Comparison of 5-Fluorouracil Pharmacokinetics in Patients Receiving Continuous 5-Fluorouracil Infusion and Oral Uracil Plus N1-(2′-Tetrahydrofuryl)-5-fluorouracil

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ABSTRACT

Plasma 5-fluorouracil (5-FU) levels were compared in the same patients after approximately equimolar doses (1.9 mmol/m2/day) of 5-day continuous i.v. infusion of 5-FU (CIFU) and oral administration of a formulation of two combined pharmacological agents, uracil (U) plus N1-(2′-tetrahydrofuryl)-5-fluorouracil (florafur or FT), a prodrug of 5-FU. Ten patients received CIFU for 5 days, then, after a week wash-out period, began the 28-day oral UFT regimen, which was given in three daily divided doses. Following 1 h of CIFU, the plasma 5-FU levels reached a steady state of 0.6 ± 0.2 µM (mean ± SD; day 1), which was maintained for the entire 5-day infusion period (0.6 ± 0.1 µM). In contrast, the maximum 5-FU concentrations (Cp, max) generated from oral UFT at 1 h after dose administration on days 1 and 5 were 2.1 ± 1.5 µM and 2.3 ± 1.9 µM, respectively, which were higher than the steady-state levels during CIFU. These high 5-FU levels disappeared with an apparent elimination half-life (t1/2,α) of 5.2 ± 2.4 h (day 1) and 7.2 ± 3.9 h (day 5). On day 1 of both regimens, CIFU patients had significantly larger 5-FU area under the concentration versus time curve (AUC0–s) values (4.4 ± 1.3 µM·h) than the AUC value they received the UFT regimen (2.6 ± 1.7 µM·h; P = 0.02). However, by day 5, there were no significant differences between AUC0–s values in patients receiving CIFU and UFT, respectively (4.8 ± 1.5 µM·h versus 3.8 ± 2.2 µM·h; P = 0.30). On day 5, the average concentration of the metabolite 5-FU at steady-state (C, ave) within dose interval of 8 h (0.48 ± 0.28 µM) for the oral UFT treatment is comparable with the C, ave values of 5-FU from CIFU-treated patients. The post-UFT generated 5-FU pharmacokinetic parameters (higher Cp, max, comparable C, ave, equal AUC values, and longer apparent t1/2,α of 5-FU) may make oral UFT a preferred method of delivering this fluoropyrimidine over CIFU. In addition, oral UFT would eliminate the incidence of venous thrombosis and catheter-related infections sometimes seen in patients treated with CIFU. Furthermore, the convenience and decreased cost of oral administration may be preferable for many patients, particularly those receiving 5-FU for palliation.

INTRODUCTION

5-FU has been used extensively to manage advanced colorectal carcinoma. Various doses, schedules, methods, and routes of administration have been applied including: oral; i.v. bolus; and short-term, continuous, and protracted infusions. Response rates have improved with increasing doses and prolonged infusion (1–5). With indwelling venous catheters and portable infusion pumps, constant and protracted infusion of chemotherapeutic agents can be given on an out-patient basis (2). However, portable infusion pumps are still inconvenient, and indwelling catheters may produce complications such as venous thrombosis or catheter infections. Oral administration that produced a similar level of 5-FU would be a desirable alternative. FT, a chemical depot form or a prodrug of 5-FU (6), has been shown to be effective against adenocarcinoma when given p.o. (6, 7). U was found to slow 5-FU catabolism in rodent tumor cells (8). When U was administered along with FT, 5-FU levels generated from FT in the AH 130 tumor were much greater than those of animals given FT alone. Additionally, 5-FU levels in the tumor declined slowly (9) in the presence of coadministered U. Thus, oral use of two combined pharmacological agents of U and FT (UFT) was investigated. Phase I and II trials of UFT have been performed in Japan (10–13) and the United States (14–16). In this report, we compare 5-FU pharmacokinetics of an oral UFT dose, which is the recommended Phase II dose on a 28-day administration schedule (370 mg/m2/day as FT) to that of a 28-day schedule of 5-FU infusion (250 mg/m2/day). Our goal was to obtain samples for representate pharmacokinetics in a 5-day study of CIFU and oral UFT in the same patient at a dose that is commonly administered for 28 days. Equitoxic doses for this study could not be applied, because observed toxicities of these two regimens are not the same. Notably, there is an absence of neutropenia, stomatitis, and hand-foot syndrome in UFT treatment, and diarrhea is the dose-limiting toxicity (5, 14). The pharmacology of FT and U in patients treated with UFT will be reported elsewhere.
MATERIALS AND METHODS

UFT capsules containing 224 mg of U and 100 mg of FT (molar ratio of U:FT, 4:1) were supplied for clinical use by Taiho Pharmaceutical Co., Ltd. (Tokyo, Japan). Fl', Taiho (molar ratio of U:Fl', 4:1) were supplied for clinical use by Sigma Chemical Co. (St. Louis, MO). [12N2]U and [15N2]5-FU were purchased from Isotec (Miamisburg, OH).

Patients. Four female and six male patients (age 62 ± 9 years, mean ± SD; range, 45-75 years) participated in this pharmacology study. All patients had to be 18 years old or older with histological proof of malignancy (solid tumor). Tumor types included a rectal squamous carcinoma and nine adenocarcinomas (seven colon, one esophagus, and one stomach). Patients had to have been off all previous chemotherapy or radiotherapy for 3 weeks prior to entering this study and had to show signs of recovery from the toxic effects of previous treatments.

Study Plan. 5-FU (250 mg/m²/day or 1.9 mmol/m²/day) was continuously infused into 10 patients for 5 days via a Provider 6000 infusion pump. The total dose for a 5-day course was mixed in 1 liter of 5% dextrose in water; the infusion rate was 200 ml/24 h. Prior to use, pumps were tested in the laboratory. The drug solution and bags were weighed before and after infusion, and the amount of drug remaining in the bag and infusion cassette was subtracted from the original weight so that the actual amount of drug infused was obtained and subsequently used for calculations. After a week wash-out period, oral UFT was given with 4-8 ounces of water every 8 h for 28 consecutive days. No food was consumed from 1 h before to 1 h after the medication was ingested. The daily UFT dose (370 mg/m²/day or 1.9 mmol/m²/day) as defined by the FT dose was an approximately equimolar dose to CIFU. Because UFT capsule contains 100 mg of FT, the calculated UFT dose was rounded off to the nearest 100 mg. When the daily UFT doses could not be divided evenly, the highest dose was given in the morning. Written informed consent was obtained from patients according to institutional policy.

Sample Collection. Baseline heparinized blood samples were collected prior to treatment. On CIFU treatment days 1 and 5, blood samples were obtained at 1, 2, 4, 5, and 6 h after the start of the infusion. On days 2-4, two blood samples were obtained 2 h apart at the beginning of each 24-h cycle. After the first dose of oral UFT on days 1 and 5, blood samples were drawn at 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, and 5 h. On days 2-4 of the UFT regimen, one sample (tough) was collected 1 h before the first dose of the day was given, and a second sample ("peak") was collected 1 h after that dose. The exact sampling times were always recorded for later use in calculations. Samples were immediately placed in normal plasma, et al. Aliquots of plasma were frozen in glass tubes at 301/303 for 5-FU and 7.7 psi; U at 70°C.

Pharmacokinetics. The highest plasma drug concentration measured in patients after receiving oral UFT. After day 1 baseline, steady-state drug concentrations were averaged from a total of 16 samples (10 collected on days 1 and 5 and 6 collected on days 2-4) in patients following the start of CIFU. Tmax is the time of the highest concentration observed. The trapezoidal rule method was used to calculate the area under the concentration versus time curve (AUC0-t) of 5-FU for CIFU and the AUC0-8 for 5-FU generated from the FT of oral UFT treatment. The average concentration of the metabolite 5-PU at steady state (C stead) within a dosing interval was calculated [AUC/dosing interval (8 h)] for the oral UFT-treated patients (18). Apparent distribution half-life (t1/2,a) and elimination half-life (t1/2,b) were calculated by biexponential curve-fitting using RSTRIP (MicroMath, Salt Lake City, UT). For patients receiving CIFU, the 5-FU AUC0-8 h value was used to further calculate the total clearance (CLf; Ref. 19), and the volume of distribution at steady state (Vdss) was also calculated using the methods described by Rowland and Tozer (18). The values are presented as means ± SD of the 10 patients.

The GraphPad InStat program (GraphPad Software, San Diego, CA) was used for statistical analyses. This program uses the Student’s t test for paired, parametric analyses. Two-tailed P values less than or equal to 0.05 were considered to be significant (20).

RESULTS

5-FU and U Pharmacology of CIFU. Fig. 1 shows the plasma 5-FU and endogenous uracil levels in the 10 patients during CIFU on days 1 and 5. It appears that the Cmax of 5-FU was reached very rapidly when measured in plasma at 1 h and was maintained for the entire 6 h measured on days 1 (Fig. 1A) and 5 (Fig. 1B) and throughout the entire 5-day regimen (Fig. 2A). The CLf for days 1 and 5 was 2.6 ± 0.7 and 2.4 ± 0.7 L/min/m², respectively. The Vdss for days 1 and 5 was 647 ± 157 and 598 ± 218 L/m², respectively. The endogenous U level remained constant throughout the infusion period.

5-FU Pharmacology of Oral UFT. The 5-FU levels generated from FT of patients who received oral UFT are presented in Fig. 1C (day 1) and Fig. 1D (day 5). FT generated 5-FU Cmax of 2.0 ± 1.4 and 2.3 ± 1.7 μM at Tmax of 1.1 ± 0.5 and 1.2 ± 0.7 h for days 1 and 5, respectively. The plasma levels of 5-FU were sustained near the Cmax for about another one-
half to 1 h, and it then declined following a biphasic curve. The apparent 5-FU $t_{1/2,a}$ for days 1 and 5 was 0.34 ± 0.26 and 0.41 ± 0.34 h, respectively, and the corresponding apparent $t_{1/2,b}$ was 5.2 ± 2.4 and 7.2 ± 3.9 h, respectively. The mean trough 5-FU values at 5 h after UFT (the last measured value) were 0.10 ± 0.09 μM and 0.23 ± 0.15 μM for days 1 and 5, respectively. The calculated 5-FU trough levels at 8 h were 0.07 ± 0.08 μM and 0.15 ± 0.12 μM for days 1 and 5, respectively. The 5-FU trough levels measured on days 2 through 5 remained fairly constant and were significantly higher than the trough concentration calculated on day 1 (Fig. 2B).

**Comparisons of 5-FU Pharmacokinetics in Patients Treated with CIFU and Oral UFT.** The 5-FU pharmacokinetic results are compared in Table 1 for patients receiving CIFU and oral UFT treatment. Within the day of drug administration (both days 1 and 5), the 5-FU $C_{p,a}$ in patients receiving CIFU was statistically lower than $C_{p,max}$ of 5-FU generated from FT in patients given oral UFT, as also seen in Fig. 2. The 5-FU $t_{1/2,B}$ (0.19 h) of patients receiving CIFU (21) is significantly shorter than the apparent 5-FU $t_{1/2,B}$ generated from FT when they received oral UFT. On day 1, patients receiving CIFU yielded significantly larger 5-FU $AUC_{0-8 h}$ values (4.4 ± 1.3 μM-h) than the 5-FU $AUC_{0-8 h}$ values (2.6 ± 1.7 μM-h) from FT when they received the UFT regimen. However, by day 5, the 5-FU $AUC_{0-8 h}$ values (4.8 ± 1.5 μM-h versus 3.8 ± 2.2 μM-h) were not different when patients received either CIFU or UFT. On day 5, the $C_{a,aver}$ values of 5-FU generated from FT in patients treated with oral UFT are comparable to the $C_{p,a}$ values in CIFU-treated patients.

**DISCUSSION.**

Human liver contains very high levels of dihydropyrimidine dehydrogenase (22), which is the rate-limiting enzyme for the inactivation of U and 5-FU. Harris et al. (23) showed that this enzyme in the human peripheral blood mononuclear cells reflected its level in human liver (23). The mononuclear cells enzyme activity undergoes diurnal changes, which influence 5-FU levels in the blood of patients receiving 5-FU. Recently, Muggia et al. (15) also reported this circadian cycle of 5-FU levels in patients after oral UFT treatment. Blood sampling for the pharmacology studies always started around 9 a.m. with specific intent to minimize this circadian problem within our small patient population.

The $C_{p,a}$ levels (0.6 μM) achieved in our patients are proportional to that (6.6 μM) of those patients given continuous infusion of 5-FU at a ~10-fold higher dose (24). Due to the rapid disappearance of 5-FU and the low levels of 5-FU anticipated at this CIFU dose level, no attempt was made to study the 5-FU half-lives after CIFU. For comparison, we therefore used the reported 5-FU $t_{1/2,B}$ (mean ± SD) values of 0.21 ± 0.06 h from 11 published studies carried out between 1964–1979 (21). These values were not different from a study of patients receiving continuous infusion of 5-FU at 400 mg/m²/day

**Table 1 Comparison of 5-FU pharmacokinetic parameters in 10 patients receiving CIFU and oral UFT.**

<table>
<thead>
<tr>
<th>5-FU Parameters (units)</th>
<th>Therapy</th>
<th>Day 1</th>
<th>Day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{p,a}$ (μM)</td>
<td>CIFU</td>
<td>0.60 ± 0.31</td>
<td>0.61 ± 0.14</td>
</tr>
<tr>
<td>$C_{p,max}$ (μM)</td>
<td>UFT</td>
<td>2.04 ± 1.35</td>
<td>2.30 ± 1.59</td>
</tr>
<tr>
<td>Apparent $t_{1/2,B}$ (h)</td>
<td>UFT</td>
<td>2.5 ± 0.6</td>
<td>2.3 ± 0.9</td>
</tr>
<tr>
<td>$AUC_{0-8 h}$ (μM-h)</td>
<td>CIFU</td>
<td>6.4 ± 1.3</td>
<td>4.8 ± 1.5</td>
</tr>
<tr>
<td>$AUC_{0-8 h}$ (μM-h)</td>
<td>UFT</td>
<td>2.5 ± 0.6</td>
<td>3.8 ± 2.2</td>
</tr>
<tr>
<td>$C_{a,aver}$ (μM), dosing interval, 8h</td>
<td>UFT</td>
<td>0.33 ± 0.21</td>
<td>0.48 ± 0.28</td>
</tr>
</tbody>
</table>

* All of the results are presented as mean ± SD.

* b Within-day values of 5-FU parameters from CIFU are significantly different from those values generated from FT after oral UFT treatment (P < 0.0001 to 0.02).

* On day 5, $C_{a,aver}$ of 5-FU generated from FT after oral UFT treatment is comparable with those $C_{p,a}$ of 5-FU in patients receiving CIFU.
(t1/2,B, 0.3 h). In the present study, the FT in the UFT-treated patients generated much longer apparent 5-FU t1/2,B from CIFU than the published 5-FU t1/2,B from CIFU. Peak 5-FU levels generated from FT when patients received oral UFT every 8 h are higher than the steady-state level of 5-FU from CIFU at equimolar doses. The trough levels, although initially low on dose 1 of day 1, reached a steady-state level by day 2 that was maintained for the remaining 4 days. Both the CIFU and UFT regimens yielded comparable values of 5-FU AU(0-8) on day 5. Furthermore, on day 5, the Cmax of 5-FU generated from FT within 8-h dosing interval of UFT treatment is comparable with the Cmax of 5-FU values of CIFU-treated patients, which suggests that the AUC values from these two regimens are comparable. These results support preliminary findings of comparable response rates, although with a small patient population, observed with oral UFT regimen and with CIFU therapy.

Although 5-FU Cmax generated from FT in patients treated with oral UFT is higher than that observed with CIFU at equimolar doses, toxicity (neutropenia or oral mucositis) was not observed with oral UFT administration. Furthermore, the hand-foot syndrome known to complicate CIFU therapy was also not observed (5, 14–16, 25, 26). Diarrhea is the dose-limiting toxicity for the patients treated with oral UFT at a dose of 370 mg/m²/day for 28 days, and escalation of doses beyond 370 mg prevents administration of a 28-day schedule (14, 25). Oral UFT may also eliminate the incidence of venous thromboembolism and catheter-related infections sometimes caused by CIFU. The advantages of the longer apparent half-life, similar Cmax, and equivalent AUC values of 5-FU from FT may make oral UFT a preferential method for delivering fluoropyrimidine.

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Comparison of 5-fluorouracil pharmacokinetics in patients receiving continuous 5-fluorouracil infusion and oral uracil plus N1-(2'-tetrahydrofuryl)-5-fluorouracil.

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