Phase I and Pharmacokinetic Study of Oral UFT, a Combination of the 5-Fluorouracil Prodrug Tegafur and Uracil

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ABSTRACT

UFT is an oral preparation combining the 5-fluoura-
cril (FU) prodrug tegafur (FT) and uracil (U) in a 1:4 ratio, which is commercially available in Japan for the treatment of breast and gastrointestinal cancers. We sought to determine the tolerance of daily oral UFT and to relate this tolerance to the pharmacokinetics of FT and/or the derived FU, while exploring the possibility of circadian FU kinetics contributing to the results. A 28-day schedule followed by 2 weeks rest was begun at the initial level of 300 mg/m²/day administered either at 8 a.m. or at 6 p.m. At the following level, 400 mg/m²/day patients were randomly assigned to a split-dose administration or to the above single, timed dose administration. Intolerance to single dosing was clearly demonstrated, and only the split dosing was advanced to 500 mg/m²/day. When this level proved too toxic, 400 mg/m² was studied further on a 7 a.m., 3 p.m., and 11 p.m. (every 8 h) schedule. Pharmacology was determined on selected patients. In the single dose administration, areas under the curves of FU were higher following p.m. dosing, although substantial interpatient variation was present. Toxicities (diar-rhea and neutropenia) were more severe in patients receiving the drug in single daily doses. We conclude that the kinetics of FT are saturable, with disproportionate increases in area under the curve (and toxicities) as dose levels are increased. With divided dosing, tolerance improves. UFT at a dose of 400 mg/m²/day administered as three divided doses (every 8 h) is suitable for Phase II studies, although toxicity requiring cessation of drug administration prior to completion of 28-day cycles will occur in some patients.

INTRODUCTION

The fluoropyrimidine FT (also known as tegafur, Ftorafur, and Futrafur), a prodrug of FU, was synthesized in Latvia and initially studied in the Soviet Union under the name of Ftorafur (1). It had a brief trial in the United States by the iv. route in the 1970s, prior to investigations by the oral route (2, 3). Subsequently, Japanese investigators devised an oral formulation in combination with uracil at a 1:4 molar ratio, because it yielded high FU blood levels (through the interference of uracil with its catabolism) and the optimal antitumor effects against murine tumors (4). Packaged commercially as UFT (Taiho Pharmaceutical Co., Tokyo, Japan), this preparation is widely used in Japan for the treatment of gastrointestinal and breast cancers (5). UFT is usually administered at a total daily dose of 600 mg (as amount of FT) in two or three divided doses; it is given continuously until the appearance of toxicity and is subsequently restarted upon recovery. The toxicities of UFT are both dose and duration dependent; they are typical of FU (i.e., gastrointestinal toxicity and myelosuppression), with diarrhea being the predominant dose-limiting manifestation.

The current Phase I and pharmacological study was stimulated by our encouraging results with continuous infusions of FU in advanced colorectal cancer with or without leucovorin (6, 7). Although substantial pharmacological and tolerance information is available from Japanese trials (8), the current study was designed to evaluate a daily schedule and to elucidate: (a) the role of divided dosing in determining pharmacological parameters and toxicity; and (b) the relationship of FU area under the concentration × time (C × T) curve plot (AUC) to toxic events. We were also influenced in the design of this study by the known circadian pharmacokinetics of FU infusions, which are related to the circadian activity of the catalytic enzyme dihydropyrimidine dehydrogenase (9).

PATIENTS AND METHODS

This Phase I and pharmacological study was designed to evaluate the daily oral administration of UFT in a 28-day course followed by a rest interval of 2 weeks. The initial dose level was 300 mg/m² as a single daily dose given either at 8 a.m. (step 1) or at 6 p.m. (step 2). This starting dose level was selected based on the known tolerance of this dose from the Japanese literature (5, 8). The next dose levels consisted similarly of single dose administration of 400 mg/m², given at either of the above times (steps 4 and 5), or split administration at both these times (step 3). Random assignment to either step 1 or 2 was planned for an evaluable cohort of 8 patients (4 per step completing the 28-day course), and similar random assignment was used for 12 evaluable patients to be entered in steps 3 to 5. Calculated doses were rounded off to the nearest hundredth, and in the event of an uneven total dose (e.g., 700 mg), a greater amount was given in the morning. The same dosing rules were applied when, after all

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2 To whom requests for reprints should be addressed, at USC/Norris Cancer Center, 1441 Eastlake Avenue, Los Angeles, CA 90033. Phone: (213) 764-3920; Fax: (213) 764-0061.

3 The abbreviations used are: FT, 1-(tetrahydro-2-furanyl)-5-fluorouracil; FU, 5-fluorouracil; AUC, area under the curve; ECOG, Eastern Cooperative Oncology Group; PR, partial response; U, uracil; FUH,

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patients had completed one course at the preceding steps, the
dose was escalated in a subsequent four-patient cohort to 500
mg/m², given in two divided doses (step 6). The single-dose
schedules of 500 mg/m² were omitted because of toxicities
observed using the single-dose schedules at the preceding dose
level. The split-dose schedule of 500 mg/m² was also found to
exceed the limits of tolerance (the unacceptable toxicity at a
given dose was to be defined by the occurrence of grade 3 or 4
toxicities in two or more patients). The dose of UFT was then
decreased to 400 mg/m² daily but divided into three doses given
every 8 h (step 7). In this last divided-dose schedule, patients
were carefully instructed to fix times of administration within
1 h of 7 a.m., 3 p.m., and 11 p.m. Entry of a minimum of six
evaluable patients was planned to complete step 7. Patient entry
began on August 1990, and this stage of the study was com-
pleted on May 1991. The drug was supplied by the Taiho
Pharmaceutical Co. in the usual commercial formulation of
100-mg capsules containing 100 mg of FT and uracil in a 1:4
molar ratio of FT to uracil.

The study called for interrupting courses of treatment if a
grade 2 or greater toxicity became manifest. Under this circum-
stance, the second or subsequent courses were not administered
until all toxicities had cleared and at least 1 week had elapsed,
with the absence of disease progression. Patients manifesting
grade 2 or 3 toxicities (usually diarrhea) interrupted the treat-
ment cycle. After full recovery or a minimum of 2 weeks,
patients were re-dosed with a shorter cycle length by stopping
its administration 1 day prior to when the drug interruption had
occurred in the preceding cycle. Grade 4 toxicities, on the other
hand, mandated one level of dose reductions on subsequent
cycles.

The trial was approved by the Institutional Review Board of
the University of Southern California upon obtaining our own
IND, and all patients signed an informed consent to participate.
Eligibility for this clinical study consisted of adult patients with
surgically incurable, histologically confirmed advanced dissem-
inated cancers either refractory to prior therapies or known to
be resistant to all conventional agents. Adequate bone marrow
(granulocytes >1500/mm², and platelets >100,000/mm³), renal
(serum creatinine <2.0 mg/dl) and hepatic function (bilirubin
<1.5 mg/dl; alanine aminotransferase, aspartate aminotrans-
ferase <3 times normal) was required, as was a Karnofsky
performance status of better than 50% (Zubrod scale of 2 or
better). Some preference for entry was given to patients with
malignancies usually sensitive to fluoropyrimidines (Table 1).
However, prior treatment failure with a FU-containing regi-
men was not an exclusion, considering the Phase I end points
and since patients with colorectal cancer usually have no
other attractive systemic therapeutic alternatives. Moreover,
some patients with breast cancer have been documented to
benefit from fluoropyrimidines, even after failing treatment
with initial FU containing-combinations (10). Measurable
disease was not required, but all patients had some assess-
ment of disease status at the beginning of every cycle (i.e.,
every 6 weeks). Because many of these patients had gastro-
intestinal cancer and were pretreated, disease progression
leading to non-completion of therapy was relatively common.
This accounts for the high number of patients not completing
cycle 1 (thus, evaluable).

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number</th>
<th>Prior Chemo</th>
<th>Prior FU</th>
<th>Prior RT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colon</td>
<td>11</td>
<td>11</td>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>Rectum</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other gastrointestinal (stomach, pancreas)</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Breast</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Lung, non-small cell</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ovary</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cervix</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age median (range)</td>
<td>59.5 (35–85 y)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Karnofsky Performance (%)</td>
<td>100%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Status (number)</td>
<td>90%</td>
<td>(5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>80%</td>
<td>10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>70%</td>
<td>5%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60%</td>
<td>1%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Excludes 10 patients who withdrew before completing cycle 1 with: subjective complaints (other than gastrointestinal or hematologic toxicity); disease progression without toxicity; or failure to comply.

Analysis of toxicities during cycle 1 was performed by the
Common Toxicity Criteria of the Cancer Therapy Evaluation
Program, National Cancer Institute, on observations recorded
weekly. From Japanese trials (5), it was anticipated that diarrhea
and other gastrointestinal symptoms would be the most common
toxicities observed. Accordingly, special attention was paid to
such symptoms, and a questionnaire with daily entries by the
patients was given and collected on a weekly basis, together
with weekly determination of hemoglobin, WBC count, differen-
tial, and platelets. The questionnaire and capsule counts were
used to assess treatment compliance. The criteria of tumor
response, whenever applicable, included ECOG standard reduc-
tion of >50% of the sum of cross-sectional diameters for all
indicator lesions lasting at least 1 month to qualify for a PR and
other ECOG criteria (11). Patients were deemed not fully evalu-
able for toxicity if they failed to comply with the study, volun-
tarily withdrew from the study with subjective complaints other
than gastrointestinal complaints and lacked any toxicity infor-
mation prior to cycle 1 completion, or went off the study with-
out toxicity because of disease progression before completing
cycle 1.

All patients in dose steps 1, 2, 3, and 6 were to have
pharmacokinetic determinations during treatment cycle 1. In
addition, some patients had serial determinations designed to
explore intrapatient variation and issues of drug accumulation.
Heparinized blood samples (5 ml each) were collected at time 0,
0.5, 1, 2, 10, 11, and 12 h after first and second dosing. These
times were deemed sufficiently informative based on prior ex-
perience with FT (5). Immediately after collection, plasma was
separated from RBCs by centrifugation at 1000 × g for 10 min,
and plasma samples were stored at −20°C until analysis.
Determination of FT, U, FU, and FUH₂ in these samples were
performed usually within 2 weeks. FT was analyzed by modi-
fication of the published method (12). The modification in-
volved the change of the high-performance liquid chromatog-
Table 2  Number of patients experiencing grade 3 and 4 toxicities during cycle 1 by dose and schedule of UFT

<table>
<thead>
<tr>
<th>Step</th>
<th>Daily dose of UFT (mg/m²)</th>
<th>Schedule</th>
<th>No. of patients registered</th>
<th>No. evaluable for all toxicities</th>
<th>Diarrhea</th>
<th>Vomiting</th>
<th>Nausea</th>
<th>Stomatitis</th>
<th>Esophagitis</th>
<th>Hand-foot syndrome</th>
<th>Fatigue</th>
<th>Dizziness</th>
<th>Leukopenia</th>
<th>Granulocytopenia</th>
<th>Thrombocytopenia</th>
<th>Anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>300 @ a.m.</td>
<td>a.m.</td>
<td>5</td>
<td>4</td>
<td>0/0</td>
<td>1/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>1/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>2</td>
<td>300 @ p.m.</td>
<td>p.m.</td>
<td>4</td>
<td>4</td>
<td>0/0</td>
<td>1/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>3</td>
<td>400 @ a.m./p.m.</td>
<td>a.m./p.m.</td>
<td>6</td>
<td>3</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>4</td>
<td>400 @ a.m.</td>
<td>a.m.</td>
<td>3</td>
<td>3</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>2/1</td>
<td>1/1</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>5</td>
<td>400 @ p.m.</td>
<td>p.m.</td>
<td>2</td>
<td>2</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>1/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>6</td>
<td>500 @ a.m/p.m.</td>
<td>a.m/p.m.</td>
<td>8</td>
<td>4</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>3/0</td>
<td>1/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
<td>0/0</td>
</tr>
<tr>
<td>7</td>
<td>400 q 8 h*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

"q 8 h, every 8 h.

Table 3  Cycle 1: nadirs absolute neutrophil counts (ANC) per mm³

<table>
<thead>
<tr>
<th>UFT dose (mg/m²) and schedule</th>
<th>ANC at baseline</th>
<th>Nadir ANC on cycle 1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of patients</td>
<td>Median</td>
</tr>
<tr>
<td>300 @ a.m.</td>
<td>3</td>
<td>6.7</td>
</tr>
<tr>
<td>300 @ p.m.</td>
<td>3</td>
<td>4.0</td>
</tr>
<tr>
<td>400 @ a.m./p.m.</td>
<td>4</td>
<td>3.3</td>
</tr>
<tr>
<td>400 @ a.m.</td>
<td>2</td>
<td>5.1</td>
</tr>
<tr>
<td>400 @ p.m.</td>
<td>2</td>
<td>5.8</td>
</tr>
<tr>
<td>500 @ a.m./p.m.</td>
<td>3</td>
<td>4.0</td>
</tr>
<tr>
<td>400 q 8 h*</td>
<td>7</td>
<td>4.4</td>
</tr>
</tbody>
</table>

"q 8 h, every 8 h.

RESULTS

Toxicity. Six separate dose-steps were studied in the dose-escalation stage, and a seventh cohort received the 400 mg/m² daily dose as three divided doses. All toxicities during cycle 1 are summarized in Table 2, and neutrophil and platelet nadirs are summarized in Table 3. Moderately severe (grade 3) to severe (grade 4) gastrointestinal and myelosuppressive toxicities were observed during cycle 1 with increasing frequency from steps 3 to 6. Three patients each on step 1 (300 mg/m²/day) were evaluable, and all but one completed 28 days without interruption. At 400 mg/m²/day (steps 3–5), four of the six registered patients receiving the drug in two divided doses (step 3) completed 4 weeks; on the other hand, the four evaluable patients on the single-dose administration, whether given in the morning or in the evening, had to interrupt treatment before 3 weeks (median, 2 weeks) because of the appearance of grade 3 or 4 diarrhea. One of the patients receiving 400 mg/m² in the evening required a 25-day hospitalization for severe diarrhea followed by prolonged neutropenia, fever, and i.v. antibiotics.

Only the divided-dose schedule was, therefore, advanced to 500 mg/m²/day. Three of four patients were fully evaluable for toxicity, and one refused further treatment at day 17 after 1 week of nausea, vomiting, and fatigue. The three experienced at least grade 2 myelosuppression and grade 3 diarrhea, with none of the three patients receiving treatment beyond 2 weeks. Since UFT is provided as 100-mg capsules, the actual doses per m² received were 484, 508, and 511 mg/m², respectively. All three of these patients required hospitalization for 3, 4, and 10 days, respectively, for symptoms of severe enteritis-associated abdominal
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Table 4  Summary of relevant pharmacokinetic parameters of FT and 5-FU in patients receiving UFT at dose step 1: 300 mg/m² at 8 a.m.

<table>
<thead>
<tr>
<th>Patient profile</th>
<th>mg given</th>
<th>FT</th>
<th>FT</th>
<th>FU</th>
<th>FT</th>
<th>FT</th>
<th>FU</th>
<th>FT</th>
<th>FT</th>
<th>FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>600</td>
<td>6.3</td>
<td>11.6</td>
<td>0.7</td>
<td>1</td>
<td>1</td>
<td>5.0</td>
<td>120</td>
<td>3.9</td>
<td></td>
</tr>
<tr>
<td>2a</td>
<td>600</td>
<td>7.7</td>
<td>18.2</td>
<td>1.06</td>
<td>0.5</td>
<td>0.5</td>
<td>2.8</td>
<td>211</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>2b</td>
<td>600</td>
<td>9.9</td>
<td>18.5</td>
<td>1.0</td>
<td>0.5</td>
<td>1</td>
<td>3.8</td>
<td>157</td>
<td>4.4</td>
<td></td>
</tr>
<tr>
<td>3b*</td>
<td>700</td>
<td>7.9</td>
<td>10.1</td>
<td>0.2</td>
<td>2</td>
<td>1</td>
<td>5.2</td>
<td>134</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>4a</td>
<td>500</td>
<td>2.8</td>
<td>6.9</td>
<td>0.02</td>
<td>2</td>
<td>2</td>
<td>9.8</td>
<td>51.0</td>
<td>0.51</td>
<td></td>
</tr>
<tr>
<td>4b</td>
<td>500</td>
<td>2.1</td>
<td>10.5</td>
<td>0.08</td>
<td>2</td>
<td>1</td>
<td>7.3</td>
<td>68.3</td>
<td>0.10</td>
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</tr>
<tr>
<td>4c</td>
<td>500</td>
<td>5.4</td>
<td>13.3</td>
<td>1.03</td>
<td>1</td>
<td>1</td>
<td>3.5</td>
<td>145</td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td>4d</td>
<td>500</td>
<td>5.3</td>
<td>9.0</td>
<td>0.3</td>
<td>2</td>
<td>1</td>
<td>5.1</td>
<td>98.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Median*</td>
<td>7.1*</td>
<td>10.8*</td>
<td>0.5*</td>
<td>1.0*</td>
<td>1*</td>
<td>1*</td>
<td>5.1*</td>
<td>127*</td>
<td>2.2*</td>
<td></td>
</tr>
</tbody>
</table>

* See Fig. 2d for earlier profile on patient 3.
* Median based on the average value of each patient.
* Not statistically different from the equivalent value on Table 5 at P > 0.05 (Wilcoxon rank sum test based on average for each patient).

Table 5  Summary of relevant pharmacokinetic parameters of FT and 5-FU in patients receiving UFT at dose step 2: 300 mg/m² at 6 p.m.

<table>
<thead>
<tr>
<th>Patient profile</th>
<th>mg given</th>
<th>FT</th>
<th>FT</th>
<th>FU</th>
<th>FT</th>
<th>FT</th>
<th>FU</th>
<th>FT</th>
<th>FT</th>
<th>FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>600</td>
<td>7.5</td>
<td>15.5</td>
<td>1.0</td>
<td>2</td>
<td>2</td>
<td>2.7</td>
<td>221</td>
<td>7.0</td>
<td></td>
</tr>
<tr>
<td>5b</td>
<td>600</td>
<td>7.9</td>
<td>18.7</td>
<td>1.1</td>
<td>1</td>
<td>2</td>
<td>2.7</td>
<td>219</td>
<td>7.8</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>600</td>
<td>7.7</td>
<td>14.7</td>
<td>0.3</td>
<td>0.5</td>
<td>1</td>
<td>4.0</td>
<td>150</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>600</td>
<td>9.2</td>
<td>15.0</td>
<td>0.1</td>
<td>2</td>
<td>2</td>
<td>1.9</td>
<td>324</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8a</td>
<td>500</td>
<td>7.1</td>
<td>14.0</td>
<td>3.8</td>
<td>0.5</td>
<td>1</td>
<td>5.8</td>
<td>86.1</td>
<td>19.0</td>
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<td>3.5</td>
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<td>155</td>
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<td>46.2</td>
<td>3.0</td>
<td>0.04</td>
<td>0.5</td>
<td>0.5</td>
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<td>117</td>
<td>0.21</td>
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<tr>
<td>Median*</td>
<td>8.4*</td>
<td>14.8*</td>
<td>0.7*</td>
<td>1.0*</td>
<td>1.0*</td>
<td>1.7*</td>
<td>3.4*</td>
<td>185*</td>
<td>7.4*</td>
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</table>

* Median based on the average value of each patient.
* Not statistically different from the equivalent value on Table 4 at P > 0.05 (Wilcoxon rank sum test based on average for each patient).

Pharmacokinetics. Pharmacokinetics were investigated in patients receiving single or split daily UFT doses. At 300 mg/m², four patients were studied after drug administration at 8 a.m. (Table 4) and four at 6 p.m. (Table 5). For each treatment period, one patient was studied on four occasions, and one on two occasions, giving a total of eight profiles. Fig. 1 shows selected profiles after single and divided dose administration; relevant pharmacokinetic parameters of FT and FU corresponding to these dose steps were estimated from curve fitting to appropriate pharmacokinetic models. A limited number of time points were determined but for FU were deemed sufficient to estimate AUCs from a one-compartment model. The a.m. to p.m. comparisons were made on several of the pharmacokinetic parameters based on the nonparametric Wilcoxon test. The mean value for each patient was used in each comparison. No difference between a.m. and p.m. dosing was observed in FT pharmacokinetic parameters, although the mean AUC value of FU from P M administration of UFT tended to be higher than that from the a.m. administration, respectively (P = 0.22). The T_max for FU at a.m. also tended to be lower than that at p.m. (P = 0.10), but the accuracy of the T_max estimation is questionable based on the sparse time points.

The pharmacokinetic parameters obtained from patients receiving split doses are presented in Table 6. Plasma concentrations of FT for the first or second doses reached the maximum level between 0.5 and 2 h. Plasma concentrations of FU also
reached the maximum level within the first 2 h with both doses. Six patients attained FU peak plasma levels exceeding 0.5 μg/ml and four above 1 μg/ml. The mean AUC (μg/ml/h) value of FT normalized in relation to UFT dose was statistically higher for the second (p.m.) dose than for the first (a.m.) dose, suggesting drug accumulation or circadian kinetics. Formal comparison of plasma FU levels between administration at 8 a.m. or 6 p.m. under this dose splitting setting was not meaningful since there was no sufficient washout period between doses. Clinical toxicities in patients who had peak levels of FU exceeding 0.5 μg/ml exceeded grade 2 in every instance and included life-threatening hematological toxicities as well in patients 14 and 15. FT pharmacology was less variable (see also Fig. 1), but some patients showed rather unusual disposition of FT. Fig. 1d (patient 3 profile) indicates an anomalous pharmacokinetic pattern on a patient who manifested slow increase in FT plasma levels and no appreciable levels of either FU or U. In all patients, plasma FUH₂ levels were inversely related to U, confirming the role of U in blocking catabolism of FU.

Therapeutic Effects. Disease status assessments were systematically carried out by tumor measurements using ECOG criteria whenever feasible (11). Two patients experienced objective responses that qualify as PR: one patient with breast cancer and pulmonary metastases who had failed FU + leucovorin given on a weekly schedule. The duration of their response was 3 and 6 months, respectively, both having required dose reductions from cycle 1 because of grade 4 gastrointestinal and hematological toxicity. Four other patients were continued on treatment because of stable disease or improvement (decrease in tumor measurements not qualifying as PR, or improvement in tumor markers). These therapeutic effects included a decline in carcinoembryonic antigen coupled with improvement in performance status in two patients with bowel cancers and similar effects in two patients with breast cancer. These four patients remained on treatment ranging from 7 to 10.5 months.

DISCUSSION

This study complements the extensive observations that have been made in Japan during Phase I and subsequent trials of UFT (5, 8). In their vast experience, the usually recommended method of administration was 600 mg/body given continuously daily in two to three divided doses. With a minimum of escalation steps and fixed time dosing in this study, we were able to establish the importance of split daily administration in attenuating the toxicities associated with 400 mg/m²/day of UFT.
Escalation to 500 mg/m²/day, even in two divided doses, led to severe gastrointestinal toxicities and myelosuppression. This may be explained by both the steep dose-dependent pharmacokinetics and cumulative levels of FT, leading to marked increases in the AUC of FU as the dose of UFT is increased and given in less than three divided doses. In fact, a study of weekly UFT beginning at 600 mg/m²/week was terminated after dose escalations to 900 and to 1200 mg/m² because of prohibitive toxicity, striking dose-dependent FT clearance, and resulting increases in FU AUC. The AUCs of FT increased from 0.8 to 2.0 and to 8.1 m²h at these three levels, whereas the FU AUCs were 0.16, 0.37, and 2.17 m²h, respectively (14). The increases on this weekly schedule are unlikely to result from accumulation of FT given earlier, since the FT half-life is only 6–7 h. These results indicate marked nonlinear pharmacokinetics, as FT dose increases.

In the current study, there is a suggestion of circadian pharmacokinetics of FU derived from FT. Patients receiving a single p.m. dose showed usually higher levels of FU than patients receiving a similar dose in the a.m. However, when administered in two divided doses, these circadian effects were in part confounded by cumulative FT levels on repeated administration at 10 h. More detailed pharmacokinetic study is required to establish a circadian effect. Circadian behavior of FU would be expected to be accentuated by coadministration with uracil, since this agent is also subject to the same catabolism of FU by the enzyme dihydroxypirimidine dehydrogenase, the activity of which is circadianly regulated (9). One might also expect that a deficiency of this enzyme would accelerate the development of toxic manifestations following UFT.

We shifted our interest to the schedule in three divided doses (given at 8-h intervals) with an aim to arrive at a practical dose schedule that would mimic our continuous infusion FU experience (6, 7). Our findings indicate that 400 mg/m²/day in three divided doses may be tolerated without interruptions for 28 days by more than one-half of patients, but some will require earlier cessation of treatment because of the appearance of gastrointestinal toxicities. The toxicities observed were those already described in Japanese trials (5, 8). Most impressive was a syndrome of severe enteritis observed particularly in patients at the highest doses or those receiving single daily doses. This syndrome was characterized by abdominal cramps, nausea and vomiting, and incessant diarrhea leading to dehydration and metabolic acidosis. Rechallenges at lower drug doses were well tolerated by patients, indicating that such occurrence was probably due to severe FU toxicity. These toxicities resemble those of FU in the early i.v. push studies when the drug was given on an every other day basis until toxicity, after a 5-day period of "loading." This pattern of toxicity differs from the continuous infusion FU, which has stomatitis and the hand-foot syndrome as major dose-limiting toxicities (6).

Pharmacokinetic correlations with toxic events are providing some insight into factors determining FU toxicity (14–21). In spite of the long history of this drug in cancer chemotherapy, the relevance of its pharmacokinetic behavior in an individual patient to the toxic or therapeutic manifestations observed has been inadequately studied. The current experience reiterates the finding that patients attaining the highest FU AUCs experience severe toxic manifestations. With adequate data points, correlations should emerge between FU AUC and toxicity from UFT. Also, insufficient determinations were performed to establish whether the disposition of FU exhibits circadian variations.

The availability of UFT provides the opportunity for prolonged exposure to FU. Protracted FU i.v. infusion schedules or daily oral UFT may prove advantageous by allowing one to titrate FU better to the point of mild toxicity, maximizing exposure perhaps to a more "therapeutic" AUC. On the other hand, intermittent exposure to FU may lead to a pattern of

### Table 6
Summary of relevant pharmacokinetic parameters of FT and FU from patients treated with UFT split doses given 10 h apart (dose steps 3 and 6)

<table>
<thead>
<tr>
<th>Patient profile</th>
<th>Dose step</th>
<th>mg given</th>
<th>C&lt;sub&gt;max&lt;/sub&gt; (µg/ml)</th>
<th>T&lt;sub&gt;max&lt;/sub&gt; (h)</th>
<th>Normalized AUC&lt;sub&gt;10 h&lt;/sub&gt; (µg · h/ml)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>FT</td>
<td>FU</td>
<td>FT</td>
</tr>
<tr>
<td>9</td>
<td>3</td>
<td>300</td>
<td>13.7</td>
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<td>0.5</td>
</tr>
<tr>
<td>10</td>
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<td>0.38</td>
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<td>18.1</td>
<td>0.15</td>
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<tr>
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<td>500</td>
<td>20.3</td>
<td>0.70</td>
<td>0.5</td>
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<tr>
<td>15</td>
<td>6</td>
<td>500</td>
<td>18.1</td>
<td>0.15</td>
<td>11</td>
</tr>
<tr>
<td>Median for first dose (normalized to dose)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Median for second dose</td>
<td></td>
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</table>

<sup>a</sup> a.m. and p.m. values are not statistically significantly different at the 0.05 level (i.e., P > 0.05), based on the Wilcoxon signed rank test using the difference between the a.m. and p.m. value for each patient.

<sup>b</sup> a.m. and p.m. values are statistically significantly different at the 0.05 level (i.e., P = 0.02), based on the Wilcoxon signed rank test using the difference between the a.m. and p.m. value for each patient.
resistance that is quite different from what is observed during continuous exposure (22). Pharmacological as well as biochemical rationale, based on the dual actions of FU on DNA and RNA, may help explain why patients failing one schedule of FU subsequently show response to another schedule of administration.

In this study, we documented several responses to UFT in patients who had received prior FU and some prior FU and leucovorin: greater dose intensity and/or different biochemical actions related to continuous exposure, or alternatively, some preferential tumor-related activation of FT to FU could have contributed to these results. We conclude that UFT at 400 mg/m² daily in three divided doses for 28-day courses appears suitable for Phase II studies seeking to evaluate the role of prolonged exposure to FU without requiring central venous catheters and ambulatory pumps. Future studies with UFT will be assessing whether leucovorin modulation may further enhance the therapeutic index over currently available fluoropyrimidine therapy. In fact, there have been encouraging Phase II studies using daily doses of 350 mg/m² given in three divided doses (23, 24).

ACKNOWLEDGMENTS

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