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, Cmax, Tmax, AUC(0-∞), and T1/2 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 T1/2 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 T1/2 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-∞) 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 T1/2, 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

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/m² 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/mm³ but <12,000/mm³, platelets ≥10 x 10⁴/mm³, total bilirubin ≤1.5 mg/dl, GOT GPT < 10 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/m² (half the recommended dose of 80 mg/m² per day). The drug was administered within 30 min after breakfast at a dose of 40 mg (20 mgxtwo capsules) for body surface area (BSA) <1.25 m², 50 mg (25 mgxtwo capsules) for BSA 1.25–1.50 m², and 60 mg (20 mgxtree capsules) for BSA >1.50 m². 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 by 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 (Cmax), maximum plasma concentration time (Tmax), AUC, and half-life (T1/2) 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