Short Communication

Pharmacokinetics of 5-Fluorouracil in Elderly Japanese Patients with Cancer Treated with S-1 (a Combination of Tegafur and Dihydropyrimidine Dehydrogenase Inhibitor 5-Chloro-2,4-dihydroxypyridine)

Received February 6, 2009; accepted April 21, 2009

ABSTRACT:

S-1 is an oral anticancer agent that combines tegafur, a prodrug of 5-fluorouracil (5-FU), and 5-chloro-2,4-dihydroxypyridine (CDHP), an inhibitor of dihydropyrimidine dehydrogenase. We examined the effects of aging on the pharmacokinetics of these compounds in elderly patients. The median area under the concentration-time curve (AUC) of active 5-FU did not significantly differ between 10 patients 75 years or older and 53 patients younger than 75 years (P = 0.598, Mann-Whitney U test). It is interesting to note that the median oral clearance of tegafur in patients 75 years or older was significantly lower than that in patients younger than 75 years (P = 0.011). Furthermore, the median AUC of CDHP was significantly higher in patients 75 years or older than in those younger than 75 years (P = 0.004). This effect was caused by reduced renal function in the elderly, because CDHP is excreted in the urine by glomerular filtration. The opposing effects of aging on the oral clearance of tegafur and the AUC of CDHP may offset each other, leading to unchanged systemic exposure of 5-FU.

The elderly comprise the most rapidly growing segment of the population that requires chemotherapy for the treatment of cancer. Aging is associated with various physiological changes, including decreased renal function (Brenner et al., 1982) and hepatic metabolism (Sotaniemi et al., 1997), the processes of which may increase the risk of unpredictable toxicity during anticancer therapy. It is unfortunate that adequate data to support evidence-based decisions about the use of chemotherapy in elderly patients are scarce. This paucity of data are mainly attributed to the minimal participation of older patients in clinical trials and to the lack of systematic clinical evaluations of chemotherapy (Yee et al., 2003). Most previous studies of chemotherapy have been retrospective subset analyses, in which older patients comprise only a fraction of subjects. Prospective pharmacokinetic studies in elderly patients with cancer are particularly scarce, although chemotherapy-induced toxicity can often be caused by age-related changes in pharmacokinetics (Lichtman et al., 2007).

S-1 (Taiho Pharmaceutical, Tokyo, Japan) is an oral anticancer agent that combines tegafur with 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate (Kubota, 2008). The structure of these chemicals is reported by Hirata et al. (1999). Tegafur is a prodrug of cytotoxic 5-fluorouracil (5-FU). The bioactivation of tegafur to 5-FU is catalyzed mainly by CYP2A6 (Ikeda et al., 2000), which is highly polymorphic (Nakajima et al., 2006). CDHP increases the plasma 5-FU level by competitively inhibiting dihydropyrimidine dehydrogenase (DPD) (Tatsumi et al., 1987).

S-1 is widely used as a standard option for chemotherapy in patients with gastric cancer in Japan (Kubota, 2008). Because of its oral formulation, high effectiveness, and relatively low toxicity, S-1 may be particularly suited for the treatment of cancer in elderly patients (Lee et al., 2008). However, little information is available about the effects of aging on the pharmacokinetics of tegafur, CDHP, and the active metabolite 5-FU in patients who are receiving S-1 capsules. One underlying reason for this limited information is the fact that clinical trials of S-1 have only involved participation of patients 75 years or younger (Hirata et al., 1999; Yamada et al., 2003). Given that the pharmacokinetics of these compounds are potentially affected by aging, current dosage recommendations for S-1 might not produce adequate serum levels of the active metabolite 5-FU in elderly patients.

Therefore, we compared the areas under the concentration-time curves (AUCs) of 5-FU and CDHP and oral clearance of tegafur between patients 75 years or older and those younger than 75 years to assess the effects of aging on the pharmacokinetics of the components of S-1.

Materials and 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 0 to 3, and had not received chemotherapy or radiotherapy within the last 4 weeks. Each patient was confirmed to have adequate bone marrow function (neutrophil count, at least 1.5 × 10^9/liter; platelet count, at least 100 × 10^9/liter), and hepatic and renal function within normal limits.

This work was supported in part by a grant-in-aid for Cancer Research [Grant 17-8]; a Health and Labour Sciences Research grant from the Ministry of Health, Labour and Welfare of Japan (2005-Clinical Cancer Research-008); a grant-in-aid for Scientific Research from the Japan Society for the Promotion of Science [Grant A-16200038]; and a grant from the Japan Research Foundation for Clinical Pharmacology.
liver function (serum bilirubin level, less than 3.0 mg/dl; transaminases, less than 2.0 times the upper limit of normal), and renal function (serum creatinine level, less than 2.0 mg/dl). All patients gave written informed consent to participate in the study and for 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.** Patients were divided into two categories, 75 years or older and younger than 75 years. S-1 was given orally, twice daily for 28 consecutive days, followed by 2 weeks of rest. The dose of S-1 was based on the patients’ body surface area as recommended by the package insert in Japan.

**CYP2A6 Genotyping.** CYP2A6 genotyping (*4A, *7, and *9) was performed by the methods described previously (Fujita et al., 2008).

**Measurement of Tegafur, 5-FU, and CDHP in Plasma.** Blood samples for pharmacokinetic analysis were obtained on day 1 of treatment as described previously (Fujita et al., 2008). Plasma concentrations of tegafur and 5-FU were analyzed by high-performance liquid chromatography and those of CDHP were determined by gas chromatography mass spectrometry, as reported elsewhere (Fujita et al., 2008). Plasma concentrations of tegafur and 5-FU for pharmacokinetic analysis were obtained on day 1 of treatment as described previously (Fujita et al., 2008). The parameter was calculated with Cockcroft-Gault equation. Pharmacokinetic data are reported as median values with standard deviation (SD), unless stated otherwise. Statistical comparisons between groups were done using a Mann-Whitney U test, and \( P < 0.05 \) was used as a cutoff for significance.

**Results and Discussion**

A total of 63 Japanese patients, including 10 patients 75 years or older, was enrolled between November 2005 and July 2008. The patient characteristics are shown in Table 1. The median Ccr level in patients 75 years or older was significantly lower than that in patients younger than 75 years (54.5 ± 9.3 versus 85.0 ± 26 ml/min, \( P = 0.000006 \)).

The AUCs of 5-FU and CDHP, and oral clearance of tegafur in patients 75 years or older were compared with those in patients younger than 75 years. The median AUC of active 5-FU did not significantly differ between patients 75 years or older and those younger than 75 years (8.78 ± 2.3 versus 9.76 ± 3.7 \( \mu M \cdot h \), \( P = 0.598 \)) (Fig. 1). The median oral clearance of tegafur in patients 75 years or older was significantly lower than that in patients younger than 75 years (1.82 ± 1.3 versus 2.80 ± 1.1 \( \mu M \cdot h \), \( P = 0.011 \)). On the other hand, the median AUC of CDHP was significantly higher in patients 75 years or older than in those younger than 75 years (10.4 ± 2.5 versus 7.42 ± 1.9 \( \mu M \cdot h \), \( P = 0.004 \)).

In view of the age-dependent change in oral clearance of tegafur and the altered exposure to CDHP, the lack of any obvious effect of age on the pharmacokinetics of 5-FU after the administration of S-1 was somewhat unexpected. Indeed, it was anticipated that advancing age might be associated with decreased conversion of tegafur to 5-FU, which is mainly catalyzed by CYP2A6, resulting in decreased production of 5-FU in patients 75 years or older than in those younger than 75 years. An age-related decline in CYP2A6 activity is supported by the previous observation that decreased coumarin clearance in the elderly was associated with reduced CYP2A6 activity (Sotaniemi et al., 1997). It should be pointed out that we previously found that the oral clearance of tegafur was predominantly affected by CYP2A6 genotype and not by age (Fujita et al., 2008). In that previous study, age was analyzed as a continuous variable, whereas age was analyzed as a categorical variable in the present study. In addition, the distribution of variant CYP2A6 genotypes in patients 75 years or older did not differ significantly from that in patients younger than 75 years (\( \chi^2 \) test) (Table 1), although the power of the statistical analysis might be low because of the small number of elderly patients. Given these results, the lower median oral clearance of tegafur in patients 75 years or older relative to that in younger patients seems to primarily reflect an age-dependent change in oral clearance of tegafur.

With regards to CDHP, it is worth mentioning that this agent is known to predominantly undergo urinary excretion through glomerular filtration.

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**TABLE 1**

**Patient characteristics**

<table>
<thead>
<tr>
<th>Category of Patients</th>
<th>&lt;75 Years</th>
<th>≥75 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>59 (33–74)*</td>
<td>78.5 (75–85)</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>32/21†</td>
<td>7/3</td>
</tr>
<tr>
<td>Performance status (0/1/≥2)</td>
<td>85.0 (51.0–174)*</td>
<td>54.5 (39.0–66.0)</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>0.4 (0.3–1.5)*</td>
<td>0.45 (0.2–0.7)</td>
</tr>
<tr>
<td>Total bilirubin (mg/dl)</td>
<td>22</td>
<td>4</td>
</tr>
<tr>
<td>CYP2A6 genotype</td>
<td>19</td>
<td>5</td>
</tr>
<tr>
<td>Wild type</td>
<td>12</td>
<td>1</td>
</tr>
<tr>
<td>One-variant allele</td>
<td>35/5/8</td>
<td>4/4/1/1</td>
</tr>
<tr>
<td>Two-variant alleles</td>
<td>3/21/29</td>
<td>0/8/2</td>
</tr>
</tbody>
</table>

* Values are expressed as medians, with ranges in parentheses.
† Number.
‡ Creatinine clearance was calculated with Cockcroft-Gault equation.
ular filtration (Hirata et al., 1999). In our patient population, the median Ccr in patients 75 years or older was significantly lower than that in younger patients (Table 1), which is consistent with previous observations that renal function often decreases with advancing age (Brenner et al., 1982). Consequently, the median AUC of CDHP was significantly higher in patients 75 years or older than in those younger than 75 years. Because CDHP is not metabolized by DPD (Tatsumi et al., 1987), the decrease of glomerular filtration might directly cause the increase of CDHP concentration in elderly patients. The anticipated pharmacologic implication of the increased exposure of CDHP in elderly patients would be a greater degree of inhibition of DPD activity, which, in turn, would lead to a higher AUC of 5-FU in patients 75 years or older. The opposing effects of aging on the oral clearance of tegafur and the AUC of CDHP are likely to offset each other, leading to a similar AUC of 5-FU in patients 75 years or older compared with those younger than 75 years.

One limitation of the current study is the relatively small number of elderly patients that was studied, suggesting that the study might have limited power to detect subtle group differences in the pharmacokinetic profile of 5-FU and that confirmatory analyses in a larger patient population are warranted. Furthermore, although the median AUC of 5-FU was similar in older and younger patients, additional investigation is required to examine the effects of aging on pharmacodynamic factors associated with S-1 chemotherapy.

In conclusion, no significant difference in AUC of active 5-FU between patients 75 years or older and those younger than 75 years was found.

Acknowledgments. We thank Alex Sparreboom (St. Jude Children’s Research Hospital, Memphis, TN) for review of the manuscript.

References


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