UFT Plus Oral Leucovorin: 
A New Oral Treatment for Colorectal Cancer

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ABSTRACT

UFT is an oral antineoplastic agent that combines the 5-fluorouracil (5-FU) prodrug tegafur with uracil in a 1:4 molar ratio. Uracil is added because it competitively inhibits the degradation of 5-FU, resulting in increased plasma and tumor 5-FU concentrations. Although UFT has been available in Japan since 1984, it has only recently been in clinical development in the United States. Beginning in 1991, phase I/II trials of UFT have been conducted in the United States to establish a maximum tolerated dose, evaluate its pharmacokinetics, and assess its efficacy and safety in advanced colorectal cancer. Pharmacokinetic studies demonstrated that UFT 300 mg/m²/day administered in divided doses every 8 h for 28 days provides an effective oral method of delivering a prolonged exposure to 5-FU. UFT plus oral leucovorin is well tolerated, with diarrhea as the dose-limiting toxicity. Unlike i.v. administered 5-FU, UFT is not associated with significant myelosuppression, mucositis, hand-foot syndrome, or alopecia, and patients have a decreased risk of toxicity-related hospitalization. In a phase II trial in advanced colorectal cancer, UFT plus oral leucovorin produced an objective response rate of 42%, with survival similar to weekly i.v. 5-FU plus leucovorin. The reduced toxicity, efficacy comparable to i.v. 5-FU, and the convenience and cost savings of an orally administered regimen have potential pharmacoeconomic advantages.

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INTRODUCTION

UFT (Taiho Pharmaceutical Ltd.; Tokyo, Japan; BMS-200604, Bristol-Myers Squibb; Princeton, New Jersey) is an oral antineoplastic agent combining tegafur (florafur, a prodrug of 5-fluorouracil [5-FU]) and uracil in a 1:4 molar ratio. The development of UFT is based on the pioneering work of Fujii more than 20 years ago and builds on the observation that uracil inhibits the degradation of 5-FU, generated from tegafur [1]. Although UFT has been commercially available in Japan since 1984 and is widely prescribed in that country for the treatment of solid tumors, knowledge and experience with the drug in other countries is relatively limited.

Tegafur was evaluated in the United States in the 1970s by the National Cancer Institute, with most clinical trials using short-duration i.v. dosing schedules that resulted in high peak plasma concentrations of tegafur and 5-FU [2]. Although objective responses were observed in colorectal, breast, and gastric tumors, these administration schedules were complicated by severe diarrhea, mucositis, and central nervous system toxicity [3-5]. Tegafur appeared no more efficacious than i.v. 5-FU, but was associated with significantly more diarrhea and central nervous system toxicity; based on these findings, further development of tegafur in the United States was suspended [4].

In contrast, the Japanese strategy in developing tegafur was to use the drug as an oral agent administered in divided doses over a prolonged period with few interruptions. This approach resulted in moderate efficacy with a mild toxicity profile [6, 7]. In early clinical trials in Japan, investigators observed activity in a variety of tumors (e.g., breast cancer, head and neck tumors, and gastrointestinal cancer) with mild toxicity. The recognition that uracil modulated 5-FU metabolism led to the subsequent development of UFT [1, 8].

Many early Japanese trials did not use conventional toxicity criteria, definitions of maximum-tolerated dose (MTD), dose escalations, and response criteria that have been carefully defined by investigators in the United States over the past two decades [9]. Thus, investigators in the United States initiated conventional phase I trials of UFT in 1990, despite its commercial availability in Japan. These studies also were
Figure 1. Metabolism of 5-fluorouracil. 5-FU: 5-fluouracil; R-1-P: ribose monophosphate; dR-1-P: deoxyribose monophosphate; Pi: phosphate; FUR: fluorouracil; FUMP: fluorouracil monophosphate; FUDP: fluorouracil diphosphate; RNA: ribonucleic acid; PRPP: 5′-phosphoribosyl-1-pyrophosphate; PPI: pyrophosphate inositol; FdU: fluorouracil (fluorouridine); FdUMP: 5-fluoro-2′-deoxyuridine monophosphate; FdUDP: 5-fluoro-2′-fluorouridine diphosphate; dUMP: deoxyuridine-5′-monophosphate; dUTP: deoxyuridine-5′-triphosphate; DNA: deoxyribonucleic acid; 5,10-CH₂FH₄ 5,10-methylenetetrahydrofolate.

The current development of UFT with leucovorin represents an effort to bridge the drug development philosophies of Japan and the United States. Prolonged UFT oral dosing schedules were based on Japanese trials. Prolonged oral exposure to fluorinated pyrimidines was also consistent with an emerging concept that protracted i.v. 5-FU infusions may be the optimum dosing schedule [10-12]. Based on phase I trial methodology used in the United States, UFT was evaluated at doses approximating an MTD, considering that the optimal dose intensity of prolonged oral dosing must allow for the fewest toxicity-related dose interruptions. In addition, there was extensive experience in the United States with the biochemical modulation of 5-FU by leucovorin, principally administered by the i.v. route [13-15]. This experience, incorporating leucovorin (given orally) to modulate UFT-generated 5-FU, allowed the development of a completely oral treatment regimen.

**MECHANISM OF ACTION**

Tegafur is a prodrug of 5-FU; it is slowly metabolized to 5-FU via several metabolic pathways, but especially through hepatic microsomal cytochrome P450 [16-18]. Once tegafur is converted to 5-FU, the drug has a metabolism and cytotoxic activity identical to that of i.v. 5-FU (Fig. 1).

The cytotoxic activity of 5-FU is believed to result from its metabolism to two active nucleotides, fluorodeoxyuridine monophosphate (FdUMP) and fluorouridine triphosphate (FUTP). FdUMP acts by forming a complex with thymidylate synthase, an integral component of DNA synthesis. The other active metabolite, FUTP, is integrated into cellular RNA and may alter RNA processing and function [7, 19].

In addition to its conversion to these active metabolites, 5-FU is also metabolized to inactive metabolites, primarily by the enzyme dihydropyrimidine dehydrogenase (DPD). Uracil is a natural pyrimidine that is also metabolized by DPD. Thus, when tegafur and uracil are coadministered, uracil competitively binds to DPD, decreasing 5-FU degradation. This results in a more prolonged half-life of 5-FU and its active metabolites than with the administration of tegafur alone, producing an enhancement of the cytotoxic effects of the drug [7]. In preclinical studies, coadministration of tegafur and uracil enhanced the concentration of 5-FU in tumors and resulted in increased antitumor activity [2, 20, 21]. In rats bearing subcutaneous colorectal tumors, UFT demonstrated greater antitumor activity than tegafur alone, and this activity was further increased with leucovorin biomodulation [22]. The higher concentration of 5-FU achieved in tumor tissue with UFT has been confirmed in humans [23-25]. In patients with a variety of solid tumors, the tumor-to-normal-tissue ratio of 5-FU was 4.1:1 in patients receiving UFT compared with a ratio of 1.6:1 in those receiving tegafur alone [23]. The 1:4 molar ratio of tegafur:uracil was determined to be the optimal ratio for the combination [2, 23, 26].

The FdUMP/thymidylate synthase complex that forms after 5-FU administration depends on the presence of adequate concentrations of reduced folate [19, 27-29]. Leucovorin is a derivative of tetrahydrofolic acid, the reduced form of folic acid. The addition of leucovorin increases the intracellular concentration of reduced folates, thus stabilizing the FdUMP/thymidylate synthase enzyme complex, providing the biochemical rationale for adding leucovorin to 5-FU and tegafur chemotherapy regimens. The addition of leucovorin to i.v. 5-FU regimens has been evaluated in a number of clinical trials, and a meta-analysis has demonstrated a significantly higher response rate with the combination compared with the administration of 5-FU alone [30]. This earlier experience provided the basis for the United States experience with UFT.

In the United States, clinical experience with UFT was initiated in 1991. These trials included phase I studies to determine the pharmacokinetics and optimal dosage regimen of UFT with and without oral leucovorin, as well as phase II trials evaluating the efficacy and safety of UFT plus oral leucovorin in the treatment of advanced colorectal cancer.
**Phase I Trials**

**Pharmacokinetics**

In initial phase I studies, the pharmacokinetics of tegafur, 5-FU, and uracil following administration of UFT were evaluated in 21 patients with solid tumors [31]. Two dose-escalation administration schedules were studied: (A) administering 345 mg/m²/d and escalating to 900 mg/m²/d for five days, and (B) administering 160 mg/m²/d and escalating to 450 mg/m²/d for 28 days. The daily dose was given in three divided doses every eight h. At all time points measured, plasma concentrations were highest for tegafur, followed by uracil and 5-FU. Peak plasma concentrations of 5-FU were achieved between approximately 0.5 and two h after a dose and were generally dose-dependent.

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

In another study, the single-dose pharmacokinetics following escalating doses of UFT plus oral leucovorin and the steady-state pharmacokinetics of UFT plus oral leucovorin during the 28-day administration schedule were analyzed [32]. One week prior to initiating continuous therapy with UFT and leucovorin, 18 patients with refractory colorectal cancer received a single dose of UFT 100 (n = 6), 200 (n = 6), or 400 mg (n = 6) and leucovorin. One week after this single-dose phase, all patients received oral UFT 300 mg/m²/d plus leucovorin 75 mg/d, both drugs given in divided doses every eight h for 28 days followed by a seven-day rest period.

Single-dose UFT (100 to 400 mg) administration resulted in maximum plasma concentrations and areas under the plasma concentration-time curve (AUC) for uracil, tegafur, and 5-FU that increased with escalating doses of UFT [32]. Steady-state plasma concentration data for tegafur, uracil, and 5-FU showed a consistent peak and trough appearance during each eight-h dosing interval and were similar to single-dose administration; there was no evidence of accumulation. Plasma 5-FU concentrations peaked 0.5-1 h after dosing, with mean peak plasma concentrations ranging from 304 to 403 ng/ml during the 28-day schedule. Mean trough 5-FU concentrations ranged from 31 to 46 ng/ml. Median plasma 5-FU AUC_{0-5h} on days 8, 15, and 28 were 926, 758, and 770 ng/ml•h, respectively. Plasma 5-FU concentrations remained detectable throughout the entire eight-h dosing interval, with relatively low intrapatient variability in plasma 5-FU exposure [32]. Continuous plasma exposure of reduced folates was evident throughout the dosing period with little variation; this schedule provided adequate reduced folate exposure for each dose of UFT given during the 28-day schedule.

**Comparison to Protracted 5-FU Infusion**

Compared with i.v. bolus schedules of 5-FU, protracted low-dose 5-FU infusions are associated with decreased toxicity and at least comparable efficacy. However, protracted i.v. infusion requires a central venous catheter and portable infusion pump. As many as 30% of patients receiving these regimens have central line complications including infections, line slippage, thrombosis, or septicemia; these complications require line replacement in 11% of patients [33]. An oral treatment regimen that would provide protracted delivery of 5-FU eliminates the need for central venous catheters and infusion pumps. The pharmacokinetics of i.v. 5-FU with oral UFT administered in equimolar dosages were compared in 10 patients [34]. In this study, patients first received a protracted infusion of low-dose 5-FU 250 mg/m²/d over five days, and then after a one-week wash-out period, received UFT 300 mg/m²/d plus oral leucovorin 75 mg/d administered in divided doses every eight h over 28 days. The results are presented in Table 1. Following initiation of the protracted 5-FU infusion, plasma 5-FU levels rapidly reached a steady-state concentration (C_{ss}) that was maintained for the entire five days. After administration of UFT, the mean peak plasma concentration (C_{max}) of 5-FU ranged from 0.30 to 0.35 µg/ml over the first five days of administration. By day 25, the mean C_{max} was 0.44 µg/ml. These values exceeded the mean C_{max} produced by the continuous i.v. infusion (0.08 µg/ml). Although the 5-FU AUC was greater for the i.v. infusion on day 1, the AUC values for the two regimens were similar by day 5. The elimination half-life of 5-FU after administration of UFT was 7.2 h. This is considerably longer than the half-life previously reported for i.v. 5-FU (0.21 h) [35].

These studies indicate that, at equimolar dosages, UFT delivers higher peak plasma 5-FU concentrations with similar systemic 5-FU exposure compared with a low-dose protracted infusion of 5-FU.

**Table 1.** Plasma 5-FU concentrations after oral UFT and continuous infusion of 5-FU [34]

<table>
<thead>
<tr>
<th>Pharmacokinetic parameter</th>
<th>UFT</th>
<th>5-FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C_{max} (µg/ml)</td>
<td>0.30</td>
<td>0.08*</td>
</tr>
<tr>
<td>AUC_{0-5} (µg/ml•h)</td>
<td>0.34</td>
<td>0.35</td>
</tr>
<tr>
<td>Day 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C_{max} (µg/ml)</td>
<td>0.35</td>
<td>0.08*</td>
</tr>
<tr>
<td>AUC_{0-5} (µg/ml•h)</td>
<td>0.50</td>
<td>0.38</td>
</tr>
</tbody>
</table>

*Steady-state plasma concentration.

5-FU = 5-fluouracil; C_{max} = maximum plasma concentration; AUC_{0-5h} = area under the plasma concentration-time curve for hours 0 to 5.
DOSE-RANGING TRIALS

Single-Agent UFT

Between 1990 and 1994, several phase I dose-ranging trials with UFT were conducted (Table 2). Initially, UFT was studied as a single agent. Schedules for these studies included five days of dosing repeated every 21 days, and 28 days of dosing repeated every 35 days. The daily UFT dose was divided into three doses administered every eight hours. With the five-day schedule, UFT dosages ranging from 360 to 900 mg/m²/d were evaluated [36]. No toxicity was observed at the 360- and 720-mg/m²/d dosage levels; however, at 900 mg/m²/d, grade 4 granulocytopenia was seen in four of five patients. The dose was subsequently de-escalated to 800 mg/m²/d in an additional eight patients. At this dosage, only one patient developed grade 4 granulocytopenia, while an additional two patients experienced grade 3 toxicity (nausea [n = 1], thrombocytopenia [n = 1]). Using the 28-day schedule, dosages of 180 to 450 mg/m²/d were evaluated [36]. No grade 3/4 toxic reactions occurred at the 180-mg/m²/d dosage level. At 450 mg/m²/d, two patients developed grade 4 toxicity (granulocytopenia [n = 1], diarrhea [n = 1]), and grade 3 toxicity occurred in three patients (diarrhea [n = 2], oral mucositis [n = 1]). A subsequent dosage reduction to 400 mg/m²/d produced grade 3/4 diarrhea in three of eight patients.

These trials demonstrated that single-agent UFT possessed schedule-dependent toxicity differences. The dose-limiting toxicity (DLT) with the five-day schedule was granulocytopenia, which was observed at 900 mg/m²/d; the DLT with the 28-day schedule was diarrhea, which occurred at 400 mg/m²/d. In addition, with the 28-day schedule, a steep dose-toxicity relationship was observed; no patients receiving 360 mg/m²/d developed diarrhea. Grade 3/4 diarrhea

<table>
<thead>
<tr>
<th>Reference</th>
<th>n Patients</th>
<th>UFT dosage range (mg/m²/d)</th>
<th>Schedule (in divided doses)</th>
<th>Leucovorin dose (mg/d)</th>
<th>Grade 3/4 toxicities (n patients) daily dosage (schedule in divided doses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pazdur et al., 1996 [34]</td>
<td>19</td>
<td>360-900</td>
<td>q 8 h x 5 d; repeat q 21 d</td>
<td>none</td>
<td>800 mg/m²/d (q 8 h): granulocytopenia (1/8); nausea (1/8); thrombocytopenia (1/8)</td>
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<td></td>
<td></td>
<td></td>
<td>900 mg/m²/d (q 8 h): granulocytopenia (4/5); stomatitis (1/5); skin rash (1/5); fatigue (1/5)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>360 mg/m²/d (q 8 h): fatigue (1/6)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>400 mg/m²/d (q 8 h): diarrhea (3/8), mucositis (1/8)</td>
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<td></td>
<td></td>
<td></td>
<td>450 mg/m²/d (q 8 h): diarrhea (3/6), mucositis (1/6), granulocytopenia (1/6)</td>
</tr>
<tr>
<td>Muggia et al., 1996 [37]</td>
<td>26</td>
<td>300-500</td>
<td>q 8 h x 28 d; repeat q 35 d</td>
<td>none</td>
<td>300 mg/m²/d (QD): diarrhea (1/8); vomiting (2/8); fatigue (1/8)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>400 mg/m²/d (QD): diarrhea (4/4); vomiting (3/4); nausea (3/4); stomatitis (1/4); fatigue (2/4); dizziness (1/4); leukopenia (2/4); granulocytopenia (1/4); thrombocytopenia (1/4); anemia (1/4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>400 mg/m²/d (BID): leukopenia (1/3)</td>
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<td></td>
<td></td>
<td></td>
<td>400 mg/m²/d (q 8 h): diarrhea (2/8); nausea (1/8); stomatitis (1/8); fatigue (4/8); dizziness (1/8); anemia (1/8)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>500 mg/m²/d (BID): diarrhea (3/3); vomiting (1/3); nausea (3/3); fatigue (3/3); dizziness (1/3); leukopenia (2/3)</td>
</tr>
<tr>
<td>Pazdur et al., 1995 [38]</td>
<td>12</td>
<td>350-400</td>
<td>q 8 h x 14 d; repeat q 28 d</td>
<td>150</td>
<td>350 mg/m²/d (q 8 h): diarrhea (1/6); vomiting (1/6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>400 mg/m²/d (q 8 h): diarrhea (4/6); nausea (1/6); vomiting (1/6); abdominal cramping (1/6)</td>
</tr>
<tr>
<td>Jaiyesimi et al., 1994 [39]</td>
<td>26</td>
<td>200-400</td>
<td>q 8 h x 28 d; repeat q 35 d</td>
<td>150</td>
<td>350 mg/m²/d (q 8 h): diarrhea (6/14)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>400 mg/m²/d (q 8 h): diarrhea (2/3)</td>
</tr>
</tbody>
</table>

QD = one dose daily; BID = two divided doses daily.
generally began during the fourth week of treatment and required prolonged hospitalizations. Grade 2 diarrhea generally resolved within two to three days, allowing patients to resume UFT without dose reduction. Therefore, the recommended phase II dosages of UFT without oral leucovorin were 800 mg/m²/d using the five-day schedule and 360 mg/m²/d with the 28-day schedule. These dosages were well tolerated, and patients did not develop significant neutropenia, oral mucositis, acral erythema (hand-foot syndrome), or diarrhea.

**UFT Plus Oral Leucovorin**

Two phase I studies to evaluate the addition of oral leucovorin 150 mg/d to UFT using either a 14- or 28-day schedule were performed at the MD Anderson Cancer Center (Table 2). With the 14-day schedule, dosages of 400 mg/m²/d administered to six patients produced grade 3 diarrhea (n = 4), vomiting (n = 1), nausea (n = 1), and abdominal cramping (n = 1) [38]. In contrast, among six patients receiving 350 mg/m²/d, there were only two episodes of grade 3 toxicity (diarrhea [n = 1], vomiting [n = 1]). In another study combining UFT and oral leucovorin, UFT dosages ranging from 200 to 400 mg/m²/d for 28 days were evaluated [39]. No grade 3/4 toxicities were observed among nine patients receiving dosages of 300 mg/m²/d or less. Grade 3 diarrhea was dose limiting in two of three patients receiving 400 mg/m²/d and in six of 14 patients receiving 350 mg/m²/d.

Similar to the single-dose results, diarrhea was the DLT at 350-400 mg/m²/d. The shorter treatment duration (14-day) did not allow a significant increase in the UFT starting dose, and diarrhea remained the DLT [38]. Therefore, a UFT dosage of 300 mg/m²/d for 28 days when administered with leucovorin 150 mg/d was recommended for phase II trials [39]; this dosage allowed delivery of a greater UFT dose intensity. Subsequent reduction of the leucovorin dosage to 75 or 90 mg/d (25-30 mg every eight h) was made based on the saturable oral absorption of leucovorin beyond these lower dosages [40].

**Phase II Trial**

Between April 1993 and January 1994, 45 patients with advanced metastatic colorectal carcinoma were enrolled in a trial evaluating the efficacy of UFT plus oral leucovorin [41, 42]. These patients had not received prior chemotherapy or biologic therapy, and only three patients had received prior adjuvant therapy. Based on phase I results, the first seven patients received UFT 350 mg/m²/d and leucovorin 150 mg/d in divided doses every eight h for 28 days, followed by a seven-day rest period. However, since five of the first seven patients developed grade 3 diarrhea, the starting dosage for the remaining 38 patients was reduced to 300 mg/m²/d. Patient characteristics for this study are summarized in Table 3.

The toxicities of the two dosage regimens are summarized in Table 4. The 300 mg/m² regimen was much better tolerated than the 350 mg/m² regimen, with grade 3 diarrhea occurring in 11% and 71% of these dosage groups, respectively. There was no significant neutropenia, thrombocytopenia, hand-foot syndrome, oral mucositis, or alopecia.

In patients receiving 300 mg/m²/d, treatment delays were insignificant. Of 127 courses of treatment at this dosage, only 11 courses in three patients had interruptions of 5 to 10 days and only one course was delayed more than 10 days. In contrast, among the patients receiving 350 mg/m²/d, 17% of courses were delayed between 5 and 10 days, and 20% of courses were delayed for longer than 10 days [41].

There were 15 partial responses (39%) and one complete response (3%) among the 38 patients treated with UFT 300 mg/m²/d [41]. Three of seven patients (43%) receiving 350...
mg/m²/d also responded. The overall response rate for the two dosage groups combined was 42% (95% confidence interval: 28%-58%). Sites of response included liver (n = 18), lung (n = 6), and bone (n = 1). Of the 19 responding patients, six developed progressive disease after response durations ranging from 15 to 38 weeks. An analysis of survival data indicates that the survival curve of patients in this trial is similar to that of patients treated with weekly i.v. 5-FU and leucovorin at the MD Anderson Cancer Center (Fig. 2) [42].

The results of this trial compare favorably with those of other phase II trials conducted in the United States and Europe (Table 5) [43-45]. Although these trials evaluated slightly different dosage regimens for both UFT and leucovorin, objective response rates ranged from 25% to 40%, which corroborates the objective response rate observed in the trial described. Together, these results support the ongoing evaluation of UFT and oral leucovorin in phase III clinical trials.

Figure 2. The survival of patients treated in the phase II trial of UFT plus oral leucovorin is compared to patients treated with an i.v. schedule of weekly 5-FU plus leucovorin (LV) treated at MD Anderson Cancer Center during this same time period (reprinted with permission from [42]).

### Table 5. Phase II trials evaluating UFT and oral leucovorin in metastatic colorectal and rectal cancer

<table>
<thead>
<tr>
<th>Reference</th>
<th>UFT dosage</th>
<th>Leucovorin dosage</th>
<th>n evaluable patients</th>
<th>OR</th>
<th>Median overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pazdur et al., 1994 [41]</td>
<td>300-350 mg/m²/d × 28 d</td>
<td>150 mg/d × 28 d p.o.</td>
<td>45</td>
<td>42%</td>
<td>15.8 mo*</td>
</tr>
<tr>
<td>Gonzalez-Baron et al., 1995 [43]</td>
<td>390 mg/m²/d × 14 d</td>
<td>500 mg/m² i.v. × 1; 30 mg/d d2-14 p.o.</td>
<td>75</td>
<td>39%</td>
<td>13.5 mo</td>
</tr>
<tr>
<td>Saltz et al., 1995 [44]</td>
<td>350 mg/m²/d × 28 d</td>
<td>15 mg/d × 28 d p.o.</td>
<td>20</td>
<td>25%</td>
<td>12+ mo</td>
</tr>
<tr>
<td>Sanchez, Milla 1994** [45]</td>
<td>600 mg/m²/d × 14 d</td>
<td>90 mg/m²/d × 14 d</td>
<td>52</td>
<td>40%</td>
<td>8.2 mo***</td>
</tr>
</tbody>
</table>

*Updated data analysis.
**Rectal cancer only.
***Median time to progression; median overall survival not reported.
OR = overall response; p.o. = oral; i.v. = intravenous.
of the patients who have significant morbidity or who require hospitalization when receiving i.v. 5-FU and leucovorin have diarrhea concomitantly with neutropenia. These patients have a compromised epithelial membrane and an increased risk of sepsis. Since UFT is not associated with significant neutropenia, this risk is markedly reduced and may be one of the reasons for the substantially lower rate of hospitalizations observed with UFT.

PHARMACOECONOMICS

When evaluating the financial impact of a new therapy, pharmacoeconomic analyses should evaluate the effect of the treatment on overall healthcare costs rather than simply compare drug acquisition costs. UFT has properties that have the potential to reduce overall treatment costs. The lower propensity of UFT to cause severe adverse events such as neutropenia and stomatitis should result in decreased toxicity-induced hospitalizations and may be associated with a decreased need for laboratory monitoring. The oral route of administration also means that drug administration costs are reduced, since there is no need for i.v. lines or infusion pumps, and treatment can be administered on an outpatient basis. These advantages should improve patient quality of life.

In a recent pharmacoeconomic evaluation of UFT versus i.v. 5-FU in the treatment of metastatic colorectal cancer in Brazil and Argentina, a panel of experts from each country developed a model that identified clinical practices associated with chemotherapy administration and adverse event management [49]. Practice patterns and clinical events were then evaluated for resource utilization trends. Cost data were derived from a survey of local healthcare institutions. These data were used to calculate the average cost per patient receiving either a six-cycle course of i.v. 5-FU with levmisole and/or leucovorin or a modeled oral UFT plus leucovorin regimen. In Argentina, the oral UFT regimen cost $Arg1,188 ($Arg1.0 = $US1.0, June 1997) less than the i.v. regimen ($Arg12,367 versus $Arg13,555), whereas in Brazil oral UFT cost $Brz335 ($1.0Brz = $US0.93, June 1997) less than i.v. 5-FU ($Brz10,901 versus $Brz11,236). The differences were primarily due to the lower costs for managing adverse events and to lower costs for drug administration with UFT. This study suggests that UFT plus leucovorin is a viable economic alternative to standard i.v. 5-FU in the treatment of metastatic colorectal cancer.

DISCUSSION

Current experience indicates that UFT plus oral leucovorin provides a convenient, well-tolerated, and effective alternative to i.v. 5-FU/leucovorin for the treatment of advanced colorectal cancer. Pharmacokinetic studies have demonstrated that UFT produces maximum 5-FU plasma concentrations that are greater than those produced by an equimolar dosage of 5-FU administered by continuous infusion. However, the total drug exposure (as measured by AUC) of the two regimens is similar. These data demonstrate that UFT is an effective method for delivering prolonged 5-FU exposure.

At the recommended dosage of 300 mg/m²/d administered every eight h for 28 days in combination with oral leucovorin 25-30 mg every eight h, UFT is well tolerated. The most commonly reported adverse effect is diarrhea; however, severe diarrhea is infrequent and is not associated with significant neutropenia. In contrast to i.v. 5-FU, UFT is not associated with significant myelosuppression, mucositis, hand-foot syndrome, or alopecia. It is also not associated with the central nervous system toxicity observed with i.v. tegafur. This improved tolerability profile means that the rate of drug-toxicity-induced hospitalization is much lower with UFT than with i.v. 5-FU. With i.v. 5-FU, the incidence of toxicity-related hospitalization is approximately 20% to 30%, whereas only one of 100 patients enrolled in phase II trials at MD Anderson Cancer Center was hospitalized for drug-related toxicity. The low toxicity of this regimen also improves compliance. Among those receiving UFT 300 mg/m²/d plus oral leucovorin, only 11 of 127 courses had interruptions of 5 to 10 days and only one course was delayed more than 10 days.

The oral UFT regimen offers a number of advantages (Table 6). It may be administered without visits to the hospital or clinic, resulting in decreased cost and increased convenience for the patient. The oral schedule also allows patients to temporarily hold a dose of the drug when adverse events such as grade 2 diarrhea first emerge, preventing the toxicity from becoming severe, and allows the patient to restart the medication after one to two days when

<table>
<thead>
<tr>
<th>Table 6. Potential advantages of UFT</th>
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<tbody>
<tr>
<td>▲ Oral treatment</td>
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<tr>
<td>▲ No significant neutropenia, stomatitis, hand-foot syndrome, or alopecia</td>
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<td>▲ No need for weekly complete blood counts</td>
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<td>▲ Reduced toxicity-related hospitalization</td>
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the diarrhea resolves. In contrast, when administering i.v. 5-FU on a five-day schedule, the toxicity generally does not appear until after the regimen is complete, making it difficult to prevent the occurrence or minimize the severity of adverse events for that particular course of therapy.

The successful clinical application of an oral treatment regimen such as oral UFT plus leucovorin administered for a prolonged time requires collaboration between the physician, nurse, and patient. The patient must be educated on the importance of compliance and the management of diarrhea, the DLT associated with oral UFT plus leucovorin. Simply eliminating several doses at the onset of early-stage diarrhea can prevent its progression to a serious or life-threatening toxicity which would require hospitalization. At MD Anderson Cancer Center, patients receive written information about the medication and its adverse effects and are contacted weekly by nurses to monitor compliance and toxicity development. Patients are carefully instructed to stop UFT therapy when they develop grade 2 diarrhea. They then contact the physician’s office and receive instructions on how to monitor this toxicity and when to restart UFT therapy.

The improved tolerability profile of UFT has potential pharmacoeconomic and quality-of-life implications. The use of UFT should be associated with decreased treatment costs because of the lower propensity for toxicity-induced hospitalization. UFT is also associated with decreased drug administration costs because i.v. lines and pumps are not required, and there is a decreased need for laboratory monitoring. This advantage was demonstrated in a recent study from South America in which the use of UFT plus leucovorin was associated with lower overall treatment costs compared with i.v. 5-FU in patients with metastatic colorectal cancer [49]. The oral route and reduced toxicity should improve overall patient quality of life.

Phase II studies of UFT plus leucovorin for advanced colorectal cancer suggest response rates comparable to those achieved with i.v. 5-FU/leucovorin with better tolerability. These promising results have prompted randomized phase III comparative trials in previously untreated patients with metastatic colorectal cancer (Table 7). In addition to traditional end points, particularly survival, these studies will evaluate pharmacoeconomics and quality of life. Adjuvant trials in patients with colon carcinoma or rectal cancer are also ongoing. The NSABP C-06 trial is currently ongoing, comparing UFT and oral leucovorin to a weekly regimen of i.v. 5-FU plus leucovorin in 1,500 patients who have had stage II or III colon cancer resected surgically. UFT plus leucovorin is also being explored as a radiation sensitization agent in the preoperative treatment of rectal cancer [50].

**ACKNOWLEDGMENTS**

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**Table 7. Ongoing trials of UFT plus oral leucovorin in the treatment of colorectal cancer**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient population</th>
<th>Protocol</th>
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<tr>
<td><strong>Phase III comparative trials</strong></td>
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<tr>
<td>Study 011*</td>
<td>Previously untreated colorectal cancer</td>
<td>UFT 300 mg/m²/d + oral leucovorin 75-90 mg/d × 28 d repeated q 35 d versus i.v. 5-FU 425 mg/m²/d + i.v. leucovorin 20 mg/m²/d × 5 d repeated q 28 d</td>
</tr>
<tr>
<td>Study 012*</td>
<td>Previously untreated colorectal cancer</td>
<td>UFT 300 mg/m²/d + oral leucovorin 90 mg/d × 28 d repeated q 35 d versus i.v. 5-FU 425 mg/m² + i.v. leucovorin 20 mg/m²/d × 5 d repeated q 35 d</td>
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<tr>
<td><strong>Adjuvant Trials</strong></td>
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<tr>
<td>NSABP C-06</td>
<td>Stage II/III colon cancer</td>
<td>Randomized after surgery to either i.v. 5-FU + i.v. leucovorin or UFT + oral leucovorin; projected accrual: 1,500 patients</td>
</tr>
<tr>
<td>MD Anderson Cancer Center</td>
<td>T3 and T4 rectal lesions</td>
<td>Pelvic radiotherapy (4,500 cGy/d) with concomitant UFT + oral leucovorin followed in four to six weeks by surgery; UFT + oral leucovorin × 28 d repeated q 35 d × 4 courses</td>
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</table>

*Primary endpoint of Study 011 is survival; primary endpoint of Study 012 is time to progression.*
REFERENCES


22. Rustum YM. Mechanism-based improvement in the therapeutic selectivity of 5-FU prodrug alone and under conditions of metabolic modulation. Oncology 1997;54(suppl 1):7-11.


