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ORIGINAL ARTICLE

**Masataka Ikeda · Hiroshi Furukawa · Hiroshi Imamura
Jyunzo Shimizu · Hideyuki Ishida · Seizo Masutani
Masayuki Tatsuta · Takatoshi Kawasaki
Takashi Satomi**

Pharmacokinetic study of S-1, a novel oral fluorouracil antitumor agent in animal model and in patients with impaired renal function

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Abstract *Purpose:* S-1 is a novel oral fluorouracil antitumor drug that combines tegafur (FT), 5-chloro-2,4-dihydroxypyridine (CDHP), which inhibits dihydropyrimidine dehydrogenase (DPD), and potassium oxonate (Oxo). As 50% of CDHP is excreted in the urine, renal dysfunction may directly affect the DPD inhibitory effect and lead to increased 5-fluorouracil (5-FU) concentrations. We sought to determine the influence of impaired renal function on the pharmacokinetics of S-1 in an animal model and in patients with gastric cancer. *Methods:* An experimental renal failure model induced by cisplatin was developed in rabbits, and plasma concentrations of FT, 5-FU, CDHP and Oxo were determined after S-1 injection. Four patients with various degrees of renal impairment with unresectable gastric cancer were recruited to the study, and the pharmacokinetics in these four patients were analyzed following single and consecutive S-1 administrations. *Results:* In experimental renal failure, plasma clearance of CDHP and 5-FU was retarded corresponding to the degree of renal impairment and there was a close correlation between creatinine clearance (CLcr) and plasma CDHP and 5-FU clearance. In the single administration study, half standard dose was used in three patients (CLcr ≥50 ml/min) and one-third in the other (CLcr < 50 ml/min). In patients with CLcr more than 75 ml/min, C_{max}, T_{max}, $AUC_{(0-\infty)}$, and $T_{1/2}$ of 5-FU and CDHP were not different between single and consecutive administrations. In contrast, in patients with mild and moderate renal dysfunction (CLcr 55 and 36 ml/min, respectively), the $T_{1/2}$ values of CDHP with consecutive administrations (7.6 and 15.3 h, respectively) were longer than the values with single administration (4.6 and 8.2 h, respectively). The $T_{1/2}$ of 5-FU was 5.7 h with single administration and 8.5 h with consecutive administration in patients with moderate renal impairment. The $AUC_{(0-\infty)}$ of 5-FU with consecutive administrations (3089.7 ng·h/ml) was far greater than with single administration (430.4 ng·h/ml). There was also a strong correlation between CLcr and plasma CDHP clearance. Based on the pharmacokinetics following multiple consecutive administrations, S-1 administration resulted in no severe adverse reactions in any of the four patients. *Conclusions:* CDHP clearance was prolonged in the presence of renal impairment, leading to a delayed $T_{1/2}$, and high AUC of 5-FU. These findings demonstrate that administration of S-1 to patients with impaired renal function may need individualized dosing and pharmacokinetic monitoring.

Keywords Gastric cancer · S-1 · CDHP (5-chloro-2,4-dihydroxypyridine) · 5-FU · Renal dysfunction

M. Ikeda (✉)
Department of Surgery and Clinical Oncology (E2),
Graduate School of Medicine, Osaka University,
2-2 Yamadaoka Suita, Osaka 565-0871, Japan
E-mail: mikeda@surg2.med.osaka-u.ac.jp
Tel.: +81-6-68793251
Fax: +81-6-68793259

M. Ikeda · H. Furukawa · H. Imamura
J. Shimizu · H. Ishida · S. Masutani · M. Tatsuta
T. Kawasaki · T. Satomi
Department of Surgery,
Sakai Municipal Hospital,
Osaka 590-0064, Japan

Introduction

S-1 is a novel oral agent that combines three pharmacological agents: tegafur (FT), which is a prodrug of 5-fluorouracil (5-FU), 5-chloro-2,4-dihydroxypyridine (CDHP), which inhibits dihydropyrimidine dehydrogenase (DPD) activity, and potassium oxonate (Oxo), which reduces gastrointestinal toxicity [5, 21]. S-1 can maintain therapeutic plasma 5-FU concentration by inhibiting DPD activity while reducing gastrointestinal side effects, which is one of the dose-limiting toxicities of 5-FU [19]. A late phase II study of S-1 in advanced gastric cancer conducted in Japan has shown an overall response rate of 46% [11, 18]. On the basis of these results, a regimen comprising 80 mg/m^2 per day given in two divided doses after breakfast and supper for 28 days consecutively followed by 14 days rest is recommended [11, 18]. S-1,

therefore, is a promising drug in terms of patient convenience and response rate in advanced gastric cancer.

However, the incidence of adverse reactions was 78% in a late phase II study [18]. In particular, the incidence of adverse reactions including myelosuppression was higher in patients with impaired renal function than in those with normal renal function. Because more than 52.8% of CDHP is excreted in the urine, renal function is critical for plasma CDHP clearance [9]. Lower CDHP clearance leads to prolonged high concentrations of plasma CDHP, which causes sustained high plasma concentrations of 5-FU. This may lead to severe adverse events.

In the clinical setting, we often encounter patients with impaired renal function, for example elderly patients and patients with prior chemotherapy. Creatinine clearance (CLcr) decreases significantly with age and precautions must be taken during cancer chemotherapy in the elderly [1, 10]. There is a previous report of successful S-1 treatment in patients with renal dysfunction [12]. However, we have no definite data on the safe administration of S-1 in patients with impaired renal function. It may be necessary to monitor pharmacodynamics to achieve optimal administration of antitumor drugs in elderly patients and patients with impaired renal function. With cisplatin, which shows renal toxicity, monitoring plasma platinum concentration and estimating the area under the plasma concentration versus time curve (AUC) has been recommended to monitor adverse events [2, 24].

The primary objective of this study was to investigate the pharmacokinetics of S-1 in an animal experimental renal failure model and in patients with impaired renal function. The secondary objective was to document adverse events in patients with impaired renal function based on the pharmacokinetic results.

Materials and methods

Experimental renal failure in rabbits induced by cisplatin

Male NZW rabbits purchased from Kitayama Rabesu (Nagano, Japan) were used in this study. All rabbit procedures were carried out in accordance with the guidelines and with the approval of the Taiho Pharmaceutical Company (Tokyo, Japan). In order to induce renal dysfunction, 1, 2 or 3 mg/kg of cisplatin was administered intravenously into an ear vein once a day for three consecutive days. As a control 6 ml/kg of saline was used. S-1 solution (FT concentration 5 mg per 2 ml per kg) was injected into an ear vein 24 h after the final administration of each concentration of cisplatin. Then 50 mg per 2 ml per kg of creatinine solution was added to the S-1 solution to determine CLcr. Blood (4 ml) was drawn into heparinized tubes at 15 and 30 min, and 1, 2, 4, 8 and 24 h after injection of S-1. The blood was then centrifuged at 3000 rpm for 10 min at 4°C, and the plasma was collected and stored at –80°C until use. Blood urea nitrogen (BUN) and creatinine were also determined.

Patients

Four patients, all men, with a median age of 66.5 years, ranging from 56 to 79 years, participated in this study between November 2000 and March 2001 at Sakai Municipal Hospital. To be eligible, patients had to have unresectable gastric cancer and meet the following criteria: (1) Eastern Cooperative Oncology Group (ECOG) performance status of 2 or better; (2) adequate bone marrow, liver, heart and lung functions (hemoglobin ≥9.0 g/dl, WBC ≥4000/mm^3 but $<12{,}000/mm^3$, platelets $\geq 10\times10^4/mm^3$, total bilirubin ≤ 1.5 mg/dl, GOT GPT <100 U); (3) renal function (serum creatinine >1.1 mg/dl (our institutional upper limit), CLcr >20 ml/min). Patients with clinical signs of brain metastasis, active gastrointestinal bleeding, and those under hemodialysis treatment were excluded. The protocol for this study was approved by the institutional review board and was conducted in accordance with good clinical practice guidelines. Written informed consent was obtained from all patients before enrollment into the study. Grading of toxicity was scored according to the National Cancer Institute Common Toxicity Criteria. Before administration of S-1, CLcr was calculated from the serum creatinine concentration in 24-h urine samples.

Study design

S-1 was available as capsules in which FT, CDHP, and Oxo were combined at a molar ratio of 1:0.4:1. Each capsule contained 20 or 25 mg FT. The single administration and then the 5-day consecutive administration were carried out. The selected dose for the single administration study was 40 mg/m^2 (half the recommended dose of 80 mg/m^2 per day). The drug was administered within 30 min after breakfast at a dose of 40 mg (20 mg×two capsules) for body surface area (BSA) <1.25 m^2, 50 mg (25 mg×two capsules) for BSA 1.25–1.50 m^2, and 60 mg (20 mg×three capsules) for BSA >1.50 m^2. In the consecutive-day administration study, the daily dose was determined according to the pharmacokinetic results of 5-FU obtained in the single administration study.

Sample collection

For the single administration, blood samples were obtained before administration, and at 2, 4, 6, 10 and 24 h after. For the 5-day consecutive administration, blood was drawn before administration on day 5 in the morning, and at 2, 4, 6, 10 and 24 h after. The blood (5 ml each time) was obtained from the antecubital vein and collected into heparinized tubes. The blood was then centrifuged at 3000 rpm for 10 min at 4°C, and the plasma was collected and stored at –80°C until use.

Drug assay and pharmacokinetic parameters

FT, 5-FU, CDHP and Oxo were analyzed using high-performance liquid chromatography and gas chromatography/negative ion chemical ionization mass spectrometry, according to the method of Matsushima et al. [14]. Pharmacokinetic parameters, including maximum plasma concentration (C_{max}), maximum plasma concentration time (T_{max}), AUC, and half-life ($T_{1/2}$) were calculated using noncompartmental methods, using a program renewed in FORTRAN based on a program by Yamaoka and Tanigawa [25], validated by comparison with Nonlin results. The values are expressed as means ± SD. Measured values of plasma levels with consecutive-day administration were plotted on a simulation curve, prepared based on the single administration results. The data from the two groups were analyzed using a two-sided Student's *t*-test.

Results

Experimental renal failure in rabbits induced by cisplatin

Renal dysfunction induced by cisplatin is caused by proximal tubular necrosis [3]. In our renal failure model, plasma clearance of creatinine decreased with increasing

doses of cisplatin as shown in Fig. 1. The CLcr in the control group was 1.59 ± 0.24 ml/min per kg, and in the groups injected with 1 mg/kg, 2 mg/kg and 3 mg/kg of cisplatin were 0.75 ± 0.20, 0.36 ± 0.11, and 0.23 ± 0.03 ml/min per kg, respectively (Fig. 1). Plasma BUN levels after cisplatin injection increased dose dependently, demonstrating the occurrence of impaired renal function in our model (data not shown).

Pharmacokinetics of FT, 5-FU, CDHP and Oxo in experimental renal failure

Figure 2 shows the serial changes in the plasma concentrations of FT (Fig. 2A), 5-FU (Fig. 2B), CDHP (Fig. 2C) and Oxo (Fig. 2D) after intravenous administration of S-1. Plasma FT concentrations in the control group were similar to those in the three experimental renal failure groups, suggesting that the pharmacokinetics of FT were not affected by renal dysfunction (Fig. 2A). Plasma 5-FU, CDHP and Oxo concentrations after intravenous administration of S-1 increased in proportion to the dose of cisplatin injected (Fig. 2B, C, D). The $AUC_{(0-\infty)}$ values of 5-FU, CDHP and Oxo were significantly elevated in the experimental renal failure groups compared to the control group (data not shown).

Correlation between CLcr and clearance of 5-FU and CDHP

There was a very close correlation between CLcr and clearance of 5-FU ($n = 18$, $r = 0.970$, $P < 0.0001$) and CDHP ($n = 18$, $r = 0.989$, $P < 0.0001$), and between 5-FU and CDHP ($n = 18$, $r = 0.966$, $P < 0.0001$) (Fig. 3).

Patient characteristics

The characteristics of the patients are summarized in Table 1. All patients had unresectable gastric carcinoma and three patients had had prior gastric surgery. Two patients had previously had chemotherapy, one with oral 5-FU and the other with CPT-11 plus cisplatin. The serum creatinine level and CLcr of each patient are also shown in Table 1. The dose of S-1 for the single and consecutive administration studies, treatment dose, cycles of treatment performed, and treatment toxicity are summarized in Table 2.

Pharmacokinetics of FT, 5-FU, CDHP and Oxo after single and consecutive administrations

The solid lines in Fig. 4 show the FT (Fig. 4A), 5-FU (Fig. 4B), CDHP (Fig. 4C) and Oxo (Fig. 4D) pharmacokinetics in each patient after a single administration, and the dotted lines show the pharmacokinetics after consecutive administration. Table 3 shows C_{max}, T_{max}, $AUC_{(0-\infty)}$ and $T_{1/2}$ values for all four patients. In patients 3 and 4, with CLcr more than 75 ml/min, these four pharmacokinetic parameters were not different between single and consecutive administrations. In contrast, in patients 1 and 2 with apparent renal dysfunction, C_{max}, $AUC_{(0-\infty)}$ and $T_{1/2}$ values of CDHP and 5-FU after consecutive administrations were greater than after a single administration.

Correlation between CLcr and clearance of CDHP

As shown in Fig. 5, in the consecutive S-1 administration study there was a strong linear relationship between the clearance of plasma CDHP and the CLcr ($r = 0.979$,

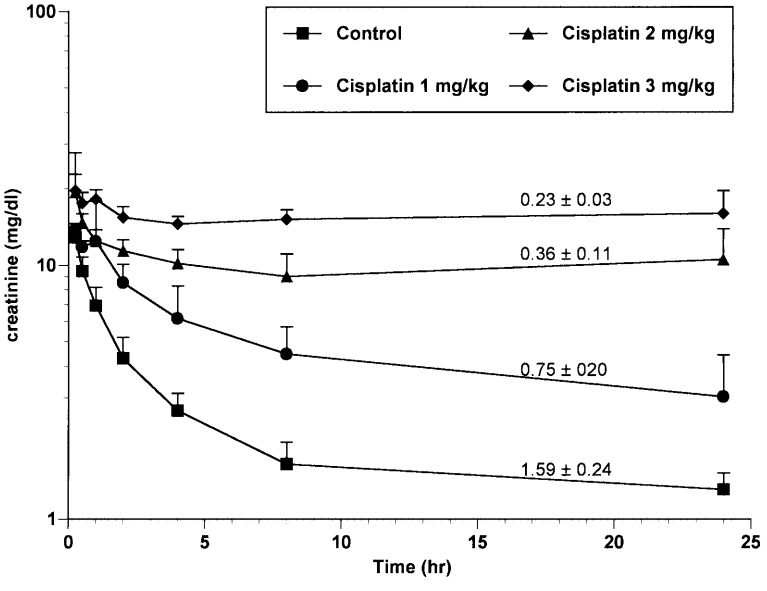

Fig. 1. Serum creatinine concentrations in a renal failure rabbit model induced by cisplatin. The values are means ± SD ($n = 5$, control and cisplatin 1 mg/kg groups; $n = 4$, cisplatin 2 mg/kg and 3 mg/kg groups). The numbers on each line indicate the CLcr (ml/min/kg) of that group

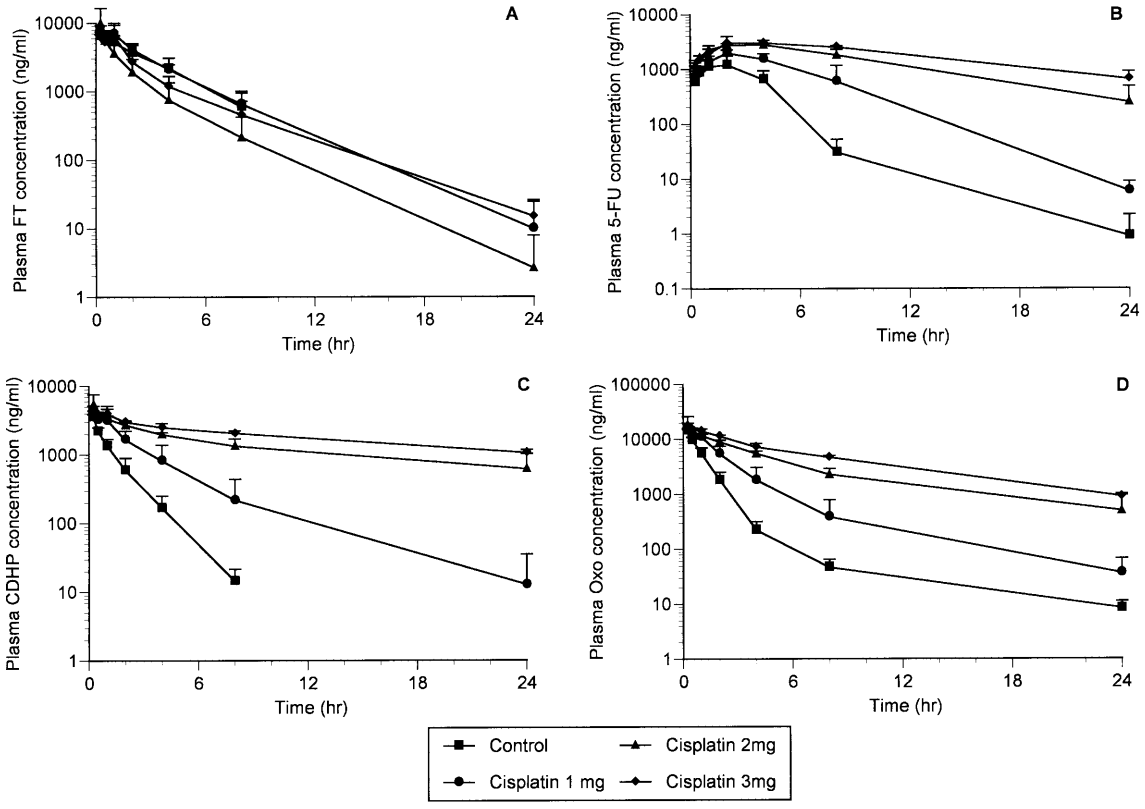

Fig. 2A–D. Plasma concentrations of FT (**A**), 5-FU (**B**), CDHP (**C**) and Oxo (**D**) after intravenous administration of S-1 to rabbits with renal failure induced by cisplatin

$P = 0.0262$), as seen in the experimental renal failure model.

Toxicity

After the consecutive administration study, treatment was initiated with the doses and cycles shown in Table 2. In patient 1, S-1 administration was discontinued on day 15 due to progression of disease. S-1 treatment was ongoing at the time of this report for the rest of the patients. During all seven cycles with therapeutic doses, toxicity of grades 1–2 was noted in three patients, but toxicity of grades 3–4 was not observed. No patient developed diarrhea. However, as shown in Fig. 6, in patient 1 during the consecutive administration study, there was a marked discrepancy between the actual plasma 5-FU concentration and the simulated 5-FU concentration calculated from the single administration results. Because of this prolonged high concentration of 5-FU, patient 1 developed grade 3 thrombocytopenia, and a grade 1 serum transaminase increase, which were successfully managed by conservative treatment. Patient 3 experienced an unrelated intraperitoneal bleeding twice because of peritoneal metastasis resulting in the cessation of S-1 for a short time.

Fig. 3A–C. Relationship between creatinine clearance (CLcr) and clearance (CLp) of 5-FU and CDHP after intravenous administration of S-1 to rabbits with renal failure induced by cisplatin (*solid line* regression line). The coefficient of correlation (r) and the significance level (P) are shown

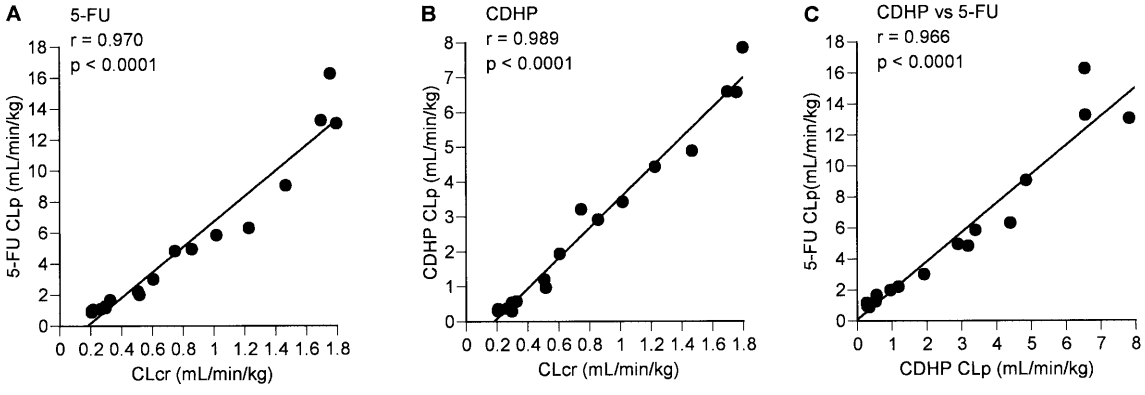

Table 1. Patient characteristics

Patient no.	Sex	Age (years)	BSA (m^2)	Performance status (ECOG)	Creatinine (mg/dl)	CLcr (ml/min)	Gastrectomy	Prior chemotherapy	Site of metastases
1	M	79	1.72	1	1.53	36.3	Partial	None	Peritoneum
2	M	66	1.68	0	1.15	54.9	None	CPT-11, CDDP	Lymph nodes[a]
3	M	56	1.72	0	1.32	79.7	Partial	5-FU	Peritoneum
4	M	67	1.60	0	1.14	86.5	Partial	None	Liver

[a]Lymph nodes along the common hepatic artery

Table 2. S-1 dose for pharmacokinetic study and subsequent treatment and toxicity

Patient no.	S-1 dose (mg)			No. of cycles	Toxicity (NCI-CTC grade)
	Single administration	Consecutive administration	Treatment		
1	40	50×2	50×1	0.5	Anemia (1), thrombocytopenia (1), GOT (1)
2	60	60×1	60×1	3	Total bilirubin (2), leukopenia (1), thrombocytopenia (1)
3	60	60×1	50×2	2	None
4	60	60×1	50×2	2	Anemia (1), neutropenia (2), GOT, GPT (1)

Discussion

Until recently, oral administration of fluoropyrimidines has not been widely accepted in the mainstream of treatment in spite of its convenience because of erratic intestinal absorption, unpredictable 5-FU plasma

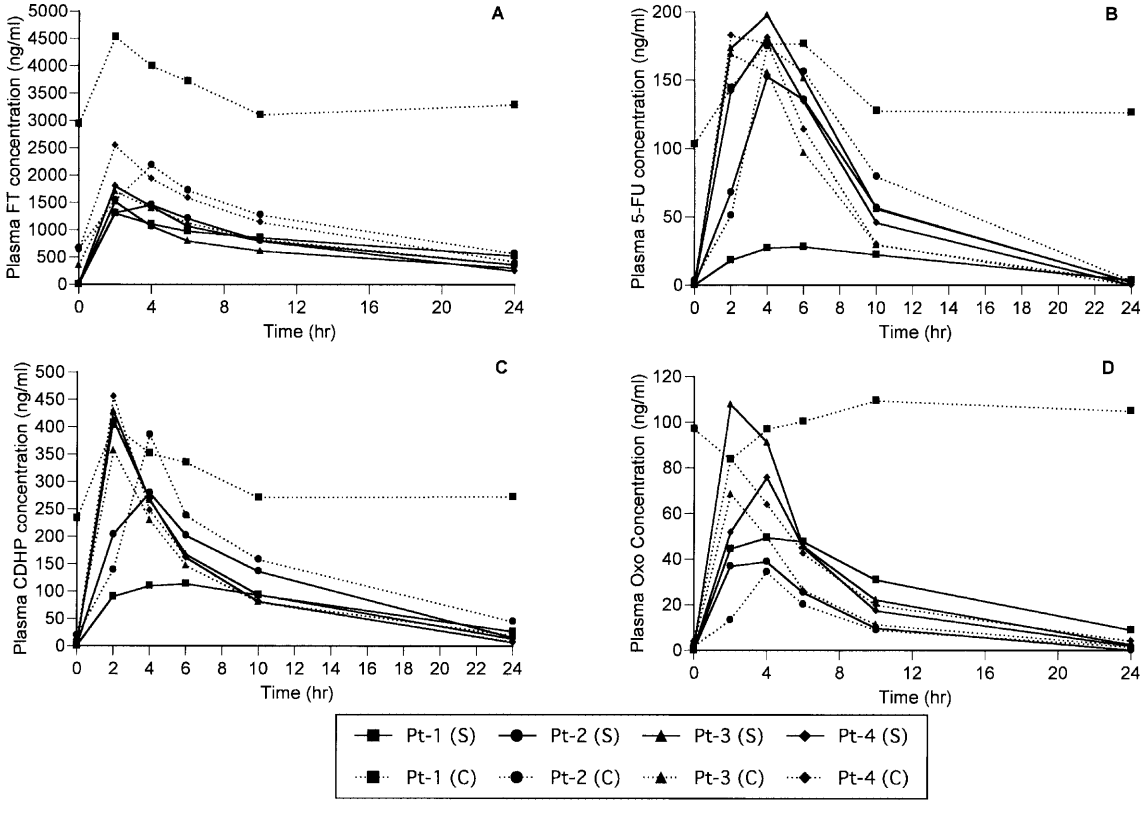

Fig. 4A–D. Plasma concentration-time curves of FT (**A**), 5-FU (**B**), CDHP (**C**), and Oxo (**D**). The *solid lines* show the pharmacokinetics in each patient after a single administration and the *dotted lines* show the pharmacokinetics after consecutive administrations

Table 3. S-1 pharmacokinetic data after single and 5-day consecutive administration (*NC* not calculated)

Administration	Drug	C_{max} (ng/ml)				T_{max} (h)				$AUC_{(0-\infty)}$ (ng·h/ml)				$T_{1/2}$ (h)			
		Patient 1	Patient 2	Patient 3	Patient 4	Patient 1	Patient 2	Patient 3	Patient 4	Patient 1	Patient 2	Patient 3	Patient 4	Patient 1	Patient 2	Patient 3	Patient 4
Single	FT	1304	1458	1516	1802	2	4	2	2	34,453	24,777	20,860	21,609	20.2	11.2	10.8	8.4
	5-FU	27.9	152.4	197.5	180.9	6	4	4	4	430.4	1,378.0	1,722.6	1,329.0	5.7	3.0	3.0	2.9
	CDHP	113.8	279.5	428.5	411.1	6	4	2	2	2,081.1	3,003.9	2,918.2	2,657.0	8.2	4.6	4.4	3.8
	Oxo	49.3	38.7	107.7	75.5	4	4	2	4	763.8	286.9	763.6	566.5	7.6	2.9	4.2	4.1
Consecutive	FT	4527	2185	1708	2546	2	4	2	2	110,088	38,190	26,040	33,197	16.2	11.6	10.5	9.4
	5-FU	176.6	174.6	169.2	182.6	4	4	2	2	3,089.7	1,673.7	1,233.4	1,215.1	8.5	3.1	2.9	2.2
	CDHP	403.1	385.9	357	456.0	2	4	2	2	9,285.6	4,003.3	2,679.0	2,715.5	15.3	7.6	5.3	4.1
	Oxo	109.3	34.2	68.3	83.8	10	4	2	2	NC	254.5	444.0	661.9	NC	5.0	5.3	5.4

concentration and toxicity, and subsequent uncertain antitumor activity. However, with the advent of S-1 which contains CDHP, a DPD inhibitor, oral treatment has achieved a higher level of acceptance. Oral drugs enable patients to receive treatment as outpatients, and therefore contribute to maintaining the patients' quality of life. S-1 has shown considerable antitumor activity in gastric and colorectal cancer [11, 17, 18]. We decided to investigate the pharmacokinetics of S-1 in patients with impaired renal function.

First we established an experimental renal failure model, and we demonstrated a decrease in 5-FU and CDHP plasma clearance in the presence of impaired renal function. There was a close correlation between plasma 5-FU, CDHP and CLcr, indicating the importance of renal function in the metabolism of S-1. In the clinical setting, the $T_{1/2}$ and the AUC of 5-FU in patients with renal impairment were longer and greater than in patients with normal renal function [9]. A significant difference was also observed in $T_{1/2}$ and the AUC of CDHP between single and consecutive administrations [9]. There was no difference in the pharmacokinetic parameters of Oxo between patients with impaired renal function and those with normal renal function. Therefore, in patients with impaired renal function, an increase in $T_{1/2}$ of 5-FU and CDHP was observed, confirming our hypothesis that retention of CDHP due to renal dysfunction leads to prolonged plasma 5-FU concentrations, and subsequent AUC increase. A post-marketing survey of S-1 in 3294 patients with advanced gastric cancer in Japan has demonstrated a close relationship between the incidence of grade 3 or worse hematological toxicities and renal function (Taiho Pharmaceuticals Company, data on file). Pharmacological studies of topotecan and lobaplatin in patients with impaired renal function have been conducted and plasma clearance of these drugs are significantly reduced requiring dose adjustment to prevent adverse events [16, 23].

In patient 1 given 50 mg of S-1 twice daily in the consecutive administration study, plasma concentrations of 5-FU and CDHP after a 5-day consecutive administration was far greater than we calculated, resulting in grade 3 thrombocytopenia. In this case, the $T_{1/2}$ values of 5-FU and CDHP were 5.7 h and 8.2 h, respectively, which were considerably longer than the values in patients with normal renal function [9]. In the consecutive administration study, the $T_{1/2}$ of 5-FU was 8.5 h and of CDHP was 15.3 h, which resulted in actual plasma 5-FU concentration much greater than we simulated. At the end of the consecutive administration study, the serum creatinine level was 1.86 mg/dl, suggesting the occurrence of additional renal dysfunction. Accumulated CDHP and 5-FU after a multiple dosing schedule may further interfere with the clearance of 5-FU. Therefore, we gave 50 mg S-1 once daily. 5-FU concentrations at 4, 6 and 24 h after administration of 50 mg S-1 were 19.0, 44.1 and 4.0 ng/ml, respectively, and no severe toxicity was observed. In patient 2, with mild renal dysfunction,

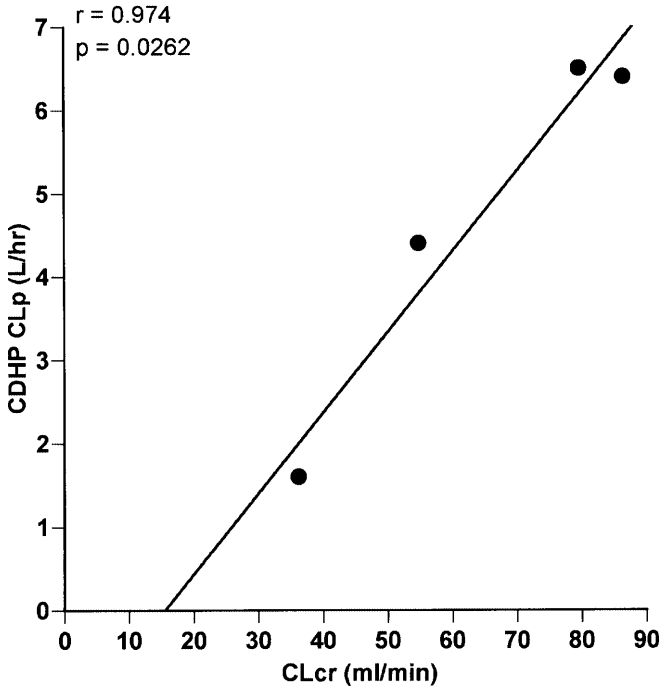

Fig. 5. Plot of clearance of CDHP (CDHP CLp) against creatinine clearance (CLcr) (*solid line* regression line). The coefficient of correlation (*r*) and the significance level (*P*) are shown

the $T_{1/2}$ values of 5-FU and CDHP with consecutive administration were 3.1 h and 7.6 h, respectively. A dose of 60 mg S-1 once daily was safely administered for three cycles without any severe side effects. For patients 3 and 4, S-1 was safely administered with dose reduction (from 60 mg twice daily to 50 mg twice daily).

There is a significant correlation between 5-FU plasma concentration, in particular the 5-FU AUC, and therapeutic activity and toxicity [6, 8, 13, 15, 19, 22]. Prospective trials of 5-FU dose adjustment based on 5-FU AUC have been conducted [4, 7]. These trials have shown good therapeutic tolerability in dose-adjusted groups, with a lower incidence of adverse events and good objective response rate. The 5-FU AUC after a single administration of S-1 at the recommended dose in Japanese and European studies were 723.9 ± 272.7 ng·h/ml (range 356.6–1145.9 ng·h/ml) and 1493.8 ± 418.7 ng·h/ml, respectively [9, 22]. The difference between the Japanese study and the European study may have been due to differences between Asian and Caucasian populations. The 5-FU AUC corresponding to a daily dose has been calculated to be at least about 1500 ng·h/ml (range 720–2300 ng·h/ml) for Japanese and 3000 ng·h/ml for Caucasians. In this study, the 5-FU $AUC_{(0–10\ h)}$ of patient 1 was 1528.7 ng·h/ml resulting in grade 3 thrombocytopenia. The calculated 5-FU $AUC_{(0–24\ h)}$ values with the treatment dose for the four patients in this study were 2580.8, 1659.4, 2229.9, 2406.2 ng·h/ml, respectively. Therefore, even in patients with impaired renal function, S-1 can be safely given by dose adjustment aiming at a 5-FU $AUC_{(0–24\ h)}$ between 1500 and 2300 ng·h/ml for Japanese without sacrificing tumor-killing activity.

Plasma FT clearance was not affected by renal function in experimental renal failure. The pharmacokinetic parameters of FT in these four patients were also comparable to those reported in patients with normal renal function [9]. Oxo is an inhibitor of orotate phosphoribosyltransferase and a protector against 5-FU-induced gastrointestinal toxicity. Plasma Oxo clearance was dependent on renal function in experimental renal failure, so elevation of plasma Oxo concentration may reduce the antitumor activity of S-1, although Oxo is preferentially distributed in the gastrointestinal tract after oral administration [20]. However, pharmacokinetic parameters of Oxo in four

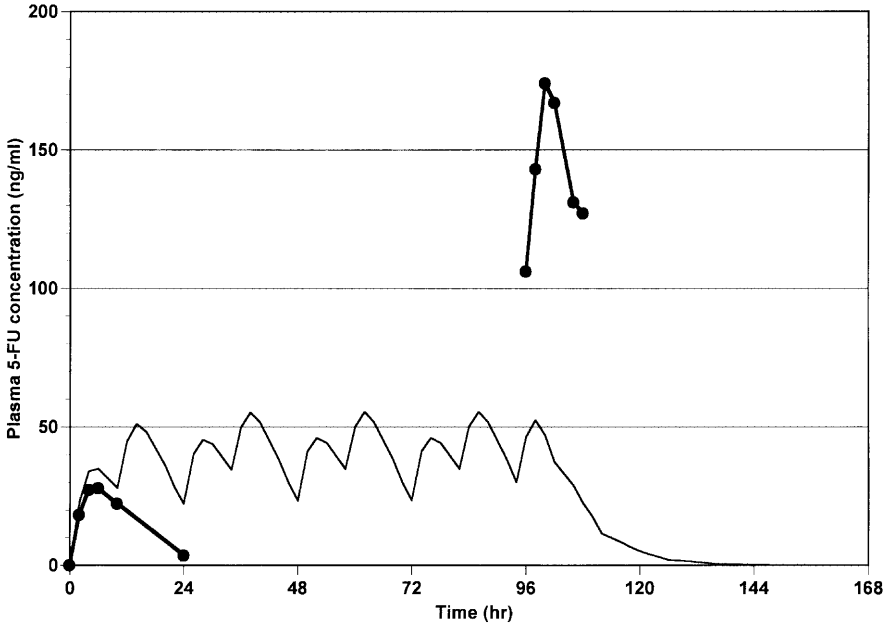

Fig. 6. Simulation curve of plasma 5-FU concentration prepared based on the single administration study (S-1 40 mg), and actual 5-FU concentration after consecutive administration (S-1 50 mg×2). The *closed circles connected with solid lines* indicate the actual 5-FU concentrations after a single and consecutive administrations of S-1, and the *solid line with no data points* indicates simulated 5-FU concentrations with 50 mg of S-1 twice daily

patients with renal dysfunction were not different from the data obtained in patients with normal renal function, suggesting that the effect on antitumor activity of renal impairment affecting the Oxo concentration is negligible.

In conclusion, we demonstrated higher and longer 5-FU concentration and subsequent AUC increases in an experimental renal failure model and in patients with renal impairment due to the retention of CDHP. Individual dose adjustment with pharmacokinetic monitoring would be useful in patients with impaired renal function. A formal S-1 organ dysfunction study must be conducted in larger numbers of patients with moderately or even severely impaired renal function in order to obtain clinically useful dosing recommendations.

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