Fixed dosing and pharmacokinetics of S-1 in Japanese cancer patients with large body surface areas

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Background: S-1 is an oral anticancer agent that combines tegafur (FT) with 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate. The recommended initial dose of S-1 is 120 mg/day for patients with a body surface area (BSA) of ≥1.5 m² in Japan.

Methods: We examined the effects of using this fixed dose on the pharmacokinetics of FT, CDHP, and active 5-fluorouracil (5-FU) on the basis of actual BSA. The pharmacokinetics was compared between patients with a BSA of 1.5–1.75 m² and those with a BSA of ≥1.75 m².

Results: The median areas under the time–concentration curves (AUCs) of 5-FU and CDHP were significantly lower in patients with a BSA of ≥1.75 m² than in those with a BSA of 1.5–1.75 m² (P = 0.005 and 0.006, respectively; Mann–Whitney U-test). There was no difference between the groups in the median AUC of FT.

Conclusion: Systemic exposure to 5-FU is significantly lower in Japanese cancer patients with a large BSA of >1.75 m² who received the recommended fixed dose of S-1.

Key words: 5-FU, Japanese, large body surface area, pharmacokinetics, S-1

introduction

S-1 (Taiho Pharmaceutical, Tokyo, Japan) is an oral anticancer agent that combines tegafur (FT) with 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate [1]. FT is a prodrug of cytotoxic 5-fluorouracil (5-FU). The bioactivation of FT to 5-FU is predominantly catalyzed by the liver drug-metabolizing enzyme CYP2A6 [2], which is highly polymorphic [3]. CDHP increases the plasma 5-FU level by competitively inhibiting dihydropyrimidine dehydrogenase [4], the rate-limiting enzyme responsible for 5-FU metabolism [5]. S-1 is widely used as a standard option for chemotherapy in patients with gastric cancer in Japan [1].

Clinically, how doses of anticancer drugs should be adjusted for patients with large body surface areas (BSAs) remains poorly understood. In many cases, extrapolation of dosing recommendations to those patients with large BSA must be carried out arbitrarily when the dose is required to be standardized by particular patient demographics including BSA [6]. The package insert of S-1 in Japan recommends an initial fixed dose of 120 mg/day for patients with a BSA of ≥1.5 m².

The pharmacokinetics of a drug cannot be reliably predicted on the basis of BSA [6, 7]. The drug clearance of 5-FU does not clearly correlate with BSA in patients who receive capecitabine [6]. Dosage recommendations for capecitabine have not been definitively established (i.e. a fixed dose or a BSA-based dose) although the package insert recommends that the dose is based on BSA [8]. In contrast, the area under the time–concentration curve (AUC) of 5-FU strongly correlates with BSA after oral administration of uracil/FT (UFT) with leucovorin (LV) [9]. A BSA-based dose of UFT plus LV is therefore recommended for the treatment of colorectal cancer.

To date, little information is available on the relation of BSA to the pharmacokinetics of FT, CDHP, and the active metabolite 5-FU in patients who are taking S-1 capsules. If the pharmacokinetics of these compounds is affected by BSA, the currently recommended fixed dose of S-1 for patients with a BSA of ≥1.5 m² might not produce adequate serum levels of the active metabolite 5-FU in such patients. We therefore examined the AUC of 5-FU, CDHP, and FT in patients with a BSA of ≥1.5 m² who received S-1 in a fixed dose of 120 mg/day.

methods

eligibility

Eligible patients were 20 years or older and had histologically confirmed metastatic or recurrent solid tumors treated with S-1, a World Health
Organization performance status of zero to three, and no history of chemotherapy or radiotherapy within the last 4 weeks. Each patient was confirmed to have adequate bone marrow and liver function [10], as well as adequate renal function (a creatinine clearance of ≥50 ml/min as calculated by the Cockcroft–Gault equation). All patients gave written informed consent to participate in the study and their peripheral blood samples and medical information to be used for research purposes. The study protocol was approved by the Institutional Review Board of Saitama Medical University.

**treatment**
S-1 was given orally, twice daily for 28 consecutive days, followed by 2 weeks of rest. The dose of S-1 was fixed based on the patients’ BSA according to the package insert in Japan. The dose was 120 mg/day for patients with a BSA of ≥1.5 m².

**determination of FT, 5-FU, and CDHP**
Blood samples for pharmacokinetic analysis were obtained on day 1 of treatment as described by Fujita et al. [10]. Plasma concentrations of FT and 5-FU were analyzed by high-performance liquid chromatography and those of CDHP were determined by gas chromatography mass spectrometry, as reported elsewhere [10].

**pharmacokinetic variables**
The AUCs (µM h) of FT, 5-FU, and CDHP were calculated by the linear trapezoidal rule (until the peak plasma concentration) and the linear-log trapezoidal rule (until the last measurable concentration), using a computer program (WinNonlin version 5.1 software, Pharsight Corporation, Mountain View, CA), as described previously [10].

**statistical analysis**
The Mann–Whitney U-test was used to compare the AUCs of 5-FU, CDHP, and FT according to two BSA categories, 1.5–1.75 and ≥1.75 m² (JMP version 6 software, SAS Institute, Inc., Cary, NC). A P value of <0.05 was considered to indicate statistical significance.

**results and discussion**
A total of 26 Japanese patients (21 men, 5 women) with a BSA of ≥1.5 m², including six patients with a BSA of ≥1.75 m², were enrolled from November 2005 through April 2007 at Saitama Medical University. Patient characteristics are shown in Table 1. The median BSA was 1.58 m² (range 1.5–1.91). The median age was 58 years (range 35–80). The median creatinine clearance was 87.5 ml/min (range 55–174).

To examine the effects of BSA on the pharmacokinetics of S-1 components in patients receiving a fixed dose of 120 mg/day, the patients were subdivided into two categories: those with a BSA of 1.5 to <1.75 m² and those with a BSA of ≥1.75 m². These categories were based on the 0.25-m² interval of current BSA-based dosage recommendations for S-1 in Japan (<1.25, 1.25–1.5, and ≥1.5 m²). Characteristics of patients in each group are shown in Table 1.

Since the dose of S-1 normalized to BSA (mg/m²/day) decreased as the BSA increased, the normalized dose of S-1 in the patients with a BSA of ≥1.75 m² (64.0 ± 1.9 mg/m², median ± standard deviation (SD)) was significantly lower than that in the patients with a BSA of 1.5–1.75 m² (77.4 ± 3.2 mg/m², median ± SD) (P = 0.0003, Mann–Whitney U-test). The median AUC of 5-FU in the patients with a BSA of ≥1.75 m² (6.63 ± 1.4 µM·h, median ± SD) was significantly lower than that in the patients with a BSA of 1.5–1.75 m² (11.5 ± 3.1 µM·h, median ± SD) (P = 0.005, Mann–Whitney U-test) (Figure 1). The median AUC of CDHP was also significantly lower in the patients within a BSA of ≥1.75 m² (5.96 ± 0.7

**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th>BSA (m²)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5–1.75</td>
<td>2≥1.75</td>
</tr>
<tr>
<td>Agea</td>
<td>61.5 (46–80)</td>
</tr>
<tr>
<td>Sexb</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>15</td>
</tr>
<tr>
<td>Female</td>
<td>5</td>
</tr>
<tr>
<td>Performance statusb</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>12</td>
</tr>
<tr>
<td>1</td>
<td>8</td>
</tr>
<tr>
<td>≤2</td>
<td>0</td>
</tr>
<tr>
<td>Serum creatinine (mg/dla)</td>
<td>0.73 (0.51–0.98)</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)a</td>
<td>79 (55–126)</td>
</tr>
<tr>
<td>Total bilirubin (mg/dla)</td>
<td>0.4 (0.3–1.1)</td>
</tr>
<tr>
<td>Tumor typeb</td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>13</td>
</tr>
<tr>
<td>Colorectal</td>
<td>3</td>
</tr>
<tr>
<td>Others</td>
<td>4</td>
</tr>
<tr>
<td>Prior chemotherapy regimensb</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>1</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

aValues are expressed as medians, with ranges in parentheses.

bNumber.
μM·h, median ± SD) than in those with a BSA of 1.5–1.75 m² (9.76 ± 2.0 μM·h, median ± SD) \( (P = 0.006\), Mann–Whitney U-test) (Figure 2). In contrast, the AUC of FT did not differ significantly between the groups (114 ± 28 μM·h for 1.5–1.75 m² and 110 ± 35 μM·h for ≥1.75 m², median ± SD) \( (P = 0.927\), Mann–Whitney U-test) (Figure 3).

The median AUC of 5-FU may have differed according to BSA group for the following reasons: (i) As shown in our previous study [10, 11], the AUC of 5-FU is primarily affected by the AUC of CDHP, not that of FT. (ii) CDHP is predominantly excreted in the urine by glomerular filtration [12]. Since the glomerular filtration area is directly related to BSA [7, 13], the AUC of CDHP decreased as the BSA increased (Figure 2). (iii) Therefore, the lower median AUC of 5-FU in patients with a BSA of ≥1.75 m² is attributed to the BSA-dependent decrease in the AUC of CDHP.

Since the interpatient variability in the AUC of FT caused by \textit{CYP2A6} genotype is larger than that by the BSA in Japanese patients with cancer [10], the AUC of FT did not differ significantly between the two groups.

According to the present results, we could hypothesize that Japanese patients with a BSA of ≥1.75 m² may insufficiently benefit from S-1 treatment because of the low systemic exposure to active 5-FU after administration of a fixed dose of S-1 (120 mg/day). In addition, the dose of S-1 in patients with BSA >1.5 m² should be subdivided into more categories as a phase II study for first-line advanced gastric cancer carried out with Western patients where the dose of S-1 (50 mg/m²/day) was subdivided into seven categories according to the BSA of patients (<1.29 m², 60 mg/day; 1.3–1.49 m², 70 mg/day; 1.5–1.69 m², 80 mg/day; 1.7–1.89 m², 90 mg/day; 1.9–2.09 m², 100 mg/day; 2.1–2.29 m², 110 mg/day; ≥2.3 m², 120 mg/day) [14]. This fine categorization may not induce the low systemic exposure to active 5-FU in Western patients with large BSA. Even in a multi-institutional phase II study of S-1 monotherapy in advanced gastric cancer which carried out with Korean patients, the dose of S-1 (70 or 80 mg/m²/day) was reasonably subdivided into six categories with the BSA of the patients (<1.36, 1.36–1.57, 1.58–1.78, 1.79–1.92, 1.93–2.07, and ≥2.08 m²) [15]. In this Korean study, response rate was reported to be 19% that was significantly lower than that expected. The examination of the relation between the response and \textit{CYP2A6} genotype and CDHP exposure might be helpful for the better understanding the unexpected results.

It should be noted that the results of the present study were obtained by low number of patients. Therefore, a prospective clinical study with a large number of homogeneous patients

**Figure 1.** Relation between the area under the time–concentration curve (AUC) of 5-fluorouracil (5-FU) and body surface area (BSA). Bars indicate medians.

**Figure 2.** Association between the area under the time–concentration curve (AUC) of 5-chloro-2,4-dihydroxypyridine (CDHP) and body surface area (BSA). Bars indicate medians.

**Figure 3.** Area under the time–concentration curve (AUC) of tegafur (FT) versus body surface area (BSA) plots. Bars indicate medians.
should be carried out to analyze between exposure of 5-FU and clinical outcome.

**funding**

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**references**