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ORIGINAL ARTICLE

Phase II study of S-1 as first-line treatment for elderly patients over 75 years of age with advanced gastric cancer: the Tokyo Cooperative Oncology Group study

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Abstract
Purpose This prospective multicenter phase II study was carried out to investigate the efficacy, safety and pharmacokinetics of S-1 monotherapy in elderly patients over 75 years of age, with unresectable advanced or recurrent gastric cancer.
Methods Patients had measurable or evaluable lesions according to the Japanese Classification of Gastric Carcinoma. S-1 (25–60 mg determined by the body surface area and creatinine clearance) was given orally, twice daily. A course of treatment consisted of 4-week administration followed by a 2-week rest period, and the patients received repeated courses.
Results Thirty-three patients were enrolled. Pharmacokinetics of S-1 was studied in six patients, and the maximum plasma concentrations of respective metabolites after S-1 administration were found to be similar to those reported for younger cancer patients. The overall response rate in 33 patients was 21.2% (95% CI, 10.7–37.8%), and median progression-free survival was 3.9 months, with a median overall survival of 15.7 months. Frequently noted adverse events include leukopenia, neutropenia, anemia, anorexia, and fatigue. As for serious adverse events, relatively higher frequencies of anemia (9%) and anorexia (12%) of grade 3 severity were found, but there were no grade 4 episodes.
Conclusions The results suggest that S-1 monotherapy is safe and useful for elderly patients with unresectable

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advanced or recurrent gastric cancer when the dose is selected with caution, taking into account renal function.

Keywords S-1 · Gastric cancer · Elderly · Phase II study

Introduction

Gastric cancer is the second most frequent cause of cancer death in the world; there are reportedly 700,000 deaths from gastric cancer annually. The incidence of gastric cancer varies greatly among different regions. The frequencies of gastric cancer are said to be highest in East Asia, Eastern Europe, and one part of Latin America. In Japan, gastric cancer has been second, after lung cancer, among cancer-related deaths since 1999. The number of deaths due to gastric cancer in this country was 49,500 in 2003, accounting for 16% of all cancer deaths [1, 2].

The prognosis of unresectable advanced or recurrent gastric cancer is unfavorable. Although a number of relevant randomized studies have been carried out in both Western and Asian countries, no standard treatment for this condition has yet been established. In Japan, the JCOG9205 study conducted by the Japan Clinical Oncology Group (JCOG) demonstrated combination therapy with 5-fluorouracil (5-FU) and cisplatin to be significantly superior to 5-FU monotherapy in terms of the response rate and progression-free survival (PFS), but there was no significant benefit in overall survival (OS) [3]. Therefore, the subsequent JCOG9912 study examined the superiority of irinotecan/cisplatin combination therapy and the non-inferiority of S-1 monotherapy with OS as the primary endpoint, to that of 5-FU monotherapy used as the reference arm [4]. S-1 is an oral anticancer drug, based on biochemical modulation, which consists of a mixture of the 5-FU prodrug tegafur (FT) and two modulators, i.e., 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo), in a molar ratio of 1:0.4:1 [5]. CDHP inhibits the degradation of 5-FU strongly and reversibly by inhibiting the activity of dihydropyrimidine dehydrogenase, an enzyme that degrades 5-FU, thereby achieving prolonged high concentrations of 5-FU in blood and tumor tissue [6]. Oxo is distributed in the gastrointestinal tract at a high concentration after oral administration, and alleviates gastrointestinal toxicities by competitively and reversibly inhibiting orotate phosphoribosyltransferase, an enzyme participating in the phosphorylation of 5-FU [7]. The JCOG9912 study showed that both the irinotecan/cisplatin combination therapy and S-1 monotherapy achieved significantly better response rates and PFS than 5-FU monotherapy. In regard to OS, however, no superiority of the irinotecan/cisplatin combination therapy to 5-FU monotherapy was demonstrated, although S-1 monotherapy was found to be non-inferior to 5-FU monotherapy [4]. In addition, the superiority to the reference arm S-1 monotherapy was examined by the SPIRITS trial for S-1/cisplatin combination therapy [8], and by the GC0301/TOP002 trial for S-1/irinotecan combination therapy [9]. As a result, the S-1/cisplatin therapy showed a significant survival benefit as compared with S-1 monotherapy, whereas the S-1/irinotecan therapy failed to show such benefit. Thus, in Japan the practical standard therapy for patients with unresectable advanced or recurrent gastric cancer is currently the S-1/cisplatin combination therapy in patients who can tolerate cisplatin, whereas it is S-1 monotherapy in patients who are not suitable for cisplatin.

However, since patients enrolled in these randomized trials were restricted to those under the age of 75 years, the significance of chemotherapy with S-1 in elderly gastric cancer patients, a patient population that has been growing annually, remains unclear. The Tokyo Cooperative Oncology Group (TCOG) GI group speculated that S-1 monotherapy would be useful for elderly gastric cancer patients since it is highly effective for gastric cancer with minimal adverse reactions [10, 11]. Thus, this prospective multicenter phase II study was carried out to examine the clinical efficacy, safety and pharmacokinetics (PK) of S-1 monotherapy in elderly patients over 75 years of age, with unresectable advanced or recurrent gastric cancer.

Materials and methods

Patients

Patients over 75 years of age who had histologically confirmed gastric adenocarcinoma were enrolled. All had measurable or evaluable lesions according to the Japanese Classification of Gastric Carcinoma, 13th edition [12]. The patients had no history of prior treatment and 6 months or more had elapsed since end of postoperative adjuvant chemotherapy (those who had postoperative adjuvant chemotherapy with S-1 were excluded). Their Eastern Cooperative Oncology Group (ECOG) performance status was 0-2. They showed adequate organ function, with the following laboratory data: leukocyte count $\geq$4,000/mm^3 but $<$12,000/mm^3, platelet count $\geq$100,000/mm^3, hemoglobin $\geq$8.0 g/dL, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) $\leq$2.5$\times$ the upper limit of normal (ULN) (left to the investigator's discretion when deviation was attributable to the underlying disease, e.g. hepatic metastasis), total bilirubin $\leq$ULN, serum creatinine $\leq$1.2 mg/dL, and creatinine clearance (Ccr) $\geq$30 mL/min. Survival of at least 3 months was expected for these patients. Written informed consent was obtained from each patient. The participating facilities were approved by institutional review boards.

Toxicity and response criteria

Adverse events were evaluated at least once every 2 weeks during the study period according to the NCI-Common Toxicity Criteria, version 2.0. The tumor response was evaluated every 4–6 weeks after the beginning of therapy according to the Japanese Classification of Gastric Carcinoma, 13th edition [12]. Two important elements in the Japanese criteria were: (1) using X-ray and endoscopic findings to assess primary gastric lesions and (2) a new methodology to evaluate diffusely infiltrating tumors. Under the Japanese criteria, primary lesions were classified as: (a) measurable, (b) evaluable but not measurable, and (c) diffusely infiltrating lesions [13, 14].

Treatment dose and schedule

S-1 was given orally after meals, twice daily. A course of treatment consisted of 4-week administration followed by a 2-week rest period, and the patients received repeated courses. The starting dose was determined by the body surface area (BSA) and Ccr (Table 1). Ccr values were the observed or predicted values obtained from the Cockcroft–Gault formula [15]. When thrombopenia of grade 2 or more, leukopenia or neutropenia of grade 3 or more, non-hematologic toxicities (diarrhea, stomatitis, vomiting, anorexia) of grade 2 or more, hepatic dysfunction of grade 2 or more (elevated total bilirubin, elevated AST/ALT), and renal dysfunction (serum creatinine >1.2 mg/dL, Ccr < 30 mL/min) occurred, S-1 therapy was discontinued, and then resumed after recovery. When resuming S-1 therapy, modification of therapy by a one-level dose reduction and/or reduction of the administration period (e.g., 2-week administration followed by a 1-week rest period) was considered. When there was no recovery from adverse events even after a 4-week drug-free interval, disallowing resumption of S-1 therapy, the protocol treatment was discontinued.

PK study

When PK measurement was feasible, blood was sampled 2, 4 and 6 h after S-1 administration in the morning of the 5th to 10th days of S-1 therapy. Plasma was then separated and stored at −80°C. Measurement of plasma concentrations of FT, CDHP, 5-FU and Oxo according to the method of Matsushima et al. [16] was entrusted to FALCO Biosystems Ltd. (Kyoto, Japan).

Table 1 Starting dose of S-1

BSA (m^2)	Creatinine clearance (mL/min)		
	≥50	≥30 but < 50	<30
≥1.5	60 mg bid	50 mg bid	
≥1.25 but <1.5	50 mg bid	40 mg bid	Do not administer
<1.25	40 mg bid	25 mg bid	

BSA body surface area, *bid* twice daily

Statistical analysis

On the premise that the threshold response rate is 10%, and the expected response rate 30%, the necessary number of subjects was calculated to be 24 with $\alpha = 0.1$ (one-tailed) and $\beta = 0.1$. Taking possible ineligible patients into account, the target number of patients was 30. The primary endpoint of this study was the response rate, with the response determined by the Response Evaluation Committee, based on imaging findings. Secondary endpoints were the time to treatment failure (TTF; including progression, death or early discontinuation of protocol treatment), PFS, OS and safety. TTF, PFS and OS were estimated by the Kaplan–Meier method using the enrollment date as the initial date of reckoning.

Results

Patient characteristics

A total of 33 patients comprising 20 males and 13 females were enrolled between July 2004 and September 2006. The patient characteristics are shown in Table 2. The median age was 80 years (19 patients; 76–80 years, 9; 81–85 years, and 5; 86–91 years), and the starting dose determined by BSA and Ccr was 60 mg in four patients, 50 mg in 14, 40 mg in 12, and 25 mg in 3. Twenty-nine patients had gastric lesions, which were included among the target lesions for evaluating the tumor response.

Response to therapy

Table 3 shows the response rates determined by the Response Evaluation Committee, which analyzed the results on an intention-to-treat basis. Among the 33 patients, complete response (CR) was achieved in one and partial response (PR) in 6, resulting in a response rate of 21.2% (80% CI, 13.6–31.6%; 95% CI, 10.7–37.8%). The lower limit of the 80% CI (13.6%) exceeded the threshold value (10%), and the primary endpoint was met. The disease control rate including 13 patients showing no change was 61%. Of the 29 patients who had primary gastric lesions, one had CR, and two had PR, showing a response rate of 10.3%, with only four patients having progressive disease (PD). The patient with CR underwent surgery, and the CR was confirmed pathologically [17].

Table 2 Patient characteristics

Characteristics	No. of patients (%)
Enrolled	33
Age (years)	
Median	80
Range	76–91
Gender	
Male	20 (61)
Female	13 (39)
ECOG performance status	
0	14 (42)
1	17 (52)
2	2 (6)
Body surface area (m^2)	
<1.25	9 (27)
≥1.25 but <1.5	17 (52)
≥1.5	7 (21)
Creatinine clearance (mL/min)	
≥50	21 (64)
≥30 but <50	12 (36)
Initial actual dose (mg bid)	
60	4 (12)
50	14 (42)
40	12 (36)
25	3 (9)
Histology	
Well-moderate differentiated	16 (48)
Poorly differentiated	17 (52)
Site of disease	
Stomach	29 (88)
Liver	14 (42)
Lymph node	16 (48)
Others	17 (52)

ECOG Eastern Cooperative Oncology Group, *bid* twice daily

Table 3 Response rate

No. of patients	CR	PR	NC	PD	NE	Response rate (%)
33	1	6	13	7	6	21.2 (95% CI 10.7–37.6)

CR complete response, *PR* partial response, *NC* no change, *PD* progressive disease, *NE* not evaluable, *CI* confidence interval

Progression of disease occurred in 26 patients, and 24 died over a median follow-up period of 14.8 months. Median TTF was 3.2 months (95% CI, 2.6–5.6 months), median PFS 3.9 months (95% CI, 2.6–8.0 months), and median OS 15.7 months (95% CI, 10.4–22.7 months) (Fig. 1). Second-line treatment was given to 18 patients (54.5%) (paclitaxel in 12, irinotecan-containing regimens in 5, and tegafur/uracil in 1), and 8 of the 18 patients received third-line treatment.

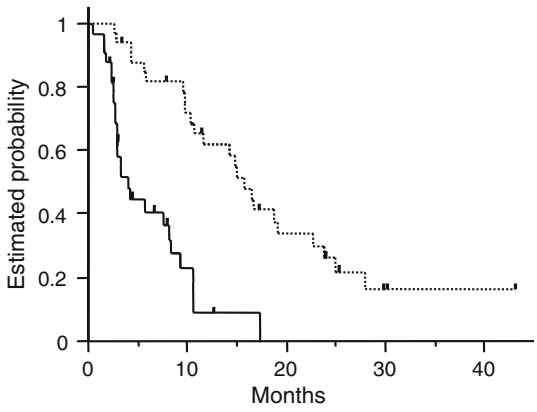

Fig. 1 Progression-free survival (*solid-line*) and overall survival (*dotted-line*)

Table 4 Adverse events

	No. of patients (%)		
	All grade	Grade 3	Grade 4
Leukopenia	14 (42)	0	0
Neutropenia	14 (42)	1 (3)	0
Anaemia	13 (39)	3 (9)	0
Thrombocytopenia	8 (24)	0	0
Elevated AST	3 (9)	0	0
Elevated ALT	1 (3)	0	0
Hyperbilirubinaemia	3 (9)	0	0
Elevated creatinine	1 (3)	0	0
Mucositis	7 (21)	0	0
Anorexia	14 (42)	4 (12)	0
Nausea	5 (15)	2 (6)	0
Vomiting	2 (6)	1 (3)	0
Diarrhea	4 (12)	0	0
Pigmentation disorder	7 (21)	0	0
Fatigue	10 (30)	2 (6)	0

AST aspartate aminotransferase, *ALT* alanine aminotransferase

Safety

Table 4 shows hematologic and non-hematologic adverse events. Frequent adverse events include leukopenia (all grade, 42%), neutropenia (42%), anemia (39%), anorexia (42%), and fatigue (30%). As for serious adverse events, anemia (9%) and anorexia (12%) of grade 3 were relatively frequent, but there were no grade 4 episodes.

PK

Pharmacokinetics measurement was carried out in a total of 6 patients, 4 males and 2 females. Their median age was 81 years (range 78–91 years), with Ccr being at least 50 mL/min in 2 and 30 mL/min to 50 mL/min in 4. The

Table 5 Pharmacokinetics

	Plasma concentration (ng/mL)		
	2 h	4 h	6 h
FT	3690.3 ± 1196.4	3739.2 ± 1240.2	3213.8 ± 1027.5
CDHP	197.6 ± 33.1	248.5 ± 68.8	154.7 ± 45.0
5-FU	98.7 ± 30.3	138.1 ± 27.7	100.4 ± 27.0
Oxo	53.7 ± 9.4	60.6 ± 17.6	39.5 ± 12.5

FT tegafur, *CDHP* 5-chloro-2,4-dihydroxypyridine, *5-FU* 5-fluorouracil, *Oxo* potassium oxonate

S-1 dose was 40 mg in 3 patients, 50 mg in 2, and 60 mg in one. The plasma concentrations of FT, CDHP, 5-FU and Oxo all peaked 4 h after administration, and the mean concentrations at 4 h (C_{max}) were 3739.2, 248.5, 138.1, and 60.6 ng/mL, respectively (Table 5).

Discussion

The aging process varies widely among individuals, and elderly people of the same age do not necessarily have similar physical conditions. However, in general, elderly people are likely to have decreased major organ functions and may have a number of concomitant diseases. Therefore, chemotherapy in elderly patients requires particular caution. Previous phase II studies have demonstrated that S-1 achieves high response rates with extremely low frequencies of serious adverse events in patients with advanced or recurrent gastric cancer [10, 11]. Since the possible usefulness of this therapy in elderly patients with gastric cancer was thus suggested, this study was designed to investigate this issue. However, since CDHP, a component of S-1, is excreted by the kidneys, decreased renal function leads to decreased clearance of CDHP, resulting in a markedly elevated concentration of 5-FU in blood; this may cause strong adverse events [18]. In this regard, Ccr and BSA were taken into consideration when determining the dose of S-1.

Hirata et al. carried out a pharmacokinetic study of S-1 in 12 patients with cancer (median age 54 years), and determined PK parameters after a single dose and after multiple dosing for 28 consecutive days [19]. They reported that the number of days required to reach a steady-state plasma concentration was about 4 days for FT, and about 2 days for CDHP, 5-FU and Oxo. Based on these findings, blood was sampled 5–10 days after the beginning of S-1 therapy in this study. In our PK study, we used only three sampling points, i.e., 2, 4 and 6 h after S-1 administration, and only C_{max} was obtained, to minimize the number of blood sampling points in view of the subjects' advanced ages. C_{max} values (at 4 h) of FT, CDHP, 5-FU and Oxo were almost the same as those reported by Hirata et al. [19]. The PK data in our study were obtained from only six patients, and did not allow calculation of PK parameters other than C_{max}, but were sufficient to allow as to assume that the S-1 doses used in this study did not correspond to over-dosages. In fact, there were hardly any serious hematologic adverse events in this study, supporting this assumption.

Since the stomach is a hollow viscus, gastric lesions often infiltrate diffusely, making evaluation of tumor response difficult. Therefore, the response evaluation criteria in solid tumors (RECIST) criteria, which are widely used internationally, focus on only metastatic lesions as the target lesions for evaluation of the response of gastric cancer and exclude primary lesions from the target lesions [20]. In Japan, where the incidence of gastric cancer is high, patients with gastric cancer often have primary lesions. Evaluation of the response of primary lesions seems to be important because their response is closely related to the quality of life (QOL) of the patient and because the survival period is reported to be longer in responders than in non-responders [14, 21, 22]. Thus, the present study included primary lesions in the target lesions, and evaluated tumor responses according to the Japanese Classification of Gastric Carcinoma (Japanese criteria). Although the response rate for primary lesions was lower than the corresponding rate for target lesions as a whole, there were only four cases with PD, suggesting decreased QOL due to progression of primary lesions to be relatively rare.

As phase III studies of S-1 monotherapy in patients 75 years of age or younger with advanced or recurrent gastric cancer, the JCOG9912 study demonstrated that the response rate was 28%, median TTF 4.0 months, median PFS 4.2 months, and median OS 11.4 months, whereas the SPIRITS trial reported that the response rate was 31%, median TTF 3.9 months, median PFS 4.0 months, and median OS 11.0 months [4, 8]. Lee et al. carried out a randomized phase II study in elderly patients aged 65 or over (median age 71 years), with advanced or recurrent gastric cancer, and reported that S-1 monotherapy yielded a response rate of 29%, median TTF of 3.0 months, median time to progression of 4.2 months, and median OS of 8.1 months [23]. In comparison with these studies, the present study achieved better results in terms of OS, although the response rate was lower. The response rate in this study was not necessarily satisfactory, but the PD rate was low, and disease control was achieved to a considerable extent. The OS prolongation observed in this study may have resulted from the following scenario: S-1 monotherapy for elderly gastric cancer patients was effective to control not only metastatic but primary lesions and was associated with minimal adverse events, rarely causing patients' QOL to decrease, and thus allowing more than half of the enrolled patients to proceed to second-line treatment.

The results of two phase II studies carried out in Italian elderly patients with advanced or recurrent gastric carcinoma were recently reported. First, Graziano et al. used a combination regimen consisting of weekly cisplatin, 5-FU, and folinic acid (PLF) and achieved a response rate of 43%, median time to progression of 5.3 months, and median OS of 8.6 months in 58 enrolled patients [24]. Subsequently, Santini et al. used oxaliplatin instead of cisplatin in a combination regimen of weekly oxaliplatin, 5-FU and leucovorin (OXALF), and reported that the response rate was 45%, median time to progression 5.0 months, and median OS 9.0 months in 42 patients [25]. Both combination regimens, known as being similarly tolerable by elderly and younger patients, were reported to be promising. However, the median age of patients in the study by Graziano et al. was 76 years (range 67–82 years), and 52% required administration of granulocyte colony-stimulating factor. The study by Santini et al. included patients with a median age of 73 years (range 70–81 years), 33.3% of whom had neurotoxicity (all grades). Although these combination regimens may be useful for patients who can tolerate cisplatin or oxaliplatin therapy, it seems that S-1 monotherapy is more promising for gastric cancer patients over 75 years of age, i.e. the elderly, like those examined in our study because this therapy is associated with minimal adverse events and is expected to contribute to prolongation of the survival period. The balance between the benefits and risks of S-1-based combined regimens for elderly gastric cancer patients should be considered and such regimens should probably be cautiously assessed in the future.

In conclusion, the primary endpoint of this study was met and our results suggest that S-1 monotherapy would be a safe and useful form of chemotherapy for elderly patients, i.e. those aged over 75, with unresectable advanced or recurrent gastric cancer, although further confirmation of these findings is necessary because of the small number of patients examined in this study. When prescribing S-1 for elderly patients, advanced age alone does not require dose reduction, but it is important to select the therapeutic dose with caution, taking into account the patient's renal function level.

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