A Phase II Trial of UFT-E and Oral Leucovorin in Advanced Colorectal Cancer

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**Purpose:** To determine the efficacy and toxicity of UFT-E plus oral calcium leucovorin in the treatment of patients with advanced colorectal cancer.

**Materials and Methods:** Forty-three patients with advanced, bidimensionally measurable colorectal adenocarcinoma were enrolled in the trial. No patients had received prior palliative chemotherapy. The patients that had received previous adjuvant chemotherapy were enrolled when more than 6 months had elapsed after the completion of adjuvant therapy. Patients were treated with 300 mg/m²/day of UFT-E (tegafur-based) plus 90 mg/day of leucovorin administered orally in three divided daily doses, every 8 hours for 28 days followed by a 7-day rest period. Response was evaluated after two or three courses of therapy.

**Results:** Thirty-six of forty-three patients were evaluable for response; seven dropped out due to infection, toxicity and patients’ refusal. Ten patients had partial responses and one patient complete response (response rate, 31%; 95% confidence interval, 16–46%). The median response duration for the UFT-E plus leucovorin regimen was 28 weeks. Grade III toxicity was seen in one case, with diarrhea.

**Conclusion:** This oral regimen proved effective and well tolerated. This schema also avoided inconveniences, such as hospitalization and the use of infusion pumps, which are associated with 5-FU infusion regimens. The regimen used showed minimal toxicity, especially in the upper digestive tract, with good patient compliance. (Cancer Research and Treatment 2001;33:225–228)

**Key Words:** Colorectal neoplasm, Chemotherapy, UFT-E, Oral leucovorin

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**INTRODUCTION**

Fluorouracil (5-FU) is regarded as the standard treatment for palliation in advanced colorectal cancer for decades. However, it gives rise to an objective response in less than 20% of patients with colorectal cancer (1–3). Attempts to improve the therapeutic effectiveness of 5-FU have focused on the scientific principles of biochemical modulation: the alteration of tumor cell metabolism to selectively enhance cytotoxicity. One of the current biochemical modulations involves the use of folinic acid (leucovorin), and another involves the combination of tegafur and uracil. Calcium leucovorin is widely used to modulate 5-FU biochemically (4). Uracil may inhibit the activity of hepatic dihydropyrimidine dehydrogenase, an enzyme involved in 5-FU catabolism, and thus when tegafur is administered with uracil 5-FU levels are increased (5). UFT plus oral leucovorin were found to produce an objective response rate of up to 40% (6), and the combination of UFT and leucovorin is receiving widespread acceptance as a therapy for advanced colorectal cancer.

Poor compliance with the medication is a big obstacle of effective oral chemotherapy, and usually results from side effects on the upper gastrointestinal tract, such as nausea, vomiting and epigastric pain, which may be aggravated by the gastrointestinal mucosal irritation of 5-FU, which is converted from tegafur by spontaneous degradation.

Therefore, UFT-E (the enteric coated form) was produced to reduce upper digestive tract toxicity by reducing spontaneous conversion of tegafur to fluorouracil in the upper gas-
tointestinal tract.

Some phase II clinical researches of UFT-E were carried out and these showed minor side effects on the upper gastrointestinal tract (7). We report here results of a phase II study on the UFT-E and leucovorin regimen in patients with advanced colorectal cancer.

MATERIALS AND METHODS

1) Patient population and eligibility

Forty-three patients with advanced colorectal cancer were enrolled in this trial between November 27, 1998 and November 11, 1999.

The patients characteristics are listed in Table 1. Study patients were required to have histologically proven colorectal adenocarcinoma. The disease had to be measurable, with at least one lesion having dimensions ≥ 1×2 cm at the longest diameter and the diameter perpendicular to this at the widest part of the tumor. Patients were excluded from the study if they had received prior systemic chemotherapy for metastatic disease, although prior adjuvant chemotherapy was allowable if it had been completed at least 6 months before the entry into study.

Requisite laboratory criteria included the following values: absolute granulocyte count ≥ 1,500/mm³, platelet count ≥ 100,000/mm³, serum bilirubin level ≤ 1.5 mg/dL, and serum creatinine level ≤ 1.5 mg/dL. Informed consent was obtained from all patients.

The initial dose of UFT-E was 300 mg/m²/day for 28 days followed by a 7-day rest period. The total daily dose was administered orally in three divided doses every 8 hours (approximately 7 AM, 3 PM, and 11 PM). The UFT-E dose was rounded up or down to the nearest 100 mg. If the pack dose could not be divided equally, the highest dose was administered in the morning and the lower doses in the evening. Leucovorin was supplied as 15-mg tablets and administered orally at a dose of 90 mg/day. Leucovorin was administered concurrently with UFT-E. Patients consumed no food 1 hour before and after ingestion of the medications. A course of therapy was defined as 28 consecutive days of treatment followed by a 7-day rest period.

Dose-modification criteria were designed to allow a reduction of the UFT-E dose; however, the dose of leucovorin remained at 90 mg/d. If UFT-E was withheld because of toxic effects, patients resumed UFT-E at the same dose after the effects had completely resolved. Days on which therapy was withheld because of drug toxicity were counted as treatment days. In the event of grade 3 or 4 toxic effects, the UFT dose was reduced by 50 mg/m²/day in the subsequent courses of treatment. When grade II hematologic toxicity was encountered, therapy was withheld until the absolute neutrophil and platelet counts exceeded 1,500/mm³ and 100,000/mm³, respectively. Standard criteria for response and toxicity were used (8). After two courses of therapy, response was evaluated by computed tomography (CT). In patients who demonstrated a more than 50% reduction in bidimensionally measurable disease, another CT scan was performed 2 months after the first to confirm that the response was of at least 1-month duration.

Patient compliance was verified by counting the remaining packs of UFT-E at the end of each week for the first treatment course, and then at the end of each treatment course. All patients received education before therapy was started. If any toxicity developed, the patients were instructed to contact the research nurse or the physician responsible.

The distribution of time to progression from the first day of treatment to progression was estimated by using the Kaplan-Meier method.

The distribution of overall remission duration from the onset of partial response (even if patient had a complete response later) to progression was also estimated by using the Kaplan-Meier method.

RESULTS

Forty-three patients entered this trial. Patient and disease characteristics are listed in Table 1. The majority of patients (39/43) had a relatively good performance status (ECOG performance grade ≤ 1). The median age of patients was 57 years, ranging from 30 to 74. Of the 43 patients, 7 dropped out due to infection (urinary tract infection, cholangitis and bacterial peritonitis), grade III diarrhea (N=1), and refusal to receive further chemotherapy (N=3) while on the first chemotherapy course, though these 3 patients dropped out with no evidence of progression. Two of them had grade I nausea and grade I epigastric discomfort and the other grade II toxicity of vomiting and diarrhea.

1) Response to chemotherapy

Response to treatment included one complete response (CR) and ten partial responses (PR). The overall response rate (complete response + partial response) of the 36 patients was 31% (95% confidence interval, 16% to 46%). Disease
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Table 2. Tumor response in patients with colorectal cancer receiving oral UFT-E and oral leucovorin

<table>
<thead>
<tr>
<th>Response</th>
<th>No. of patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>10 (28%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>9 (25%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>16 (44%)</td>
</tr>
</tbody>
</table>

Table 3. Number of patients who experienced toxic reactions

<table>
<thead>
<tr>
<th>Toxic reaction</th>
<th>Toxicity grade (No. of patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>17</td>
</tr>
<tr>
<td>Epigastric pain</td>
<td>3</td>
</tr>
<tr>
<td>Hepatic dysfunction</td>
<td>1</td>
</tr>
<tr>
<td>Skin rash</td>
<td>1</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>2</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
</tr>
</tbody>
</table>

No. of evaluable patients: 43

2) Toxicity

This regimen was well tolerated (Table 3) and had no serious toxic effect occurred except in one patient who developed grade 3 diarrhea and dropped out of this trial.

The most frequently encountered toxic reaction was nausea and vomiting, which was slight to moderate in degree. Diarrhea occurred infrequently though it was recognized as the dose limiting toxicity. Neither serious mucositis nor hand-foot syndrome was observed. No significant neutropenia or thrombocytopenia was observed. Therefore, a dose reduction was performed in no patient, and the does-intensity was 100% of the projected does.

Four median chemotherapy cycles were administered (range, 1 to 10+).

DISCUSSION

Phase II studies have shown that oral UFT/leucovorin is an active and well-tolerated regimen in patients with previously untreated colorectal cancer (9–11). The objective response rate is comparable or superior to that typically observed with the leucovorin modulated IV bolus 5-FU regimen (12–16). Improved efficacy of UFT plus leucovorin in metastatic colorectal cancer could result from the prolonged fluoropyrimidine exposure achieved, through repeated oral dosing and the increased tumor 5-FU concentration caused by competitive inhibition of 5-FU degradation by uracil. The overall response rate of the UFT-E and oral leucovorin regimen used in this study is comparable to that of UFT/leucovorin regimen (17, 18). In terms of toxicity, UFT-E plus leucovorin is likely to provide a significant advantage over the bolus 5-FU and leucovorin regimens, including improved tolerability, decreased toxicity-related hospitalizations, and decreased laboratory monitoring costs (19–21). UFT-E and UFT, unlike the continuous infusion of 5-FU, are rarely associated with mucositis or hand-foot syndrome (18,22,23). However, infections developed in three patients, who were dropped out because of it. Usually chemotherapy-related infection is mainly contributed to neutropenia and the disruption of mucosal barrier. However, in...
any severe mucositis or neutropenia. In another UFT study, infection was also noted to occur infrequently (18–23). Therefore, the infections developed during this study are not considered to result from UFT-E/LV chemotherapy.

In a Japanese study (24), UFT-E showed less gastrointestinal toxicity than UFT. This study also showed minimal toxicity on the upper gastrointestinal tract. It should be emphasized that this side effect is associated with patient compliance with oral chemotherapy.

**CONCLUSIONS**

Our data suggest that UFT-E plus oral leucovorin is an effective and convenient regimen, with minimal toxicity for patients with colorectal cancer

**REFERENCES**


6. Paulo M. Hoff, Richard Pazdur. UFT plus oral leucovorin: an effective regimen with low toxicity for any severe mucositis or neutropenia. In another UFT study, infection was also noted to occur infrequently (18–23). Therefore, the infections developed during this study are not considered to result from UFT-E/ LV chemotherapy.


