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ORIGINAL ARTICLE

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Oral uracil and Ftorafur plus leucovorin: pharmacokinetics and toxicity in patients with metastatic cancer

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Abstract *Purpose*: To assess the pharmacokinetics of Ftorafur (tegafur, FT), 5-fluorouracil (5-FU), and uracil in 31 cancer patients who were enrolled in phase I studies of oral uracil and FT (UFT). The correlation between pharmacokinetic parameters and toxic effects of UFT was evaluated. *Methods*: Uracil and FT were orally administered in a 4:1 molar ratio at FT doses of 200–400 mg/m^2 per day. Patients also received leucovorin at 150 mg/day. Daily doses were divided into three doses and administered at 8-h intervals for 28 consecutive days. Plasma FT concentrations were measured by high-performance liquid chromatography, and plasma 5-FU and uracil concentrations were determined using gas chromatography-mass spectrometry. National Institutes of Health Common Toxicity Criteria were used for assessment of toxicity. *Results*: The concentrations of FT, 5-FU, and uracil showed wide interpatient variations. Maximum plasma concentrations (Cp_{max}) of all three compounds were achieved in 0.3 to 4.0 h. At the various study doses, the terminal half-life ($t_{1/2\beta}$) of FT ranged from 3.9 to 5.9 h, the area under the concentration-versus-time curve (AUC_{0-6h}) ranged from 16,220 to 52,446 (ng/ml)h, the total clearance (Cl_T) ranged from 100 to 175 ml/min, and the steady-state volume of distribution (Vd_{ss}) ranged from 18.3 to 28.7 l. The 5-FU generated from FT had an apparent distribution half-life ($t_{1/2\alpha}$) and an apparent elimination half-life ($t_{1/2\beta}$) of 0.3–1.3 h and 4.9–7.0 h, respectively. The AUC_{0-6h} of 5-FU ranged from 120 to 325 (ng/ml)h. Uracil had a $t_{1/2\alpha}$ of 0.2–0.5 h and the level quickly returned to the endogenous level. The AUC_{0-6h} for uracil ranged from 605 to 3764 (ng/ml)h, the Cl_T ranged from 3225 to 7748 ml/min, and the Vd_{ss} ranged from 341 to 1354 l. The Cp_{max} and AUC_{0-6h} of both FT and uracil were significantly correlated with FT doses (*P*-values of 0.0244 and 0.0112) and with uracil doses (*P*-values of 0.0346 and 0.0083), respectively. In addition to interpatient variations, intrapatient variations were also observed in six patients who had pharmacology studies done on days 1 and 26 ± 2 at the same study dose. We found that the repeated treatment with UFT caused cumulative increases in the values of Cp_{max}, C_{trough}, and AUC_{0-6h} of FT and 5-FU. The major toxic effects observed were diarrhea and nausea and vomiting. The occurrence of these toxic effects correlated significantly with the Cp_{max} and AUC_{0-6h} of 5-FU. *Conclusions*: The pharmacology studies showed that FT and uracil were readily absorbed orally and that FT was rapidly converted to 5-FU. The preliminary findings suggest that determination of plasma levels of 5-FU after oral administration of UFT may help predict subsequent toxic effects.

Key words Ftorafur (tegafur) · 5-FU · UFT · Pharmacology · Toxicity

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Introduction

Ftorafur (tegafur, FT), a prodrug of 5-FU [6], has been shown to have a broad spectrum of antitumor activity

when administered intravenously [29] or orally [2, 28]. These studies have suggested that the clinical activity of FT may be attributable to the slow release of 5-FU. One of the actions of 5-FU is the inhibition of thymidylate synthase by fluorodeoxyuridine 5′-monophosphate (FdUMP), the active metabolite of 5-FU. The inhibition requires a cofactor, 5,10-methylene tetrahydrofolate, and subsequently interferes with DNA synthesis [17]. The cytotoxicity of 5-FU is enhanced by giving leucovorin (5-formyl tetrahydrofolate; LV), which is a precursor to 5,10-methylene tetrahydrofolate and has been used in clinical trials of advanced colorectal cancer to modulate the anticancer activity of 5-FU [3, 22, 23]. LV is orally bioavailable [8, 16] and has been administered orally in combination with 5-FU for the treatment of advanced colorectal adenocarcinoma [9].

In vitro studies have shown that uracil retards the degradation of 5-FU by acting as a competitive inhibitor of dihydropyrimidine dehydrogenase. In rodent tumors, much higher and sustained levels of 5-FU have been noted when uracil is coadministered with FU than when 5-FU is administered alone [5, 12]. Enhancement of antitumor activity by administering FT with uracil (UFT; Taiho Pharmaceutical, Tokyo, Japan; BMS-200604, Bristol-Myers Squibb, Princeton, N.J.) has also been reported [4, 5, 19]. Preliminary studies of the pharmacokinetics of UFT [18, 19] and UFT plus LV [15, 20, 21] have previously been reported along with the clinical studies. The clinical development and the potential treatment of cancer with oral UFT and LV have been reviewed [11]. In this study, we extended the pharmacologic study of oral UFT plus LV in 31 patients from The University of Texas M. D. Anderson Cancer Center and Roswell Park Cancer Institute, and evaluated the degree of correlation between the toxic effects observed in these patients and the pharmacokinetic parameters of FT, 5-FU, and uracil. The pharmacology of LV has been reported elsewhere [8, 15, 16].

Materials and methods

Drugs

UFT was supplied by Taiho Pharmaceutical Co. (Tokyo, Japan). Each UFT capsule contained 224 mg uracil and 100 mg FT (uracil/FT molar ratio 4:1). LV, a 6*R*,*S*-racemic mixture, was supplied as 15-mg tablets by Lederle Laboratories (Wayne, N.Y.). [$^{15}N_2$]Uracil and [$^{15}N_2$]5-FU were purchased from Merck Sharp & Dohme Isotopes-Canada (Dorval, PQ, Canada).

Patients

A total of 52 patients took part in the phase I trial of oral UFT plus LV for metastatic carcinoma, and 17 patients from M. D. Anderson Cancer Center and 14 patients from Roswell Park participated in the pharmacology study. Written informed consent was obtained from the patients according to institutional policies. To be eligible for this study, patients had to be at least 18 years old with histologic proof of metastatic solid tumor unsuitable for surgical resection. Patients also had to have completed all previous treatment at least 3 weeks earlier and had to show signs of recovery from the toxic effects of previous treatment.

Protocol

Doses of UFT are expressed in terms of the FT doses. The starting oral dose of UFT was 200 mg/m^2 per day of FT, and the daily oral LV dose was 150 mg. Doses were given every 8 h with 4–8 oz of water for 28 consecutive days. In successive patient cohorts, the UFT dose was escalated to 400 mg/m^2 per day of FT in 50-mg increments. Because UFT capsules contain 100 mg FT, the calculated UFT dose was rounded off to the nearest 100 mg. When the daily UFT doses could not be divided evenly, the highest dose was given in the morning. Patients consumed no food from 1 h before to 1 h after medication was ingested.

Sample collection and preparation

Baseline heparinized blood samples were collected before treatment. Additional samples were collected at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, and 6 h after the first dose on the first day of treatment. Approximately the last day of treatment, a second 6-h pharmacology study was conducted in the morning on patients who were able to return. Plasma was separated by centrifuging the blood for 15 min at 1000*g* at 4 °C, and 0.5-ml aliquots were frozen in glass tubes at −70 °C and later assayed for 5-FU, uracil, and FT as described below.

5-FU and uracil determinations

5-FU and uracil were assayed using the procedure of Marunaka et al. [14]. The assay samples were prepared by adding 0.5 ml water or 0.5 ml standards in water, 0.5 ml patients' or normal subjects' plasma and 0.1 ml each of [$^{15}N_2$]uracil (2.5 μg/ml) and [$^{15}N_2$]5-FU (0.5 μg/ml) in water. Additional water was added to a final sample volume of 2 ml. After adding 50 μl 1 *N* HCl, the samples were extracted four times with 15 ml chloroform. The aqueous layer containing uracil and 5-FU was neutralized by the addition of 80 μl 1 *N* NaOH and ammonium bicarbonate to saturation and then extracted with 40 ml ethyl acetate, which was evaporated under nitrogen at room temperature. To the residue, 25 μl of pyridine and 75 μl of *N*-methyl-*N*-(*t*-butyl-dimethyl-silyl)trifluoroacetamide were added. The mixture was heated at 70 °C for 30 min, and the concentrations of 5-FU and uracil were determined by gas chromatography-mass spectrometry using a Finnigan INCOS 50 mass spectrometer (Finnigan Corporation, San Jose, Calif.) with an electron impact ionization source. The mass fragment chromatography analysis was made at m/z 301/303 for 5-FU/[$^{15}N_2$]5-FU and at 283/285 for uracil/[$^{15}N_2$]uracil. 5-FU standard concentrations were 0.005, 0.01, 0.05, 0.1, 0.2, and 0.25 μg/ml. The r^2 value for the standard curve was 0.9991, and the extraction efficiency was 70%. The uracil standard concentrations were 0.01, 0.02, 0.1, 0.5, 1, 2, 4, and 5 μg/ml. The r^2 value was 0.9990. The extraction efficiency was 75%.

FT determinations

To 0.5-ml samples of patients' plasma or standard in plasma, 50 μl thymidine at a concentration of 50 μg/ml (internal standard) was added. Ethyl acetate (4 ml) was then added, and the mixture was shaken for 10 min. The organic layer was removed after centrifugation, and the aqueous layer was reextracted once with an additional 4 ml ethyl acetate. The combined ethyl acetate layers were evaporated under nitrogen at 40 °C. The residue was reconstituted in 200 μl of the mobile phase solvent (3% methanol in 10 m*M* ammonium acetate, pH 4.2) used for high-performance liquid chromatography analysis. Of the reconstituted residue, 20 μl was injected for FT measurement at 265 nm, using a 10-cm Spherisorb ODS [2] column (Phenomenex, Torrance, Calif.) with a 3 μm particle size at a flow rate of 1 ml/min. The retention times for thymidine and FT were 13 min and 24 min, respectively. FT standards were 0.1, 0.5, 1, 5, 10, 20, and 30 μg/ml. The r^2 value was 0.9989, and the extraction efficiency was 79%.

Pharmacokinetics

FT, uracil, and 5-FU generated from FT were measured in patients after oral administration of UFT. Half-lives of FT and uracil and the apparent distribution half-life ($t_{1/2\alpha}$) and elimination half-life ($t_{1/2\beta}$) for 5-FU were calculated by biexponential curve-stripping using RSTRIP (MicroMath, Salt Lake City, Utah). The linear trapezoidal rule method was used to calculate AUC_{0-6h}. For FT and uracil, the AUC values were then used to calculate the total clearance (CL_T) [24] and the volume of distribution at steady state (Vd_{ss}) was calculated using the methods described by Rowland and Tozer [25]. PHARM/PCR version 4.0, based on the methods of Tallarida and Murray [27], was used for pharmacologic calculations. The National Institute of Health Common Toxicity Criteria were used for assessment of toxicity [1]. The GraphPad InStat program (GraphPad Software, San Diego, Calif.) was used for statistical analyses [13]. This program uses Student's *t*-test for paired parametric analyses. Two-tailed *P*-values ≤0.05 were considered to be statistically significant [26]. For statistical correlations of pharmacokinetic parameters with toxicity, both Kruskal-Wallis nonparametric ANOVA and Spearman's rank nonparametric tests were used [13, 26].

Results

The patients ranged in age from 38 to 76 years (mean ± SD 59 ± 9 years). Tumor types were as follows: 24 adenocarcinomas (17 of the colon, 3 of the rectum, 1 each of the appendix, stomach, cecum, and lung); 2 squamous cell carcinomas (1 of the lung and 1 of the esophagus); 1 adenoid cystic carcinoma; 1 large-cell lung carcinoma; 1 renal cell carcinoma; 1 anaplastic carcinoma; and 1 melanoma.

Pharmacokinetic studies

The pharmacologic study of 1 of the 31 patients was discontinued approximately 2 h after the administration of UFT due to poor vascular access for blood collections. Therefore, only the results of her Cp_{max} and T_{max} were included in the analyses of the data.

Uracil, FT, and the generated metabolite of FT, 5-FU, were rapidly measurable in the plasma of patients following oral administration of UFT (Fig. 1). At all time-points, the plasma FT concentrations were highest, and the plasma 5-FU concentrations were lowest. 5-FU levels appeared to parallel uracil levels (Fig. 1). T_{max} differed from patient to patient. For example, the T_{max} of patient B (Fig. 1B) was approximately eight times longer than those of patients shown in Fig. 1A,C (4 h vs 0.5 h). However, in individual patients, all three compounds usually had the same T_{max}. After reaching Cp_{max}, the initial 5-FU and uracil concentrations declined rather rapidly and then declined more slowly. 5-FU concentrations stabilized at low trough levels, and uracil decreased to its endogenous levels (Fig. 1). Wide interpatient variations were observed among the three patients (Fig. 1A-C). The Cp_{max} and AUC_{0-6h} for FT were higher in patient C [1012 ng/ml and 517 (ng/ml)h], respectively than in patient A [129 ng/ml and 105 (ng/ml)h] or patient B [134 ng/ml and 163 (ng/ml)h].

Table 1 summarizes the pharmacokinetic data for FT, 5-FU, and uracil in all the patients studied. Significant correlations between FT and uracil doses and their Cp_{max} and AUC were found (*P*-values of 0.008 to 0.0346). For simplicity, the results are presented in four different dose groups in Table 1. In addition to the wide interpatient variations reflected in the large standard deviations (Tables 1 and 2), intrapatient variations were also observed in six patients who had pharmacology studies done on days 1 and 26 ± 2 at the same study dose. Comparison of day-1 and day-26 values in each individual patient suggested that the effects of UFT on the values of Cp_{max}, C_{trough}, and AUC_{0-6h} of FT and 5-FU were cumulative (Table 2).

The major toxic effects observed were nausea and vomiting, and diarrhea. As shown in Table 3, significant correlations were observed between the Cp_{max} and AUC_{0-6h} of 5-FU and the occurrence of diarrhea or nausea and vomiting (*P*-values ranged from ≤0.001 to 0.033).

Discussion

Comparison of pharmacokinetics on days 1 and 26 ± 2 in each individual patient suggested that the repeated treatment with UFT caused cumulative increases in the

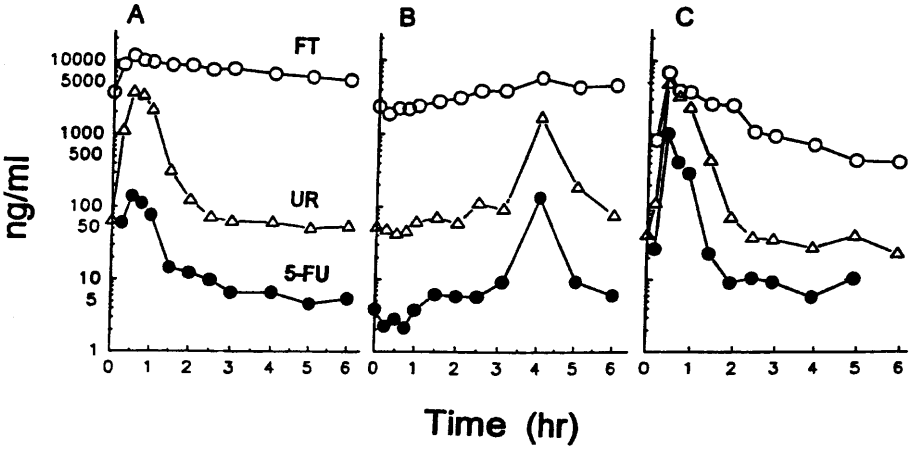

Fig. 1A–C Plasma levels of FT (○), uracil (Δ), and 5-FU (●) in three patients after oral administration of UFT (**A** 100 mg/m^2 per study dose, **B** 150 mg/m^2 per study dose, **C** 125 mg/m^2 per study dose)

Table 1 FT, 5-FU, and uracil pharmacokinetic parameters in patients receiving various oral UFT doses

UFT[a] (mg/m^2/study dose)	Compound	No. of patients	Cp_{max} (ng/ml)	C_{trough} (ng/ml)	T_{max} (h)	$t_{1/2\alpha}$ (h)[b]	$t_{1/2\beta}$ (h)[b]	AUC_{0-6h} (ng/ml)h	Cl_T (ml/min)	Vd_{ss} (l)
61	FT	1	3300	1566	1.6	NA[c]	5.9	16,220	103	21.7
100	FT	13	8462 ± 3316	3098 ± 618	1.1 ± 0.6	NA	3.9 ± 1.6	26706 ± 6745	133 ± 37	22.7 ± 7.6
125	FT	11	5526 ± 1247	2603 ± 974	1.5 ± 0.9	NA	3.9 ± 1.2	19968 ± 4934	175 ± 78	28.7 ± 8.1
125 (day 26[d])	FT	6	12017 ± 7746	7715 ± 4716	2.2 ± 0.5	NA	5.1 ± 1.2	52446 ± 35854	100 ± 68	18.3 ± 13.3
150	FT	5[e]	9227 ± 1827	3983 ± 1407	1.1 ± 0.4	NA	4.1 ± 1.0	34304 ± 9028	143 ± 32	25.0 ± 4.7
61	5-FU	1	17	4.6	1.0	0.9	NA	48	NA	NA
100	5-FU	13	109 ± 65	4.9 ± 5.4	1.0 ± 0.6	0.3 ± 0.1	5.4 ± 1.9	120 ± 93	NA	NA
125	5-FU	11	110 ± 129	11 ± 13	1.0 ± 0.6	1.3 ± 0.9	4.9 ± 2.3	171 ± 151	NA	NA
125 (day 26)	5-FU	6	114 ± 57	18 ± 7	2.1 ± 1.2	0.5 ± 0.2	7.0 ± 3.4	234 ± 131	NA	NA
150	5-FU	5	305 ± 254	8.6 ± 0.5	1.1 ± 0.5	0.4 ± 0.3	5.7 ± 3.8	325 ± 261	NA	NA
61	Uracil	1	325	17	1.6	0.2	NA	605	6175	800
100	Uracil	13	2004 ± 1353	52 ± 36	1.0 ± 0.5	0.3 ± 0.1	NA	1930 ± 904	5726 ± 4653	559 ± 574
125	Uracil	11	1685 ± 2285	76 ± 83	1.0 ± 2.0	0.5 ± 0.2	NA	2115 ± 1768	6542 ± 5278	909 ± 946
125 (day 26)	Uracil	6	1191 ± 617	70 ± 37	2.3 ± 1.0	0.4 ± 0.3	NA	1845 ± 1158	7748 ± 8435	1354 ± 1575
150	Uracil	5	3899 ± 2992	48 ± 25	1.2 ± 0.5	0.4 ± 0.1	NA	3764 ± 1991	3225 ± 1017	341 ± 186

[a] With the exception of the results for the 61 mg/m^2/study dose, all of the results are presented as mean ± SD; [b] $t_{1/2,\alpha}$ and $t_{1/2,\beta}$ of 5-FU are apparent half-lives; [c] Not applicable; [d] Pharmacokinetic parameter values of dose 1, day 1 were not significantly different from those of dose 1, day 26; [e] One patient's study was discontinued ~2 h after UFT administration, so only the Cp_{max} and T_{max} values were included in the data analyses

values of Cp_{max}, C_{trough}, and AUC_{0-6h} of FT and 5-FU. We also found inter- and intrapetient variations in the pharmacokinetics of FT, uracil, and 5-FU. There are several possible causes of such variations. Differences in drug absorption can always be a major cause of these variations. They might also have been caused by diurnal variations in the activity of dihydropyrimidine dehydrogenase, the rate-limiting enzyme that catabolizes both 5-FU and uracil [7]. Harris et al. have shown that in patients receiving continuous infusions of 5-FU, 5-FU levels peak when the dehydrogenase activity is lowest, at 6 a.m. and 3 p.m. In a study of oral administration of a single UFT dose, the mean AUC values for 5-FU were higher at 6 p.m. than at 8 a.m. [18]. Our pharmacology studies were always started between 8 a.m. and 9 a.m. with the intention of minimizing the effect of this circardian cycle. Another possible explanation for the wide interpatient variation in pharmacokinetic parameters is that dihydropyrimidine dehydrogenase, which is present predominantly in the liver, varies widely in activity in different individuals [10]. This variation could have caused the differences in the degradation of 5-FU and uracil. Variation in the activity of liver microsomal oxidase, which hydroxylates FT and converts it to 5-FU [30], is yet another possible explanation for the wide patient variations in pharmacokinetic parameters.

There were many differences among patients in this study with respect to tumor types, tumor burdens, previous drug treatments, and extent of liver metastases. All these factors could have affected the 5-FU levels. Furthermore, the effect of food on drug absorption could also have been a factor even though patients were instructed not to consume food from 1 h before to 1 h after drug ingestion. The time interval between the last meal and drug administration in this trial may not have been long enough, because it can take as long as 6 h for food to transit the stomach. Our preliminary experiments showed that administering an oral dose of UFT in the morning to rats denied food overnight yields significantly higher plasma levels of 5-FU than in rats that had been fed (Ho, unpublished data). This question of food effect is now being explored clinically (Pazdur, personal communication).

Not only the individual factors cited above but also combinations of these factors might have influenced the pharmacokinetics of FT, uracil, and 5-FU. For example, the drugs in the patient whose results are shown in Fig. 1C were rapidly absorbed, and this yielded a fast T_{max}. The fast half-life of FT (1.2 h) and the relatively high 5-FU concentrations indicate that high levels of microsomal oxidase and soluble hydrolytic enzymes rapidly generated 5-FU from FT [6, 30]. The metabolic pathways of FT have been reviewed and detailed by Grem [6]. Low dehydrogenase activity could also have contributed to the high levels of 5-FU and uracil. On the other hand, in the patient whose results are shown in Fig. 1B, FT was absorbed rapidly, but a smaller amount was absorbed than in the patients whose results are shown in Fig. 1A and C. The uracil levels were low

Table 2 FT and 5-FU pharmacokinetic parameters compared in patients receiving UFT on day 1 vs day 26

Patient no.	Study day	Cp_{max} (ng/ml)		$C_{(trough)}$ (ng/ml)		AUC_{0-6h} (ng/ml)h	
		FT	5-FU	FT	5-FU	FT	5-FU
1	1	3,800	16	1,480	5	15,275	62
	26	7,310	18	6,890	17	39,346	84
2	1	6,550	156	2,660	4	17,393	216
	26	7,570	177	3,370	13	27,158	248
3	1	4,790	25	2,770	11	18,160	64
	26	7,610	122	4,810	23	32,963	224
4	1	4,890	351	1,680	37	16,579	454
	26	23,230	149	15,510	29	112,363	475
5	1	7,130	39	4,200	6	25,518	80
	26	20,610	81	11,200	13	80,100	190
6	1	6,000	70	2,830	4	26,880	143
	26	5,770	140	4,510	11	22,747	185

Table 3 5-FU pharmacokinetic parameters in relation to diarrhea and nausea/vomiting grade in patients receiving UFT (numbers in parentheses are the numbers of patients)[a]. The Cp_{max} and AUC_{0-6h} values were correlated with diarrhea and nausea/vomiting grade (P-values ranging from ≤0.001 to 0.033)

Parameter	Diarrhea grade				Nausea/vomiting grade			
	0	1	2	3	0	1	2	3
Cp_{max} (ng/ml)	97 ± 74 (16)	208 ± 140 (4)	378 ± 375 (7)	211 ± 141 (4)	100 ± 70 (13)	225 ± 212 (12)	176 ± 130 (5)	1019 (1)
AUC_{0-6h} (ng/ml)h[a]	140 ± 91 (16)	152 ± 86 (4)	290 ± 227 (7)	559 ± 286 (3)	149 ± 103 (13)	231 ± 195 (12)	349 ± 338 (4)	528 (1)

[a] (ng/ml)h

initially in the baseline range, which indicates that uracil had not been absorbed and/or that the activity of dehydrogenase, which catabolizes uracil as soon as it is absorbed, was too high. This could also partially explain the fact that the 5-FU concentrations in this patient were very low. An additional explanation for the low 5-FU levels could be that not enough liver microsomal oxidase was available to convert the prodrug FT to 5-FU. At present, no explanation can be offered as to why the concentrations of the three compounds significantly increased at 4 h (Fig. 1B).

The 28-day oral UFT plus LV regimen causes neither neutropenia nor oral mucositis [15, 18, 21] that often occur with intravenous 5-FU treatment. The observed major toxic effects in this current oral UFT study – nausea and vomiting, and diarrhea – correlated significantly with 5-FU Cp_{max} and AUC values. Similar results have been reported with intravenous 5-FU [6]. These preliminary results suggest that measuring plasma 5-FU levels after oral UFT administration may assist in identifying individuals at risk for toxic effects. Further studies are needed to substantiate this finding.

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References

1. Ajani JA, Welch SR, Raber MN, Fields WS, Krakoff IH (1990) Comprehensive criteria for assessing therapy-induced toxicity. Cancer Invest 8: 149
2. Ansfield FJ, Kallas GJ, Singson JP (1983) Phase I-II studies of oral tegafur (Ftorafur). J Clin Oncol 1: 107
3. Budd GT, Fleming TR, Bukowski RM, McCracken JD, Rivkin SE, O'Bryan RM, Balcerzak SP, Macdonald JS (1987) 5-Fluorouracil and folinic acid in the treatment of metastatic colorectal cancer: a randomized Southwest Oncology Group study. J Clin Oncol 5: 272
4. Fujii S, Shirasaka T, Ikenaka K, Kitano S (1979) Effect of uracil on antitumor activity of 1-(2-tetrahydrofuryl)-5-fluorouracil. In: Nelson JD, Grassi C (eds) Current chemotherapy and infectious disease: proceedings of the 11th International Congress of Chemotherapy and 19th Interscience Conference of Antimicrobial Agents and Chemotherapy. American Society of Microbiology, Washington DC, p 1529
5. Fujii S, Kitano S, Ikenaka K, Shirasaka T (1979) Effect of coadministration of uracil or cytosine on the antitumor activity of clinical doses of 1-(2-tetrahydro-furyl)-5-fluorouracil and level of 5-fluorouracil in rodents. Gann 70: 209
6. Grem JL (1990) Fluorinated pyrimidines. In: Chabner BA, Collins JM (eds) Cancer chemotherapy, principles and practice. Lippincott, Philadelphia, p 180
7. Harris BE, Song R, Soong S, Diasio RB (1990) Relationship between dihydropyrimidine dehydrogenase activity and plasma 5-FU levels with evidence for circadian variation of enzyme activity and plasma drug levels in cancer patients receiving 5-fluorouracil by protracted continuous infusion. Cancer Res 50: 197
8. Hines JD, Zakem MH, Adelstein, DJ, Giroski P, Blum MR, Rustum YM (1987) Bioavailability of high-dose oral leucovorin. J Natl Cancer Inst Monogr 5: 57
9. Hines JD, Zakem MH, Adelstein DJ, Rustum YM (1988) Treatment of advanced-stage colorectal adenocarcinoma with fluorouracil and high-dose leucovorin calcium: a pilot study. J Clin Oncol 6: 142
10. Ho DH, Townsend L, Luna MA, Bodey GP (1986) Distribution and inhibition of dihydrouracil dehydrogenase activities in human tissues using 5-fluorouracil as a substrate. Anticancer Res 6: 781

11. Hoff PM, Pazdur R, Benner SE, Canetta R (1998) UFT and leucovorin: a review of its clinical development and therapeutic potential in the oral treatment of cancer. Anticancer Drugs 9: 479
12. Ikenaka K, Shiraska T, Kitano S, Fujii S (1979) Effect of uracil on metabolism of 5-fluorouracil in vitro. Gann 70: 353
13. INSTAT Instant Biostatistics. GraphPad Software, San Diego, 1990–92
14. Marunaka T, Umeno Y, Yoshida K, Minami Y, Fujii S (1980) High pressure liquid chromatographic determination of Ftorafur [1-(tetrahydro-2-furanyl)-5-fluorouracil] and uracil in biologic materials after oral administration of uracil plus ftorafur. J Pharm Sci 69: 1296
15. Meropol NJ, Rustum YM, Petrelli NJ, Rodriquez-Bigas M, Frank C, Ho DH, Kurowski M, Creaven PJ (1996) A phase I and pharmacokinetic study of oral uracil, Ftorafur, and leucovorin in patients with advanced cancer. Cancer Chemother Pharmacol 37: 581
16. Meropol NJ, Noel D, Sonnichsen DS, Birkhofer MJ (1998) Oral UFT plus leucovorin in patients with relapsed or refractory colorectal cancer. Oncology 11: 22
17. Mini E, Morrison BA, Bertino JR (1987) Cytotoxicity of fluorouridine and 5-fluorouracil in human T-lymphoblast leukemia cells: enhancement by leucovorin. Cancer Treat Rep 71: 381
18. Muggia FM, Wu X, Spicer D, Groshen S, Jeffers S, Leichman CG, Leichman L, Chan KK (1996) Phase I and pharmacokinetic study of oral UFT, a combination of the 5-fluorouracil prodrug tegafur and uracil. Clin Cancer Res 2: 1461
19. Nakajima O, Kuniyuki I, Takoko I, Akira M, Masayo K, Yukio I, Yoshiyuki K, Tadashi K (1980) Phase I and II studies on a mixture of 1-(2-tetrahydrofuryl)-5-fluorouracil and uracil (UFT). Jpn J Chemother 7: 1558
20. Pazdur R (1998) Phase I and pharmacokinetic evaluations of UFT plus oral leucovorin. Oncology 11: 35
21. Pazdur R, Lassere Y, Rhodes V, Ajani JA, Sugarman SM, Patt YZ, Jones DV Jr, Markowitz AB, Abbruzzesse JL, Bready B, Levin B (1994) Phase II trial of uracil and tegafur plus oral leucovorin: an effective oral regimen in the treatment of metastatic colorectal carcinoma. J Clin Oncol 12: 2296
22. Petrelli N, Douglas HO, Herrera L, Russell D, Stablein DM, Bruckner HW, Mayer RJ, Schinella R, Green MD, Muggia FM, Megibow A, Greenwald ES, Bukowski RM, Harris J, Levin B, Gaynor E, Loutfi A, Kalser MH, Barkin JS, Benedetto P, Woolley PV, Nauta R, Weaver DW, Leichman LP (1989) The modulation of fluorouracil with leucovorin in metastatic colorectal carcinoma. A prospective randomized phase III trial. J Clin Oncol 7: 1419
23. Poon MA, O'Connell MJ, Moertel CG, Wieand HS, Cullinan SA, Everson K, Krook JE, Mailliard JA, Laurie JA, Tschetter LK, Wiesenfeld M (1989) Biochemical modulation of fluorouracil: evidence of significant improvement in survival and quality of life in patients with advanced colorectal carcinoma. J Clin Oncol 7: 1407
24. Ritschel WA (1976) Handbook of basic pharmacokinetics. Drug Intelligence Publications, Hamilton, Ill, p 235
25. Rowland M, Tozer TN (1989) Clinical pharmacokinetics: concepts and applications, 2nd edn. Lea & Febiger, Philadelphia, p 415
26. Sokal RR, Rohlf FJ (1982) Biometry, 2nd edn. W.H. Freeman & Co., New York
27. Tallarida RJ, Murray RB (1990) Manual of pharmacological calculations with computer programs. Springer, New York
28. Unemi N, Harima K, Daidai Y, Oshiro U, Fujihara H, Fujii S (1971) Experimental studies of N_1-(2′-tetrahydrofuryl)-5-fluorouracil (FT-207). Gan No Rinsho 17: 731
29. Valdivieso M, Bodey GP, Gottlieb JA, Freireich EJ (1976) Clinical evaluation of Ftorafur (pyrimidine deoxyribose N_1-2′-furanidyl-5-fluorouracil). Cancer Res 36: 1821
30. Wu AT, AU JL, Sadee W (1978) Hydroxylated metabolites of *R*,*S*-1-(tetrohydro-2-furanyl)-5-fluorouracil (ftorafur) in rats and rabbits. Cancer Res 38: 210