A Phase I Study Evaluating the Effect of CDHP as a Component of S-1 on the Pharmacokinetics of 5-Fluorouracil

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Abstract. *The purpose of this study was to investigate the effect of gimeracil (CDHP), a reversible dihydropyrimidine dehydrogenase (DPD) inhibitor, on the pharmacokinetics of 5-fluorouracil (5-FU) and other related metabolites by comparing the pharmacokinetic (PK) profile of S-1 (tegafur [FT] + CDHP + oteracil potassium [Oxo]) to that of FT alone. Patients and Methods: Patients with advanced solid tumors received single oral doses of S-1 (50 mg) and FT (800 mg) on days 1 and 8 in a randomized crossover fashion. Plasma samples were collected on days 1, 2, 3, 8, 9 and 10. Single-dose PK parameters were determined for FT, 5-FU and α-fluoro-β-alanine (FBAL). Following the single-dose crossover period, patients entered an extension phase and received treatment with S-1 b.i.d. for 14 days followed by a 7-day rest, repeated every 3 weeks. Results: A total of 12 patients were enrolled; median age was 59 years and mean body surface area was 1.94 m^2. Following S-1 administration, 5-FU exposure was significantly greater (approximately 3-fold) compared to FT alone ($p \leq 0.0007$ for $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, and C_{max} of 5-FU) despite the 16-fold higher dose of FT administered alone compared to S-1, while plasma concentrations of FT and FBAL were significantly lower with S-1 ($p<0.0001$ for all comparisons). Following both single- and multiple-dose administration of S-1, the average maximum DPD inhibition was observed at 4 h post-dose. The extent of inhibition was similar following single and multiple dosing. Following single- and multiple-dose administration of S-1, plasma concentrations of uracil returned to baseline levels within approximately 48 h of dosing, indicating reversibility of DPD inhibition by CDHP. Conclusion: Despite the differences in the FT dose administered, exposure to 5-FU was significantly greater following S-1 administration compared to FT administration. Conversely, exposure to FT and FBAL were significantly less following S-1 administration compared to FT administration. Thus, the DPD inhibitory action of CDHP contributes to a decrease in 5-FU catabolism and to significantly higher blood levels of 5-FU compared to FT alone.*

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The effectiveness of 5-fluorouracil (5-FU) as an anticancer drug depends on maximizing exposure of blood and tumor tissue to 5-FU. When 5-FU is administered alone intravenously, 90% of the drug is rapidly catabolized in the liver by dihydropyrimidine dehydrogenase (DPD) and excreted in the urine as α-fluoro-β-alanine (FBAL) (1, 2) (Figure 1). Repeated intravenous administrations or protracted infusions are inconvenient for patients. Other oral 5-FU prodrugs with new pharmacological characteristics are now emerging in the area of clinical oncology (3). These 5-FU prodrugs differ markedly in their mode of activation, their pharmacokinetic (PK) behavior, particularly in terms of DPD inhibition, and their pharmacologic modulation. Gimeracil (5-chloro-2,4-dihydroxypyridine, CDHP), a component of S-1, inhibits the catabolism of 5 FU by reversibly inhibiting the activity of DPD. The DPD inhibitory action of CDHP is approximately 180-fold more potent than the inhibitory activity of uracil (4). S-1 is a new generation oral fluoropyrimidine that combines tegafur (5-fluoro-1-(tetrahydro-2-furyl)uracil, FT), an oral prodrug of 5-FU, with two modulators, CDHP, which inhibits 5-FU degradation by DPD inhibition, and oteracil potassium (monopotassium 1,2,3,4-tetrahydro-2,4-dioxo-1,3,5-triazine-6-carboxylate, Oxo), which inhibits 5-FU phosphorylation in the digestive tract. This combination of the three compounds is rationally designed to achieve enhanced antitumor effects while decreasing adverse events (AEs) (5).

In preclinical studies, blood concentrations of 5-FU have been compared after the administration of 10 mg/kg FT with CDHP *versus* 10 mg/kg FT with uracil (UFT). The results

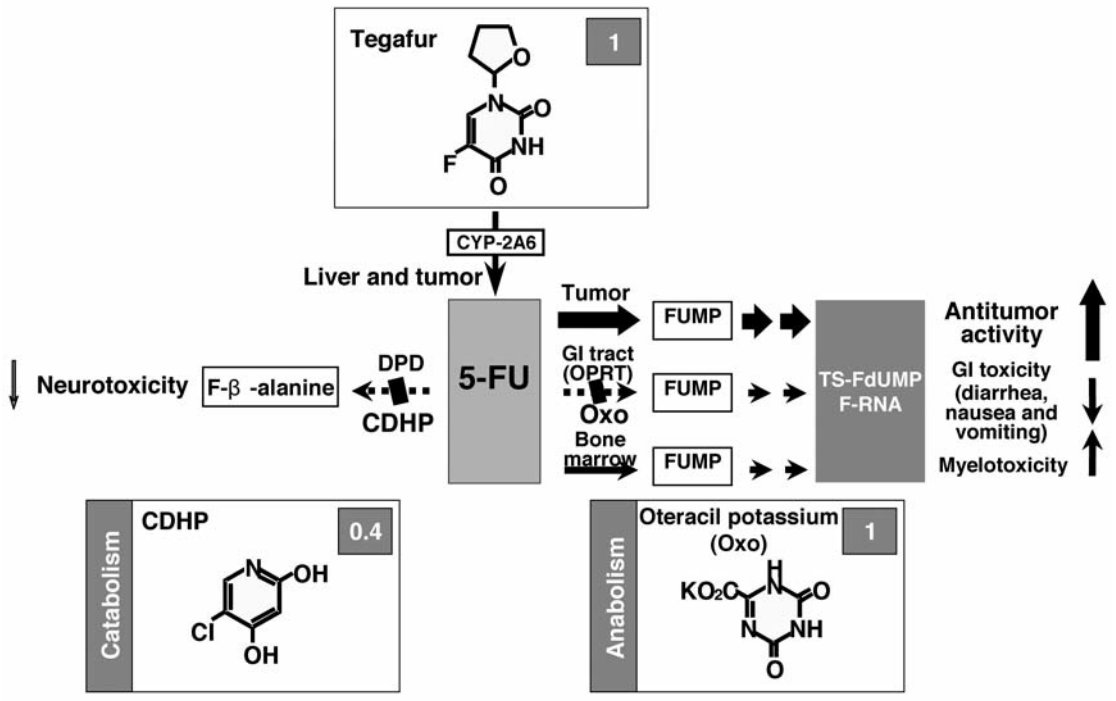

Figure 1. *Components of S-1 and their role in the metabolism of 5-FU.*

indicate that the combination of FT and CDHP produces a much higher level of 5-FU for a longer period of time than that seen with UFT (6, 7). The primary significance of CDHP is that inhibition of DPD by CDHP helps to maintain plasma and, presumably, tumor concentrations of 5-FU for a prolonged time period following oral dosing with FT; hence, PK is similar to that seen with the protracted intravenous infusion of 5-FU (8). Furthermore, due to the shift of metabolism of 5-FU towards anabolism, formation of FBAL is reduced. This may lead to a reduction of hand–foot syndrome (9). In the several clinical studies conducted in Asia and the West, S-1 has been shown to be effective and safe, especially in reducing hand–foot syndrome for patients with gastrointestinal cancer (10-13).

The present phase I study compared the PK of S-1 (FT + CDHP + Oxo) and FT to demonstrate the inhibitory effect of CDHP on 5-FU metabolism in patients with solid tumors.

Patients and Methods

Patient selection. Eligible patients had a pathologically confirmed, advanced solid tumor that was refractory to conventional treatment or for which no standard therapy existed. Eligibility criteria also included the following: age ≥18 years, ECOG performance status of 0 to 2, life expectancy of more than 12 weeks, absolute granulocyte count ≥1,500/μl, platelet count ≥100,000/μl, a hemoglobin value ≥ 9.0 g/dl, bilirubin ≤1.5 times the upper limit of normal (ULN), transaminases AST (SGOT) and ALT (SGPT) ≤2.5 × ULN or AST (SGOT) and ALT (SGPT) may be ≤5 × ULN if related to underlying malignancy, a calculated creatinine clearance >60 ml/min (by Cockcroft-Gault formula), and measurable or evaluable disease. Patients were required to have discontinued chemotherapy, immunotherapy and radiotherapy for at least three weeks before entry into the study (six weeks for nitrosoureas or mitomycin C). Pregnant and breast-feeding women were excluded from this study and fertile patients were required to practice effective contraception. Patients with known brain metastasis or leptomeningeal disease were not eligible. Patients gave written informed consent as per institutional and federal regulatory requirements and the protocol was approved by the Institutional Review Board.

Study design and treatment. S-1 and FT was supplied by Taiho Pharma USA, Inc. (Princeton, NJ, USA). Each capsule of S-1 contained 20 or 25 mg of FT. Individual doses were rounded as closely as possible to the calculated dose, given the available formulation. This was a phase I, open-label, randomized, two-sequence, crossover, PK study evaluating the effect of the DPD inhibitory action of CDHP as an S-1 component compared with FT alone on the PK of 5-FU in patients with advanced solid tumors. The study was conducted in two parts: Crossover PK phase and S-1 extension phase. Each cycle of the S-1 extension phase lasted 21 days (14 days' S-1 treatment, 7 days' recovery). Study treatment continued until disease progression (PD), occurrence of intolerable side-effects and removal by the investigator or withdrawal of consent. Because potassium oxonate is unstable under acidic conditions, patients were instructed to take the capsules under fasting conditions. During the crossover PK phase, patients were randomly assigned to

receive one of the following treatment sequences: Sequence A: Single dose of 50 mg S-1 (2 capsules of 25 mg) on day one followed by a single dose of 800 mg FT (8 capsules of 100 mg) on day 8 and Sequence B: Single dose of 800 mg FT on day 1 followed by a single dose of 50 mg S-1 on day eight.

During only cycle 1 in the S-1 extension phase, the final (evening) dose on day 14 was not administered in order to obtain PK assessment of the duration of DPD inhibition after multiple dosing with S-1. Efficacy assessments and additional supportive safety information were also collected during this phase of the study. Safety monitoring began at the time of a signed and dated informed consent form and continued for 30 days after the last dose of study medication. The crossover PK phase of the study lasted 11 days from day-1 (12 h prior to the first study drug dose on day 1) to day 10 (48 h after the second study drug dose on day 8). The end of study for the crossover PK phase was defined as prior to the first dose of the extension phase or 30 days after the last drug administration of the crossover PK phase for those not participating in the extension phase.

Patients completing the crossover PK phase were eligible to enter the optional S-1 extension phase immediately, where S-1 only was administered according to body surface area (BSA). All patients received only S-1 at 30 mg/m^2 twice daily for 14 days followed by a one-week recovery period, the recommended phase II dose (14). This cycle was repeated every three weeks. Study treatment continued until PD, occurrence of intolerable side-effects, removal by the investigator or withdrawal of consent. The end of study for the S-1 extension phase was 30 days after the last dose of S-1. Study treatment continued until all patients had discontinued treatment or 12 months from the date of the first day of treatment of the S-1 extension phase of the last patient, whichever came first. At that point, treatment would continue at the discretion of the investigator and in agreement with the sponsor.

Dose modifications. No dose modification of S-1 or FT was permitted during the crossover PK phase. For the extension phase, S-1 was held until recovery for nonhematological toxic effects of grade ≤1, granulocytopenia ≥1,000/μl and thrombocytopenia ≥50,000/μl. The protocol specified one level of dose reduction for patients with grade 3 or 4 toxicity. For patients with grade 2 toxic effects, S-1 was held until recovery to grade ≤1 and then resumed at the same dose level.

Toxicity and efficacy assessment. All patients had a complete medical history and physical examination at the time of enrollment and a repeat physical examination at each clinic visit. Likewise, complete blood counts (CBCs) and serum chemistry profile, plain radiographs, computed tomography scans and electrocardiograms were performed before enrollment. CBCs were obtained at least weekly while the patients were receiving S-1 or FT. All patients receiving any dose of S-1 or FT were evaluable for toxicity. Patients receiving a minimum of two courses were evaluable for response, unless there was rapid PD after the first course, in which case, PD was declared and patients were removed from the study. The extent of disease was assessed every two cycles using the same radiographic method used initially to demonstrate measurable or evaluable disease. Responses were determined based on RECIST (15). All of the partial and complete responses were to be confirmed four weeks after their initial documentation. Patients with stable disease were allowed to continue in the study, at the discretion of the treating physician, until the disease clearly progressed. Patients returned any unused capsules and their study calendars to the research nurse at each clinic visit, to verify compliance with the treatment.

PK blood sampling. During the crossover PK phase, serial blood sampling for PK analysis occurred on days 1 and 8 immediately prior to dosing and 0.5, 1, 2, 4, 6, 8, 12, 24, and 48 h post-dose. In addition, urine samples were collected quantitatively for the 12-h interval (approximate) before each dose (*i.e.*, on days -1 and 7) and for the periods of 0 to 6, 6 to 12, 12 to 24, 24 to 36 and 36 to 48 h after administration of S-1 or FT. During cycle 1 only, serial blood samples were collected immediately prior to the morning (AM) dose on day 14 and 2, 4, 8, 24, 48, and 72 h post-dose.

PK analyses. During single-dose crossover, plasma concentration-time data obtained after single doses of FT and S-1 were summarized using descriptive statistics and presented graphically by time point. The primary PK parameters were $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$ and C_{max} of 5-FU, which were analyzed using a single-dose, crossover model with fixed effects for treatment (S-1 or FT), sequence and period and a random effect for patient. Ninety-five percent confidence intervals (CIs) were constructed about the estimated treatment difference (S-1 *minus* FT). The data were log-transformed prior to analysis and the 95% CIs and point estimates obtained from the model were exponentiated after analysis such that the results were presented as a ratio. Identical methods were used to analyze the $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$ and C_{max} for FT, uracil (excluding $AUC_{0\text{-}inf}$) and FBAL. Summary statistics for the ratio of single-dose $AUC_{0\text{-}48}$ were presented for both 5-FU/FT and FBAL/5-FU. Percentage DPD inhibition was calculated (using plasma uracil concentration as a surrogate marker) at each time point after administration of a single dose of S-1 and summarized using descriptive statistics. Excretion of 5-FU, FT, FBAL, CDHP, Oxo and uracil in urine over the 48-h period after a single dose of S-1 or FT was summarized. During S-1 extension (cycle 1), plasma concentration-time data obtained after multiple S-1 doses (cycle 1, day 14) were summarized using descriptive statistics and presented graphically. PK parameters (AUCs and C_{max}) for FT, 5 FU, CDHP, Oxo, FBAL and uracil were determined and summarized using descriptive statistics. Percentage DPD inhibition (using plasma uracil concentration as a surrogate marker) was calculated at each time point and summarized using descriptive statistics.

Results

Demographics and baseline characteristics. Twelve patients, seven men and five women, were enrolled; median age was 59 years (range: 41-73 years). Eleven patients were Caucasian and one patient was Asian (Table I). All 12 patients were included in the primary PK analysis (single-dose crossover PK phase). All 12 patients entered the S-1 extension phase and initiated at least one cycle of S-1 treatment (safety population). Eleven patients were included in the PK analysis assessing DPD inhibition following multiple dosing with S-1 (day 14, cycle 1). Eleven patients were included in the assessment of tumor response. Locations of primary lesions were: pancreas (three patients), lung (two patients) and head and neck, liver, ovary,

Table I. *Summary of patient demographic characteristics.*

Patient characteristics (N=12)			
Gender	N	BSA, m^2	
Male	7	Mean	1.939
Female	5	Range	1.57-2.48
Age, years		Prior chemo	N
Median	59.0	0	5
Range	41-73	1	6
		2	1
Race	N	Primary cancer	N
Caucasian	11	Pancreas	3
Asian	1	Lung	2
		Head and neck	1
		Liver	1
		Ovary	1
		Colorectal	1
		Anus	1
		Neuroendocrine system	1
		Unknown primary	1
Performance status	N		
0	5		
1	6		
2	1		
Type of study	N		
Randomized	12		
PK evaluable	12		
Extension phase	12		
Safety	12		
Efficacy evaluable	11		

BSA, Body surface area.

colorectal, anus, neuroendocrine system and unknown primary lesion (one patient in each location). All patients (12) had prior chemotherapy and/or immunotherapy, including five patients who were treated with more than two regimens for advanced or metastatic disease.

PK results. Summary statistics for single-dose plasma PK parameters during the single-dose crossover phase are presented in Table II. The mean values of $AUC_{0\text{-inf}}$, $AUC_{0\text{-48}}$ and C_{max} for 5 FU were approximately 3-fold greater following administration of S-1 than following administration of FT alone, while $AUC_{0\text{-inf}}$, $AUC_{0\text{-48}}$ and C_{max} values for FT and FBAL were approximately 15- to 22 fold higher following administration of FT than following administration of S-1. The results of the statistical analysis of single-dose plasma PK parameters for 5-FU, FT, FBAL and uracil following administration of S-1 or FT are presented in Table III. The ratio of geometric mean point estimates and 95% CIs for $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$ and C_{max} indicated a significantly greater exposure to 5-FU following administration of S-1 compared to FT alone ($p \leq 0.0007$ for all three parameters). The point estimates and 95% CIs for $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$ and C_{max} of FT and FBAL indicated significantly lower exposure to these analytes following administration of S-1 compared to FT alone ($p<0.0001$ for all comparisons). Although exposure to 5-FU was greater after administration of S-1 (a 5-FU prodrug), the mean apparent half-life of 5-FU following administration of S 1 was shorter than that observed following administration of FT alone (1.75 *versus* 8.81 h). Urinary excretion results after single-dose administration of S-1 or FT are shown in Table IV. The amounts of FT, 5-FU and FBAL recovered in urine were consistent with plasma PK of these analytes: 3-fold higher amount of 5-FU excreted after S-1 than after FT and approximately 20 fold higher amounts of FT (unchanged) and FBAL excreted after FT than after S-1. The percentage of parent dose excreted as unchanged FT and FBAL was similar following S-1 and FT administration and, as expected, as a result of CDHP in S-1, the percentage of parent dose excreted as 5-FU differed following S-1 and FT administration.

Duration of DPD inhibition. During the single-dose crossover phase, immediately prior to dosing with 50 mg S-1 or FT, mean plasma uracil concentrations were 17.48 and 17.98 ng/ml, respectively. There was no marked change in plasma uracil concentrations after administration of a single dose of FT; the mean peak plasma concentration was 21.79 ng/ml (range, 14-31 ng/ml). Therefore, the average uracil concentration over 24 h after FT administration was used as a baseline value to calculate the percent DPD inhibition for each patient during the single-dose crossover and the S-1 extension (multiple dose) phases. Plasma uracil levels increased markedly after administration of a single dose of S-1 (reflecting increased DPD inhibitory activity); the mean peak plasma concentration was 830.17 ng/ml (range, 533-1110 ng/ml). After a fixed dose of 50 mg S-1, the average maximum percentage DPD inhibition was observed at 4 h post-dose (Table V). Median (range) T_{max} values for plasma uracil were 4.0 (3.95-6.07) h after S-1 administration and 3.0 (0.0-48.5) h after FT administration. Considering that uracil is an endogenous compound and the apparent lack of effect of FT on plasma uracil concentrations, it is not surprising that T_{max} values were variable after administration of FT alone. Minimum plasma uracil concentrations observed after -28 ng/ml) and FT (range, 9-24 ng/ml), indicating a return to baseline levels after S-1 administration. During the multiple-dose S-1 extension phase, after multiple dosing with S-1 (30 mg/m^2), the mean plasma uracil concentration, immediately prior to administration of the AM dose on day 14, was 266.7 ng/ml, which reflected a mean DPD inhibition of 33.42% (Table V). Plasma uracil levels increased markedly after administration of S-1 on day 14 (mean C_{max}, 779.64 ng/ml). The average maximum DPD inhibition after multiple dosing was observed at 4 h post-dose. Plasma uracil concentrations returned to baseline levels within

Table II. *Summary statistics for single-dose plasma PK parameters.*

Analyte parameter	S-1 (50 mg)		FT (800 mg)	
	N	Mean±SD	N	Mean±SD
5-FU				
C_{max} (ng/ml)	12	125.02±55.39	12	40.68±41.75
T_{max} (h)[a]	12	2.00 (1.00, 4.00)	12	1.02 (0.50, 2.00)
AUC_{0-inf} (ng h/ml)	12	546.62±225.56	10	189.63±79.21
AUC_{0-48} (ng h/ml)	12	546.62±225.57	10	183.00±76.46
$T_{1/2}$ (h)	12	1.75±0.58	10	8.81±4.51
FT				
C_{max} (ng/ml)	12	1426.67±443.08	12	21375.00±7233.27
T_{max} (h)[a]	12	1.00 (0.48, 4.00)	12	1.49 (0.50, 2.02)
AUC_{0-inf} (ng h/ml)	12	14712.51±8171.01	12	261303.6±126669.1
AUC_{0-48} (ng h/ml)	12	13298.93±5251.23	12	238005.1±90798.28
$T_{1/2}$ (h)	12	11.30±6.66	12	11.87±5.23
CDHP				
C_{max} (ng/ml)	12	273.33±133.89	ND	
T_{max} (h)[a]	12	1.01 (0.50, 4.00)	ND	
AUC_{0-inf} (ng h/m)	12	1095.12±335.81	ND	
AUC_{0-48} (ng h/m)	12	1093.68±337.06	ND	
$T_{1/2}$ (h)	12	3.79±1.92	ND	
FBAL				
C_{max} (ng/ml)	12	83.61±28.75	12	1863.00±843.68 (45.29)
T_{max} (h)[a]	12	5.99 (1.10, 12.00)	12	3.98 (1.92, 6.00)
AUC_{0-inf} (ng h/ml)	11	1279.94±386.14	12	25578.88±7231.88 (28.27)
AUC_{0-48} (ng h/ml)	11	1235.84±368.80	12	24317.35±7404.83 (30.45)
$T_{1/2}$ (h)	11	8.13±3.69	12	10.95±4.57
Oxo				
C_{max} (ng/ml)	12	58.26±60.66	ND	
T_{max} (h)[a]	12	1.53 (0.50, 3.95)	ND	
AUC_{0-inf} (ng h/ml)	8	294.89±268.50 (91.05)	ND	
AUC_{0-48} (ng h/ml)	9	310.42±255.46 (82.29)	ND	
$T_{1/2}$ (h)	8	2.72±1.23	ND	
Uracil				
C_{max} (ng/ml)	12	830.17±166.57 (20.06)	12	21.79±4.50 (20.67)
T_{max} (h)[a]	12	4.00 (3.95, 6.07)	12	3.00 (0.00, 48.50)
AUC_{0-inf} (ng h/ml)	5	10063.61±2915.57 (28.97)	1	1482.26 (n=1)
AUC_{0-48} (ng h/ml)	11	8025.14±2802.27 (34.92)	8	735.52±158.22 (21.51)
$T_{1/2}$ (h)	5	9.30±2.06	1	52.44

[a]Median (min, max) is presented for T_{max}; ND, could not be determined due to plasma concentrations below the lower limit of quantitation.

48 h after the morning dose administered on day 14 (no evening dose administered). Minimum plasma uracil concentrations observed after T_{max} ranged from 7 to 30 ng/ml.

Efficacy results. Of the 11 evaluable patients, two had partial response (PR) as their best overall response, six had stable disease (SD) and the remaining three had PD.

Safety results. During the single-dose crossover PK phase, ten patients reported 16 AEs; all but one of these AEs were of grade 1/2 severity. One patient experienced grade 3 non-cardiac chest pain (reported as a serious AE unrelated to study medication). No patients discontinued during the single-dose crossover PK phase. During the S-1 extension phase, across all cycles, all patients (12) reported at least one AE and 11 patients experienced at least one treatment-related AE. The most common treatment-related AEs among all cycles were nausea (seven patients), rash (six patients) and diarrhea, fatigue and anorexia (five patients each). Three patients died within 30 days after receiving the last dose of study medication; two of the three patients had malignant disease noted as the primary cause of death and the third patient died due to head injuries sustained in a car accident. The majority of patients (8/12) discontinued their study participation during the S-1 extension phase due to objective PD.

Table III. *Statistical analysis of single-dose plasma PK parameters for 5-FU, FT, FBAL and uracil following administration of S-1 or FT.*

Analyte parameter	Study treatment (N=12)	Geometric mean	Ratio of geometric mean point estimate (95% CI)[a]
5-FU			
C_{max} (ng/ml)	S-1	111.07	
	FT	29.28	0.2636 (0.1734, 0.4006)
$AUC_{0\text{-inf}}$ (ng h/ml)[b]	S-1	476.21	
	FT	176.79	0.3712 (0.2411, 0.5717)
$AUC_{0\text{-last}}$ (ng h/ml)	S-1	484.90	
	FT	160.26	0.3305 (0.2285, 0.4781)
FT			
C_{max} (ng/ml)	S-1	1368.14	
	FT	20218.41	14.7780 (11.438, 19.094)
$AUC_{0\text{-inf}}$ (ng h/ml)	S-1	13174.52	
	FT	238519.5	18.1046 (16.197, 20.237)
$AUC_{0\text{-last}}$ (ng h/ml)	S-1	12193.25	
	FT	223356.3	18.3180 (16.504, 20.331)
FBAL			
C_{max} (ng/ml)	S-1	79.05	
	FT	1676.09	21.2026 (18.438, 24.382)
$AUC_{0\text{-inf}}$ (ng h/ml)c	S-1	1236.49	
	FT	24899.06	20.1368 (18.916, 21.437)
$AUC_{0\text{-last}}$ (ng h/ml)	S-1	1100.13	
	FT	23330.98	21.2075 (19.427, 23.151)
Uracil			
C_{max} (ng/ml)	S-1	814.14	
	FT	21.34	0.0262 (0.0227, 0.0302)
$AUC_{0\text{-inf}}$ (ng h/ml)	S-1	ND	ND
	FT	ND	ND
$AUC_{0\text{-last}}$ (ng h/ml)	S-1	7693.86	
	FT	707.02	0.0919 (0.0707, 0.1194)

[a]Contrast: FT *versus* S-1 (parameter estimates for CDHP and Oxo were not available after administration of F.); [b]N=10; [c]N=11; ND, could not be determined; only one patient with $AUC_{0\text{-inf}}$ calculated after both S-1 and FT.

Discussion

This study was designed to investigate the effect of the DPD inhibitory action of CDHP (as a component of S-1) on the PK of 5-FU by comparing the PK of S-1 (FT + CDHP + Oxo) with that of FT alone using a single-dose, crossover design. In addition, the duration of DPD inhibition was assessed following single and multiple dosing of S-1. Despite the 16-fold higher dose of FT administered as FT alone (800 mg) compared to S-1 (50 mg), exposure to 5-FU was approximately 3-fold greater following administration of S-1 compared to that following FT alone. Conversely, exposure to FBAL, a 5-FU metabolite, and FT was approximately 15- to 22 fold higher following administration of FT alone than following administration of S-1. The half-life of 5-FU after short intravenous injection is 5 to 20 minutes (16-18). The apparent elimination half-life of 5-FU observed after administration of S-1 (a 5-FU prodrug) was longer than that after intravenous administration of 5-FU, but shorter than that observed after administration of FT alone. This is not unexpected because the apparent 5-FU half-life of S-1 depends on the inhibitory effect of CDHP, while the apparent 5-FU half-life of FT depends on the elimination rate of FT. As the contribution of CDHP to S-1 is to enhance 5-FU exposure, the increase in 5-FU exposure after administration of S-1 does not require a half-life of 5-FU that is longer than that after FT administration. Consistent with plasma levels of analytes, urinary excretion of 5-FU was approximately 3-fold higher following administration of S-1 while that of FBAL and unchanged FT were approximately 20-fold lower in patients receiving a single dose of S-1 when compared with patients receiving a single dose of FT. The percent of parent dose excreted as unchanged FT and FBAL was similar following S-1 and FT administration and, as expected, as a result of CDHP in S-1, the percentage of parent dose excreted as 5-FU differed following S-1 and FT administration. In the present study, the duration of DPD inhibition was assessed using plasma uracil concentrations as a marker for DPD activity following both single- (50 mg) and multiple-dose (30 mg/m^2) administration of S-1. Plasma uracil concentrations remained at predose levels after administration of FT, *i.e.*, there was no DPD inhibition in the absence of CDHP. Plasma uracil levels increased markedly after administration of a single dose of S-1, reflecting DPD inhibitory activity of CDHP. Maximum mean percent DPD inhibition was observed at 4 h after both single- and multiple-dose administration of S-1. The extent of inhibition was similar following single and multiple dosing. Following single- and multiple-dose administration of S-1, plasma concentrations of uracil returned to baseline levels within approximately 48 h after dosing, indicating reversibility of DPD inhibition by CDHP. Taking into consideration minor differences in dosage and sampling times, AUC and C_{max} values for S-1 components and metabolites are similar across the phase I PK studies completed to date (19, 20). S-1 was generally well tolerated in this patient population, with no unexpected AEs reported.

Oral fluoropyrimidines differ, particularly regarding their PK profile and, especially, in the delivery of circulating 5-FU. The DPD inactivator eniluracil is administered with 5-FU in a 10:1 ratio and produces 5-FU directly in the blood compartment. 5-FU PK during multiple oral dosing of eniluracil and 5-FU showed that the elimination half-life of 5-FU is approximately 4.0 h (21). Between day 2 and day 29, the main PK parameters remained constant, notably for the values of the total body clearance. Another randomized, open-label, crossover study compared continuous venous infusion (CVI) of 5-FU to 5-FU/eniluracil combination (22). The results showed that individual 5-FU concentrations during 5-FU CVI were highly variable, whereas those after 5-FU/eniluracil were more

Table IV. *Urinary excretion results after single-dose administration of S-1 or FT. Data are expressed as mean±standard deviation.*

Analyte:	FT (unchanged)		5-FU		FBAL	
Single-dose treatment:	S-1	FT	S-1	FT	S-1	FT
Parameter						
Amount recovered in urine after 48 h (mg)	2.18±1.31	43.17±20.42	2.04±0.83	0.63±0.14	14.74±3.62	286.84±27.88
Percent of parent dose excreted in 48 h	4.36±2.62	5.40±2.55	6.29±2.56	0.12±0.03	55.10±13.52	67.02±6.51
Renal clearance (l/h)	0.18±0.10	0.18±0.07	4.35±1.98	3.92±1.36	13.30±6.02	12.34±4.62

reproducible. The lower variability in 5-FU concentrations following 5-FU/eniluracil is attributable to the inhibition of DPD. The PK of 5-FU following the administration of S-1 at a standard dose of 80 mg/m^2 were first reported in 1995 (9). This relative stability in the 5-FU PK during S-1 treatment was not consistent with the results of a study by Peters *et al*. (23) who reported an increase in 5-FU and uracil plasma concentrations during repeated daily administration of S-1. Therefore, more data are needed about the time-stability of the S-1 PK during repeated administration. Elimination half-life of 5-FU during S-1 treatment was reported to be in the range of 1.9-2.9 h. This demonstrated 5-FU elimination (compared to 5-FU given alone) reflects the presence of the DPD inhibitor in S-1. The fate of 5-FU following the administration of BOF-A2 was also examined during a phase I dose-escalating trial (200 mg/m^2 twice daily to 300 mg/m^2 three times daily) (24). In this study, the mean steady-state concentration of plasma 5-FU was in the range of 30-100 ng/ml. A lack of variation of 5-FU levels within a day at steady state may be explained by the suppression of circadian variations in 5-FU concentrations due to DPD inhibition (25). Average plasma concentrations of 5-FU generated from FT in patients treated with oral UFT were comparable to those observed in continuous venous infusion (CVI)-treated patients (26). Owing to the presence of uracil, the 5-FU elimination half-life was markedly higher during UFT treatment (7.2±3.9 h on day 5) as compared to CVI (0.19 h). Muggia *et al*. (27) examined 5-FU AUC levels as a function of the timed dose of UFT, 300 mg/m^2 (morning *versus* evening dose). Although not significant, higher 5-FU blood exposures (AUC) were observed in the evening dose as compared to the morning dose.

This is the first study that assessed a reversible inhibitory effect of CDHP on 5-FU in humans. A single dose of 50 mg S-1 was compared to a single dose of 800 mg FT, a bio-equivalent dosage. Despite the difference in the FT dose administered, exposure to 5-FU was significantly greater following S-1 administration compared to FT administration. Conversely, exposure to FT and FBAL were significantly less following S-1 administration compared to FT administration. Thus, the DPD inhibitory action of CDHP contributes to a decrease in 5-FU catabolism and significantly higher blood levels of 5-FU compared to FT alone.

Table V. *Percentage inhibition of DPD after single and multiple dose administration of S-1.*

Post-dose time point[a] (h)	Single dose S-1 (50 mg)		Multiple dose S-1 (30 mg/m^2 twice daily)	
	N	Mean (SD)	N	Mean (SD)
0	12	0.06 (0.48)	10	33.42 (17.84)
0.5	12	3.74 (3.38)	---	---
1	12	19.01 (9.95)	---	---
2	12	49.98 (18.03)	10	81.41 (14.82)
4	12	95.14 (10.04)	11	99.82 (0.55)
6	12	87.23 (13.64)	---	---
8	9	62.93 (18.81)	11	51.24 (16.52)
12	8	22.69 (11.29)	---	---
24	12	2.94 (2.87)	11	2.03 (2.72)
48	12	0.21 (0.78)	10	–0.42 (1.30)
72	---	---	9	–0.83 (0.62)

[a]Percentage inhibition at a time point calculated as [CT-BL]/[C_{max}-BL] × 100, where C_T is the uracil concentration at the time point, BL is baseline plasma uracil concentration and C_{max} is the maximum observed concentration across all time points following single-dose administration of S-1 (50 mg) for each patient. Baseline for each patient was the mean of all plasma uracil concentrations obtained for that patient up to 24 h after administration of single FT dose in the single-dose crossover PK phase.

In summary, despite the 16-fold higher dose of FT administered as FT alone (800 mg) compared to S-1 (50 mg), 5-FU exposure by AUC determinations were significantly greater (approximately3-fold), following administration of S-1. Plasma concentrations of FT and FBAL were significantly lower with S-1 than with FT alone. Along with plasma uracil concentrations, these results confirmed the DPD inhibitory effect of CDHP as a component of S-1. Clinically, S-1 was generally well-tolerated.

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