Development of a Pharmacokinetic Model to Optimize the Dosage Regimen of TS-1, a Combination Preparation of Tegafur, Gimeracil and Oteracil Potassium

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Summary: Background: TS-1 is a combination preparation of tegafur, a prodrug of 5-fluorouracil (5-FU), with gimeracil, a potent inhibitor of dihydropyrimidine dehydrogenase (DPD), which mediates the inactivation of 5-FU. UFT is a combination preparation of tegafur with uracil, which also inhibits DPD, though less potently; UFT has a higher content of tegafur than that in TS-1. We aimed to develop a pharmacokinetic model to describe the kinetics of tegafur and 5-FU after the administration of TS-1 and UFT.

Methods: We developed a model incorporating the inhibition of DPD by gimeracil and uracil, and fitted the model to the observed kinetics of tegafur and 5-FU after the administration of TS-1 and UFT. Then, we simulated the plasma 5-FU profiles in patients with renal dysfunction and those after replacement of TS-1 with UFT and compared them with the observed profiles.

Results: The developed model could appropriately describe the plasma concentration profiles of 5-FU and tegafur after the administration of TS-1 in patients with normal and impaired renal function.

Conclusion: The developed model may be useful to optimize the dosage regimen of TS-1 under various clinical conditions.

Key words: dihydropyrimidines; renal dysfunction; dosage optimization

Introduction

TS-1 is a combination preparation consisting of tegafur (FT), gimeracil (CDHP) and oteracil potassium in a stoichiometric ratio of 1:0.4:1. CDHP potently and reversibly inhibits the function of dihydropyrimidine dehydrogenase (DPD), which is expressed in the liver and mediates the rate-limiting process of 5-fluorouracil (5-FU) elimination, thereby increasing the plasma concentration of 5-FU. UFT is another combination preparation consisting of FT and uracil in a stoichiometric ratio of 1:4. Although uracil, like CDHP, inhibits DPD, its inhibitory potency is far weaker than that of CDHP. Therefore, the content of FT in UFT is 3- to 5-fold higher than that in TS-1.

Clinically, TS-1 is sometimes replaced with other fluorouracil formulations, such as UFT. However, when TS-1 is replaced by UFT, for example, the dose of FT is increased 3- to 5-fold. If CDHP remains in the patient’s body, it may inhibit the metabolism of UFT-derived 5-FU and thus increase its level. Therefore, concomitant use of TS-1 and other fluorouracil formulations is contraindicated, and a delay of seven days or more before administration of fluoropyrimidine derivatives is advised after the cessation of TS-1. However, in patients with renal dysfunction, a longer period may be necessary, because CDHP is excreted unchanged into urine.

The aim of this study was to develop a pharmacokinetic model incorporating the inhibition of DPD by CDHP and uracil to describe the kinetics of FT and 5-FU after the administration of TS-1 and UFT, and to
determine the required interval between cessation of TS-1 and starting UFT in patients with various degrees of renal dysfunction by estimating the plasma concentration profiles of 5-FU following the replacement of TS-1 with UFT after various intervals.

**Methods**

**Pharmacokinetic parameters of 5-FU**

A conventional 1-compartment model as described by Eq. (1) was fitted to the plasma concentration profile of 5-FU after bolus intravenous administration of 500 mg of 5-FU to cancer patients by a non-linear least-squares method with Marquardt-Levenberg iterative curve-fitting algorithm (MLAB, Civilized Software Inc., MD, USA) to estimate the pharmacokinetic parameters of 5-FU, keFU and VdFU.

\[
CpFU(t) = \frac{Dose}{VdFU} \cdot \exp (-keFU \cdot t) \tag{1}
\]

where \(CpFU\), keFU and VdFU represent the plasma concentration (\(\mu\)mol/L), elimination rate constant (hr\(^{-1}\)) and distribution volume (L), respectively.

**Pharmacokinetics of FT, 5-FU and uracil after administration of UFT**

To estimate the pharmacokinetic parameters of uracil, we analyzed the report of Nakashima et al., which deals with the plasma concentration profile of uracil after the oral single administration of UFT (containing 672 mg [6.00 mmol] of uracil) to cancer patients. Plasma concentration of uracil reached a steady-state 6 hours after the administration of UFT, and we assumed this to be the physiological (basal) concentration of uracil. A 1-compartment model with first-order absorption and with the physiological concentration of uracil (\(C0u\) [\(\mu\)mol/L]), as described by Eq. (2), was fitted to the plasma concentration profile of uracil by a non-linear least-squares method to estimate the pharmacokinetic parameters of uracil.

\[
Cpu(t) = C0u + \frac{Dose \cdot kau}{Vdu \cdot (kau - keu)} \{\exp (-keu \cdot t) - \exp (-kau \cdot t)\} \tag{2}
\]

where Cpu, kau, keu and Vdu represent the plasma concentration (\(\mu\)mol/L), absorption rate constant (hr\(^{-1}\)), elimination rate constant (hr\(^{-1}\)), apparent volume of distribution (L) and physiological concentration of uracil, respectively. These parameters, estimated here, were used as constants in the following analysis.

The inhibitory constant, Ki, of uracil (Kiu; \(\mu\)mol/L) was calculated from the in vitro IC\(_{50}\) value reported by Tatsumi et al. using Eq. (3) to be 14 \(\mu\)mol/L.

\[
Ki = \frac{IC_{50}}{1 + \frac{[S]}{Km}} \tag{3}
\]

To estimate the pharmacokinetic parameters of FT, we analyzed the same report of Nakashima et al., which provides plasma concentration profiles of FT and 5-FU after oral single administration of UFT (containing 300 mg [1.50 mmol] of FT). After oral administration of TS-1, plasma 5-FU shows distinctive profile; it disappears faster than FT (the parent drug) in the early phase (~12 hr). This characteristics cannot be explained at all by a model in which 5-FU is formed only from FT in the systemic circulation. Therefore, we incorporated two rate constants for the metabolism of FT into 5-FU, i.e., the conversion rate constant during the first-pass metabolism (ka2A6; hr\(^{-1}\)) and that in the systemic circulation (k2A6; hr\(^{-1}\)) (Fig. 1). We assumed that uracil only competitively inhibits the elimination of 5-FU. The Eqs. (4)–(7), which represent the pharmacokinetic model of UFT (Fig. 1), were simultaneously fitted to the observed concentration profiles of FT and 5-FU by a non-linear least-squares method to estimate the pharmacokinetic parameters of kaFT, keFT, ka2A6, k2A6 and VdFT.

\[
\frac{dXaFT}{dt} = -kaFT \cdot XaFT - ka2A6 \cdot XaFT \tag{4}
\]
\[
\frac{dCpFT}{dt} = kaFT \cdot \frac{XaFT}{VdFT} - \text{keFT} \cdot \text{CpFT} - k2A6 \cdot \text{CpFT} \tag{5}
\]

\[
\frac{dCpFU}{dt} = k2A6 \cdot \frac{\text{CpFT} \cdot VdFT}{VdFU} + kaA6 \cdot \frac{XaFT}{VdFU} - \frac{keFU}{1 + \frac{\text{Cpu}}{\text{Ki}u}} \cdot \text{CpFU} \tag{6}
\]

\[
\text{Cpu}(t) = C0u + \frac{\text{Dose} \cdot kau}{Vdu \cdot (\text{kau} - \text{keu})} \cdot \{ \exp (-\text{keu} \cdot t) - \exp (-\text{kau} \cdot t) \} \tag{7}
\]

\[
\text{Cpg}(t) = \frac{\text{Dose} \cdot \text{kag}}{Vdg} \cdot \left\{ \frac{k21g - \text{kag}}{(\alpha - \text{kag}) \cdot (\beta - \text{kag})} \cdot \exp (-\text{kag} \cdot t) + \frac{k21g - \alpha}{(\text{kag} - \alpha) \cdot (\beta - \alpha)} \cdot \exp (-\alpha \cdot t) \right. \\
+ \left. \frac{k21g - \beta}{(\text{kag} - \beta) \cdot (\alpha - \beta)} \cdot \exp (-\beta \cdot t) \right\} \tag{8}
\]

where \(\text{Cpg}, \text{kag}, \text{keg}, \text{k12g}, \text{k21g}\) and \(\text{Vdg}\) represent the plasma concentration (\(\mu\text{mol/L}\)), absorption rate constant (hr\(^{-1}\)), elimination rate constant (hr\(^{-1}\)), transfer rate constant from the central to the peripheral compartment (hr\(^{-1}\)), from the peripheral to the central compartment (hr\(^{-1}\)) and the apparent distribution volume of CDHP (L), respectively.

**Simulation of the concentration profiles of FT and 5-FU after oral administration of TS-1**

The pharmacokinetic model of FT described above, which incorporates two distinct rate constants, \(ka2A6\) and \(k2A6\), for the conversion of FT into 5-FU, was also applied to describe the profile of 5-FU after oral administration of TS-1 (Fig. 1). We assumed that CDHP only competitively inhibits the elimination of 5-FU and that basal uracil also competitively inhibits the elimination of 5-FU. The Ki value of CDHP (Ki) was calculated from the IC50 value reported by Tatsumi et al., using Eq. (3), to be 0.078 \(\mu\text{mol/L}\). The value of plasma unbound fraction (fug) used for the following simulation is 0.7.\(^{30}\)

Plasma concentration profiles of FT and 5-FU after administration of TS-1 were simulated by assigning the pharmacokinetic parameters of FT, 5-FU and CDHP estimated in the above sections to the model for 5-FU (Fig. 1), and compared with the observed profiles reported by Hirata et al.\(^6\) The mass-balance equation for plasma 5-FU is given by Eq. (9).

\[
\frac{dCpFU}{dt} = k2A6 \cdot \frac{\text{CpFT} \cdot VdFT}{VdFU} + kaA6 \cdot \frac{XaFT}{VdFU} - \frac{\text{keFU}}{1 + \frac{\text{fug} \cdot \text{Cpg}}{\text{Ki}} + \frac{\text{C0u}}{\text{Ki}u}} \cdot \text{CpFU} \tag{9}
\]

**Estimation of the renal excretion ratio (r) of CDHP**

To calculate the profile of CDHP in patients with renal dysfunction, we estimated the ratio of renal elimination to total elimination (r). We assumed that only the elimination rate (keg) is affected by renal dysfunction. The elimination rate constant (keg’) in a patient with a creatinine clearance of \(CLcr’\) can be described by Eq. (10).

\[
\text{keg’} = (1 - r) \cdot \text{keg} + r \cdot \text{keg} \cdot \frac{\text{CLcr’}}{\text{CLcr}} \tag{10}
\]

where keg and CLcr represent the elimination rate constant (hr\(^{-1}\)) and creatinine clearance (mL/min) in subjects with normal renal function. CLcr was assigned to be 120 mL/min. Plasma CDHP profiles after the oral single administration of TS-1 in four patients with...
Fig. 2. Model-based simulation of the plasma concentration profiles of FT, 5-FU and CDHP after oral administration of TS-1 (55 mg of FT and 15.95 mg of CDHP) to patients with normal renal function. Insets show the same profiles as normal plots. Each line represents the profile estimated by the developed model using the parameters listed in Table 1. Each symbol represents the mean ± S.D. of the observed concentrations cited from the report of Hirata et al. (1999).

Pharmacokinetic model for TS-1 various grades of renal dysfunction was used to estimate the r value. The elimination rate constant of CDHP (keg) in Eq. (8) was substituted with Eq. (10), and the resultant equations for the CLcr’ values were simultaneously fitted to the aforementioned profiles of plasma CDHP to estimate the r value.

Simulation of the time profiles of FT, 5-FU and CDHP in patients with renal dysfunction after the administration of TS-1

Plasma concentration profiles of FT and 5-FU in four patients with renal dysfunction were simulated with the model by using the pharmacokinetic parameters of TS-1, i.e., keFU, VdFU, kau, keu, Vdu, C0u, kaFT, keFT, kaA6, k2A6, VdFT, kag, k12g, k21g and Vdg, and the keg’ value calculated from r, keg and CLcr’ of the respective patients. We assumed that parameters other than elimination rate constant, such as apparent volume of distribution (which reflects both distribution volume and bioavailability) and absorption rate constant, are not affected by renal dysfunction. The calculated profiles were compared with the observed profiles reported.

Simulation of plasma 5-FU concentration profile under the manufacturer’s dosage guideline for patients with renal dysfunction

Plasma concentration profiles of 5-FU during repetitive oral administration of TS-1 to patients with various grades of renal function in accordance with the manufacturer’s guideline, i.e., 60 mg b.i.d. for a patient with CLcr of 120 or 80 mL/min, 50 mg b.i.d. for a patient with CLcr of 50 mL/min and 40 mg b.i.d. for a patient with CLcr of 30 mL/min, were simulated with the developed model.

Simulation of plasma 5-FU profile in patients with renal dysfunction after replacement of TS-1

Plasma concentration profiles of 5-FU in patients with renal dysfunction after replacement of TS-1 at the aforementioned doses with UFT at a dose of 200 mg, t.i.d., with a 12-hour interval, were simulated with the developed model. The AUC (area under the blood concentration-time curve) values were calculated by numerical integration using the trapezoidal rule.

Results

Development of the model and estimation of parameters

Plasma concentration profiles of FT, 5-FU, uracil and CDHP after oral administration of UFT and TS-1 to patients with normal renal function were successfully described by the model; all the fitting lines fell within a range of observed mean ± S.D. The estimated pharmacokinetic parameters are shown in Table 1. The
plasma concentration profiles of FT and 5-FU after oral administration of TS-1 were well simulated with the model using parameters obtained from the pharmacokinetic analysis of UFT and CDHP and the in vitro inhibitory constant of CDHP on DPD; the simulated line fell within a twofold range of the observed values (Fig. 2).

The plasma concentration profile of CDHP in a patient with renal dysfunction could be estimated from creatinine clearance by using the estimated renal excretion ratio (r) of 0.939. Figure 3 shows the predicted plasma concentration profiles of FT and 5-FU after oral administration of TS-1 to patients with renal dysfunction, obtained with the model using the pharmacokinetic parameters of TS-1 and the keg' value calculated from r, keg and CLcr of the respective patients along with the observed profiles. The estimated lines for CDHP concentration are shown along with the observed data.

Simulation of plasma 5-FU concentration profile under the manufacturer’s dosage guideline for patients with renal dysfunction

Figure 4 shows the predicted plasma concentration profiles of 5-FU during repetitive administration of TS-1 (−12 to 0 hr) and after the replacement of TS-1 with UFT (0–60 or 84 hr) with a 12-hour interval in patients with various grades of renal dysfunction. The doses of TS-1 are those recommended by the manufacturer for the respective CLcr values.3) During the repeated administration of TS-1 at the recommended dose, maximum plasma concentrations of 5-FU (as shown between −12 to 0 hr) were predicted to be similar regardless of renal function. The increase in the plasma 5-FU concentration was not large in patients with normal renal function (CLcr = 120 mL/min) after the replacement of TS-1 with UFT with a 12-hour interval (Fig. 4(A), 0–60 hr). However, in patients with renal dysfunction, the greater the renal dysfunction, the larger the predicted increase of plasma 5-FU concentration after the replacement of TS-1 with UFT with a 12-hour interval (Fig. 4(B–D), 0–60 or 84 hr). The AUC values from 0 to 12 hours were increased 1.7-, 2.7-, 4.4- and 6.5-fold in comparison with the AUC0–12 value after the single dose of UFT, as shown in Fig. 4 (A–D vs. E).

Discussion

The developed model could successfully predict the plasma concentration profiles of FT and 5-FU by using
Fig. 4. (A–D) Estimated concentration profiles of 5-FU before and after the replacement of TS-1 with UFT with a 12-hour interval in patients with normal renal function and several grades of renal dysfunction. (E) Simulation of the plasma concentration profiles of 5-FU during repeated administration of UFT. T and U represent the administrations of TS-1 and UFT, respectively. Doses of TS-1 and UFT are shown in each panel.

Pharmacokinetic model for TS-1

The pharmacokinetic parameters obtained by analysis of the profiles of 5-FU, FT and uracil following the administration of 5-FU and UFT to patients with normal renal function (Fig. 2). Moreover, the model could also appropriately simulate the plasma concentration profiles of FT, 5-FU and CDHP after the administration of TS-1 in patients with various grades of renal dysfunction by taking into account the change in the elimination rate of CDHP based on the CLcr value. Therefore, the developed model is considered to be useful to predict the kinetics of FT and 5-FU after the administration of TS-1 to a wide range of patients under any dosage regimen. However, the model tended to overestimate the concentration of FT after the administration of TS-1. A speculative explanation for this overestimation is the difference between UFT and TS-1. We calculated the pharmacokinetic parameters of FT from its concentration profile after administration of UFT and used them to simulate the kinetics of FT after administration of TS-1. The former concentration profile was nearly 10-fold higher than the latter. Moreover, the absorption kinetics and availabilities may be possibly different between UFT and TS-1. During the first-pass metabolism of FT, its metabolite (5-FU) may be further metabolized before being removed from the liver by blood flow. This ‘succeeding metabolism’ may be also inhibited by CDHP. However, we cannot quantitatively estimate the contribution of succeeding metabolism during the first-pass process, so that we did not take it into consideration in the present study.

We estimated the renal excretion ratio (r) of CDHP to be 0.939, which suggests that CDHP is almost entirely excreted unchanged into urine in humans. It was reported that 52.8% of CDHP in orally administered
TS-1 was recovered in patients with normal renal function within 72 hrs. Although the bioavailability of CDHP in humans remains to be investigated, that in rats is reported to be 58% or 36% under fasting or non-fasting conditions, respectively. Therefore, the r value obtained in this analysis seems reasonable, and we conclude that the kinetics of CDHP can be predicted from the CLcr value.

We assumed that distribution volumes of FT and 5-FU are not affected by renal dysfunction. While plasma albumin concentration is decreased under disease state such as renal dysfunction, the plasma protein binding of FT and 5-FU is as low as 48.9–55.7% and 16.7–20.0%, respectively, suggesting that the decrease in the plasma albumin may not have a significant impact on the pharmacokinetics of FT and 5-FU.

Prediction of plasma 5-FU profiles after the replacement of TS-1 with UFT indicated that plasma 5-FU would be only slightly increased in patients with normal renal function even with only a 12-hour dosing interval. In contrast, the extent of increase in 5-FU after the replacement becomes greater in proportion to the deterioration of renal function. However, when UFT was administered 72 hrs after the last dose of TS-1 in patients with moderate renal dysfunction (CLcr = 30 mL/min), the increase was estimated to be only 1.2-fold in terms of AUC, suggesting that the interval of 72 hrs (3 days) may enough to avoid a significant increase in the plasma 5-FU concentration, even in patients with moderate renal dysfunction. (TS-1 is contraindicated for patients with severe renal dysfunction.) The manufacturer of TS-1 recommends a 7-day interval in replacing TS-1 with other fluoropyrimidines. From the viewpoint of pharmacokinetic interactions, the present analysis confirmed that seven days is sufficient to avoid a substantial increase in the plasma 5-FU level. Of course, the present analysis does not imply that the replacement of TS-1 with other fluoropyrimidines with only a 3-day interval is necessarily safe, because other factors, such as the recovery rate of the hematogenetic function of bone marrow, should also be taken into consideration.

In conclusion, we have developed a pharmacokinetic model that can appropriately predict the plasma concentration profiles of 5-FU after administration of TS-1 and UFT to patients with normal or impaired renal function under any dosage regimen. The model predicts that, in replacing TS-1 with UFT, the 7-day interval recommended by manufacturer is sufficient to avoid pharmacokinetic interactions. The developed model may be useful to optimize the dosage regimen of TS-1 under various clinical conditions.

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