-1} when it was administered by 5-day continuous infusion with 500 mg m^{-2} day^{-1} of leucovorin [2]. On the other hand, Vokes et al were able to administer a 5-day continuous infusion of FUdR at 0.3 mg kg^{-1} day^{-1} in conjunction with 100 mg leucovorin given p.o. every 4 h for the duration of the infusion [16]. Potentiation of FUdR toxicity, unfortunately, suggests that the postulated biochemical interaction among these three drugs may occur at the level of the gastrointestinal epithelial cell, although we have no direct biochemical evidence to support this hypothesis. In the relatively few patients whose disease remained stable, there was no evidence of cumulative toxicity over several cycles of chemotherapy. The recommended doses for future phase II studies of this regimen are 0.15 mg kg^{-1} day^{-1} of FUdR by continuous infusion and 2 g/day of oral hydroxyurea when combined with a continuous infusion of folinic acid at 500 mg m^{-2} day^{-1}.

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