Phase I and Pharmacokinetic Evaluations of UFT Plus Oral Leucovorin

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The phase I development program of tegafur and uracil (UFT) in the United States has included evaluation of the drug as a single agent and subsequent studies of its biochemical modulation by oral leucovorin. Phase I trials of single-agent UFT examined both a 5-day schedule repeated every 21 days and a 28-day schedule repeated every 35 days. In all of the trials the total dose was divided by three and administered three times daily at 8-hour intervals. Like intravenous schedules of fluorouracil (5-FU), UFT has schedule-dependent toxicity, with granulocytopenia being the dose-limiting toxicity for the 5-day regimen and diarrhea being the dose-limiting toxicity for the 28-day regimen. The suggested phase II doses for UFT administered without leucovorin were 800 mg/m²/day for the 5-day schedule and 360 mg/m²/day for the 28-day schedule. Subsequent phase I studies combining UFT with oral leucovorin used a 28-day schedule repeated every 35 days. Diarrhea was the dose-limiting toxicity, and the recommended phase II dose was UFT, 300 mg/m²/day, plus leucovorin, 90 mg/day. Pharmacokinetic evaluation showed that single-dose UFT results in maximum plasma levels and an area under the concentration-time curve that increased with escalating UFT doses. In addition, 5-FU levels were detectable throughout the 28-day dosing period; however, there was no evidence of significant accumulation of uracil, tegafur, or 5-FU. The administration of leucovorin in this trial provided continuous exposure of d,l-leucovorin and 5-methyltetrahydrofolate with little variation between doses or days.[ONCOLOGY 11(Suppl 10):35-39, 1997]

Introduction

UFT, a combination of uracil and tegafur in a 4:1 molar concentration, was developed by Fujii and co-workers[1] based on reports of uracil’s biochemical modulation of tegafur. In preclinical studies, the coadministration of uracil with tegafur (which is converted to fluorouracil [5-FU] in vivo) enhanced the concentration of 5-FU in tumors and resulted in increased antitumor activity.[2] With UFT, 5-FU concentrations in tumors were 5 to 10 times higher than with tegafur alone.[3-5] Although UFT has been commercially available in Japan since 1984 and is widely used in that country to treat advanced cancers and for adjuvant therapies, clinical trials of the compound were not initiated in the United States until 1990. No well-defined maximum tolerated dose of UFT has been established in Japanese studies, but the dose and schedule most commonly used is 200 to 300 mg administered 2 or 3 times daily until disease progresses. Although UFT has shown activity in colon, gastric, breast, and pancreatic cancers, its activity has not been uniformly assessed by criteria as defined in trials conducted in the United States. Thus, it has been difficult to establish the efficacy of UFT relative to that of intravenous (IV) 5-FU.[6]

In the United States, phase I trials have been conducted to evaluate UFT, both as a single agent and in combination with oral calcium leucovorin.[7-10] Calcium leucovorin is widely used to modulate 5-FU biochemically, and its combination with UFT received widespread acceptance as therapy for advanced colorectal carcinoma. In clinical trials, UFT demonstrated improved response rates over those achieved with single-agent 5-FU.[11] We conducted phase I trials of UFT plus oral leucovorin in an attempt to biochemically modulate the 5-FU generated by UFT, and with hopes of developing a completely oral treatment regimen for colorectal cancer. [12,13] The phase I clinical trials program of single-agent UFT and UFT plus oral leucovorin is described here.

Phase I Trials of UFT

Without Leucovorin
At The M.D. Anderson Cancer Center we selected two administration schedules for evaluation of UFT: A 5-day schedule repeated every 21 days and a 28-day schedule repeated every 35 days.[9] UFT was administered three times daily at 8-hour intervals. Dose levels examined on the 5-day schedule were 360, 720, and 900 mg/m²/day, with subsequent de-escalation to 800 mg/m²/day. Dose levels examined with the 28-day schedule were 180, 360, and 450 mg/m²/day, with subsequent de-escalation to 400 mg/m²/day. With the 5-day schedule, the dose-limiting toxicity was granulocytopenia, seen at 900 mg/m²/day, with four of five patients experiencing grade 4 granulocytopenia at that dose level. With the 28-day schedule, the dose-limiting toxicity was diarrhea, observed in three of six patients treated at 450 mg/m²/day and in three of eight patients treated at 400 mg/m²/day.

These trials demonstrated that single-agent UFT possessed schedule-dependent differences. Granulocytopenia, the dose-limiting toxicity with the 5-day schedule, was uncommon in the 28-day schedule, whereas grade 3 to 4 diarrhea was dose limiting with the longer schedule. We noted a steep dose-toxicity relationship with the 28-day UFT schedule. Three of the six patients given 450 mg/m²/day and three of the eight patients who received 400 mg/m²/day developed severe diarrhea, while no patients treated with 360 mg/m²/day were so affected.

Grade 3 or 4 diarrhea generally began during the fourth week of treatment and led to prolonged hospitalization. Grade 2 diarrhea resolved itself, usually within 2 to 3 days, allowing patients to resume UFT treatment without dose reduction. Efforts should be made to avoid progression of diarrhea beyond grade 2, and patients should be instructed on how to discontinue UFT and initiate loperamide in the presence of grade 2 or greater diarrhea. Phase II doses of UFT administered without oral leucovorin were 800 mg/m²/day on the 5-day schedule and 360 mg/m²/day on the 28-day schedule. At these doses, UFT was well tolerated; patients did not develop significant neutropenia, oral mucositis, hand-foot syndrome, or diarrhea.[9]

The pharmacokinetics of UFT were analyzed. tegafur was measured by high-performance liquid chromatography (HPLC), and uracil and the 5-FU generated by metabolism of the tegafur were measured by gas chromatography-mass spectrometry.[8] Plasma levels were highest for tegafur, followed by uracil and 5-FU at all time points. Maximum plasma levels for tegafur, uracil, and 5-FU were achieved at 0.6 to 2.1 hours, 0.6 to 4.1 hours, and 0.7 to 2.0 hours, respectively. We observed that lower UFT doses yielded more rapid decay of 5-FU and uracil levels.

**Phase I Trials of UFT With Oral Leucovorin**

Trials of UFT in North America and Europe have generally used the 28-day schedule, because of superior UFT dose intensity deliverable with that schedule. Subsequent to establishing the benefits of the 28-day schedule, development of UFT in the United States involved combining it with oral leucovorin. Based on reports that IV leucovorin modulated IV 5-FU biochemically,[14] we were interested in developing an oral regimen in which leucovorin would modulate the 5-FU generated from tegafur. Although the optimal leucovorin dose required to modulate 5-FU biochemically is unknown, levels of extracellular leucovorin greater than 1 mmol/L appear to be necessary.[15]

A phase I trial was carried out to examine the dose-limiting toxicities and maximum-tolerated dose of UFT administered for 28 consecutive days followed by a 7-day rest period,[10,12,13] and then repeated every 35 days. Dose levels examined were UFT 200 mg/m²/day, with planned escalations to 250, 300, 350, and 400 mg/m²/day. The leucovorin dose remained at 150 mg/day (50 mg tid) a dose known to produce the requisite extracellular leucovorin concentrations. A minimum of 3 patients were entered at each dose level. Similar to the phase I trials of single-agent UFT, the total daily doses of both UFT and leucovorin were divided by three and administered at 8-hour intervals. Diarrhea became the dose-limiting toxicity at 400 mg/m²/day, with grade 3 diarrhea observed in two of three patients treated at that dose level. To further define a phase II starting dose, 3 additional patients were entered at the UFT 350-mg/m²/day dose level[3] of the 6 patients treated at this level developed grade 3 toxic effects. The recommended phase II starting dose of UFT with leucovorin is therefore 300 mg/m²/day plus 150 mg leucovorin per day. Subsequent reductions of leucovorin to 75 or 90 mg/day (25 or 30 mg every 8 hours) were made once absorption of leucovorin reached saturation beyond doses of 25 to 30 mg.[16]

Since neutropenia, significant mucositis, and hand-foot syndrome were not observed with UFT plus leucovorin, the toxicity profile of this regimen appears more favorable than that of IV 5-FU plus leucovorin.[14,17] This phase I trial of UFT plus leucovorin served as the basis for a phase II trial demonstrating a 42% response rate in patients with advanced colorectal cancer[12]. It was also the basis for subsequent phase III trials, as well as for the adjuvant colon cancer trial currently being
conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP).

**Pharmacokinetic Comparison of UFT vs Protracted 5-FU Infusion**

Compared with IV bolus administration, protracted low-dose infusions of 5-FU have been associated with a reduction in toxic effects, with at least comparable efficacy. However, protracted IV infusions require a central venous catheter and a portable infusion pump. Up to 30% of patients treated with these protracted infusion regimens have central-line complications such as infections, line slippage, thrombosis, or septicemia, requiring line replacement in 11% of patients.[17] An oral treatment regimen that would provide protracted delivery of 5-FU obviates the need for central venous catheters and infusion pumps. We therefore compared levels of 5-FU attained with a low-dose infusion of 5-FU vs levels of 5-FU attained from UFT.[18,19]

Ten patients received protracted low-dose infusions of 5-FU, 250 mg/m$^2$/day, for a trial period of 5 days. After a 1-week interval, patients began treatment with UFT, 370 mg/m$^2$/day in 3 divided doses administered every 8 hours for 28 consecutive days. UFT generated higher maximum plasma levels than the protracted 5-FU infusions with similar area under the concentration-time curve (AUC) values.[18]

**Single-Dose and Steady-State Pharmacokinetics**

The pharmacokinetic aim of this study conducted at The M.D. Anderson Cancer Center was to characterize the single-dose pharmacokinetics of escalating doses of UFT and the steady-state pharmacokinetics of UFT plus leucovorin over a 28-day schedule.[19]

Eighteen enrolled patients were evaluated for both the single-dose and steady-state pharmacokinetics of UFT plus leucovorin. One week before starting continuous therapy, patients received single doses of UFT plus leucovorin in the morning. The 18 patients were then divided into three groups of six: group 1 received 100 mg UFT, group 2 received 200 mg UFT, and group 3 received 400 mg UFT. One week after the single-dose study, all patients began a continuous therapeutic regimen of oral UFT plus leucovorin. Patients received oral UFT, 300 mg/m$^2$/day, and leucovorin, 75 mg/day in three daily doses for 28 consecutive days, followed by a 7-day rest period. Tegafur, folinic acid, and 5-methyltetrahydrofolate were assayed using HPLC-ultra violet, and 5-FU and uracil were assayed using sensitive gas chromatography-mass spectrometry with a 1-ng/mL lower limit quantitation for 5-FU.

Pharmacokinetic analysis of the single-dose study showed that uracil, tegafur, and 5-FU plasma concentrations typically rose quickly following dosing, with maximum plasma concentrations achieved in approximately 1 hour. In contrast to tegafur but consistent with their very short plasma half-lives, plasma concentrations of both uracil and 5-FU declined rapidly after the maximum plasma concentration was achieved. However, 5-FU plasma concentrations remained detectable for 8 hours after a single 200- or 400-mg dose. The profile of the plasma 5-FU AUC generally followed that of uracil, thus corroborating uracil’s competitive effect on 5-FU elimination. In summary, single-dose administration of 100 to 400 mg of UFT resulted in maximum plasma concentrations and AUCs for tegafur, 5-FU, and uracil that increased with escalating doses of UFT.

Steady-state plasma concentration data for tegafur, uracil, and 5-FU demonstrated a consistent peak and trough appearance during each 8-hour dosing interval. Figure 1 illustrates the plasma concentrations of tegafur, 5-FU, and uracil during an 8-hour period on day 8 of the 28-day cycle. Exposure parameters of the maximum plasma concentration and AUC were comparable on days 8, 15, and 28 for uracil, tegafur, and 5-FU, revealing that significant accumulation did not occur over the 28-day regimen.

Plasma 5-FU concentrations peaked 0.5 to 1 hour after dosing at approximately 200 ng/mL and remained detectable for the entire 8-hour dosing interval. As with the single-dose study, plasma uracil and 5-FU concentrations were variable across the study population. Although variability was apparent among patients for the pharmacokinetic parameters investigated, variability in plasma 5-FU exposure between treatment days for an individual patient was relatively low. There was no association between plasma concentration of UFT and leucovorin analytes and patient toxicity. The plasma concentrations of $d,l$-leucovorin and 5-methyltetrahydrofolate provided continuous exposure of reduced folates throughout the dosing period, with little variation between doses or days. Figure 2 shows plasma concentrations of $d,l$-leucovorin and 5-methyltetrahydrofolate during an 8-hour dosing period. This level of reduced folate exposure is the range deemed necessary to modulate 5-FU biochemically. Thus, this dosage schedule for oral leucovorin provided reduced folate exposure for each administration of UFT during the 28 consecutive days.

Before enrolling in this study, all 18 patients who entered had demonstrated disease progression.
with previous 5-FU regimens. Although we did not observe any objective clinical responses, the favorable toxicity profile of the UFT-oral leucovorin regimen described previously[12] was corroborated in this patient population. Patients did not experience significant neutropenia, thrombocytopenia, oral mucositis, or hand-foot syndrome. No drug-related grade 4 toxicities were observed, and no patients were hospitalized for therapy-related toxic effects.

**Conclusion**

In summary, pharmacokinetic studies demonstrated a protracted exposure of 5-FU during administration periods of the UFT-oral leucovorin regimen. A continuous exposure of d,l-leucovorin and 5-methyltetrahydrofolate was also observed. A favorable toxicity profile without severe neutropenia, mucositis, and hand-foot syndrome known to complicate intravenous dosing schedules of 5-FU was also recognized. The results of the phase I schedules presented herein provided the framework for the subsequent development of UFT plus oral leucovorin.

**References:**


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