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Neal J. Meropol · Yousef M. Rustum
Nicholas J. Petrelli · Miguel Rodriguez-Bigas
Cheryl Frank · Dah H. Ho · Marilyn Kurowski
Patrick J. Creaven

A phase I and pharmacokinetic study of oral uracil, ftorafur, and leucovorin in patients with advanced cancer

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Abstract A phase I and pharmacokinetic study of oral uracil, ftorafur, and leucovorin was performed in patients with advanced cancer. Uracil plus ftorafur (UFT) was given in a 4:1 molar ratio in three divided doses for 28 consecutive days. Patient cohorts were treated at 200, 250, 300, and 350 mg/m^2 of UFT daily. For all patients, 150 mg of leucovorin was given daily in three oral doses. A 1-week rest period followed each 28-day treatment course. Gastrointestinal toxicity, characterized by diarrhea, nausea, and vomiting, was dose-limiting at 350 mg/m^2 UFT in patients who had received prior chemotherapy. Mild fatigue and transient hyperbilirubinemia were also common. In previously untreated patients, UFT at 350 mg/m^2 was well-tolerated, suggesting this as an acceptable phase II dose in this schedule with leucovorin. Two of eight previously untreated patients with advanced colorectal cancer had partial responses with UFT (350 mg/m^2) plus leucovorin. Pharmacokinetic parameters [ftorafur, uracil, 5-fluorouracil (5-FU), 5-methyltetrahydrofolate] showed wide interpatient variations. Plasma levels of 5-FU (C_{max} 1.4 $\pm$ 1.9 μM) were comparable to those achieved with protracted venous infusions, and folate levels (C_{max} 6.1 $\pm$ 3.6 μM) were sufficient for biochemical modulation. Ongoing study will determine if this convenient oral regimen will compare favorably in terms of efficacy, toxicity, and cost with intravenous fluoropyrimidine programs.

Key words Ftorafur · Uracil · Leucovorin

N.J. Meropol (✉) · M. Kurowski · P.J. Creaven
Division of Medicine, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263, USA
(Fax (716)845–8176)

N.J. Petrelli · M. Rodriguez-Bigas
Division of Surgical Oncology, Roswell Park Cancer Institute, Buffalo, NY 14263, USA

Y.M. Rustum · C. Frank
Department of Experimental Therapeutics, Roswell Park Cancer Institute, Buffalo, NY 14263, USA

D.H. Ho
University of Texas, M.D. Anderson Cancer Center, Department of Medical Oncology, Houston, TX 77030, USA

Introduction

Ftorafur [1-(2-tetrahydrofuranyl)-5-fluorouracil] is a 5-fluorouracil (5-FU) prodrug that has a spectrum of antitumor activity similar to that of 5-FU [1, 8, 12]. Following administration, ftorafur is converted to 5-FU by two mechanisms, a hydrolytic pathway mediated by microsomal cytochrome P-450, and by soluble enzyme hydrolysis. Clinical interest in ftorafur arises because of the potential for oral administration. Whereas 5-FU shows erratic gastrointestinal absorption, ftorafur is generally 100% absorbed after oral dosing. Preclinical models have suggested that the therapeutic index of ftorafur may be improved when the drug is coadministered with uracil, by increasing the concentration of 5-FU in tumor relative to serum. The presumed mechanism involves inhibition by uracil of the degradation of 5-FU to 2-fluoro-beta-alanine [9, 10, 13]. Early clinical trials of the combination of uracil and ftorafur (UFT) in a molar ratio of 4:1 have been conducted [5, 11, 16, 18, 21, 22]. In Japanese phase II trials, UFT has shown response rates of 32% in breast cancer (50 patients), 28% in gastric cancer (188 patients), and 25% in colorectal cancer (56 patients) [21]. Phase I studies of UFT in a 28-consecutive-day schedule have been carried out in the United States, in an effort to reproduce the cellular pharmacology of prolonged infusional therapy with oral dosing [18, 22]. The recommended phase II dose range derived from these studies was 360–400 mg/m^2 given in three divided doses every 8 h. Dose-limiting toxicities were diarrhea and abdominal pain, with granulocytopenia, nausea, stomatitis, and fatigue also reported.

Intracellular reduced folates are required for and augment the binding of deoxyuridylates to thymidylate synthase. When adminstered with 5-FU, pharmacological doses of reduced folates, in the form of calcium leucovorin (5-formyl tetrahydrofolate), have been shown to potentiate fluoropyrimidine cytotoxicity. In patients with colon cancer, the addition of leucovorin improves the therapeutic index of 5-FU, increasing response rates in advanced disease [24]. In addition, the combination of 5-FU plus leucovorin improves survival in the adjuvant setting when compared to surgery alone [6, 7, 19, 27]. Although in most clinical trials the combination of 5-FU and leucovorin have been administered intravenously, there is clinical evidence that oral administration of leucovorin results in biologically significant serum levels of reduced folates, and an improved ratio of biologically active folates to the inactive 6R-leucovorin isomer [14, 26]. Given that absorption of 6S-leucovorin (the active isomer) is saturable at higher doses [26], a daily total dose of 150 mg was chosen for the present study.

An effective oral fluoropyrimidine-based therapy, including biochemical modulation with leucovorin, could be of great benefit to patients with advanced colorectal cancer in terms of symptom palliation and quality of life. In addition, given clinical evidence that the radiosensitizing effects of fluoropyrimidines are schedule-dependent [20], a daily oral regimen may provide logistical benefits when compared with protracted venous infusions of 5-FU, while still maintaining superiority over short-term intravenous bolus schedules. A phase I and pharmacokinetic trial of the combination of oral UFT and leucovorin in a 28-consecutive day schedule was therefore undertaken and the results are reported here.

Materials and methods

Patient eligibility

Eligible patients were at least 18 years old, with an Eastern Cooperative Oncology Group performance status of 0, 1, or 2 (ambulatory at least 50% of the time). Adequate bone marrow function (absolute neutrophil count $\geq 2000/\mu l$, platelets $> 100\,000/\mu l$), liver function (bilirubin ≤ 1.5 mg/dl), and renal function (creatinine ≤ 1.5 mg/dl) were required. Three weeks must have elapsed since previous chemotherapy or radiotherapy (6 weeks if mitomycin C or nitrosoureas were adminisered). Patients with an unstable medical condition, myocardial infarction within 6 months, or active infection were ineligible. This protocol was approved by the Roswell Park Cancer Institute Institutional Review Board. All patients signed written informed consent before entry.

Protocol treatment

UFT was supplied by Taiho Pharmaceutical (Tokyo) as 100-mg capsules (referring to 100 mg of ftorafur). Cohorts of patients were enrolled at escalating UFT dose levels. The first UFT dose level was 200 mg/m^2 per day, and the daily dose was increased by 50 mg/m^2 at subsequent levels. Leucovorin (Lederle) was supplied as 15-mg tablets (6R,S-racemic mixture), and administered at a total daily dose of 150 mg to all patients. UFT and leucovorin were administered concurrently in divided doses every 8 h daily for 28 consecutive days, followed by a 7-day rest period. Doses were scheduled at 0700, 1500, and 2300 hours, and were taken orally with 4–8 ounces of water. No food was permitted from 1 h before each dose until 1 h after drug ingestion. The calculated UFT dose was rounded to the nearest 100 mg, and if uneven dosing was required, the highest dose was administered in the morning. Leucovorin was administered as 60 mg with the first daily dose of UFT and 45 mg with the other two doses. Complete blood counts were obtained weekly and serum chemistries (including electrolytes, creatinine, bilirubin, and hepatic transaminases) were repeated every other week. Patients with measurable disease had disease reevaluations after every two 5-week courses of therapy. Treatment courses were repeated until disease progression, toxicity precluded continuation, or the patient expressed the wish to stop therapy.

The NIH Common Toxicity Criteria were used for toxicity assessment [2]. Chemotherapy was held for grade 3-4 hematologic or grade 2-4 non-hematologic toxicity during a treatment course. Upon resolution of toxicity, treatment was restarted, with a dose reduction of one level in those patients with grade 3–4 toxicity. A UFT dose reduction of one level was instituted in subsequent courses for grade 3–4 hematologic toxicity or grade 3 non-hematologic toxicity; grade 4 non-hematologic toxicity mandated a dose reduction of two UFT dose levels in the subsequent course. The leucovorin dose was not changed for toxicity.

Cohorts of at least three patients were treated at each dose level. The maximum tolerated dose (MTD) was defined as the highest dose at which at least 50% of treated patients were able to receive at least 75% of their proposed dose over two courses. Eight patients were enrolled at the MTD to better characterize toxicity at this dose.

In addition, to determine whether the MTD would be an acceptable phase II dose in a patient population likely to receive this regimen in phase II evaluation, eight patients with advanced colorectal cancer who were chemotherapy-naive (except for adjuvant therapy at least 6 months earlier) were treated.

Pharmacokinetic studies

Plasma levels of ftorafur, 5-FU, uracil, and folates were assessed. Plasma was obtained at $t = 0$, 0.5, 1.5, 2, 4, and 6 h following the initial doses of UFT and leucovorin. Plasma concentrations of ftorafur and 5-methyltetrahydrofolate were determined using high performance liquid chromatography as described by Creaven et al. [4]. For ftorafur, a Perkin Elmer model 410 Bio programmable pump, equipped with an LC 95 UV/V detector set at 265 nm, and an interface connected to a Sigma 10 Data system, and a Spheresorb S-3-OD52 (15 cm $\times$ 4.6 cm internal diameter) column system in series were used for analysis. Ftorafur was eluted by an isocratic buffer of 2.5 mM ammonium acetate containing 1.25% methanol (pH 5), at a flow rate of 1 ml/min. In the ftorafur analyses, thymidine was used as internal standard, and ftorafur concentrations ranging from 0.1 μg/ml to 30 μg/ml were linear. The lower limit of detection in this assay was 100 ng/ml, with interassay variation of 8.3% over 11 assay days.

Uracil and 5-FU were assayed using the GC/MS method of Marunaka et al. [17] with minor modifications. In brief, [^{15}N]-uracil and [^{15}N]-5-FU were added to samples as internal standards. After removing ftorafur from the aqueous layer with chloroform, 5-FU and uracil were extracted with ethylacetate. The ethylacetate layer was evaporated under nitrogen. Calibration curves for 5-FU were made by plotting the ratios (m/z 301/303) versus concentrations of 1–200 ng/ml. For uracil, ratios (m/z 283/285) versus concentrations of 10–5000 ng/ml were plotted. Interassay variablility for 5-FU and uracil was 4.0 and 8.0%, respectively.

Table 1 Patient Demographics. The maximum tolerated dose was defined by the previously treated patient cohort with a standard dose escalation scheme. The previously untreated cohort had advanced colorectal cancer, and were treated at a single dose level

	Previously treated	Previously untreated
Median age (range)	59(47–74)	66 (45–77)
Male/female	8/10	3/5
Performance status		
0–1	17	8
2	1	0
Disease sites		
Colorectal	11	8
Lung	4	
Stomach	1	
Esophagus	1	
Melanoma	1	
Prior chemotherapy regimens		
Median	2	
Range	1–4	

Results

Patient demographics are listed in Table 1. The MTD was defined in a heavily pretreated population. Toxicity data are presented in Table 2. At UFT dose levels of 200–300 mg/m^2 daily, toxicity greater than grade 2 was not encountered (except one patient with a transient bilirubin elevation), and none of the ten patients treated discontinued therapy because of toxicity. Eight patients who had previously failed other systemic treatment were then treated with UFT 350 mg/m^2 daily. At this dose level, one patient had grade 4 diarrhea, two had grade 3 nausea and vomiting (one of whom also had severe fatigue), and one had transient grade 3 hyperbilirubinemia. Gastrointestinal toxicity was therefore dose-limiting with this regimen.

Twelve patients were eligible for dose intensity analysis at the UFT 350 mg/m^2 dose level. Four other patients treated at this dose level discontinued therapy within the first two cycles for disease progression. Of 12 evaluable patients, 10 received at least 75% of scheduled doses over two cycles. The mean ($\pm$ SD) delivered dose intensity (as a percentage of scheduled dose) over two cycles at the UFT 350 mg/m^2 dose level was 86.9 $\pm$ 25.9%.

Transient hyperbilirubinemia was common, observed in seven patients (Table 3). This tended to occur during second or subsequent cycles of treatment, and resolved over 10–14 days. Changes in alkaline phosphatase and hepatic transaminases were not generally associated with bilirubin elevations. Hyperbilirubinemia was not clearly dose-related as all affected patients had liver metastases. It did not require treatment delay or dose modification.

In view of the frequent toxicity observed at the 350 mg/m^2 UFT dose level (weakness/fatigue in all patients, diarrhea in five out of eight, nausea/vomiting in six out of eight), dose-limiting toxicity in three of eight (38%) patients, and a steep dose-toxicity relationship for UFT at doses near the MTD [3, 25], we did not escalate the UFT dose further. However, given that most toxicities were mild, and the majority of these heavily pretreated patients were able to tolerate at least two cycles of therapy, we believed that this was likely to be an acceptable phase II dose for previously untreated patients.

To characterize the toxicity pattern in chemotherapy-naive patients, eight subjects with advanced colorectal cancer who had not been treated for advanced disease were treated with UFT 350 mg/m^2 plus

Table 2 Toxicity of oral uracil plus ftorafur (*UFT*) plus leucovorin ($n = 26$) in patients with tumor grades 1–4

Toxicity symptoms	UFT < 350 mg/m^2 ($n = 10$)				Prior therapy UFT 350 mg/m^2 ($n = 8$)				No prior therapy UFT 350 mg/m^2 ($n = 8$)			
	1	2	3	4	1	2	3	4	1	2	3	4
Abdominal Pain	1	0	0	0	2	0	0	0	2	0	0	0
Alopecia	0	0	0	0	1	0	0	0	1	0	0	0
Anemia	1	0	0	0	2	2	0	0	2	0	0	0
Anorexia	2	0	0	0	1	0	0	0	6	0	0	0
Diarrhea	0	1	0	0	1	3	0	1	2	1	1	0
Headache	1	0	0	0	1	0	0	0	0	0	0	0
Hepatic	0	1	1	0	0	2	1	0	0	0	2	0
Lacrimation	2	0	0	0	0	0	0	0	1	0	0	0
Nausea/vomiting	2	1	0	0	4	0	2	0	6	2	0	0
Neutropenia	0	0	0	0	0	0	0	0	0	0	0	0
Rash	0	0	0	0	1	0	0	0	1	0	0	0
Renal	0	0	0	0	1	0	0	0	1	0	0	0
Stomatitis	0	1	0	0	1	0	0	0	1	1	0	0
Thrombocytopenia	0	0	0	0	0	0	0	0	1	0	0	0
Weakness/fatigue	2	0	0	0	4	3	1	0	3	1	1	0

Table 3 Hyperbilirubinemia in patients treated with UFT plus leucovorin

Patient (UFT dose)	Bilirubin (mg/dl)			Liver metastases
	Baseline	Peak (day)	Last (day)	
02 (200 mg/m^2)	1.4	1.9 (49)	1.8 (72)	Yes
06 (250 mg/m^2)	0.6	1.3 (64)	1.3 (64)	Yes
11 (350 mg/m^2)	0.6	2.8 (56)	1.4 (89)	Yes
14 (350 mg/m^2)	0.4	1.4 (70)	0.9 (80)	Yes
17 (350 mg/m^2)	0.2	1.7 (140)	0.8 (243)	Yes
19 (350 mg/m^2)	0.7	2.5 (28)	1.3 (39)	Yes
20 (350 mg/m^2)	0.9	2.5 (64)	1.6 (70)	Yes

Table 4 Pharmacokinetic parameters of ftorafur, uracil, and 5-fluorouracil (5-FU) in patients treated with 350 mg/m^2 oral UFT. [C_{max} maximum concentration, AUC area under the curve (0–6 h), all values ± standard deviation]

n	Day	Ftorafur		Uracil		5-FU	
		C_{max} (μM)	AUC (μM · h)	C_{max} (μM)	AUC (μM · h)	C_{max} (μM)	AUC (μM · h)
9	1	32.4 ± 9.2	108.1 ± 41.4	22.3 ± 20.9	22.4 ± 14.1	1.8 ± 2.5	1.5 ± 1.3
6	28	59.2 ± 37.1	262.5 ± 179.7	17.2 ± 11	16.5 ± 10.3	0.8 ± 0.4	1.4 ± 0.8
15	1 + 28	45.1 ± 24.5	169.8 ± 136.5	20.3 ± 17.3	20.1 ± 12.7	1.4 ± 1.9	1.5 ± 1.1

Table 5 Plasma pharmacokinetics of 5-methyltetrahydrofolate derived from 6R, S-leucovorin (60 mg) in patients ($n = 19$) treated with UFT. [C_{max} maximum concentration, $t_{1/2}$ plasma half life, AUC area under the curve (0–6 h)].

	C_{max} (μM)	$t_{1/2}$ (h)	AUC (μM · h)
Mean	6.1 ± 3.6	4.1 ± 3.3	38.4 ± 36.1
Range	1.7–16	0.8–12.5	8.3–152.7

leucovorin 150 mg daily. The side effects seen in these patients are shown in Table 2. Two patients had partial responses in measurable liver metastases, lasting 5 months and 7 months.

Table 4 shows the plasma concentrations of ftorafur, uracil, and FU derived from oral administration of UFT at 350 mg/m^2. In general, there was no significant difference between the parameters as measured on day 1 or day 28 during treatment. In these patients, there was significant variation in the maximum concentration (C_{max} 1.4 ± 1.9 μM) and area under the curve (AUC, 1.5 ± 1.1 μM · h) of 5-FU.

5-Methyltetrahydrofolate pharmacokinetics are outlined in Table 5. A wide variation was observed in the C_{max} and AUC following oral administration of 60 mg 6R, S-leucovorin. The plasma concentrations achieved should be sufficient for modulation of 5-FU action. Using HPLC it was not possible to detect in the plasma any 6S-leucovorin, the biologically active isomer. There were no clear associations of either maximum toxicity or individual organ toxicities with plasma levels of 5-FU (data not shown).

Discussion

We found that the maximum tolerated dose of UFT when given with oral leucovorin for 28 consecutive days is 350 mg/m^2. This is equivalent to the MTD observed with UFT alone [18, 22], indicating that oral leucovorin does not alter the toxicity pattern when administered in this schedule. Two of eight previously untreated patients with colorectal cancer had partial responses in this trial; the contribution of leucovorin to this activity will require further study. The toxicity observed in our study is less than that reported by Pazdur et al. [23] with an identical regimen at the M.D. Anderson Cancer Center. Two of 16 patients treated with 350 mg/m^2 UFT in our study had dose-limiting diarrhea (one of eight previously untreated), whereas five of seven patients in the other trial had grade 3 diarrhea. The reasons for these findings are not certain. It is possible that subtle selection factors differed at each site. In addition, it is difficult to extrapolate precise population toxicity frequencies in phase I trials with the small patient numbers at each dose level. Based upon our experience, we recommend 350 mg/m^2 UFT as the starting phase II dose in future studies, although objective responses were observed in 16 of 38 patients with measurable advanced colorectal cancer treated at 300 mg/m^2 in the M.D. Anderson trial [23].

In our study, the achieved plasma concentration of 5-FU (1.5 μM) is similar to that obtained with protracted venous infusion schedules of 5-FU. Similarly, the concentrations of 5-methyltetrahydrofolate observed,

with a half-life of approximately 4 h, are sufficient to modulate 5-FU action [28]. Although we found no correlation between 5-FU or 5-methyltetrahydrofolate pharmacokinetics and toxicity, this sample size is small, and a pooled analysis of our data and that obtained in the M.D. Anderson study [23] is in progress.

There is currently evidence that protracted venous infusions of 5-FU may be superior to bolus administration in colorectal cancer, both in advanced disease and as a radiopotentiator in the adjuvant setting [15, 20]. Our 28-day oral regimen has the potential to duplicate these results without the inconvenience and expense of ambulatory infusion pumps and central venous catheters. A prospective randomized trial comparing UFT plus oral leucovorin to intravenous 5-FU plus leucovorin in advanced colorectal cancer is currently underway.

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