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ORIGINAL ARTICLE

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Bioavailability and phase II study of oral UFT plus leucovorin in patients with relapsed or refractory colorectal cancer

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Abstract *Purpose*: This study was undertaken to address the influence of concurrent administration on the pharmacokinetics of UFT (uracil plus tegafur) and leucovorin (LV), and to measure the antitumor activity of a 28-consecutive-day oral regimen of UFT plus LV in patients with relapsed or refractory colorectal cancer. *Methods*: Patients with advanced measurable colorectal cancer who had failed previous therapy with intravenous bolus 5-fluorouracil (5-FU) were eligible. Patients were treated with UFT 300 mg/m^2 per day plus LV 90 mg per day in three divided doses every 8 h for 28 days, repeated at 35-day intervals. In addition, a three-treatment by three-period crossover bioavailability comparison of oral LV 30 mg plus UFT 200 mg versus either LV or UFT alone was scheduled for the 8 days preceding the first cycle of therapy. *Results*: Of 19 patients enrolled, 18 were assessable for pharmacokinetics and response. When LV was coadministered with UFT, there were no statistically significant effects on tegafur, uracil, or 5-FU C_{max}, AUC, or T_{max}, with the exception of a delayed T_{max} for tegafur ($P = 0.03$). No statistically significant differences were found in LV and 5-methyltetrahydrofolate plasma levels when LV was administered alone or with UFT. However, wide interpatient variability was observed for all parameters. There were no antitumor responses seen. *Conclusions*: Although the T_{max} for tegafur is delayed with the concurrent administration of LV, there were no differences ($P > 0.05$) in any pharmacologic parameters that are of likely clinical significance. However, the great interpatient variability observed in UFT and LV pharmacology may have obscured true bioavailability effects in this small patient population. Daily oral UFT plus LV is inactive as second-line therapy in patients who have failed bolus 5-FU.

Key words UFT · Ftorafur · Tegafur · Leucovorin · Colorectal cancer

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Introduction

UFT is composed of a 1:4 fixed molar ratio of tegafur (ftorafur) and uracil. Tegafur is a 5-fluorouracil (5-FU) prodrug, and uracil competes with 5-FU as a substrate for dihydropyrimidine dehydrogenase, the rate-limiting enzyme responsible for 5-FU catabolism. In preclinical models, the antitumor activity of tegafur is enhanced by uracil, with an increase in the ratio of 5-FU in tumor compared to plasma or normal tissue [6, 7, 9]. Given its excellent gastrointestinal absorption, UFT is potentially attractive as an oral alternative to intravenous 5-FU. Given clinical success with adding leucovorin (LV) to 5-FU [15], UFT is being developed with oral LV as a biochemical modulator. When UFT is administered orally with LV on a 28-consecutive-day schedule, response rates of 25–43% are observed in patients with previously untreated advanced colorectal cancer [11, 13, 17]. In these studies, UFT and LV were administered concurrently. However, it is not known whether the bioavailability of UFT is affected by LV, and hence whether this administration schedule is optimal. The current study was undertaken to address the influence of concurrent administration on the pharmacokinetics of UFT and LV. In addition, the utility of a protracted schedule of oral UFT/LV in patients with colorectal cancer who had failed therapy with intravenous bolus 5-FU was assessed. This study population was chosen based upon reports of antitumor responses with infusional 5-FU in patients with colorectal cancer who fail

initial 5-FU-based therapy [12, 19], and the potential of daily oral UFT/LV to mimic the pharmacology of a protracted venous infusion of 5-FU [14].

Methods

Patient eligibility

Eligible patients had histologically confirmed colorectal adenocarcinoma that was either metastatic or locally advanced and unresectable, with bidimensionally measurable disease. Patients were at least 18 years old, with an ECOG performance status of 0–2 (ambulatory at least 50% of the time), and a life expectancy of at least 12 weeks. Patients showed progressive disease (PD) with bolus 5-FU plus LV for advanced disease, and/or relapsed within 6 months of the completion of 5-FU-based adjuvant therapy. An absolute neutrophil count $\geq 1500/\mu l$, platelet count $\geq 100\,000/\mu l$, bilirubin ≤ 1.5 mg/dl, and serum creatinine ≤ 1.5 mg/dl were required. Previous therapy with UFT or infusional 5-FU was not permitted. This protocol was approved by the Institutional Review Board at Roswell Park Cancer Institute and written informed consent was obtained from all subjects.

Treatment program

Patients were treated with UFT 300 mg/m^2 per day plus LV 90 mg per day in three divided doses every 8 h, for 28 consecutive days followed by a 1-week rest period (1 cycle = 35 days). This dose and schedule was based upon phase I and II studies [11, 13]. UFT was prepared as 100 mg (tegafur) capsules (containing 224 mg uracil). Total daily dosage was rounded to the nearest 100 mg. If the number of daily capsules did not evenly distribute over the three daily administration times, the greater number of capsules were taken in the morning and afternoon, and the smaller number of capsules in the evening. Two 15-mg oral LV tablets were taken with each UFT dose. UFT/LV was taken on an empty stomach (at least 1 h before or 2 h after food) with 8 oz of fluid.

National Cancer Institute Common Toxicity Criteria were used. Treatment was held for grade 3–4 hematologic toxicity occurring during a cycle, and resumed following recovery at the same dose level to complete a 28-day treatment course. UFT was reduced to 250 mg/m^2 per day in subsequent cycles for grade 3–4 hematologic toxicity. For grade 2–4 nonhematologic toxicity during a cycle, treatment was held until resolution, then reinstituted at full dose for grade 2, or at UFT 250 mg/m^2 per day for grade 3–4 toxicity. For grade 0–2 nonhematologic toxicity no dose modification was required in the subsequent cycle; for grade 3 or 4 nonhematologic toxicity, UFT was reduced to 250 and 200 mg/m^2 per day, respectively, in the subsequent cycle.

Disease reevaluations were repeated every two cycles and treatment continued until PD was documented or it was no longer felt to be in the patient's best interests to continue. Complete response (CR) was defined as total disappearance of all evidence of disease, lasting at least 4 weeks. Partial response (PR) was $\geq 50\%$ reduction in the sum of the products of the longest perpendicular diameters of measurable lesions lasting at least 4 weeks, without development of new lesions. Stable disease (SD) was $< 50\%$ reduction or $< 25\%$ increase in the sum of the products of the longest perpendicular diameters of measurable lesions without development of new lesions. PD was $\geq 25\%$ increase in the sum of the products of the longest perpendicular diameters of measurable lesions or the development of new lesions.

Pharmacokinetics

UFT and LV pharmacokinetics were measured with the first 18 patients on study. A three-treatment by three-period crossover bioavailability comparison of oral LV 30 mg plus UFT 200 mg versus either LV (30 mg) or UFT (200 mg) alone was scheduled for the 8 days preceding the first cycle of chemotherapy. Each patient was randomized to one of six schedules as shown in Table 1.

Table 1 Randomized schedules for pharmacokinetic sampling

Schedule	Day −8	Day −5	Day −1
A	UFT 200 mg	LV 30 mg + UFT 200 mg	LV 30 mg
B	UFT 200 mg	LV 30 mg	LV 30 mg + UFT 200 mg
C	LV 30 mg	LV 30 mg + UFT 200 mg	UFT 200 mg
D	LV 30 mg	UFT 200 mg	LV 30 mg + UFT 200 mg
E	LV 30 mg + UFT 200 mg	LV 30 mg	UFT 200 mg
F	LV 30 mg + UFT 200 mg	UFT 200 mg	LV 30 mg

Plasma samples were obtained at 0, 15, 30, 60, 90, 120, 180, 300, and 480 min after drug administration for measurement of tegafur, 5-FU, uracil, LV, and 5-methyltetrahydrofolate (5-MTHF). Plasma concentrations of tegafur were determined by a validated high-performance liquid chromatographic (HPLC) assay method [10] with a minor modification in the mobile phase [methylene chloride-hexane-ethanol (80:20:1.2) was used instead of ethylene chloride-ethanol (24:1)]. A validated gas chromatographic-mass spectroscopic (GC-MS) assay method [2] was used to quantitate 5-FU in human plasma samples. The assay method was modified to include the simultaneous quantitation of uracil as reported by Maranuka et al. [10]. Prior to analysis, interference from tegafur was eliminated by passing the samples through two 200-mg C18 solid phase extraction columns; tegafur was retained on the columns and the eluate from the second column was used for the analysis of 5-FU and uracil. This procedure resulted in more than 99.9% removal of tegafur. LV and 5-MTHF were determined by validated HPLC methods, which were modifications of previously reported methods [3, 4]. LV and 5-MTHF were extracted from plasma as described by Etienne et al. [4]. However, LV was resolved from endogenous interferences using a gradient HPLC (mobile phase A, 40% acetonitrile-50% methanol in 25 m*M* KH_2PO_4, pH 2.3; mobile phase B, 25 m*M* KH_2PO_4, pH 2.3) and 5-MTHF was resolved from endogenous interferences by isocratic HPLC using a mobile phase consisting of 5% acetonitrile-5% methanol in 25 m*M* KH_2PO_4, pH 2.3.

Individual analytical runs were considered acceptable if they met the following criteria: each run would include calibration standards assayed in duplicate at six or more concentrations; the predicted concentrations of at least three-fourths of all calibration standards were within $\pm 15\%$ (20% for 5-FU and uracil) of their individual nominal concentrations; the predicted concentrations of at least one of the duplicate lowest standard was within $\pm 20\%$ of the nominal concentration (25% for 5-FU and uracil); each analytical run would include low, medium, and high standards assayed in triplicate; and the predicted concentrations of at least two-thirds of the standards did not deviate by more than $\pm 15\%$ (20% for 5-FU and uracil) from the nominal concentrations. No internal standards were used.

For tegafur, the standard curves were linear ($R^2 \geq 0.993$) over the concentration range 50 to 20 000 ng/ml. The between-run precision and the within-run precision for analytical quality control samples were no greater than 5% and 8% RSD, respectively, with deviations of the mean observed concentrations from nominal values of no more than 7%. For 5-FU the standard curves were linear ($R^2 \geq 0.999$) over the concentration range 1 to 500 ng/ml. The between-run precision and the within-run precision for the analytical and shipping quality control samples were no greater

than 6% and 4% RSD, respectively; the deviations of the mean observed concentrations from nominal values were no more than 8%. For uracil, the standard curves were linear ($R^2 \geq 0.988$) over the concentration range 20 to 5000 ng/ml. The between-run precision and the within-run precision for the analytical quality control samples were no greater than 11% RSD. Deviations of the mean observed concentrations from nominal values were no more than 9%. For *d*,*l*-LV, the standard curves were linear ($R^2 \geq 0.998$) over the concentration range 50 to 2000 ng/ml. The between-run precision and the within-run precision for the quality control samples were no greater than 7% and 6% RSD, respectively, with deviations of the mean observed concentrations from nominal values of no more than 8%. For 5-MTHF, the standard curves were linear ($R^2 \geq 0.985$) over the concentration range 50 to 2000 ng/ml. The between-run precision and the within-run precision for the quality control samples were no greater than 13% RSD. The deviations of the mean observed concentrations of the quality control samples from nominal values were no more than 3%.

Plasma disposition of the five analytes of UFT and LV therapy – tegafur, 5-FU, uracil, LV and 5-MTHF – were summarized by calculating the area under the plasma concentration versus time curve from 0 to 8 h (AUC_{0-8}), maximum concentration (C_{max}), and time to maximum concentration (T_{max}) using standard noncompartmental methods [1].

Statistical considerations

The objectives of the study were (1) to evaluate the antitumor activity of orally administered UFT plus LV in patients with colorectal carcinoma resistant to bolus 5-FU-based therapy, and (2) to determine whether oral LV alters the bioavailability of UFT, and vice versa.

This was a phase II study with a two-stage design. A total of 18 evaluable patients were enrolled in the first stage. If none or one of the first 18 patients achieved a CR or PR to therapy, the study would be closed to further accrual, and the treatment concluded to be inactive (reject H_a: response rate $\geq 20\%$). If two or three patients achieved a CR or PR in stage 1, a total of 33 patients would be enrolled (15 patients in stage II). If four or more of the first 18 patients responded to therapy, the study would be terminated with significant activity demonstrated (reject H_0: response rate $\leq 5\%$). At the end of stage II, at least five responses would be required to reject H_0; otherwise H_a would be rejected, and the conclusion obtained that this regimen would not be of significant clinical utility in this context. With this design, the probability of erroneously concluding that the therapy was effective (rejecting H_0) was 2.5% (type I error), and the probability of erroneously concluding that the therapy was ineffective (rejecting H_a) was 20.6% (type II error), using Fleming's one-sided multiple testing procedure [5].

The effect of concurrent administration on the pharmacokinetic variables (C_{max}, $AUC_{(0-T)}$, and T_{max}) of each analyte was evaluated by an analysis of variance appropriate for a three-treatment by three-period crossover design with six sequences. Factors in the analysis were sequence, period, treatment, and first-order carryover. If carryover effects were not statistically significant at the 5% level, then treatment comparisons were based on a reduced model without carryover effect. C_{max} and $AUC_{(0-T)}$ were log-transformed and T_{max} was rank-transformed prior to analysis. Confidence intervals for the differences between the least square means on the natural log scale were converted to confidence intervals for the ratio (combination/monotherapy) on the original scale. In order to conclude lack of effect, we prospectively defined that the limits of the observed 90% confidence intervals for the ratio must fall within the predetermined range of 0.75 and 1.33. Statistical analyses were carried out using SAS STAT Version 6.07 (Cary, NC).

Results

Of 19 patients enrolled in this study, 18 were evaluable for response, toxicity and pharmacokinetics. One patient developed a bowel obstruction following the pharmacokinetic portion of the study, before receiving treatment doses of UFT/LV. Another patient underwent only 2 days of pharmacologic sampling. The study was concluded after the first stage, as there were no antitumor responses observed. The mean age was 62 years (range 37–80 years), with 13 men and 6 women. Of the 19 patients, 16 had liver metastases, and only 3 patients had a single site of metastasis. All patients had received bolus 5-FU plus LV previously, except for three patients who were treated with 5-FU plus levamisole in the adjuvant setting. The toxicity of UFT/LV is shown in Table 2. Grade 3–4 toxicities were generally gastrointestinal, including diarrhea, pancreatitis, nausea/vomiting, and hyperbilirubinemia. Severe fatigue was also observed in two patients. These toxicities were reversible in all patients. All treated patients received two courses of UFT/LV, except one patient who had PD after a single cycle. Including all patients, the median percent of the planned dose received was 99.5% (mean 96.9%) in cycle one and 99.0% (mean 80.2%) in cycle two. The best responses were SD in two patients, with PD in 16 patients.

Table 2 UFT toxicity over two cycles of treatment ($n = 18$)

	Grade			
	1	2	3	4
Anemia	0	3	0	0
Anorexia	6	1	0	0
Diarrhea	5	1	1	2
Fatigue	9	0	2	0
Hyperamylasemia/clinical pancreatitis	0	0	0	1
Hyperbilirubinemia	0	0	2	1
Nausea/vomiting	11	3	1	0
Neutropenia	1	0	0	0
Paresthesia	2	0	0	0
Rash	2	0	0	0
Stomatitis	6	1	0	0
Thrombocytopenia	1	0	0	0

Table 3 compares pharmacokinetic parameters of UFT when administered either alone or with LV. For all UFT analytes, the geometric means (derived from the least square means), ratios of the means, and the 90% confidence intervals for C_{max} and AUC are listed. Figure 1 shows uracil, tegafur, and 5-FU plasma concentrations over time. LV had no effects on tegafur C_{max} and AUC. The 90% confidence intervals for the ratios of the treatment means were within the predetermined limits of 0.75 and 1.33 for concluding lack of effect. Treatment effects were not statistically significant for uracil or 5-FU C_{max} and AUC ($P > 0.05$). However, the 90% confidence intervals for the ratios were not within the predetermined limits for concluding lack of effect. The median time to peak tegafur concentration was shorter with UFT alone (0.5 h) than with concurrent LV administration (0.75 h; $P = 0.03$), although the ranges were the same for both treatments (0.25, 3.0). For UFT alone, the median (range) time to peak uracil and

Table 3 UFT pharmacokinetic parameters ($n = 18$) (*LV* leucovorin; C_{max} mean maximum concentration, ng/ml; *AUC* mean area under the concentration × time curve, ng × min/ml)

	UFT alone	UFT + LV	Two-sided *P*-value	Point estimate	90% confidence interval
Tegafur					
C_{max}	6237.1	6031.1	0.594	0.967	0.868, 1.078
$AUC_{(0-T)}$	24220.5	26362.1	0.076	1.099	1.007, 1.176
Uracil					
C_{max}	2112.7	1691.7	0.444	0.801	0.488, 1.315
$AUC_{(0-T)}$	1714.3	1276.9	0.161	0.745	0.525, 1.057
5-FU					
C_{max}	110.2	71.1	0.068	0.645	0.437, 0.953
$AUC_{(0-T)}$	103.1	80.7	0.079	0.783	0.623, 0.983

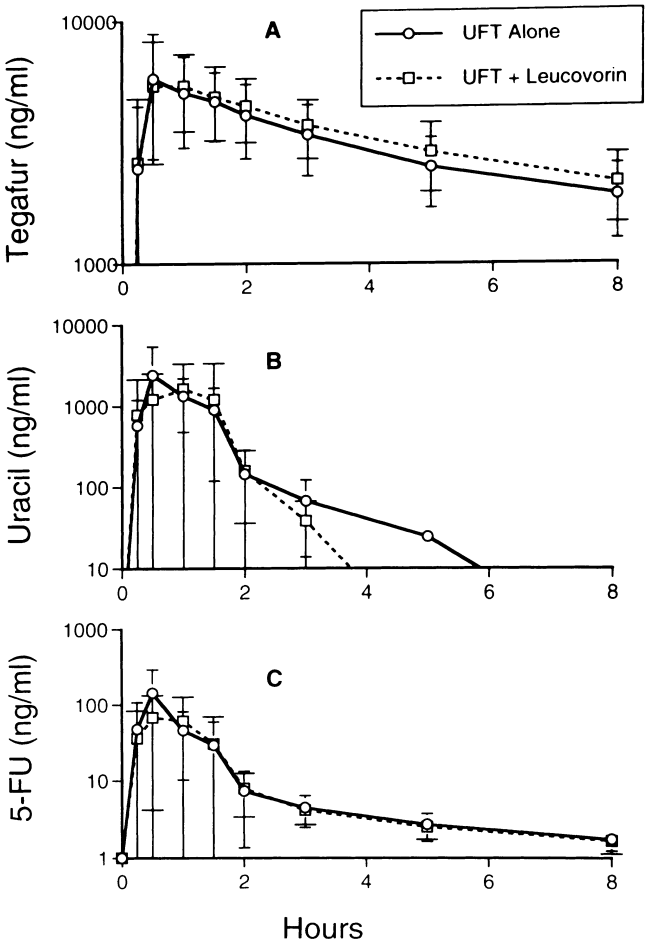

Fig. 1A–C Plasma concentrations of uracil, tegafur, and 5-FU following oral administration of UFT 200 mg alone or concurrently with LV 30 mg (**A** tegafur, **B** uracil, **C** 5-FU; *solid lines* UFT alone, *dashed lines* UFT + LV; *Error bars* show standard deviations, *wider bar* for combination)

5-FU concentration was 0.75 h (0.5, 3.0) and 0.5 h (0.25, 3.0), respectively, and for concurrent LV administration was 1.0 (0.25, 2.0) for both analytes. There were no statistically significant treatment effects for either analyte. There were no significant sequence, period, or carryover effects for any of the UFT pharmacokinetic variables analyzed.

LV and 5-MTHF plasma pharmacokinetics when 30 mg LV was administered either alone or with 200 mg UFT are shown in Table 4. The plasma levels of LV and 5-MTHF over time are shown in Fig. 2. There were no statistically significant differences in LV C_{max} and AUC when LV was given with or without UFT. However, again the ratio of the means did not fall within the *a priori* accepted range to conclude no effect. Likewise, there was no statistically significant treatment difference for MTHF AUC, but the 90% confidence interval for the ratio was not within the predetermined levels for concluding lack of effect. A carryover effect was observed for 5-MTHF AUC ($P = 0.007$), and this was included in the analysis of variance. For LV, the median (range) time to peak concentration was 2 h (1.5, 5.0) for all treatments. For 5-MTHF, the median (range) time to peak concentrations was 2 h (1.5, 3.0) for LV alone, and 2 h (1.5, 5.0) for concurrent UFT administration.

Discussion

Phase II studies have shown that oral UFT plus LV is an active and well-tolerated regimen in patients with previously untreated colorectal cancer [9, 11, 13, 17]. The standard dosing schema for this regimen calls for concurrent administration of UFT and LV. However, it was previously not known whether absorption of these agents was optimal with concurrent administration. We therefore undertook this bioavailability study, as identification of drug interactions could have important implications for dosing. In addition, prior pharmacokinetic analyses have shown that 5-FU plasma levels with a 28-day UFT schedule are similar to those obtained with protracted venous infusions of 5-FU [14]. Given the paucity of effective second-line approaches in advanced colorectal cancer, and the observation that some patients who fail bolus 5-FU therapy respond to continuous 5-FU infusions [12, 19], we also sought to determine the response rates and toxicity of daily oral UFT/LV in patients who have shown 5-FU resistance.

The pharmacokinetic data presented show that concurrent administration does not have a statistically significant impact on the gastrointestinal absorption or plasma pharmacokinetics of LV. The only effect of

Table 4 Leucovorin (*LV*) and 5-methyltetrahydrofolate (*5-MTHF*) pharmacokinetic parameters ($n = 18$) (C_{max} mean maximum concentration, ng/ml; *AUC* mean area under the concentration × time curve, ng × min/ml)

	LV alone	LV + UFT	Two-sided *P*-value	Point estimate	90% confidence interval
d,l-LV					
C_{max}	229.5	262.8	0.212	1.145	0.945, 1.374
$AUC_{(0-T)}$	1299.9	1442.2	0.466	1.110	0.868, 1.418
5-MTHF					
C_{max}	296.7	306.6	0.704	1.033	0.890, 1.199
$AUC_{(0-T)}$	1458.5	1189.3	0.112	0.815	0.660, 1.008

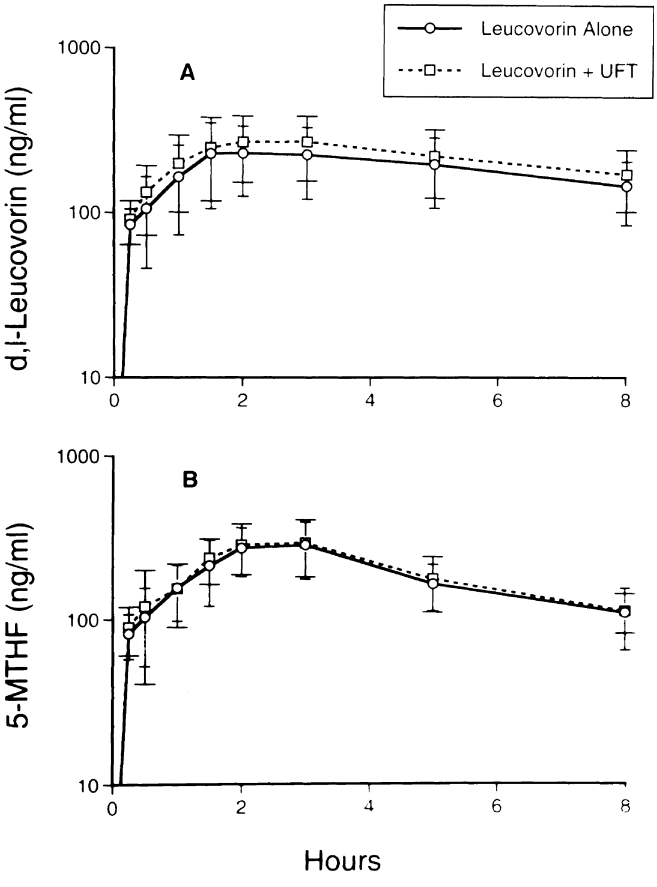

Fig. 2A,B Plasma concentrations of *d,l*-LV and 5-MTHF following oral administration of LV 30 mg alone or concurrently with UFT 200 mg (**A** *d,l*-LV, **B** 5-MTHF; *solid lines* LV alone, *dashed lines* LV + UFT; *error bars* show standard deviations, *wider bar* for combination)

coadministration on UFT pharmacology is a longer time to achieve tegafur peak concentrations. It is unlikely that this effect will be clinically meaningful, given that tegafur C_{max} and AUC are unaffected by LV, and maximum LV concentration is not achieved until after that of both tegafur and 5-FU. It is notable that several treatment comparisons did not meet our *a priori* criteria for concluding lack of effect, although differences did not reach statistical significance. There was a trend suggesting a decrease in 5-FU bioavailability when UFT was administered with LV. The mean 5-FU C_{max} was 35% lower, and the mean 5-FU AUC was 22% lower when UFT was coadministered with LV. These results suggest that this study lacked sufficient power to identify small differences in parameters with wide interpatient variations that may or may not be clinically important. A larger pharmacokinetic trial would be required to identify such differences, and a randomized study in previously untreated patients would be necessary to compare the impact on response and survival of concurrent versus delayed combination therapy.

The dose of LV used in this study (30 mg every 8 h) was chosen based upon saturable absorption at higher doses [18]. Although we did not achieve plasma concentrations defined as optimal in preclinical studies [16, 20], clinical trials of 5-FU biochemical modulation have not clearly demonstrated a dose-dependent effect [15]. Given prolonged folate half-life, it is likely that higher plasma concentrations than measured in this single-dose study would result from ongoing treatment three times daily. The mean plasma levels of 5-FU obtained in this trial were also lower than previously reported with similar UFT regimens [11, 14]. Whether these findings represent population differences or variation related to assay methodology cannot be determined from our data. There was great interpatient variability in 5-FU pharmacology, as is also typically observed with intravenous dosing.

Our data confirm the tolerability of oral UFT/LV in a heavily pretreated patient population. Unfortunately, this oral regimen did not show antitumor activity in patients who had previously shown 5-FU resistance. Phase II studies have suggested that oral UFT plus LV has similar antitumor activity to intravenous 5-FU plus LV as front-line therapy in advanced colorectal cancer [8, 11, 13, 17]. Results from completed comparative phase III studies will soon be available, and will further define the optimal role of this regimen in patients with advanced colorectal cancer.

References

1. Noncompartmental analysis based on statistical moment theory. In: Gibaldi M, Perrier D (eds) Pharmacokinetics. Marcel Dekker, New York 1982, pp 409–417
2. Anderson LW, Parker RJ, Collins JM, Ahlgren JD, Wilkinson D, Strong JM (1992) Gas chromatographic-mass spectrometric method for routine monitoring of 5-fluorouracil in plasma of patients receiving low-level protracted infusions. J Chromatogr 581: 195
3. Belz S, Frickel C, Wolfrom C, Nau H, Henze G (1994) High-performance liquid chromatograhic determination of metho-

trexate, 7-hydroxymethotrexate, 5-methyltetrahydrofolic acid and folinic acid in serum and cerebrospinal fluid. J Chromatogr 661: 109
4. Etienne M-C, Speziale N, Milano G (1993) HPLC of folinic acid diastereoisomers and 5-methyltetrahydrofolate in plasma. Clin Chem 39: 82
5. Fleming TR (1982) One-sided multiple testing procedures for phase II clinical trials. Biometrics 38: 143
6. Fujii S, Ikenaka K, Masakazu F, Shirasaka T (1978) Effect of uracil and its derivatives on antitumor activity of 5-fluorouracil and of 1-(2-tetrahydrofuryl)-5-fluorouracil. Gann 69:763
7. 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-tetrahydrofuryl)-5-fluorouracil and level of 5-fluorouracil in rodents. Gann 70: 209
8. Gonzalez-Baron M, Feliu J, de la Gandara I, Espinosa E, Colmenarejo A, Martinez-Martinez B, Blanco E, Garcia-Giron C, Jaurez F, Garrido P, Ordonez A, Zamora P (1995) Efficacy of oral tegafur modulation by uracil and leucovorin in advanced colorectal cancer. A phase II study. Eur J Cancer 31: 2215
9. Kawaguchi Y, Nagayama S, Masuda H, Yasuda A (1980) Studies on the metabolism of 1-(2-tetrahydrofuryl)-5-fluorouracil and uracil co-administered orally to tumor-bearing rats. Gann 71: 889
10. Maranuka T, Umeno Y, Yosida K, Nagamachi M, Minami Y, Fujii S (1980) High-pressure liquid chromatographic determination of ftorafur [1-(tetrahydro-2-furanyl)-5-fluorouracil and uracil in biological materials after oral administration of uracil plus ftorafur. J Pharm Sci 59: 1296
11. Meropol NJ, Rustum YM, Petrelli NJ, Rodriguez-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
12. Mori A, Bertoglio S, Guglielmi A, Aschele C, Bolli E, Tixi L, Rosso R, Sobrero A (1993) Activity of continuous-infusion 5-fluorouracil in patients with advanced colorectal cancer clinically resistant to bolus 5-fluorouracil. Cancer Chemother Pharmacol 33: 179
13. Pazdur R, Lassere Y, Rhodes V, Ajani JA, Sugarman SM, Patt YZ, Jones DV Jr, Markowitz AB, Abbruzzese 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
14. Pazdur R, Covington WP, Brown NS, Lassere Y, Diaz-Canton E, Ho DH (1996) Comparative steady state pharmacokinetics of oral UFT versus protracted intravenous 5-fluorouracil (FU) (abstract). Proc Am Soc Clin Oncol 15: 474
15. Poon MA, O'Connell J, Moertel CG, Wieand HS, Cullinan SA, Everson LK, Krook JE, Mailliard JA, Laurie JA, Tschetter LK, Wiesenfeld M (1989) Biochemical modulation of fluorouracil: evidence of significant improvement of survival and quality of life in patients with advanced colorectal carcinoma. J Clin Oncol 10: 1407
16. Rustum YM, Trave F, Zakrzewski SF, Petrelli N, Herrera L, Mittelman A, Arbuck SG, Creaven PJ (1987) Biochemical and pharmacologic basis for potentiation of 5-fluorouracil action by leucovorin. NCI Monogr 5: 165
17. Saltz LB, Leichman CG, Young CW, Muggia FM, Conti JA, Spiess T, Jeffers S, Leichman LP (1995) A fixed-ratio combination of uracil and ftorafur (UFT) with low dose leucovorin: an active oral regimen for advanced colorectal cancer. Cancer 75: 782
18. JA, Szapary D, Wynn WT (1984) Pharmacokinetics of the diastereoisomers of leucovorin after intravenous and oral administration to normal subjects. Cancer Res 44: 3114
19. Tralongo P, Di Mari A, Scibilia G, Bosco V, Giudice A, Respini D, Failla G (1995) Prolonged 5-fluorouracil infusion in patients with metastatic colon cancer pretreated with bolus schedule of the same agent. Anticancer Res 15: 635
20. Zhang Z-G, Rustum YM (1991) Effects of diastereoisomers of 5-formyltetrahydrofolate on cellular growth. Sensitivity to 5-fluoro-2′-deoxyuridine, and methylenetetrahydrofolate polyglutamate levels in HCT-8 cells. Cancer Res 51: 3476