

Two Dosages of Oral Fluoropyrimidine S-1 of 35 and 40 mg/m² bid: Comparison of the Pharmacokinetic Profiles in Korean Patients with Advanced Gastric Cancer

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Received May 14, 2009; accepted August 23, 2009

Objective: In this study, we compared the pharmacokinetic profiles of 5-fluorouracil (5-FU), tegafur, 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo) after administration of S-1 at 35 or 40 mg/m² bid for 28 consecutive days, in Cycles 1 and 3, in patients with advanced gastric cancer.

Methods: Three patients were enrolled for each dosage. S-1 dosage was assigned based on body surface area (BSA), which is different from the Japanese dosing system. The median daily dose per BSA was 76 mg/m², ranging from 70 to 88 mg/m².

Results: Plasma levels of 5-FU, tegafur, CDHP and Oxo at 4 h post-dose reached steady-state on day 8. The estimated steady-state level was dependent on S-1 dosage. There were no intercycle differences of pre-dose and 4 h post-dose levels between Cycles 1 and 3, implying no cumulative effect of S-1 was shown probably due to 2-week drug-resting period. Pharmacokinetic profiles on day 28 were similar to previous Japanese report. C_{max} and AUC_{0-48h} values of each S-1 component increased depending on S-1 dosage. Pharmacokinetic parameters were not correlated with tumor response or toxicity.

Conclusions: We suggest that these pharmacokinetic profiles of Asian population could provide a basis for schedule optimization and for additional studies on interaction with other antitumor drugs.

Key words: S-1 – gastric cancer – pharmacokinetics – Asian population

INTRODUCTION

5-Fluorouracil (5-FU) is a mainstay of chemotherapy in advanced gastric cancer. Bolus injection of 5-FU resulted in a 13–20% of response rate and its protracted continuous infusion (PCI) resulted in 18–26% of response rate (1–3). Although few full-scale trials have been conducted to directly compare these two schedules of 5-FU treatment in gastric cancer based on its association with less myelosuppression and diarrhea, PCI is considered an acceptable reference treatment (4,5). However, 5-FU concentration in plasma significantly varies with PCI schedule. Also, ~90%

of administered 5-FU is metabolized mainly to α -fluoro- β -alanine, thus abolishing its antitumor effect. Finally, dihydropyrimidine dehydrogenase (DPD) is the main factor affecting the 5-FU chemosensitivity.

S-1 is an oral fluoropyrimidine that was developed to mimic PCI of 5-FU. High 5-FU levels were maintained both in plasma and in tumor tissues, with reduced gastrointestinal toxicity, by combining tegafur with two biomodulators, 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo). Tegafur is converted to 5-FU in the liver by cytochrome P4502A6. CDHP inhibits the catabolism of 5-FU by inhibiting DPD activity. The other component,

Oxo, blocks phosphorylation of 5-FU in the intestine to reduce gastrointestinal toxicity (6,7). In the initial phase II trials conducted in Japan, S-1 monotherapy showed such a promising tumor response in gastric cancer that it was comparable to combination chemotherapies (8–10). However, subsequent studies did not reproduce this initial high tumor response but demonstrated differences in drug metabolism and toxicity among Japanese, USA and European populations. These data necessitated the evaluation of population-specific pharmacokinetic profiles to in-depth understand the ethnic differences and the pharmacologic property of S-1 (11–13). We conducted a multi-institutional phase II study of S-1 monotherapy in advanced gastric cancer, which is the first in a non-Japanese Asian population (14). The study proceeded with two dosage levels of S-1, 35 and 40 mg/m², and pharmacokinetic evaluation was planned along with the study for the purpose of obtaining further information on S-1 in Korean population.

Our aims here are (i) to investigate the changes in the plasma level of S-1 in a treatment cycle; (ii) to obtain pharmacokinetic profiles after 28 days of consecutive administration to see the dosage effect and intercycle differences with repetitive treatment of S-1 and finally (iii) to correlate with toxicity and antitumor activity.

PATIENTS AND METHODS

PATIENTS

Patients were enrolled when they have histologically confirmed gastric adenocarcinoma with inoperable or metastatic disease; age ≥ 18 years; performance status ≤ 2 according to the criteria of Eastern Cooperative Oncology Group; a life expectancy of ≥ 3 months, no prior chemotherapy for advanced disease (adjuvant chemotherapy should have been completed at least 6 months before enrollment); bidimensionally measurable lesions and adequate organ function (hemoglobin ≥ 10 g/dl, leukocyte $\geq 4000/\mu\text{l}$, platelets $\geq 100\,000/\mu\text{l}$, serum creatinine $\leq 1.5 \times$ upper limit of normal (ULN), total bilirubin $\leq 1.25 \times$ ULN and serum aminotransferase $\leq 2.5 \times$ ULN). Patients were excluded if they had other active malignancies, brain metastasis or severe comorbid conditions. The protocol was approved by the institutional review board, and written informed consent was obtained from patients according to the institutional regulation.

TREATMENT PLAN

Three patients were allocated to 35 mg/m² group, and another three patients were allocated to 40 mg/m² group. S-1 was administered twice a day within 1 h of breakfast and supper for 28 consecutive days. This was followed by a 14-day resting period. Dosage was calculated according to body surface area (BSA), which was different from Japanese dosing system (15). Planned dose intensity was

327 mg/m²/week for the 35 mg/m² group, and 373 mg/m²/week for the 40 mg/m² group. The schedule was repeated until disease progression, unacceptable toxicity or patient's withdrawal of consent. Imaging studies for tumor response were performed after each cycle, and tumor response was measured according to the World Health Organization (WHO) criteria. Adverse events were recorded every week and graded according to the NCI-common toxicity criteria (version 2.0).

PHARMACOKINETIC STUDY

A pharmacokinetic study was performed in Cycles 1 and 3. In a treatment cycle, blood samples were collected in heparinized tube immediately before and 4 h after doses on days 1, 8 and 15. And on day 28, blood was collected before as well as 1, 2, 3, 6, 8, 10, 14, 24 and 48 h after the last administration of S-1. Plasma was isolated and stored at -80°C until analysis. Urine samples were collected 12 h before the last dose of S-1 and for the periods of 0–6, 6–12, 12–18 and 18–24 h after the last dosage of S-1. After estimation of the total urine volumes, 10 ml aliquots were stored at -80°C until analysis.

Analysis of tegafur, 5-FU, CDHP and Oxo was conducted according to the method described by Matsushita et al. (16,17). Briefly, tegafur was extracted with dichloromethane from each sample and analyzed using high-performance liquid chromatography equipped with an UV absorption spectrophotometer. 5-FU and CDHP were extracted with ethyl acetate. Oxo was separately extracted using a solid extraction column. They were analyzed using a negative-ion chemical ionization gas chromatography/mass spectrophotometer. The lower measurable limit of plasma levels for tegafur, 5-FU, CDHP and Oxo was 10, 1, 2 and 1 ng/ml, respectively. The pharmacokinetic parameters were derived using non-compartmental methods with 'WinNonlin Professional' version 5.0 (Pharsight Corp., Mountain View, CA, USA). The pharmacokinetic parameters included the determination of maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under the plasma concentration-versus-time curve from time 0 to 48 h ($\text{AUC}_{0-48\text{h}}$) and plasma elimination half-life ($T_{1/2}$). Pharmacokinetic analysis for the S-1 constituents in urine included the determination of the amount excreted at each collection interval and the cumulative amount excreted over a 24 h period.

RESULTS

PATIENT CHARACTERISTICS

Three patients were enrolled for each dosage group of 35 and 40 mg/m². The six patients consisted of five men and one woman. Ages were between 28 and 66 years, and the median age was 61 years old. Three patients received prior gastrectomy. The median hemoglobin level was 11.3 (range: 10.0–13.5 g/dl). The median BSA was 1.66 m²

(range: 1.27–1.88 m²) and the median actual daily dose administered was 125 mg (range: 100–140 mg). The median daily dose divided by BSA was 71 mg/m² (range: 69–73 mg/m²) for 35 mg/m² group and 83 mg/m² (range: 79–88 mg/m²) for 40 mg/m² group. All the patients had normal baseline range of creatinine clearance, of which the median value was 80 ml/min (range: 68–112 ml/min).

CHANGE OF THE PLASMA LEVEL OF 5-FU IN ONE TREATMENT CYCLE

Figure 1 shows the changes in the mean plasma level of 5-FU, the active metabolite of tegafur, measured on days 1, 8, 15 and 28 in Cycles 1 and 3. 5-FU readily appeared in plasma from day 1. With 35 mg/m², the 4 h post-dose plasma level of 5-FU after single dose of S-1 was 56 ± 9 ng/ml. At 40 mg/m², the 5-FU plasma level increased to 191 ± 94 ng/ml. The pre-dose (trough) and 4 h post-dose 5-FU levels were similar to one another on days 8, 15 and 28, indicating that 5-FU concentration in plasma reached the steady-state level on day 8. Also, the estimated steady-state level on day 8 was also dependent on dosage. At 35 mg/m², the mean steady-state 5-FU level was 108 ± 21 ng/ml. At 40 mg/m², it was 176 ± 114 ng/ml. There were no significant differences in pre-dose and 4 h post-dose plasma levels between Cycles 1 and 3, implying that there were no inter-cyclic cumulative effect of 5-FU.

CHANGE IN PLASMA LEVELS OF TEGAFUR, CDHP AND OXO IN ONE TREATMENT CYCLE

Figure 2 shows changes in the mean plasma levels of the three components of S-1 (tegafur, CDHP and Oxo) measured in Cycles 1 and 3. At a dose of 35 mg/m², tegafur plasma

concentration was ~4000 ng/ml at each pre-dose and 4 h measurement on days 8, 15 and 28, indicating that its plasma concentration reached the steady-state which was around 4000 ng/ml. On the contrary, at 40 mg/m², both pre- and post-dose levels kept increasing as S-1 administration continued through day 28, reaching as high as 6554 ± 2344 ng/ml. This suggests a dose-related accumulation of tegafur at 40 mg/m².

CDHP and Oxo also reached steady-state on day 8. Although unclear for CDHP, Oxo plasma levels correlated with S-1 dosage. Moreover, like the case of 5-FU, there were no definite inter-cyclic differences in plasma levels between Cycles 1 and 3 for tegafur, CDHP and Oxo.

PHARMACOKINETICS AFTER 28 DAYS OF CONSECUTIVE ADMINISTRATION

Pharmacokinetic parameters of tegafur, 5-FU, CDHP and Oxo measured after the last dose on day 28 are summarized in Fig. 3 (also in Supplementary material, Table S1). At 35 mg/m², mean C_{max} for tegafur, 5-FU, CDHP and Oxo was 4484 ± 1231, 91 ± 23, 191 ± 14 and 33 ± 1.0 ng/ml, respectively. Mean AUC_{0–48h} was 99 907 ± 38 999, 750 ± 120, 1359 ± 373 and 337 ± 80 ng h/ml, respectively. Besides, the mean C_{max} of 5-FU and three S-1 components increased with S-1 dosage. AUC was also dependent on dosage, but 5-FU AUC_{0–48h} increased only marginally to 767 ± 194 ng h/ml (3%). 5-FU was eliminated from plasma with mean T_{1/2} values that did not markedly vary with the dosage.

Mean AUC_{0–48h} for 5-FU and CDHP increased in Cycle 3 compared with Cycle 1, whereas other parameters showed little inter-cyclic changes. This increase in 5-FU and CDHP might imply a correlation between DPD inhibition by CDHP

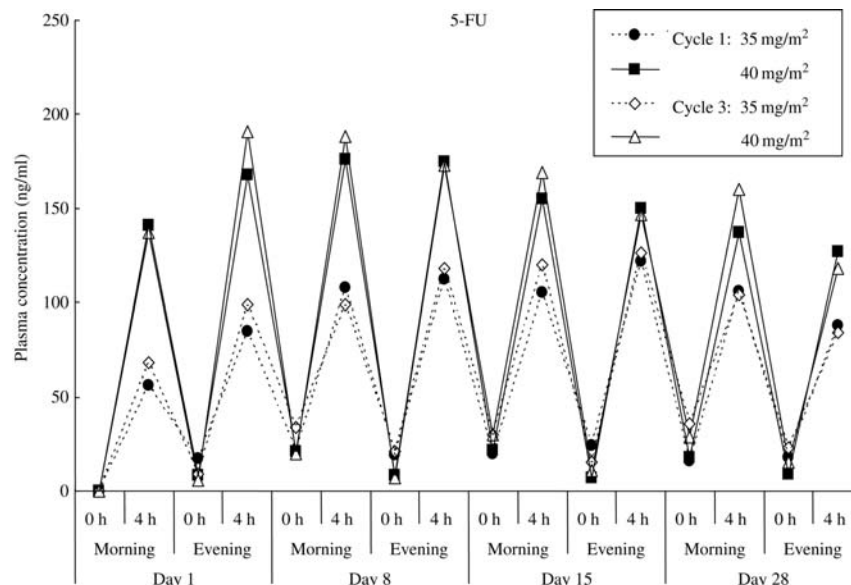


Figure 1. Changes in the average plasma level of 5-FU measured on days 1, 8, 15, and 28 after S-1 administration.

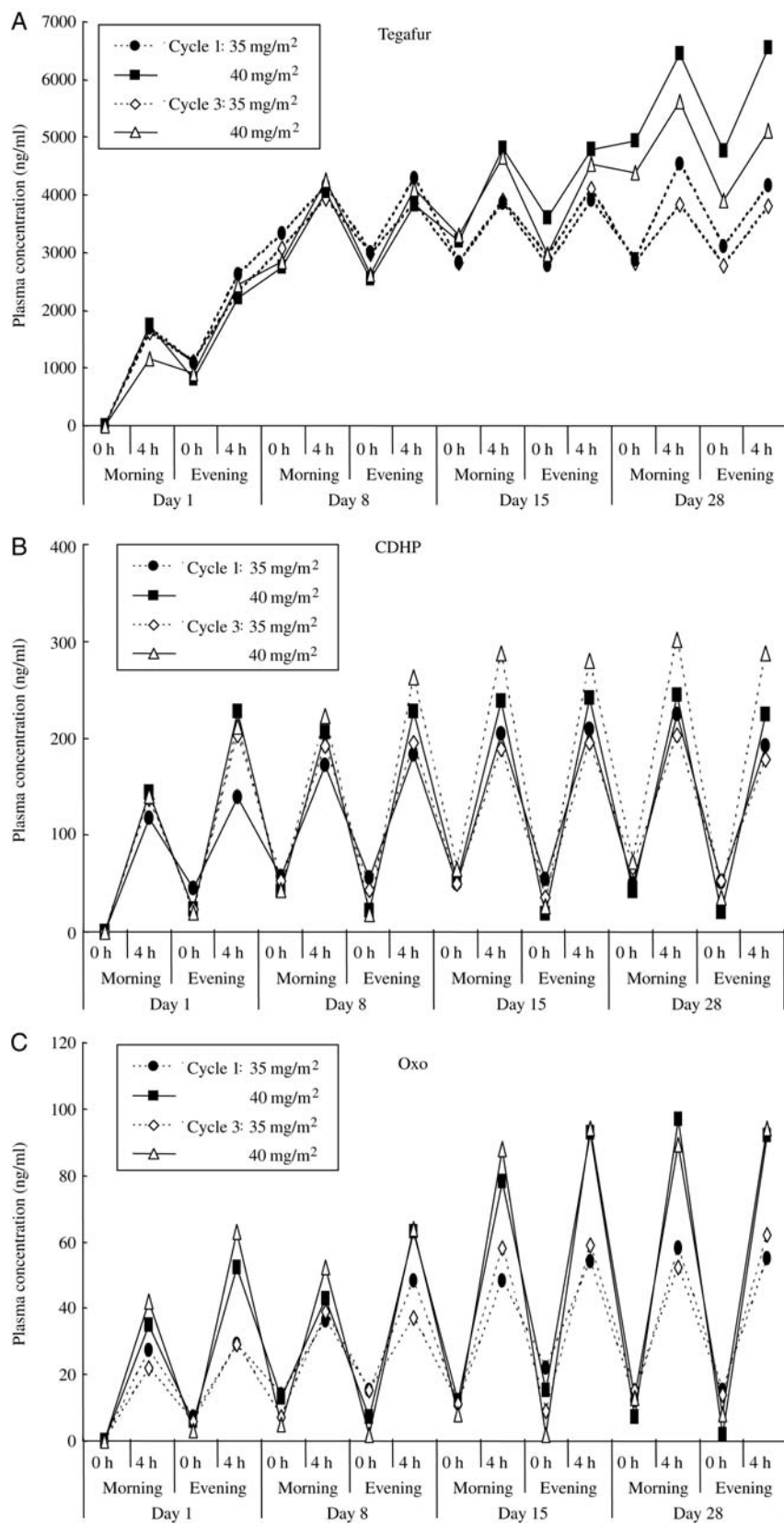


Figure 2. Change in the average plasma level of S-1 components measured on days 1, 8, 15 and 28 after S-1 administration in Cycle 1: (A) tegafur, (B) CDHP and (C) Oxo. CDHP, 5-chloro-2,4-dihydropyridine; Oxo, potassium oxonate.

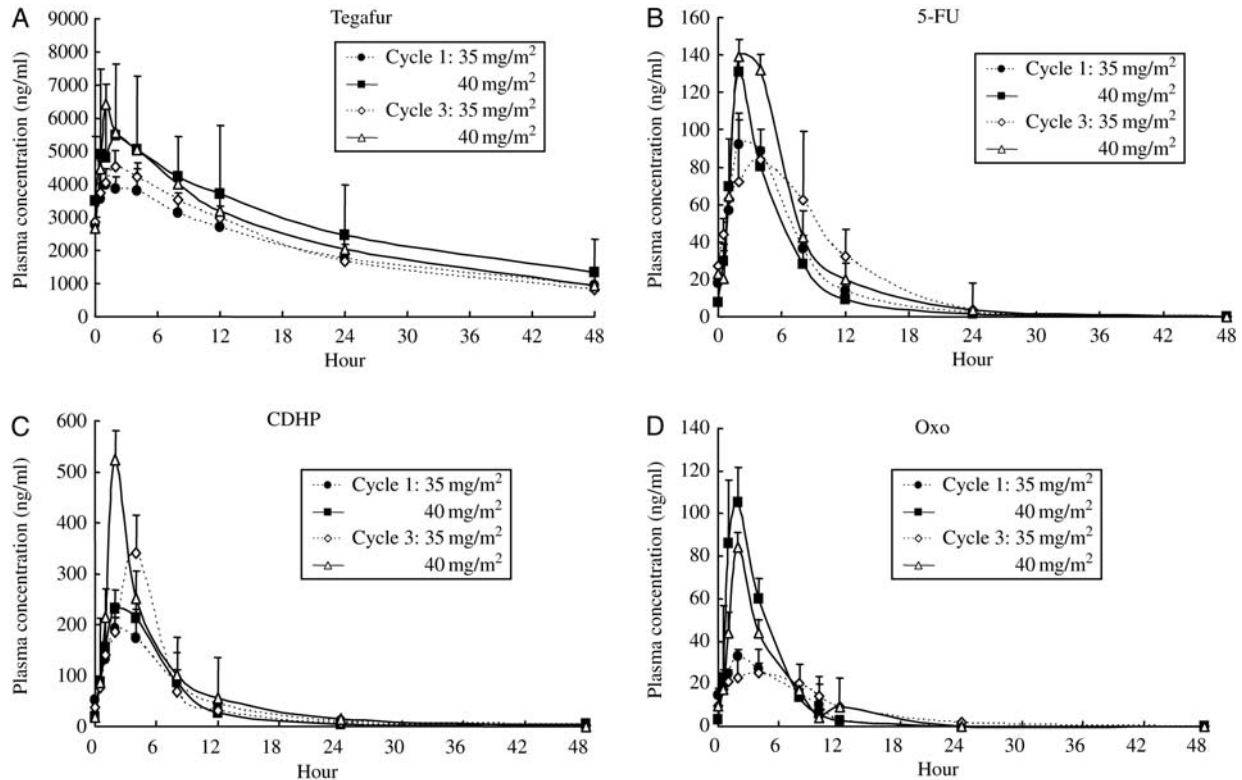


Figure 3. Pharmacokinetic profile of 5-FU and S-1 components measured on day 28 after the last dose of S-1: (A) tegafur, (B) 5-FU, (C) CDHP and (D) Oxo.

and 5-FU levels after S-1 administration. The urinary excretion of tegafur, 5-FU, CDHP and Oxo within 24 h after administration of the last dose on day 28 was 37.3 ± 15.0 , 17.1 ± 4.3 , 154.5 ± 19.7 and 5.4 ± 1.1 μg , respectively. There was no correlation of S-1 urinary excretion with its dosage or cycle.

CORRELATION WITH TOXICITY AND ANTITUMOR EFFECT

Two patients underwent 3 cycles of treatment, three patients underwent 4 cycles of treatment and the remaining patient underwent 10 cycles. Two patients—from two in the 40 mg/m^2 group—showed partial responses, whereas the disease was stable in the remaining patients. Also three patients—two in the 35 mg/m^2 group and one in the 40 mg/m^2 group—suffered Grade 3 anemia during treatment. We investigated the correlation between treatment outcome—toxicity and antitumor activity—and pharmacokinetic parameters. With Spearman's correlation coefficient, neither C_{max} nor AUC correlated with toxicity or response.

DISCUSSION

Blood pharmacokinetics of 5-FU reflect those in tumors (18). In addition, there exists a clinical correlation between 5-FU AUC and treatment outcomes (19,20). However, reports on 5-FU plasma levels with PCI are inconsistent,

which is due to its high dependency on the activity of DPD. S-1 was found to successfully allow an effect similar to that of long-term PCI of 5-FU, and the combination of a CDHP and tegafur makes the width of variation of the 5-FU plasma level narrow (15).

We conducted a pharmacokinetic study of S-1, based on the doses used in our previous multinational Phase II study, which was the first performed in non-Japanese Asian population (14). We first evaluated the changes in the 5-FU plasma level during the treatment cycle. The non-toxic concentration of 5-FU is reported to be 195 ng/ml, and the steady-state concentration (C_{ss}) of 5-FU correlates with incidence of leucopenia (21). In the previous Japanese study of S-1 pharmacokinetics, peak plasma levels were reached 3.5 h after administration, which was the basis of our measuring 4 h post-dose level of 5-FU only once in this study (15). However, our post-dose level 5-FU after a single administration was only 56 ng/ml, which is half of that measured in the Japanese study (15). We thought that this difference seemed to be overcome by dose increment of S-1 to 40 mg/m^2 . At the dose of 40 mg/m^2 , we have attained the highest dose intensity of S-1 ($367 \text{ mg/m}^2/\text{week}$) ever reported in the Phase II trials. However, the 5-FU plasma level was 181 ng/ml, which is still in the non-toxic range for 5-FU. This explains, at least partially, the favorable compliance of our patients to S-1 and the low incidence of Grade 3 neutropenia in our trial (14).

This low 5-FU level could be explained by two factors: (i) low conversion from tegafur and (ii) low activity of CDHP. CDHP attains its maximal concentration as early as 2 h in the Japanese trial, and its 4 h post-dose level was still ~ 100 ng/ml. Although it would be hasty to infer a role for CDHP in our patients from a simple extrapolation of the Japanese data, we can at least think that general CDHP levels are not much different between the two populations (22). However, changes in the tegafur plasma level could provide a clue. The mean post-dose level of tegafur after a single S-1 administration was $1.68 \mu\text{g/ml}$. In a Phase I/II study of a single administration of UFT, which is another combination formula with DPD inhibitor, and tegafur alone at 300 mg/body , the tegafur plasma level was 13.7 and $12.3 \mu\text{g/ml}$, respectively. These levels are ~ 8 -fold higher than measured in our trial (22). Considering that the overall average dose of S-1 (as tegafur) was 63 mg/body , which was higher than Japanese study (50 mg/body), our levels were only 5-fold against that of UFT and tegafur. It indicates that the value of the plasma tegafur is lower than expected. Therefore, failing to achieve appropriate plasma level of tegafur could explain the low plasma 5-FU levels seen in our patients.

In one treatment cycle, the plasma concentration of 5-FU, CDHP and Oxo readily attained the steady-state levels on day 8, which was consistent with a previous study (23). Tegafur increased in both trough and post-dose levels at the 40 mg/m^2 , but it did not necessarily accompany the increase in 5-FU level to the same extent. Taking the long half-life of tegafur into account, the result may reflect the accumulation of S-1—as the form of tegafur—and the saturation of the capacity to convert tegafur to 5-FU—such as cytochrome P4502A6 at 40 mg/m^2 of S-1 (24). The conversion level of our patients would have been comparable to that of Japanese patients when considering the alleged similar inter-ethnic profile of cytochrome P4502A6 polymorphisms in the two populations (25).

Many reports agree on the importance of evaluating potential ethnic differences in the metabolism of S-1, which lead to differential dose tolerance and toxicity. Myelosuppression was the toxicity that has precluded dose escalation in Japanese studies, whereas gastrointestinal and skin toxicity were the features of western trials. In addition, anemia was the unique toxicity encountered in a Korean Phase II study (14). Regardless, maximum tolerated doses were found to be higher in Asian studies than in western studies, and Korean study obtained the highest dose intensity ever reported with favorable compliance (14,26). Therefore, it seemed no wonder that our pharmacokinetic behaviors of S-1 and its components were more similar to those of Japanese findings rather than to those of Americans at an equivalent dose level of 35 mg/m^2 . Hoff et al. (12) noticed that AUC of 5-FU were similar among various trials, but those of tegafur were much higher in Japanese patients. This is partially explained by aforementioned ethnic variation in the cytochrome P450. Other authors speculated that this difference came from apparent difference in exposure to 5-FU resulting from different total doses due to different

body sizes, as Japanese people have lower BSA than westerns (27). Mean value of daily S-1 dose per BSA is 71 mg/m^2 in western patients and 76 mg/m^2 in Japanese patients (27). For Korean patients, this value increases to 83 mg/m^2 at 40 mg/m^2 . These findings, which are further supported by the present study, raised the question that pharmacogenomic approaches accounts for the difference in pharmacologic behavior among various ethnic groups. For tegafur, a dose-related increase in AUC was observed from 35 and 40 mg/m^2 groups. However, AUC values of 5-FU and CDHP did not so much as those for tegafur. Although this observation may result from small absolute differences between these dose levels, it adds another potential example of saturated biotransformation of tegafur converting to 5-FU.

We demonstrated little changes in AUC or C_{max} values of tegafur and Oxo between Cycles 1 and 3. This implies that a cumulative effect of S-1 is frivolous and that resting period of 2 weeks would be a reasonable wash-out period. However, we could notice the tendency that the mean AUC values and half-life of 5-FU and CDHP increased in Cycle 3 at 40 mg/m^2 . This increase might demonstrate a correlation between DPD inhibition by CDHP and 5-FU levels after S-1 administration. Allowing that all the patients maintained creatinine clearance within normal range throughout the entire treatment period, it may also suggest that the increasing risk of toxicity is plausible as treatment cycles progress in this dose level due to a cumulative effect of CDHP and 5-FU.

Although sample size is small, our data demonstrate that pharmacokinetic behaviors of S-1 could not predict response and toxicity, also consistent with previous reports (20). We suggest that S-1 could be another target for pharmacogenetic/pharmacogenomic tools for future trials. To conclude, this is the first pharmacokinetic study performed in non-Japanese Asian population that tested the highest dose intensity ever obtained as S-1 monotherapy. Our data demonstrate (i) the similar pharmacokinetic behaviors to the Japanese population at equivalent dosage, (ii) possible saturation of tegafur conversion to 5-FU at 40 mg/m^2 , (iii) negligible cumulative effects at 35 mg/m^2 between cycles and finally (iv) the poor relationship of pharmacokinetic behaviors with clinical outcomes. We believe that our data could provide a basis for schedule optimization of S-1 and for additional pharmacokinetic studies on the interaction with other antitumor agents for future clinical trial designs.

Supplementary material

Supplementary material is available at *Japanese Journal of Clinical Oncology* Online.

Acknowledgements

We thank clinical research coordinators (CRC) Seung Ah Kang, Eun Young Ju of Yonsei University College of

Medicine and Hyun Jeong Ji of Jeil Pharmaceutical Co. for their sincere help with data documentation and technical assistance. We are also grateful to Hyung Sik Choie of Jeil Pharmaceutical Co. and J. Saruta of Taiho Pharmaceutical Co. of Japan for supplying S-1 for this study.

Funding

This work was supported by the Korea Science and Engineering Foundation (KOSEF) grant funded by the Korean government (MOST) (R11-2000-082-03002-0). Funding to pay the Open Access publication charges for this article was provided by Hyun Cheol Chung.

Conflict of interest statement

None declared.

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