

Pharmacokinetic Study of S-1, a Novel Oral Fluorouracil Antitumor Drug

Koichi Hirata,¹ Noboru Horikoshi, Keisuke Aiba, Minoru Okazaki, Ryuichi Denno, Kazuaki Sasaki, Yasuyuki Nakano, Hikaru Ishizuka, Yasuhide Yamada, Shinji Uno, Tetsuo Taguchi, and Tetsuhiko Shirasaka

Department of Surgery I, Sapporo Medical University, Sapporo 060-8556 [K. H., M. O., R. D., K. S.]; Chemotherapy Cancer Center, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Tokyo 170-8455 [N. H., K. A., Y. N., H. I., Y. Y., S. U.]; Japan Society for Cancer Chemotherapy, Osaka 550-0002 [T. T.]; and Institute for Pathogenic Biochemistry in Medicine, Taiho Pharmaceutical Co., Ltd., Tokyo 101-0054 [T. S.], Japan

ABSTRACT

S-1 is a novel oral fluorouracil antitumor drug that combines three pharmacological agents: tegafur (FT), which is a prodrug of 5-fluorouracil (5-FU); 5-chloro-2,4-dihydropyridine (CDHP), which inhibits dihydropyrimidine dehydrogenase (DPD) activity; and potassium oxonate (Oxo), which reduces gastrointestinal toxicity. Phase I and early Phase II clinical trials have already been completed. On the basis of the results of these trials, 80 mg/m²/day, given daily in two divided doses after breakfast and supper, a 28-day consecutive oral regimen is recommended. In this study, we investigated the pharmacokinetics of 5-FU, intact FT, CDHP, and Oxo, after administration of S-1, at a standard dose of 80 mg/m²/day, in advanced cancer patients. Twelve patients were recruited to the study; 5 patients with gastric cancer, 4 with colorectal cancer, and 3 with breast cancer. Among them, analysis was conducted on 12 patients for single administration and on 10 patients for consecutive administration. The initial dose of S-1 for each patient was determined according to his/her body surface area (BSA) as follows: for BSA < 1.25 m², 80 mg/body/day; for 1.25 m² ≤ BSA < 1.5 m², 100 mg/day; and for 1.5 m² ≤ BSA, 120 mg/day. For single administration, half of the standard dose was used. For 28-day consecutive administration, the standard dose was given daily in two divided doses. The average single dose per BSA was 35.9 mg/m² (31.7–39.7 mg/m²). Pharmacokinetic parameters of plasma 5-FU were as follows: C_{max}, 128.5 ± 41.5 ng/ml; T_{max}, 3.5 ± 1.7 h; AUC_{0–14},

723.9 ± 272.7 ng · h/ml; and T_{1/2}, 1.9 ± 0.4 h. In the 28-day consecutive regimen, there were no fluctuations in pharmacokinetics nor any drug accumulation. Because the pharmacokinetics of orally administered S-1 is almost similar to that of continuous i.v. infusion of 5-FU, we concluded that S-1 may improve patients' quality of life.

INTRODUCTION

Since Heidelberger *et al.* (1) reported 5-fluorouracil (5-FU)² in 1957, biochemical and pharmacokinetic studies of 5-FU have been widely conducted to examine means of reinforcing its efficacy and its regimen (2). Although long-term continuous i.v. regimens of 5-FU (5-FU/CVI) are reported to be efficacious (3–5), the 5-FU concentration in plasma varies with significant disparities, and no consistent conclusion can be obtained (6–8). DPD (EC1.3.1.2), a 5-FU catabolizing enzyme, is considered to contribute to the disparities (9–11). Because of this catabolism, ~90% of dosed 5-FU is metabolized mainly to α-fluoro-β-alanine, preventing exertion of its antitumor effect (9). In addition, the circadian rhythm of DPD activity within a 24-h period may influence the catabolism of 5-FU (10, 11). Furthermore, DPD activity varies up to 100-fold, depending on the particular human cancer cells, and it might be one of the main factors that affect the sensitivity of tumors to 5-FU (12). The dose-limiting toxicities in the 5-FU/CVI method are mucositis and diarrhea (3). Animal experiments have indicated that these toxicities are induced by phosphoribosylation of 5-FU by orotate phosphoribosyltransferase (EC2.4.2.10) in the digestive tract (13), which may be a factor affecting safety in the 5-FU/CVI method.

Development of oral fluorouracil antitumor drugs started in Japan in 1971, paying attention to the fact that 5-FU acts in a time-dependent manner (14). Oral drugs enable patients to receive treatment as outpatients, and they are suitable for maintaining patients' quality of life. Presently, such medicines as UFT and 5'-deoxy-5-fluorouridine are widely used in Japan for the treatment of various cancers, such as gastrointestinal and breast cancers (15, 16). Recently, studies of UFT + leucovorin and Capecitabine have been reported in the United States (17, 18). Thus, treatment by oral administration has been highlighted (19, 20).

S-1 is a novel oral fluorouracil formulation, consisting of FT, CDHP, and Oxo, in a molar ratio of 1:0.4:1 (21, 22). As shown in Fig. 1, this drug was developed to improve the tumor-selective toxicity of 5-FU by means of modulating the action by CDHP, which is a DPD inhibitor, and Oxo, which is an orotate

Received 3/2/99; revised 5/11/99; accepted 5/14/99.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

¹ To whom requests for reprints should be addressed, at Department of Surgery I, Sapporo Medical University, 16 Nishi, Minami-Ichijyo, Chuo-ku, Sapporo 060-8556, Japan. Phone: 81-11-611-2111; Fax: 81-11-613-1678.

² The abbreviations used are: 5-FU, 5-fluorouracil; CVI, continuous i.v.; DPD, dihydropyrimidine dehydrogenase; FT, tegafur; UFT, uracil-tegafur; CDHP, 5-chloro-2,4-dihydropyridine; Oxo, potassium oxonate; Ura, uracil; BSA, body surface area; PK, pharmacokinetic; CV, coefficient of variation; EU, Eniluracil.

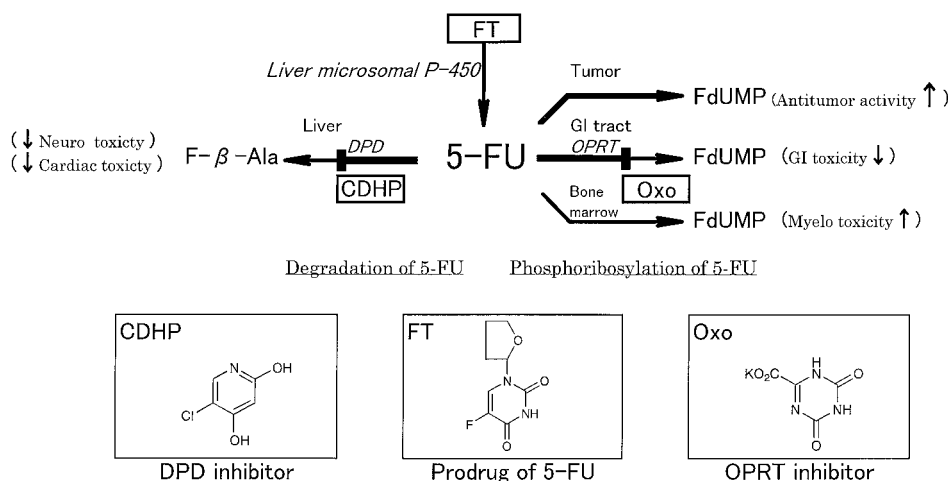


Fig. 1 Biochemical action and chemical structure of S-1 (FT + CDHP + Oxo).

phosphoribosyltransferase inhibitor, maintaining prolonged efficacious 5-FU concentrations in the blood and reducing the toxicity to the gastrointestinal tract (23). CDHP has 180-fold higher DPD inhibitory activity than that of Ura *in vitro* (24). It has been confirmed that a high blood level of 5-FU is retained when CDHP is combined with FT, a prodrug of 5-FU (22). As for Oxo, animal experiments revealed that the output of FUMP and 5-FU incorporated into RNA decreased by ~70% only in the small intestine, whereas the output decreased by 0–20% in bone marrow and tumor regions (25). This suggests that Oxo is distributed at high levels in the digestive tract after oral administration, leading to relief of gastrointestinal toxicity induced by 5-FU.

Phase I and early Phase II studies of S-1 have already been conducted in Japan (26, 27) and are ongoing in Europe and United States. In the clinical Phase I study, once-daily and twice-daily administration schedules were carried out for 28 consecutive days. The maximum allowable dose is from 150 to 200 mg/body/day for once-daily administration or from 75 to 100 mg/body/day for twice-daily administration. The dose-limiting factor in both schedule was bone marrow suppression, mainly leucopenia. Adverse reactions other than bone marrow suppression, which caused drug discontinuation, were rash and vomiting. Diarrhea and stomatitis were not severe, grade 1, therefore administration could be continued except for one patient at 200 mg/body/day (26). Pharmacokinetics was studied at 25, 50, 100, 150, and 200 mg/body. The results revealed that intact S-1 after single administration showed linearity, and that increase of both the maximum plasma concentration and the area under the curve of 5-FU, the active metabolite, depended on their dosage. On the basis of these results, it was concluded that the recommended dosage for the early Phase II study was 75 mg/body twice daily for 28 consecutive days, followed by a 14-day rest (1 course) (Ref. 26).

The early Phase II study was conducted with the regimen of 50 or 75 mg/body, twice daily for 28 consecutive days, followed by a 14-day rest (27). The response rate was 53.6% (15 of 28) for recurrent gastric cancer and 16.7% (5 of 30) for advanced colorectal cancer. Main adverse reactions were gastrointestinal symptoms and bone marrow suppression, and the

incidence of adverse reactions of grades 3 or severer was 35.7% (10 of 28). The incidence of drug discontinuation due to the occurrence of adverse reactions was obviously lower in patients at 90 mg/m²/day or less. Therefore, the recommended dose for the late Phase II study is determined to be 80 mg/m²/day.

We carried out a pharmacokinetic study of 5-FU, intact FT, CDHP, and Oxo, obtained after administration of S-1 at 40 and 80 mg/m²/day for one dose, and we also investigated Ura to confirm the inhibitory effect of CDHP on DPD and its reversibility.

PATIENTS AND METHODS

Substance. S-1 capsule, containing FT, CDHP, and Oxo in a molar ratio of 1:0.4:1, was supplied by Taiho Pharmaceutical Co., Ltd. In this study, two types of capsules were used, one containing 20 mg of FT and another containing 25 mg of FT.

Patients. Twelve patients, 5 males and 7 females, were recruited to this study. Ages were between 44 and 69 years (median, 54 years). All patients had advanced solid tumors: 5 patients had gastric cancer, 3 had breast cancer, and 4 had colorectal cancer. All of the subjects had cancers with evaluable lesions. Each patient gave informed consent prior to participation in the study. Patients who were thought to have carry-over effects of prior surgery, chemotherapy, or radiation therapy were excluded. Additional criteria included adequate marrow; liver, heart, lung, and renal functions (hemoglobin \geq 9.0 g/dl; WBCs \geq 4000/mm³ but <12,000/mm³; platelets \geq 10 \times 10⁴/mm³; total bilirubin <1.5 mg/dl; GOT \cdot GPT < 40 units; Al-P < 2 \times the upper limit of normal range adopted by the institute; creatinine less than or equal to the upper limit of normal range); and performance status of 0–2.

Study Plan. Single administration was carried out and then 28-day consecutive administration was carried out after a 7-day rest to collect blood and urine samples. Twelve patients were selected for single administration, and 10 patients were selected for 28-day consecutive regimen. The doses were determined according to BSA; a standard dose was 80 mg/m²/day, and one dose was 40 mg/m². In the single administration study, the drug was administered within 30 min after breakfast, at a

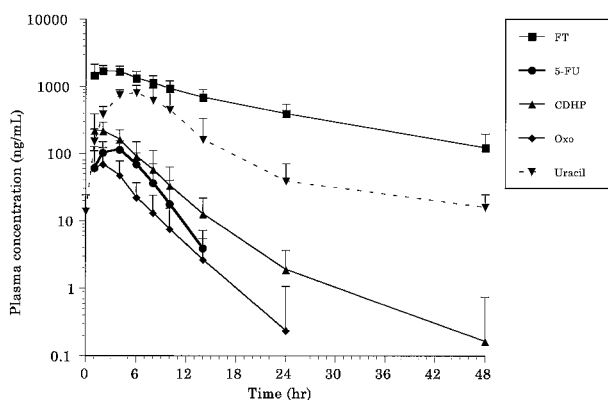


Fig. 2 Plasma concentration of FT, 5-FU, CDHP, Oxo, and uracil after single administration of S-1. Bars, S.D.

dose of 40 mg (20 mg \times two capsules) for BSA <1.25 m² 50 mg (25 mg \times two capsules) for 1.25 m² \leq BSA < 1.50 m², and 60 mg (20 mg \times three capsules) for BSA >1.50 m². In the consecutive day administration, the same daily dose used in single administration was administered twice daily (divided into two portions), given after breakfast and after the evening meal, for 28 consecutive days. On Day 28, the drug was administered only once, after breakfast. The times of drug administration were 8:00–9:00 a.m. in the morning and 5:30–7:00 p.m. in the evening. The average single dose per BSA was 35.9 mg/m² (31.7–39.7 mg/m²), not exceeding 40 mg/m².

Sample Collection. In the single administration, the blood samples were drawn on day 1, before administration, and at 1, 2, 4, 6, 8, 10, 14, 24, and 48 h after administration. In the 28-day consecutive administration, blood was drawn on days 1, 7, and 14, before administration, and at 4 h after administration in the morning and in the evening and on Day 28, before administration in the morning and at 1, 2, 4, 6, 8, 10, 14, 24, and 48 h after the last administration. Peripheral blood samples were collected into a heparinized tube at a volume of 6 ml at each sampling time and centrifuged at 3000 rpm for 15 min at 5°C; plasma was stored at -20°C . Urine was collected and pooled during the period of 12 h on the day before administration and on days 1, 2, and 3; the total volume of each sample was measured. Each of 8 ml of mixed pooled urine was stored at -20°C .

Drug Assay. Analysis of FT, 5-FU, CDHP, Oxo, and Uracil was conducted according to the method by Matsushima *et al.* (28). FT was extracted with dichloromethane from each sample and analyzed using HPLC equipped with a UV absorption spectrometer. 5-FU, CDHP, and Ura were extracted with ethyl acetate from the residue obtained after dichloromethane extraction, and pentafluorobenzyl derivatives were prepared. 5-FU and CDHP were analyzed using a negative ion chemical ionization-gas chromatograph/mass spectrometer, and Ura was assayed using electron impact ionization gas chromatography/mass spectrometry. Oxo was separately extracted from the samples using a solid extraction column; then it was decarbonated, prepared into a pentafluorobenzyl derivative, and assayed using negative ion chemical ionization-gas chromatograph/mass spectrometry. For the analysis of CDHP, Oxo, 5-FU, and Ura by gas

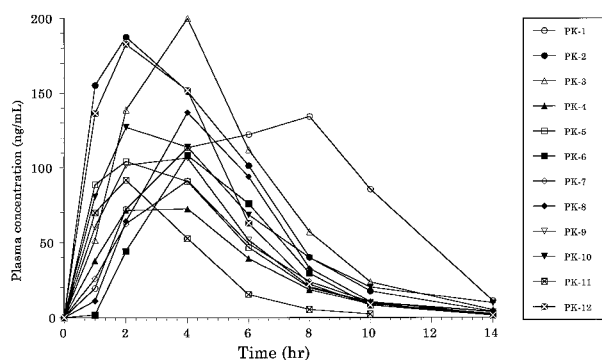


Fig. 3 Plasma concentration of 5-FU after single administration of S-1.

chromatography/mass spectrometry, a stable isotope for each compound was used as an internal reference. The measurable ranges of plasma levels were 10–4000 ng/ml for FT, 1–400 ng/ml for 5-FU, 2–800 ng/ml for CDHP, 1–200 ng/ml for Oxo, and 5–2000 ng/ml for Ura; and the measurable region of urine levels was 10-fold wider than that of plasma in each compound. The samples at high concentrations, exceeding the assay range, were appropriately diluted before analysis.

PK Parameters. PK parameters, the maximum plasma concentration (C_{\max}), the maximum plasma concentration time (T_{\max}), the area under the curve (AUC), and the half-life ($T_{1/2}$) were calculated, using plasma levels obtained from 10 samples in the single administration study or the last 10 samples in the consecutive day administration study in each patient. PK parameters were calculated according to the noncompartment method, using a program renewed in FORTRAN based on the program by Yamaoka and Tanigawa (29), validated by comparison with the Nonlin results. The values were expressed as the mean \pm SD for 12 cases of single administration and for 10 cases of consecutive day administration. Measured values of plasma levels of consecutive day administration were plotted on a simulation curve, prepared based on the single administration results. The estimated number of days required to reach steady state, the number of days when the plasma level reached $>95\%$ of the estimated steady state obtained by simulation, is indicated.

RESULTS

Pharmacokinetics of 5-FU after Single Administration.

Fig. 2 shows changes in the plasma 5-FU level in a log scale, and Fig. 3 shows those of 12 patients in a normal scale. The mean plasma levels of 5-FU at 2, 4, 6, 8, and 10 h are 104.0 ± 46.7 , 115.7 ± 39.6 , 69.9 ± 32.2 , 37.0 ± 33.4 , and 17.9 ± 22.1 ng/ml, respectively. PK parameters of 5-FU in plasma are shown in Table 1. The ranges and CVs for C_{\max} and AUC were 72.5–199.8 ng/ml, 32.3% and 356.6–1145.9 ng \cdot h/ml, 37.7%, respectively.

Pharmacokinetics of FT, CDHP, and Oxo after Single Administration.

Fig. 2 shows changes in the plasma level of FT, CDHP, and Oxo. PK parameters of FT, CDHP and Oxo are shown in Table 1. The CVs for C_{\max} and AUC were 13.6 and 27.5% for FT, 41.0 and 41.8% for CDHP, and 74.6 and 68.0% for Oxo, respectively.

Table 1 PK parameters after single and 28-day consecutive administration

	C_{\max} (ng/ml)	T_{\max} (h)	AUC^a (ng · h/ml)	$T_{1/2}$
Single administration ($n = 12$)				
FT	1971.0 ± 269.0	2.4 ± 1.2	28216.9 ± 7771.4	13.1 ± 3.1
5-FU	128.5 ± 41.5	3.5 ± 1.7	723.9 ± 272.7	1.9 ± 0.4
CDHP	284.6 ± 116.6	2.1 ± 1.2	1372.2 ± 573.7	3.0 ± 0.5
Oxo	78.0 ± 58.2	2.3 ± 1.1	365.7 ± 248.6	3.0 ± 1.4
Uracil	889.9 ± 259.4	5.3 ± 1.8	8483.3 ± 3858.9	3.0 ± 1.3
28-day consecutive administration ($n = 10$)				
FT	4166.2 ± 833.9	3.0 ± 1.8	80031.5 ± 20993.2	16.2 ± 2.4
5-FU	113.7 ± 40.5	3.4 ± 1.3	609.0 ± 170.2	2.9 ± 1.1
CDHP	276.0 ± 141.8	2.6 ± 1.8	1364.0 ± 351.6	4.2 ± 1.4
Oxo	129.5 ± 190.0	2.6 ± 2.1	549.9 ± 499.5	5.0 ± 2.5
Uracil	701.3 ± 179.5	5.4 ± 1.3	6085.8 ± 2079.7	2.8 ± 0.6

^a FT and CDHP, AUC_{0-48} ; 5-FU, AUC_{0-14} ; Oxo, AUC_{0-24} .

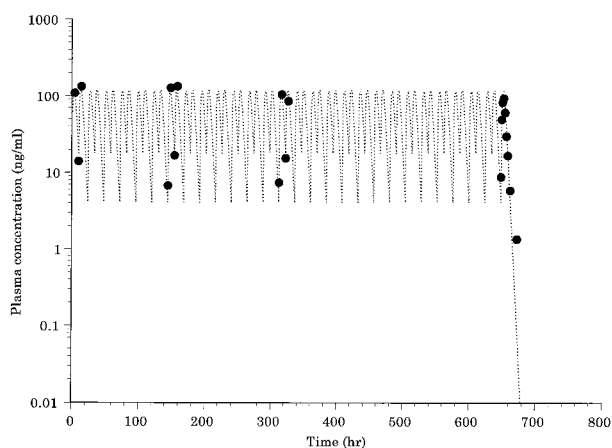


Fig. 4 Plasma concentration of 5-FU after 28-day consecutive administration of 5-FU.

Pharmacokinetics of Ura after Single Administration.

Fig. 2 shows changes in the plasma level of Ura. Although Ura is not a metabolite of S-1, the plasma level of Ura before administration is 13.8 ± 10.3 ng/ml. It increases after administration; however, at 48 h, it returns to 16.0 ± 8.5 ng/ml. PK parameters of Ura are shown in Table 1.

Pharmacokinetics after Consecutive Day Administration.

Fig. 4 shows plasma 5-FU levels measured on days 1, 7, 14, and 28 and a simulation curve prepared based on the results of the single administration study. The values of FT, CDHP, Oxo, or Ura nearly coincide with the values based on the results of the single administration study. PK parameters obtained after the final administration are shown in Table 1. Excluding FT, which has a long half-life, each parameter nearly coincides with that obtained after single administration. It was estimated that ~4 days would be required to reach the steady state for FT, 2 days for 5-FU, CDHP, and Oxo, and 3 days for Ura.

Urinary Excretion Rate. Urinary excretion within 12 h after administration of 5-FU was 47.4% for CDHP, 4.4% for FT, 7.0% for 5-FU, and 1.9% for Oxo. Urinary excretion within 72 h was 52.8% for CDHP, 7.8% for FT, 7.4% for 5-FU, and 2.2% for Oxo, indicating that urinary excretion was nearly completed by 12 h.

Influence of Gastrectomy. In the single administration study, we compared the PK parameters of 5-FU between the patients who underwent total gastrectomy (PK-2, PK-5, and PK-10 in Fig. 3) and those who did not. In the gastrectomy group, C_{\max} , T_{\max} , AUC_{0-14} , and $T_{1/2}$ are 139.5 ± 43.0 ng/ml, 2.0 ± 0.0 h, 822.8 ± 246.0 ng · h/ml and 2.1 ± 0.6 h, respectively. In the nongastrectomy group, they are 124.9 ± 43.0 ng/ml, 4.0 ± 1.7 h, 691.0 ± 286.8 ng · h/ml, and 1.8 ± 0.4 h, respectively.

Toxicity and Antitumor Effect. Three patients (PK-1, PK-2, and PK-7 in Fig. 3) encountered grade 3–4 adverse drug reactions. Two patients encountered grade 3 and 4 anemia, and one patient encountered grade 3 neutropenia. Tumor regression >50% were observed in four patients (PK-4, PK-6, PK-7, and PK-12 in Fig. 3). Both toxicity and antitumor effect have no correlation with C_{\max} and AUC of 5-FU.

DISCUSSION

5-FU, which is classified as an antimetabolite, exerts its activity only after its incorporation into tumor cells. In the PK analysis of 5-FU levels in human tumor cells using ¹⁹F-labeled nuclear magnetic resonance, it has been reported that pharmacokinetics in blood correlates with those in target tumors (30). Therefore, measuring the plasma 5-FU level is important for effects and safety. In clinical studies, there is a correlation between the AUC of 5-FU and the response (31) or toxicity (32), and the nontoxic concentration of 5-FU is determined to be 1.5 μ M, or 195 ng/ml, or less, because the steady-state concentration (C_{ss}) of 5-FU correlated with incidence of leukopenia (33).

The plasma 5-FU level in 5-FU/CVI varies by report (6–8, 34). Thus, when the dose range of 5-FU was 190–600 mg/m²/day, C_{ss} of 5-FU was 10–25000 ng/ml and AUC_{0-24} of 5-FU was 217–6600 ng · h/ml, whereas these are derived from the action of DPD, a catabolizing enzyme for 5-FU (9, 10). C_{\max} of 5-FU in single administration of S-1 was 128.5 ± 41.5 ng/ml (72.5–199.8 ng/ml), and AUC_{0-14} was 723.9 ± 272.7 ng · h/ml (356.6–1145.9 ng · h/ml). When S-1 was administered twice daily, AUC corresponding to a daily dose of S-1 was calculated to be 1447.8 ng · h/m. It is suggested that the C_{\max} and AUC of S-1 correspond to that of 5-FU administered at 300 mg/m²/day, and that the range of the plasma 5-FU level after administration of S-1 is narrower than that of CVI treatment, although S-1 is

administered orally. We concluded that exactly the combination of a DPD inhibitor makes the width of variation of the plasma 5-FU level narrower.

Pharmacokinetic studies of UFT, and 5-FU + Eniluracil (5-FU · EU), which contain DPD inhibitors, have already been conducted (34–36). When UFT at 370 mg/m² (as the amount of FT) was administered orally, C_{\max} and AUC_{0-8} of 5-FU were 265 ng/ml and 338 ng · h/ml, respectively (34). When 5-FU · EU were orally administered at 20 mg/m²/day (as the amount of 5-FU), C_{\max} and AUC_{0-24} of 5-FU were 1037.7 and 7700 ng · h/ml, respectively (35). These PK parameters are obviously different from those of S-1. The differences in C_{\max} and AUC of 5-FU were considered to be due to the difference in the inhibitory effect of DPD. The DPD inhibitory activity increases in the order of Ura, CDHP, and EU. Furthermore, their characteristics are different. CDHP is reversible, and EU is irreversible. The intensity of the DPD inhibitory activity may affect C_{\max} and AUC . Besides, it may affect the CVs for the AUC of 5-FU. In fact, the CV values of UFT, S-1, and 5-FU · EU were 65, 35, and 20%, respectively. Also, the DPD inhibitory activity is considered to affect the PK parameter of 5-FU, especially $T_{1/2}$. $T_{1/2}$ of each compound was 0.22 h for i.v. administration of 5-FU alone, 0.34 h (α -phase) for UFT, 1.9 h for S-1, and 6.1 h for 5-FU · EU (9, 34, 35). On the other hand, T_{\max} was 1.1 h for UFT, 3.5 h for S-1, and 0.76 h for 5-FU · EU. The varied values suggest that the slow-releasing effect of FT may be involved, besides the DPD inhibition activity. This means that the ratio of duration, in which the 5-FU plasma level is within a certain range (e.g., 50–200 ng/ml), is higher for S-1 in comparison with other drugs, when consecutive oral administration was used, and that the combination of CDHP and FT was successful to allow an effect similar to that of long-term 5-FU/CVI treatment to be obtained. In addition, because the T_{\max} and $T_{1/2}$ of CDHP were similar to those of 5-FU or Oxo, it is suggested that the combination of FT, CDHP, and Oxo as an oral drug is an exquisite method, from the viewpoint of PK parameters.

The plasma FT level after single administration of S-1 was 1971 ng/ml or 2.0 μ g/ml. In the Phase I/II studies of single administration of UFT alone and FT alone at 300 mg/body, the plasma FT level was 13.7 and 12.3 μ g/ml, respectively (37), which are ~6-fold higher against that of FT after administration of S-1. Because an average dose of S-1 (as FT) was 35.9 mg/m², or 50 mg/body, was about 6-fold against that of UFT and FT, the value of the plasma FT level after administration of S-1 is appropriate. On the other hand, the AUC of 5-FU after administration of S-1 was larger than that of UFT; however, the plasma FT level of S-1 was one-sixth of that of UFT. This means that S-1 is more effective than UFT, and that the incidence of adverse reactions, induced by decomposition products of FT or 5-FU, becomes smaller.

However, ~50% of CDHP is excreted into urine, indicating that renal function may directly affect the activity of S-1. Therefore, CDHP may remain in the body if renal function is impaired, and an increase in the plasma 5-FU level will be induced by a DPD inhibitory effect of CDHP after consecutive-day administration. It may lead to the occurrence of severe adverse events. Considering that S-1 is to be administered to patients with cancer, physical examinations at regular intervals, including examination of renal function, will be necessary.

Ura is present in blood as an *in vivo* constituent (shown in Fig. 2). After the administration of S-1, which contains CDHP, the plasma level of Ura attained a C_{\max} of 0.8 μ g/ml at 5 h and disappeared thereafter at $T_{1/2}$ of 3 h. From this fact, it may be confirmed that there is a DPD inhibitory activity of CDHP; the effect is reversible. In UFT, Ura is combined as a competitive inhibitor of DPD. The C_{\max} and $T_{1/2}$ of Ura of UFT were 3.0 μ g/ml and 0.5 h, respectively (37), showing a large difference from Ura's behavior after administration of S-1. This suggests that Ura produced by DPD inhibition with CDHP has little influence on the plasma 5-FU level of S-1.

If Oxo is present in the plasma, it may reduce the antitumor effect by inhibiting the phosphorylation of 5-FU in tumors. In animal experiments, [¹⁴C]Oxo was not detectable in tumors after oral administration at 10 mg/kg, although it was 0.8 nmol/g in plasma (25). It is suggested that the plasma Oxo level observed in this study has little effect.

We found that the influence of gastrectomy was small, but there were small numbers of patients; therefore, we believe that we do not need to take patients' prior gastrectomy into account for administration of S-1. Regarding pharmacodynamics, both toxicity and antitumor effect have no correlation with C_{\max} and T_{\max} of 5-FU.

From these observations, it was pharmacokinetically demonstrated that S-1 is not only an oral drug that shows a similar effect to that of long-term treatment by 5-FU/CVI but is also a next-generation drug with a self-rescuing character. Additional pharmacokinetic studies on interaction with other antitumor drugs will be necessary in the future.

ACKNOWLEDGMENTS

We thank A. Hamajima, K. Izuka, T. Hayakawa, M. Kimura, and H. Yamashita for assistance in data collection. We also thank K. Ikeda, J. Chikamoto, K. Yoshida, Y. Kusumoto, A. Urakawa, E. Matsushima, Y. Yamamoto, and S. Nagayama for collaboration with the measurement and analysis of samples.

REFERENCES

- Heidelberg, C., Chaudhuri, N. K., Danneberg, P., Mooren, D., Griesbach, L., Duschinsky, R., Schnitzer, R. J., Plevin, E., and Scheiner, J. Fluorinated pyrimidines, a new class of tumour-inhibitory compounds. *Nature (Lond.)*, 179: 663–666, 1957.
- Pinedo, H. M., and Peters, G. F. Fluorouracil: biochemistry and pharmacology. *J. Clin. Oncol.*, 6: 1653–1664, 1988.
- Vogelzang, N. J. Continuous infusion chemotherapy: a critical review. *J. Clin. Oncol.*, 2: 1289–1304, 1984.
- Lokich, J. J., Ahlgren, J. D., Gullo, J. J., Philips, J. A., and Fryer, J. G. A prospective randomized comparison of continuous infusion fluorouracil with a conventional bolus schedule in metastatic colorectal carcinoma: a Mid-Atlantic Oncology Program study. *J. Clin. Oncol.*, 7: 425–432, 1989.
- The meta-analysis group in cancer. Efficacy of intravenous continuous infusion of fluorouracil compared with bolus administration in advanced colorectal cancer. *J. Clin. Oncol.*, 16: 301–308, 1998.
- Yoshida, T., Araki, E., Iigo, M., Fujii, T., Yoshino, M., Shimada, Y., Saito, D., Tajiri, H., Yamaguchi, H., Yoshida, S., Yoshino, M., Ohkura, H., Yoshimori, M., and Okazaki, N. Clinical significance of monitoring serum levels of 5-fluorouracil by continuous infusion in patients with advanced colonic cancer. *Cancer Chemother. Pharmacol.*, 26: 352–354, 1990.
- Trump, D. L., Egorin, M. J., Forrest, A., Willson, J. K. V., Remick, S., and Tutsch, K. D. Pharmacokinetic and pharmacodynamic analysis

- of fluorouracil during 72-hour continuous infusion with and without dipyridamole. *J. Clin. Oncol.*, 9: 2027–2035, 1991.
8. Findlay, M. P. N., Raynaud, F., Cunningham, D., Iveson, A., Collins, D. J., and Leach, M. O. Measurement of plasma 5-fluorouracil by high-performance liquid chromatography with comparison of results tissue drug levels observed using *in vivo* ¹⁹F magnetic resonance spectroscopy in patients on a protracted venous infusion with or without interferon- α . *Ann. Oncol.*, 7: 47–53, 1996.
 9. Heggie, G. D., Sommadossi, J., Cross, D. S., Huster, W. J., and Diasio, R. B. Clinical pharmacokinetics of 5-fluorouracil and its metabolites in plasma, urine, and bile. *Cancer Res.*, 47: 2203–2206, 1987.
 10. Harris, B. E., Song, R., Soong, S., and Diasio, R. B. Relationship between dihydropyrimidine dehydrogenase activity and plasma 5-fluorouracil levels with evidence for circadian variation of enzyme activity and plasma drug levels in cancer patients receiving 5-fluorouracil by protracted continuous infusion. *Cancer Res.*, 50: 197–201, 1990.
 11. Zhang, R., Lu, Z., Liu, T., Soong, S., and Diasio, R. B. Relationship between circadian-dependent toxicity of 5-fluorodeoxyuridine and circadian rhythms of pyrimidine enzymes: possible relevance to fluoropyrimidine chemotherapy. *Cancer Res.*, 53: 2816–2822, 1993.
 12. Beck, A., Etienne, M. C., Cheradame, S., Fischel, J. L., Formento, P., Renee, N., and G. Milano. A role for dihydropyrimidine dehydrogenase and thymidylate synthase in tumour sensitivity to fluorouracil. *Eur. J. Cancer*, 30A: 1517–1522, 1994.
 13. Houghton, J. A., Houghton, P. J., and Wooten, R. S. Mechanism of induction of gastrointestinal toxicity in the mouse by 5-fluorouracil, 5-fluorouridine, and 5-fluoro-2'-deoxyuridine. *Cancer Res.*, 39: 2406–2413, 1979.
 14. Unemi, N., Harima, K., Daidai, Y., Fujiwara, H., and Fujii, S. Experimental studies of N^1 -(2'-tetrahydrofuryl)-5-fluorouracil (FT-207). *Gan No Rinsho*, 17: 731–742, 1971.
 15. Ota, K., Taguchi, T., and Kimura, K. Report on nationwide pooled data and cohort investigation in UFT phase II study. *Cancer Chemother. Pharmacol.*, 22: 333–338, 1988.
 16. Ota, K. Multicentre cooperative phase II study of 5'-deoxy-5-fluorouridine in the treatment of colorectal cancer. *J. Int. Med. Res.*, 16 (Suppl. 2): 19B–20B, 1988.
 17. Pazdur, R., Lassere, Y., Rhodes, V., Ajani, J. A., Sugarman, S. M., Patt, Y. Z., Jones D. V., Jr., Markowitz, A. B., Abbruzzese, J. L., Bready, B., and Levin, B. Phase II trial of uracil and tegafur plus oral leucovorin: an effective oral regimen in the treatment of metastatic colorectal carcinoma. *J. Clin. Oncol.*, 12: 2296–2300, 1994.
 18. Findlay, M., Cutsem, E. V., Kocha, W., Allman, D., Laffranchi, B., Griffin, T., Osterwalder B., Dalley D., Pazdur R., and Verweij, J. A randomised Phase II study of Xeloda™ (capecitabine) in patients with advanced colorectal cancer. *Proc. Am. Soc. Clin. Oncol.*, 16: 798, 1997.
 19. DeMario, M. D., and Ratain, M. J. Oral chemotherapy: rationale and future directions. *J. Clin. Oncol.*, 16: 2557–2567, 1998.
 20. Meropol, N. J. Oral fluoropyrimidines in the treatment of colorectal cancer. *Eur. J. Cancer*, 34: 1509–1513, 1998.
 21. Shirasaka, T., Nakano, K., Takechi, T., Satake, H., Uchida, J., Fujioka, A., Saito, H., Okabe, H., Oyama, K., Takeda, S., Unemi, N., and Fukushima, M. Antitumor activity of 1 M Tegafur-0.4 M 5-chloro-2,4-dihydropyridine-1 M potassium oxonate (S-1) against human colon carcinoma orthotopically implanted into nude rats. *Cancer Res.*, 56: 2602–2606, 1996.
 22. Shirasaka, T., Shimamoto, S., Ohsimo, H., Yamaguchi, M., Kato, T., Yonekura, K., and Fukushima, M. Development of a novel form of an oral 5-fluorouracil derivative (S-1) directed to the potentiation tumor selective cytotoxicity of 5-fluorouracil by two biochemical modulators. *Anti-Cancer Drugs*, 7: 548–557, 1996.
 23. Takechi, T., Nakano, K., Uchida, J., Mita, A., Toko, K., Takeda, S., Unemi, N., and Shirasaka, T. Antitumor activity and low intestinal toxicity of S-1, a new formulation of oral tegafur, in experimental tumor models in rats. *Cancer Chemother. Pharmacol.*, 39: 205–211, 1997.
 24. Tatsumi, K., Fukushima, M., Shirasaka, T., and Fujii S. Inhibitory effects of pyrimidine, barbituric acid and pyridine derivatives on 5-fluorouracil degradation in rat liver extracts. *Jpn. J. Cancer Res. (Gann)*, 78: 748–755, 1987.
 25. Shirasaka, T., Shimamoto, Y., and Fukushima, M. Inhibition by oxonic acid of gastrointestinal toxicity of 5-fluorouracil without loss of its antitumor activity in rats. *Cancer Res.*, 53: 4004–4009, 1993.
 26. Taguchi, T., Inuyama, Y., Kanamaru, R., Hasegawa, K., Akazawa, S., Niitani, H., Furue, H., Kurihara, M., Ota, K., Suga, S., Ariyoshi, Y., Takai, S., Shimoyama, T., Tohge, T., Takashima, S., Sugimachi, K., Hara, Y., Fujita, H., Kimura, K., Saito, T., Tsukagoshi, S., and Nakao, I. Phase I study of S-1. *Jpn. J. Cancer Chemother.*, 24: 2253–2264, 1997.
 27. Horikoshi, N., Mitachi, Y., Sakata, Y., Sugimachi, K., and Taguchi, T. S-1, new oral fluoropyrimidine is very active in patients with advanced gastric cancer (early Phase II study). *Proc. Am. Soc. Clin. Oncol.*, 15: 466, 1996.
 28. Matsushima, E., Yoshida, K., Kitamura, R., and Yoshida, K. Determination of S-1 (combined drug of tegafur, 5-chloro-2,4-dihydropyridine and potassium oxonate) and 5-fluorouracil in human plasma and urine using high-performance liquid chromatography and gas chromatography-negative ion chemical ionization mass spectrometry. *J. Chromatogr. B.*, 691: 95–104, 1997.
 29. Yamaoka, K., and Tanigawara, Y. The guide of pharmacokinetics by microcomputer, pp. 159–178. Tokyo: Nankoudou, 1983.
 30. Wolf, W., Presant, C. A., Servis, K. L., El-Tahtawy, A., Albright, M. J., Barker, P. B., Ring, R., III, Atkinson, D., Ong, R., King, M., Singh, M., Ray, M., Wiseman, C., Blayney, D., and Shani, J. Tumor trapping of 5-fluorouracil: *in vivo* ¹⁹F NMR spectroscopic pharmacokinetics in tumor-bearing humans and rabbits. *Proc. Natl. Acad. Sci. USA*, 87: 492–496, 1990.
 31. Hillcoat, B. L., McCulloch, P. B., Figueredo, A. T., Ehsan, M. H., and Rosenfeld, J. M. Clinical response and plasma levels of 5-fluorouracil in patients with colonic cancer treated by drug infusion. *Br. J. Cancer*, 38: 719–724, 1978.
 32. Van Groeningen, C. J., Pinedo, H. M., Hedders, J., Kok, R. M., De Jong, A. P. J. M., Wattel, E., Peters, G. J., and Lankelma, J. Pharmacokinetics of 5-fluorouracil assessed with a sensitive mass spectrometric method in patients on a dose escalation schedule. *Cancer Res.*, 48: 6956–6961, 1988.
 33. Au, J. L., Rustum, Y. M., Ledesma, E. J., Mittelman, A., and Creaven, P. J. Clinical pharmacological studies of concurrent infusion of 5-fluorouracil and thymidine in treatment of colorectal carcinomas. *Cancer Res.*, 42: 2930–2937, 1982.
 34. Ho, D. H., Pazdur, R., Covington, W., Brown, N., Huo, Y. Y., Lassere, Y., and Kuritani, J. Comparison of 5-fluorouracil pharmacokinetics in patients receiving continuous 5-fluorouracil infusion and oral uracil plus N^1 -(2'-tetrahydrofuryl)-5-fluorouracil. *Clin. Cancer Res.*, 4: 2085–2088, 1998.
 35. Baker, S. D., Khor, S. P., Adjei, A. A., Doucette, M., Spector, T., Donehower, R. C., Grochow, L. B., Sartorius, S. E., Noe, D. A., Hohneker, J. A., and Rowinsky, E. K. Pharmacokinetic, oral bioavailability, and safety study of fluorouracil in patients treated with 776C85, an inactivator of dihydropyrimidine dehydrogenase. *J. Clin. Oncol.*, 14: 3085–3096, 1996.
 36. Schilsky, R. L., Hohneker, J., Ratain, M. J., Janisch, L., Smetzer, L., Lucas, V. S., Khor, S. P., Diasio, R., Hoff, D. D. V., and Burris, H. A., III. Phase I clinical and pharmacologic study of eniluracil plus fluorouracil in patients with advanced cancer. *J. Clin. Oncol.*, 16: 1450–1457, 1998.
 37. Nakajima O., Ihara K., Isoda T., Matsumoto J., Komoda M., Imamura, Y., Koyama Y., and Kimura, T. Phase I/II study of combined 1-(2-tetrahydrofuryl)-5-fluorouracil and uracil (UFT). *Jpn. J. Cancer Chemother.*, 7: 1558–1568, 1980.