Oral Uracil/Ftorafur (UFT) Plus Leucovorin as First-line Chemotherapy and Salvage Therapy with Weekly High-dose 5-Fluorouracil/Leucovorin for the Treatment of Metastatic Colorectal Cancer

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Background: The purpose of this study was to determine the efficacy and toxicity of uracil/ftorafur (UFT) plus oral leucovorin (LV) as first-line chemotherapy for patients with metastatic colorectal cancer and salvage chemotherapy with weekly high-dose 5-fluorouracil (5-FU)/LV 24 h infusion.

Methods: Adult patients with no prior chemotherapy for metastatic diseases were enrolled to receive oral UFT 300 mg/m²/d plus LV 90 mg/d for 28 days. Treatment was given continuously for 28 days followed by a 7 day rest period from all treatment. For UFT failed patients, weekly 24 h infusion of 5-FU 2600 mg/m² plus LV 100 mg/m² was used as salvage therapy.

Results: Fifty-one patients with metastatic colorectal cancer were enrolled in the study. The objective response rate was 29.5% [95% confidence interval (CI), 16.8–45.2%] among the 44 evaluable patients and 25.5% in the intent-to-treat population. The median survival for all 51 patients was 16.6 months. The median time to progression was 5.9 months. Diarrhea was the major adverse effect of UFT/LV that made patients reduce dosage. Grade 3 or 4 diarrhea developed in 13.7% of patients. Twenty-six patients were treated with weekly 24 h infusional 5-FU/LV as salvage therapy and only two patients responded.

Conclusion: Our results suggest that this 28 day schedule of UFT/LV regimen may offer a well-tolerated, full oral treatment option with efficacy that appears comparable to that of intravenous 5-FU/LV regimens. Parenteral 5-FU/LV as salvage therapy for UFT refractory patients is not recommended.

Key words: UFT – leucovorin – salvage chemotherapy – metastatic colorectal cancer

INTRODUCTION

Since its discovery 40 years ago, 5-fluorouracil (5-FU) remains the most useful drug in the treatment of patients with advanced colorectal cancer (1). Although intravenous administration of 5-FU is the most widely accepted mode of administration of drug, the optimum schedule has still not been established. In general, studies have shown that the efficacy of 5-FU (at least in terms of response rate) can be improved through protracted infusion schedules and biomodulation with leucovorin (LV) (2–6). However, infusional regimens are inconvenient for patients, labor-intensive for medical staff and frequently associated with venous access-related complications. Therefore, an oral agent that avoids these problems and provides convenient, home-based therapy may replace infusional 5-FU.

Uracil/ftorafur (UFT), commercially available in Japan and several other countries, is composed of 1-(2-tetrahydrofuryl)-5-fluorouracil (Ftorafur, FT or Tegafur) and uracil in a molar ratio of 1:4 (7). Following oral administration of UFT, uracil and ftorafur are rapidly and completely absorbed from the gut into the systemic circulation. Ftorafur is subsequently metabolized to 5-FU by one of two different pathways and enzyme systems, thereby behaving as a prodrug to 5-FU (8). Uracil strongly inhibits the degradation of 5-FU to 2-fluoro-β-alanine by competitive inhibition of dihydropyrimidine dehydrogenase (DPD) (9). In addition, this inhibition predominates in tumor cells over healthy tissues, so that this combination increases the tumor concentration and antineoplastic activity of 5-FU.

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informed consent was obtained from all patients. Committee approval was obtained at our institution and elapsed since completion of radiotherapy. Appropriate ethics lesion was outside the radiation port and at least 3 weeks had prior radiotherapy was allowed, provided that the indicator treatment at least 6 months prior to enrollment in the study. Adjuvant chemotherapy had to have completed their adjuvant medication were excluded. Patients who have received prior or other conditions that restricted them from taking the study excluded. Patients with intestinal obstruction, malabsorption ease or history of any other malignancy (except appropriated treated localized cervical or epithelial skin cancer) were treated localized cervical or epithelial skin cancer) were.

The starting dose of UFT was 300 mg/m²/day and that of LV was 90 mg/day. When the UFT held, LV was also held and missed doses were skipped. No changes in LV dose were made. If diarrhea developed, patients were instructed to withhold treatment and contact their nurses. If UFT was held for toxicity during this treatment period and the toxicity resolved, patients resumed the 28 day treatment period at the same dose level, skipping missed doses. Treatment was not extended longer than 28 days from the start of the treatment cycle. During treatment, if granulocytes <1000/mm³ or platelets <50 000/mm³, UFT and LV were withheld until granulocytes increased to ≥1500/mm³ or platelets ≥100 000/mm³. UFT and LV were withheld if non-hematological toxicity ≥grade 2 and resumed when toxicity subsided to the baseline or ≤grade 1. During the next cycle, patients did not continue treatment unless granulocytes were ≥1500/mm³, platelets were ≥100 000/mm³ and non-hematological toxicities resolved to the baseline or ≤grade 1. Patients who required more than a 2 week delay in beginning treatment again were withdrawn from the study. Adjustments of the dose level were based on the highest grade of toxicity observed during the previous cycle. If the highest grade of toxicity was grade 3–4 in the previous cycle, we decreased the UFT dose by one dose level (50 mg/m²). One additional dose reduction of one dose level occurred if grade 3–4 toxicity developed again. A maximum of three dose level reductions were permitted; if patients required further reductions they were taken off the treatment.

Treatment was continued until one of the following criteria was met: disease progression, unacceptable toxicity, patients’ refusal or completion of six courses of treatment. Patients who had failed to respond to UFT/LV treatment, salvage chemotherapy with 5-FU 2600 mg/m² and LV 100 mg/m² intravenous infusion were administered 24 h per week. Patients who were refractory to this salvage therapy were allowed to receive further chemotherapy at the physician’s discretion.

PATIENTS AND METHODS

Eligibility Criteria

Patients were required to have unresectable metastasis of colorectal cancer. The eligibility criteria for patients included histologically confirmed colorectal adenocarcinoma, age ≥18 and ≤75 years, two-dimensional measurable (at least 1.5 × 1.5 cm) disease, Eastern Cooperative Oncology Group (ECOG) performance status of 0–2 and anticipated life expectancy of at least 3 months. Additional criteria included adequate bone marrow function (leukocytes ≥4000/mm³; platelets ≥100 000/mm³) and liver and renal functions (GOT and GPT ≤3× upper normal limited, serum bilirubin ≤1.5 mg/dl, serum creatinine ≤1.5 mg/dl). Patients with any prior chemotherapy for metastatic disease, active infection, concurrent major systemic disease or history of any other malignancy (except appropriately treated localized cervical or epithelial skin cancer) were excluded. Patients with intestinal obstruction, malabsorption or other conditions that restricted them from taking the study medication were excluded. Patients who have received prior adjuvant chemotherapy had to have completed their adjuvant treatment at least 6 months prior to enrollment in the study. Prior radiotherapy was allowed, provided that the indicator lesion was outside the radiation port and at least 3 weeks had elapsed since completion of radiotherapy. Appropriate ethics committee approval was obtained at our institution and informed consent was obtained from all patients.

Treatment Plan and Dose Modification

A dose of UFT 300 mg/m²/day in a 28 day schedule was chosen according to the phase I–II study of Pazdur and co-workers combined with oral LV for advanced colorectal cancer (12,13). This dose schedule appeared to be safe and effective. High-dose LV was selected in this trial because previous studies had shown increasing response rates of ~40% for UFT plus high-dose LV. This response rate seems better than with UFT plus low-dose LV or UFT alone (13–17). Further, the pharmacokinetic study of oral LV revealed that the absorption of LV was saturable at a dose between 50 and 100 mg (18). Oral LV higher than 100 mg/day was not necessary because the absorption of LV became saturable at this dose level; therefore, LV 90 mg/day was chosen.

The total daily dose of UFT was determined and rounded to the nearest 100 mg. The total daily dose of UFT was divided into three doses given 8 h apart. The times of administration were 7:00 a.m., 3:00 p.m. and 11:00 p.m. When the total number of tablets could not be evenly divided, the highest dose was given in the morning and lower doses in the afternoon or evening. Treatment occurred daily for 28 days followed by 7 days without treatment. Dosing resumed on day 36.

The starting dose of UFT was 300 mg/m²/day and that of LV was 90 mg/day. When the UFT held, LV was also held and missed doses were skipped. No changes in LV dose were made. If diarrhea developed, patients were instructed to withhold treatment and contact their nurses. If UFT was held for toxicity during this treatment period and the toxicity resolved, patients resumed the 28 day treatment period at the same dose level, skipping missed doses. Treatment was not extended longer than 28 days from the start of the treatment cycle. During treatment, if granulocytes <1000/mm³ or platelets <50 000/mm³, UFT and LV were withheld until granulocytes increased to ≥1500/mm³ or platelets ≥100 000/mm³. UFT and LV were withheld if non-hematological toxicity ≥grade 2 and resumed when toxicity subsided to the baseline or ≤grade 1. During the next cycle, patients did not continue treatment unless granulocytes were ≥1500/mm³, platelets were ≥100 000/mm³ and non-hematological toxicities resolved to the baseline or ≤grade 1. Patients who required more than a 2 week delay in beginning treatment again were withdrawn from the study. Adjustments of the dose level were based on the highest grade of toxicity observed during the previous cycle. If the highest grade of toxicity was grade 3–4 in the previous cycle, we decreased the UFT dose by one dose level (50 mg/m²). One additional dose reduction of one dose level occurred if grade 3–4 toxicity developed again. A maximum of three dose level reductions were permitted; if patients required further reductions they were taken off the treatment.

Treatment was continued until one of the following criteria was met: disease progression, unacceptable toxicity, patients’ refusal or completion of six courses of treatment. Patients who had failed to respond to UFT/LV treatment, salvage chemotherapy with 5-FU 2600 mg/m² and LV 100 mg/m² intravenous infusion were administered 24 h per week. Patients who were refractory to this salvage therapy were allowed to receive further chemotherapy at the physician’s discretion.
PATIENT EVALUATION

Prior to entry into the study, all patients provided complete medical histories and underwent physical examinations. Laboratory studies included full blood and differential counts, serum chemistry, urinalysis, carcinoembryonic antigen (CEA), electrocardiogram, chest X-ray and abdominal and pelvic computed tomography (CT) examinations. Patients were seen by physicians every 2 weeks during treatment for progress reports, physical examinations and toxicity assessments. Complete blood counts were measured every 2 weeks and serum biochemistry and CEA were examined after every course. Tumor reassessment using abdominal CT scan and/or chest X-ray was performed after every two courses thereafter. In instances of clinical suggestion of progressive disease during therapy, response to therapy was re-evaluated immediately. Determination of tumor response followed the standard WHO criteria. These toxic events were prospectively noted and evaluated according to the National Cancer Institute (NCI) Common Toxicity Criteria graduation.

STATISTICAL CONSIDERATIONS

The sample size in this study was calculated based on a target activity level of 40% and a minimum activity level of 20%, with an $\alpha$ error of 0.05 and $\beta$ error of 0.2. Therefore, the required number of evaluable patients was 43. The primary end point of this study was the response rate. All patients who received at least one dose of study medication were included in the analyses of safety parameters and survival. The time to progression was measured from the start of therapy to the date of progression. The time to progression and survival were calculated using the Kaplan–Meier method from the start of chemotherapy (19).

RESULTS

PATIENTS’ CHARACTERISTICS

Fifty-one patients with metastatic colorectal carcinoma were enrolled in the study from September 1999 through August 2000. None of the patients had received prior chemotherapy for metastatic disease and only nine patients had received 5-FU-based adjuvant chemotherapy. There were 29 men and 22 women. Their median age was 61 years (range, 29–75 years). The baseline patients’ characteristics are given in Table 1.

TREATMENT

All patients received at least one dose of UFT/leucovorin medication. Forty-one patients (80.4%) completed at least two courses of chemotherapy. Fifteen patients (29.4%) completed six courses of therapy. The median number of therapy courses completed was four. Ten patients did not complete two courses of treatment. Three of those patients had obvious clinical deterioration, which was documented by imaging studies. Another seven patients who were considered could not be evaluated for response. One patient developed intestinal obstruction on the first day of treatment, two patients had unacceptable toxicity levels (one hepatitis acute exacerbation, the other grade 4 diarrhea with sepsis), three patients for personal reasons and one patient was lost to follow-up. Only six patients had to reduce one dose level, all owing to diarrhea.

RESPONSE AND SURVIVAL

One patient achieved a complete response and 12 patients had partial responses that lasted from 2.3 to 15.9 months (median response duration, 7.5 months). This represents a 29.5% response rate (95% confidence interval (CI), 16.8–45.2%) among the 44 evaluable patients and 25.5% in the intent-to-treat population. Nineteen patients had stable disease (43.2%) and 12 patients had progressive disease (27.3%). One patient had unconfirmed response and another patient had mixed response (partial response in liver lesions, but progressive response in local recurrence). One patient had surgical resection of liver metastasis after completion of six courses of therapy and had complete remission after operation. The patient is still disease free (18.5+ months). CEA levels that normalized or decreased by $>50\%$ were found in 15 of 45 patients (33.3%).

As of August 2001, 28 patients had died and 23 were still alive. The median survival for all 51 patients was 16.6 months (95% CI, 11.7–21.5 months). The median time to progression
was 5.9 months (95% CI, 4.3–6.8 months). The overall survival rate 1 year after therapy was 58.8%.

**Salvage Chemotherapy**

Six patients who were still in remission after the completion of six courses of therapy received UFT/LV again owing to disease progression. Twenty-six patients received salvage chemotherapy with weekly 24 h infusional 5-FU/LV after UFT failure. Only two patients (7.7%) had partial responses and five patients (19.2%) were stable. Nineteen patients who had failed to both UFT/LV and 5-FU/LV received irinotecan- or oxaliplatin-based chemotherapy. In addition, seven patients received irinotecan- or oxaliplatin-based chemotherapy immediately after UFT/LV failed. Response rates to irinotecan- and oxaliplatin-based chemotherapy were 16.7 and 35%, respectively. There were 18 patients (35.3%) not receiving salvage chemotherapy: three still in remission, four with rapid progression after UFT failure and 11 refusals.

**Toxicity**

Data on toxicity for all 51 patients are shown in Table 2. Hematological toxicity was mild and no patient had grade 3 or 4 hematological toxicity. Gastrointestinal toxicities with symptoms of nausea, vomiting, diarrhea and mucositis were the most frequent toxic side effects. Grade 3 or 4 diarrhea developed in 13.7% of patients. Diarrhea was the major adverse effect that caused dose reduction in patients. Although the nausea/vomiting was usually mild because this was a daily treatment regimen, some patients could not tolerate even mild nausea or vomiting. Three patients were withdrawn from the study owing to mild nausea during the treatment. The hand–foot syndrome was infrequent in our series. Only one patient had mild hand–foot syndrome, which subsided after co-administration of vitamin B<sub>6</sub>. Hyperbilirubinemia and serum transaminase >1000 IU/ml were found in one patient after 14 days of therapy and chronic hepatitis with acute exacerbation was considered for this patient. The symptoms/signs of recovery occurred after discontinuing UFT and supportive care. Rechallenge with UFT was not performed and the patient was withdrawn from the study. Generalized exfoliative dermatitis developed in one patient after four courses of therapy. The skin lesions subsided after steroid and antihistamine therapy, but relapsed again after continuing with UFT/LV.

**DISCUSSION**

Dihydropyrimidine dehydrogenase (DPD) is the initial and rate-limiting enzyme in 5-FU metabolism. More than 85% of an administered dose of 5-FU is eliminated by catabolism through DPD (20). Since tumor DPD inversely correlated with objective response (21), the rationale for combining 5-FU with DPD inhibitor is fairly strong. Uracil competitively inhibits the degradation of 5-FU by this enzyme, which thus increases the amount of 5-FU available for its anabolic pathways and ultimately results in cell death. Ftorafur is a produg of 5-FU. Conversion to 5-FU is slow and the plasma half-life is very long (~10 h) (8). Because of these properties, repeated oral administrations of UFT/LV should simulate continuous infusion of 5-FU/LV without the inconvenience of catheter implantation or the cost of infusion pumps.

Clearly, efficacy and safety are important considerations when identifying the most suitable treatment option for individual patients. Another important factor is the patient’s convenience and the impact of the treatment on quality of life. Data from this study showed that the best clinical response was 29.5% in evaluable patients. The estimated median time to progression was 5.9 months and median survival was 16.6 months in all 51 patients treated using the study drugs. Our results suggest that the 28 day oral UFT/LV regimen for patients with metastatic colorectal cancer was well tolerated and achieved response rates similar to those achieved with an intravenous schedule of 5-FU and LV (2–6). In a preliminary report of a phase III randomized trial in patients with advanced colorectal cancer, UFT/LV produced equivalent activity to intravenous 5-FU/LV (12 vs 15%) but with significantly less toxicity (22). Because metastatic colorectal cancer is incurable, palliation of symptoms and optimization of the quality of life are critical aspects of the therapy. Compared with other regimens, this combination had the advantages of being an entirely oral regimen. This regimen, which required minimal monitoring, was more convenient for patients than regimens requiring parenteral administration of the drugs.

It is interesting that the spectrum of clinical toxicity of the 28 day schedule of UFT/LV is not similar at all to that of protracted infusion of 5-FU/LV. Like other continuous infusional 5-FU/LV regimens (2–6), the myelotoxicity was much less when compared with the Mayo Clinic regimen (23). None of the patients had grade 3 or 4 neutropenia in our series. When

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**Table 2. Maximum severity of toxicity (n = 51)**

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>NCI common toxicity criteria grade</th>
<th>% of grade 3–4</th>
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<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Leucopenia</td>
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</tr>
<tr>
<td>Anemia</td>
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<td>1</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
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<td>1</td>
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<td>Nausea</td>
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<td>6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
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<td>7</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>16</td>
<td>12</td>
</tr>
<tr>
<td>Hand–foot syndrome</td>
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</tr>
<tr>
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<td>1</td>
</tr>
<tr>
<td>Alopecia</td>
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<td>0</td>
</tr>
<tr>
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<td>1</td>
</tr>
<tr>
<td>Skin</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Infection</td>
<td>1</td>
<td>2</td>
</tr>
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compared with protracted infusional 5-FU/LV (3) or capectabine therapy (24), hand-foot syndrome occurred less frequently in this study. Despite the fact that pharmacokinetics simulated the protracted infusion of 5-FU/LV, hand-foot syndrome was rarely noted in the patients who underwent the UFT/LV regimen (13,14). In addition, serious mucositis was not observed. The most frequently observed UFT/LV-related toxicity was diarrhea. If UFT is continued in the presence of diarrhea, however, toxicity is likely to worsen, even with anti-diarrhea therapy. Patients should be instructed to discontinue UFT and initiate loperamide in the presence of grade 2 diarrhea or higher. Generally, UFT was found to be well tolerated in treating patients with metastatic colorectal cancer. However, because it is an oral daily-administered regimen, patient compliance is important. Gastrointestinal toxicity remains a major problem for oral UFT delivery, which may lead to under-dosing. Early detection and treatment of UFT-related adverse events and patient awareness of this potential toxicity are important for compliance.

Leucovorin had been widely used to modulate 5-FU biochemically and this combination had received widespread acceptance as therapy for advanced colorectal cancer (25). Several randomized trials have confirmed the advantage of 5-FU modulated with LV over 5-FU alone (23,26). However, the optimum dose or scheme or even the best route of administration of LV remain undefined. Some authors use oral LV with similar efficacy to that achieved with intravenous LV (27,28). The plasma levels of LV obtained either intravenously or orally are comparable (29). A potential advantage of oral LV administration lies in the relatively low ratios of d/l-reduced folate found in patient plasma during oral dosing. This appears to be due primarily to selective absorption of l-LV from the gastrointestinal tract (18). With regard to efficacy, results of trials that use UFT and low-dose LV are similar to those in which UFT was administered alone (14–16). These results may indicate that low doses of LV do not efficiently modulate UFT. In contrast, in phase II studies in which higher doses of LV were delivered to previously untreated patients showed increased response rates of ~40% (13,17). However, in the absence of a direct randomized comparison of UFT alone versus low- or high-dose LV, it is impossible to determine the superiority of one regimen over another.

The weekly 24 h 5-FU/LV regimen consists of a higher dose 5-FU with short-term continuous infusion, which had been the standard first-line chemotherapy for metastatic colorectal cancer in our institution. A much higher 5-FU plasma concentration (7–14 vs 0.1–2.3 μM) can be achieved compared with orally administered UFT (11,30). However, only a 7.7% response rate was obtained in UFT-refractory patients. With the arrival of new active drugs such as oxaliplatin and irinotecan, weekly 24 h high-dose 5-FU/LV is not recommended as salvage treatment for UFT-refractory patients because of the relatively low response rate.

In conclusion, our results suggest that this 28 day schedule UFT/LV regimen offers a well-tolerated, full oral treatment option with an efficacy comparable to that of intravenous 5-FU/LV regimens. In addition, UFT plus oral LV is likely to provide a significant advantage over a bolus 5-FU/LV regimen with regard to toxicity, lower administration costs, decreased toxicity-related hospitalizations and decreased laboratory monitoring costs. Parenteral 5-FU/LV is not recommended as salvage chemotherapy for UFT-refractory patients.

References


