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SHORT COMMUNICATION

Safety, efficacy and pharmacokinetics of S-1 in a hemodialysis patient with advanced gastric cancer

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Abstract
Purpose The safety and efficacy of S-1 in hemodialysis patients have not been established. We evaluated the safety and efficacy and pharmacokinetics of S-1 in a hemodialysis patient with advanced gastric cancer.
Patient A 66-year-old Japanese man with chronic renal failure, who had undergone hemodialysis three times a week for 3 years. Based on the diagnosis of stage IV gastric cancer, S-1 therapy was started. S-1 was administered 11 times at a daily dose of 23.5 mg/m^2 (40 mg/body) after hemodialysis, followed by a rest. One course was a period of 28 days. Blood samples were obtained after the first administration of S-1 and before beginning the fourth course. The concentration of 5-FU was determined by high-performance liquid chromatography.
Results Area under the concentration–time curve (AUC) of 5-FU was 2647.2 ng h/mL after administration of S-1 of 23.5 mg/m^2 (40 mg/body). During the S-1 treatment, serious adverse events such as neutropenia were not observed; however, decreases in hemoglobin level were observed (grade 3). The treatment was well tolerated. After the second course of chemotherapy, the primary lesion showed a partial response and lymph node metastases and liver metastases showed stable disease.
Conclusions Our results suggest that S-1 is an important treatment option for patients with hemodialysis with advanced gastric cancer.

Keywords S-1 · Hemodialysis · Pharmacokinetics · Advanced gastric cancer

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Introduction

S-1 is an oral fluoropyrimidine anticancer drug containing three agents: tegafur, a prodrug of 5-fluorouracil (5-FU); 5-chloro-2,4-dihydroxypyridine (CDHP), a dihydropyrimidine dehydrogenase (DPD) inhibitor; and potassium oxonate, a reducer of gastrointestinal toxicity that inhibits tegafur activation in the gastrointestinal tract [1]. S-1 monotherapy showed non-inferiority to 5-FU and achieved a high response rate of more than 40% for advanced gastric cancer [2]. Therefore, S-1 is widely used as a first-line drug for advanced gastric cancer in Japan.

The conversion of tegafur into 5-FU and the degradation of 5-FU occur mainly in the liver [3]. In contrast, CDHP is

an inhibitor of DPD, a rate-limiting enzyme of 5-FU metabolism, and about 50% of CDHP is excreted in the urine [1]. Thus, the plasma concentration of 5-FU is increased by accumulation of CDHP in patients with renal dysfunction, and the incidence of serious adverse events such as myelosupression may be enhanced [4]. However, there are only a few reports about S-1 treatment for advanced gastric cancer with renal failure [5, 6]. In addition, there are also only a few pharmacokinetic studies of S-1 in the cases with hemodialysis. Although hemodialysis patients with cancer are frequently treated with chemotherapy, the safety and efficacy of the drug have not been established in hemodialysis patients.

Therefore, we evaluated the safety, efficacy and pharmacokinetics of S-1 administered to a hemodialysis patient with advanced gastric cancer.

Patient and method

The patient was a 66-year-old Japanese man (164.2 cm, 64.0 kg, body surface area was 1.7 m^2), and his medical history included hypertension, diabetes, chronic renal dysfunction and acute myocardial infarction. The patient had undergone hemodialysis three times a week for 3 years. Hemodialysis was performed using a polyester polymer alloy dialyzer (FDY-180GW, Nikkiso, Co., Japan) with a blood flow of 180 mL/min and a bicarbonate-based dialysate flow of 500 mL/min.

The patient was diagnosed with advanced gastric cancer, stage IV according to the Japanese classification of gastric carcinoma. The Eastern Cooperative Oncology Group performance status (PS) was 1. Immediately after diagnosis, S-1 treatment was chosen for the high response rate to advanced gastric cancer. The treatment regimen was according to the method of Tanaka et al. [6]. S-1 was administered 11 times at a daily dose of 40 mg (23.5 mg/m^2) after hemodialysis, followed by a rest. One course was a period of 28 days. To our knowledge, no drug that would influence the metabolism of S-1 was administered to the patient.

In the first treatment course, blood samples were obtained at 0, 3, 5 and 24 h after the first administration of S-1 and before and at the end of the next hemodialysis. To evaluate the 5-FU accumulation, blood samples were obtained at the end of the next hemodialysis and before the beginning of the fourth course. After centrifugation at 3,000 rpm, for 10 min, plasma was collected and stored at −20°C until the analysis. The concentration of 5-FU was determined by high-performance liquid chromatography according to the method of Loos et al. [7]. Pharmacokinetic parameters were analyzed by a model-independent method using the MULTI computer program [8]. The evaluation of adverse effects was based on the Common Terminology Criteria for Adverse Events v3.0. Responses were evaluated using the Response Evaluation Criteria in Solid Tumor (RECIST) guideline. The study was approved by the institutional review board of Izumi General Medical Center, and written informed consent was obtained from the patient.

Result and discussion

This case study described the pharmacokinetics and safety of S-1 in a hemodialysis patient with advanced gastric cancer. Fig. 1 shows the plasma concentration–time profile of 5-FU after S-1 administration (23.5 mg/m^2, 40 mg/body) in the first treatment course. 5-FU was not detected at the end of the next hemodialysis and before the beginning of the fourth course. The pharmacokinetic parameters 5-FU $AUC_{0–24}$, 5-FU $AUC_{0–\infty}$ and $t_{1/2}$ were 2647.2 ng h/mL, 3276.7 ng h/mL and 8.7 h, respectively. Taguchi et al. [9] reported that 5-FU $AUC_{0–24}$ and $t_{1/2}$ after S-1 administration (100 mg/body) in the patient with adequate renal function by phase I study were 2818.5 ng h/mL and 2.8 h, respectively. The 5-FU $AUC_{0–24}$ in this case was comparable to that in a phase I study in which patients were treated with the standard dose of S-1. On the other hand, elongation of $t_{1/2}$ was observed.

The 5-FU $AUC_{0–24}$ values after S-1 administration in hemodialysis patients vary among reports. For example, the 5-FU $AUC_{0–24}$ value after S-1 administration at a dose of 33.4 mg/m^2 (50 mg/body) was 2417.7 ng h/mL in the patient maintained on hemodialysis [5], and those

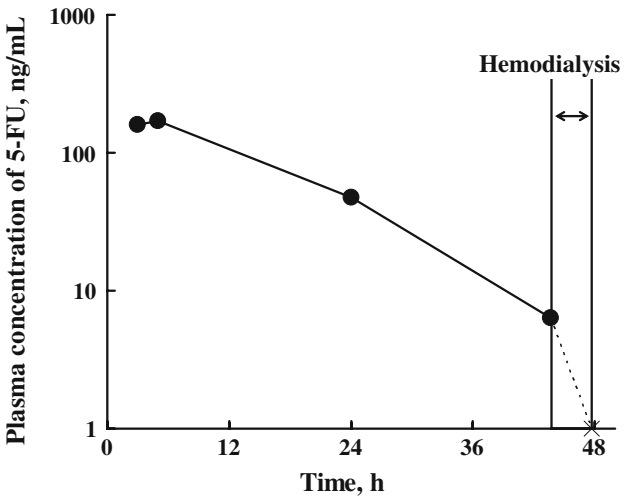

Fig. 1 Plasma concentration–time profiles of 5-FU after administration of S-1 (40 mg/body, 23.5 mg/m^2). S-1 was administered to the patient immediately after hemodialysis. After hemodialysis, 5-FU was not detected in the plasma

at a dose of 27.0 mg/m^2 (40 mg/body) and 33.8 mg/m^2 (50 mg/body) of S-1 were 2,437.0 and 3358.4 ng h/mL, respectively [6]. Additionally, several reports suggest that 5-FU AUC is correlated with therapeutic effect and adverse events [10–12]. Therefore, the evaluation of plasma 5-FU level is important in hemodialysis patients with S-1 administration.

During the S-1 treatment, PS was maintained at grade 1. Serious adverse events such as neutropenia were not observed; however, decreases in hemoglobin level were observed (grade 3). Because of the hemoglobin decrease, a red blood cell transfusion was performed after the first and second S-1 treatment. Attention to hemoglobin level is especially important in hemodialysis patients, because anemia is a frequent complication of chronic kidney disease. In fact, the patient had undergone two red blood cell transfusions before this therapeutic regimen was started. Therefore, we considered that S-1 chemotherapy might not be a direct cause of the hemoglobin decrease, and that this treatment was tolerated by the patient.

After the second course of chemotherapy, the response was assessed by computed tomography (CT) scanning and tumor markers. According to the CT scan, the primary lesion showed a partial response, while lymph node metastases and liver metastases showed stable disease. In regards to tumor markers, carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19–9 level were 5 ng/mL and 16.3 U/mL, respectively. These tumor marker values were achieved only after the second course of chemotherapy. Therefore, we consider that it is inadequate to evaluate the response to chemotherapy by this assessment alone. However, these marker values were in the normal range, and we therefore considered that at least the disease was not progressive. The patient received eight courses of chemotherapy and died 8 months after the initiation of chemotherapy. Therefore, we concluded that S-1 is safe and effective in hemodialysis patients.

Conclusion

S-1 (40 mg/body/day) was safely and effectively administered to a patient after hemodialysis. Since S-1 is administered orally, it is convenient for patients, especially for hemodialysis patient who tend to have water restrictions. Therefore, S-1 is a therapeutically useful drug from the viewpoint of quality of life. In conclusion, our results suggest that S-1 is an important treatment option for hemodialysis patients with advanced gastric cancer.

Conflicts of interest statement We declare that we have no conflict of interest.

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