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ORIGINAL ARTICLE

Phase II study of sequential treatment with S-1 and cisplatin for metastatic gastric cancer

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Abstract
Purpose This single-arm, phase II clinical study evaluated the efficacy and safety of sequential treatment with S-1 followed by cisplatin in patients with advanced or recurrent gastric cancer.
Methods Fifty patients with histologically confirmed advanced or recurrent gastric cancer and an Eastern Cooperative Oncology Group performance status of 0–2 who had measurable and/or assessable lesions and gave written informed consent were enrolled. S-1 (40 mg/m^2, bid) was administered on days 1–21, and cisplatin (70 mg/m^2) was given as an intravenous infusion on day 22 of a 35-day cycle. Treatment was continued until disease progression or intolerable adverse events. Cisplatin was administered for 6 cycles. Adverse events were assessed according to Common Terminology Criteria of Adverse Events version 3.0, and efficacy was evaluated according to the Response Evaluation Criteria in Solid Tumors version 1.0 for patients with measurable lesions and by the criteria of the Japanese Research Society for Gastric Cancer for all patients.
Results Efficacy could be evaluated in 49 of the 50 enrolled patients. The median age was 62 years. Lesions were measurable in 38 patients and assessable in 11. The response rate was 44.7% in patients with measurable lesions and 40.8% overall. The progression-free survival and overall survival were, respectively, 233 days (7.8 months) and 574 days (19.0 months) in patients with measurable lesions and 192 days (6.4 months) and 402 days (13.4 months) overall. Serious adverse events (grade 3 or higher) included neutropenia (24.5%), anemia (20.4%), and anorexia (20.4%) and were safely managed.
Conclusion The safety and effectiveness of sequential treatment with S-1 followed by cisplatin every 35 days is equivalent to that reported for conventional chemotherapeutic regimens in patients with advanced or recurrent gastric cancer.

Keywords S-1 · Cisplatin · Metastatic gastric cancer · Phase II study

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Introduction

Advanced and recurrent gastric cancer remains a serious medical problem, with a 5-year survival rate of less than 5% [1]. The standard therapeutic strategy against this disease has been systemic chemotherapy, based on the results

of randomized studies comparing chemotherapy with best supportive care (BSC) [2–4]. Recent advances in cancer chemotherapy have led to the development of various effective regimens, including 5-fluorouracil (5-FU), cisplatin, and new classes of anticancer agents [5].

S-1 is an oral fluoropyrimidine preparation combining tegafur, a prodrug of 5-FU, with 5-chloro-2,4-dihydroxypyridine, which inhibits dihydropyrimidine dehydrogenase, and potassium oxonate, which protects against tegafur-induced toxicity [6]. A randomized phase III study comparing S-1 with single-agent 5-FU and a combination of irinotecan plus cisplatin in patients with metastatic gastric cancer concluded that S-1 was noninferior to 5-FU therapy in terms of overall survival [7]. These results suggested that S-1 may be a key drug for the treatment of advanced gastric cancer. S-1 has also been combined with other agents, including cisplatin, irinotecan, and taxanes. S-1 plus cisplatin is considered one of the most promising regimens, and a phase I/II trial reported a very high response rate of 76%, with a mean survival time of 12.6 months [8]. These promising results led to a randomized phase III study comparing single-agent S-1 with S-1 plus cisplatin in patients with advanced gastric cancer. Combination chemotherapy with S-1 and cisplatin was shown to be superior to S-1 monotherapy in terms of overall survival [9]. In that study, 80 mg/m^2 of S-1 was administered for 21 days and 60 mg/m^2 of cisplatin was infused on day 8. These findings strongly suggested that a combination of S-1 plus cisplatin is a promising treatment for advanced or recurrent gastric cancer.

On the other hand, a phase III study comparing S-1 plus cisplatin for every 4 weeks with a conventional regimen of 5-FU plus cisplatin in the Caucasian population failed to show superior efficacy of the former [10]. However, the safety profiles of S-1 plus cisplatin regimen were exhibited to be more favorable than 5-FU plus cisplatin regimen.

Synergistic anti-tumor efficacy has been confirmed when 5-FU preceded cisplatin in vitro and in vivo [11, 12]. Because sequence-dependent synergistic effects were expected for a combination of S-1 and cisplatin, we conducted a phase I dose-finding study and concluded that 80 mg/m^2 of S-1 on days 1–21 and 70 mg/m^2 of cisplatin on day 22 of a 35-day cycle was the recommended dosage for further studies [13]. We now report the final results of a phase II clinical study of sequential treatment with S-1 followed by cisplatin in patients with advanced and recurrent gastric cancer.

Patients and methods

Patients

The main eligibility criteria included a histologically proved diagnosis of unresectable, locally advanced or metastatic gastric adenocarcinoma; an age of 20 to 75 years; an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less; measurable and/or assessable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0; a leukocyte count from 3,500 to 12,000/mm^3; a neutrophil count of 2,000/mm^3 or higher; a platelet count of 100,000/mm^3 or higher; a serum creatinine level within the normal range (laboratory-specific); a creatinine clearance of 50 ml/min or higher; a serum bilirubin level of less than two times the upper limit of normal (laboratory-specific); aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels of less than two times the upper limit of normal (laboratory-specific); a life expectancy of 3 months or longer; sufficient oral intake; and no prior chemotherapy or radiotherapy except for adjuvant chemotherapy completed more than 30 days before study entry. This study was approved by the local ethics committee at each institution, and patients were informed of the investigational nature of the study and provided their written informed consent before enrollment.

Patients with any of the following conditions were not eligible: central nervous system metastasis with neurologic symptoms; synchronous or metachronous double cancers; unresolved bowel obstruction or diarrhea; active gastrointestinal bleeding; interstitial pneumonia; massive pleural or peritoneal effusion; uncontrolled diabetes mellitus; a history of ischemic heart disease; or known contraindications to fluorouracil (angina pectoris, myocardial infarction in the past 6 months). Women who were pregnant, nursing infants, or wished to become pregnant were also excluded.

Study design and treatment

This single-arm, phase II study was designed to evaluate the efficacy and safety of combined chemotherapy with S-1 and cisplatin given in the fixed doses recommended by the previous phase I study [13]. The primary objective was to determine the response rate in patients with advanced or recurrent gastric cancer who had measurable lesions. Secondary objectives included the evaluation of the objective tumor response rate in patients with assessable and/or measurable tumors and the assessment of overall survival, progression-free survival, and safety.

The planned number of enrolled patients was 50, including at least 34 with measurable lesions according to RECIST version 1.0. The response of the full analysis set was analyzed according to the criteria of the Japanese Research Society for Gastric Cancer. The target number of patients was calculated on the basis of an expected response rate of 50% and a threshold response rate of 30%, with an alpha error of 0.05 and a beta error of 0.20.

Drug administration and dose modification

S-1 was orally administered on days 1–21, and cisplatin was administered on day 22 of a 35-day cycle. The dose of S-1 was 40 mg bid for a body surface area (BSA) of less than 1.25 m^2, 50 mg bid for a BSA of 1.25 to 1.50 m^2, and 60 mg bid for a BSA of greater than 1.5 m^2. Cisplatin 70 mg/m^2 was dissolved in 500 ml of saline and given intravenously (i.v.) over the course of 120-min period with appropriate hydration. A 14-day rest period followed treatment with cisplatin.

Treatment was continued until evidence of disease progression, unacceptable toxicity, or patient refusal. S-1 administration was delayed in the event of any of the following conditions on the planned day of treatment: leukopenia (a leukocyte count of less than 3,000/mm^3); a platelet count of less than 75,000/mm^3; total bilirubin, ALT, or AST levels of more than three times the upper limit of normal; serum creatinine levels of more than 1.2 times the upper limit of normal; or nonhematologic toxicity grade 3 or higher, except for nausea and vomiting. If unplanned rest of S-1 was required during 21 consecutive days of S-1 treatment period, S-1 was restarted after the resolution of the above conditions and was continued for 21 days. If the unplanned rest of longer than 8 days was required, the present course was discontinued and initiation of the next course was postponed until recovery. If the next course was not begun by 15 days after the planned day, treatment was discontinued. Treatment with cisplatin scheduled for day 22 was delayed if leukocyte counts were less than 2,000/mm^3; platelet counts were less than 50,000/mm^3; serum creatinine levels were greater than 1.2 times the upper limit of normal; creatinine clearance was less than 50 ml/min; or diarrhea of grade of 2 or higher was present. If these conditions persisted on day 31, treatment with cisplatin was skipped and the next cycle was begun after a 14-day interval. In patients with DLT, defined as the occurrence of one or more of the following National Cancer Institute (NCI) Common Toxicity Criteria (CTC): grade 3 or greater nonhematological toxicity, except for nausea and vomiting; grade 4 neutropenia lasting for more than 4 days; grade 3 neutropenic fever; or grade 4 thrombocytopenia, the dose of S-1 was reduced by approximately 20% and that of cisplatin was reduced by 10 mg/m^2. In the event of life-threatening toxicity, treatment was terminated. To prevent nausea and vomiting, 5-hydroxytryptamine-3 antagonists, dexamethasone, or both were administered i.v. before chemotherapy. Granulocyte colony-stimulating factor was given to patients who had a neutrophil count of less than 500/mm^3 or febrile neutropenia (neutrophil count, less than 1,000/mm^3).

Assessability, toxicity, and response criteria

The pretreatment evaluation included a patient history and a physical examination, a performance status assessment, a complete blood count with differential and platelet counts, a complete blood profile, carcinoembryonic antigen and carbohydrate antigen (CA) 19-9 tests, urinalysis, electrocardiography, a chest radiographic or computed tomography (CT) scan, an abdominal CT scan and/or ultrasonography, and any other appropriate diagnostic procedures to evaluate metastatic sites. During treatment, a physical examination, blood profile, and urinalysis were performed every week and a complete blood cell count was done twice a week. Sites of metastatic disease were reevaluated every 8 weeks. Chest radiography and/or an abdominal CT scanning or ultrasonography was repeated at least every 3 months if there was no evidence of lung or abdominal disease. Toxicities were monitored weekly and were scored according to the standard National Cancer Institute Common Toxicity Criteria. Responses to treatment were evaluated every 8 weeks according to RECIST version 1.0 and the criteria of the Japanese Research Society for Gastric Cancer. In criteria proposed by the Japanese Research Society for Gastric Cancer, the primary lesion was estimated by roentgen photographic and endoscopic findings, and for metastatic lesion, CT scan was used. Complete response (CR) was defined as complete disappearance of all evidence of cancer. Partial response (PR) was defined as a greater than 50% reduction in tumor volume. A new lesion or enlargement exceeding the original tumor size by 25% was defined as progressive disease (PD). All patients were categorized as having stable disease (SD).

Statistical analysis

The primary objective was to determine the response rate in patients with advanced or recurrent gastric cancer who had measurable lesions. We used a response rate of more than 30% for the null hypothesis versus a response rate of 50% for the alternative hypothesis. A total of 34 patients were recruited under the condition of a one-sided alpha error of 0.05 and a beta error of 0.20. Therefore, 34 patients with lesions measurable by the RECIST criteria version 1.0 were required. Because some patients have assessable but not measurable lesions in clinical practice, tumor responses in patients with assessable and/or measurable lesions were also assessed by the criteria of the Japanese Research Society for Gastric Cancer, version 13. The total number of patients required was estimated to be 50, because 70% of patients with assessable lesions are estimated to have measurable lesions. Fifty patients and an expected response rate of 50% would provide a 95% confidence interval of

35.5–64.5%, equivalent to 29 percentage points. The original protocol required that more than 34 patients with measurable lesions and more than 50 with assessable lesions were enrolled.

Results

Patient characteristics

Fifty patients with either advanced or recurrent gastric cancer were enrolled in this study from April 2005 to February 2008. One patient was excluded from the study before starting the protocol therapy because of a history of treatment with S-1. Among the 49 eligible patients, 39 were men and 10 were women. The median age was 62 years (range, 39–74). The ECOG performance status was 0 to 1 in 45 patients. The clinical features of the patients are shown in Table 1. Forty-one patients had unresectable tumors, and 8 had recurrent tumors. No patient had received prior chemotherapy, including adjuvant treatment. Among the 49 patients, 37 had primary gastric lesions, 36 patients had primary gastric lesions as well as metastatic lesions, and 12 had metastatic lesions alone. The major sites of metastasis were the lymph nodes, peritoneum, and liver.

Compliance

A total of 176 cycles of chemotherapy were administered. The median number of treatment cycles per patient was 3 (range, 1–10). The median and mean relative dose intensities (RDI) were, respectively, 100 and 94.4% for S-1 and 100 and 84.3% for cisplatin. The initiation of 10 treatment cycles (5.7%) was delayed because of renal dysfunction (4 cycles), myelosuppression (3 cycles), anorexia (1 cycle), or patient refusal reasons unrelated to adverse events (2 cycles). In 15 (8.5%) of the 176 cycles, cisplatin was not administered because of anorexia or nausea/vomiting (6 cycles), diarrhea (2 cycles), progressive disease (2 cycles), or other adverse events such as fatigue, renal dysfunction, myelosuppression, pneumonitis, and pneumonia (5 cycles). The dose of S-1 during protocol therapy was reduced in nine patients (18 cycles), and the dose of cisplatin was reduced in four patients (7 cycles). The dose was reduced because of adverse events in all except 1 patient, who requested that the dose was reduced for personal reasons. The protocol therapy was terminated for the following reasons: disease progression in 16 patients (32.7%), adverse events in 13 (26.5%), physician's decision in 8 (16.3%), patients' refusal in 7 (14.3%), surgical resection in 2 (4.0%), and other reasons in 3 (6.1%).

Table 1 Characteristics of subjects

	All patients	With measurable lesions
No. of patients	49	38
Gender (male/female)	39/10	32/6
Age [median (range)]	62 (39–74)	61 (39–74)
ECOG PS (0/1/2)	31/14/4	27/9/2
Inoperable/recurrent	41/8	32/6
Histology		
Intestinal	14	14
Diffuse	34	23
Unknown	1	1
Primary lesion (±)	37/12	28/10
Metastatic site		
Lymph nodes	26	24
Peritoneum	22	13
Liver	14	14
Others	4	4

ECOG Eastern Cooperative Oncology Group; *PS* performance status

Toxicity

All patients could be assessed for toxicity. There were no treatment-related deaths during any cycle of treatment in the study. Toxicities are summarized in Table 2. Forty-seven of the 49 patients (95.9%) had toxicities of any grade. Severe toxicities of grade 3 or higher according to the Common Terminology Criteria of Adverse Events occurred in 28 patients (57.1%); 24.5% had grade 3 or higher neutropenia, and 20.4% had grade 3 or higher anemia. As for nonhematologic toxicities, grade 3 anorexia occurred in 20.4% of the patients and nausea in 10.2%.

Treatment efficacy

Efficacy was evaluated in patients who had received at least one cycle of the protocol therapy; efficacy could be assessed in all 49 patients. Tumor response was assessed in 38 patients with measurable lesions. The overall response rate was 44.7% (1 complete response [CR] and 16 partial responses [PR], 95% CI: 28.6–61.7%), and the disease control rate (CR + PR + stable disease [SD]) was 89.5%. The tumor response rate assessed according to the criteria of the Japanese Research Society for Gastric Cancer in all 49 patients was 40.8% (1 CR and 19 PR, 95% CI: 27.0–55.8%), and the disease control rate was 79.6%. The median progression-free survival (PFS) of the 38 patients with measurable lesions was 233 days (7.8 months, 95% CI 149-NR), and the PFS of all patients was 192 days (6.4 months, 95% CI 149–340; Fig. 1). The median survival time (MST) was 574 days (19.0 months, 95% CI

Table 2 Toxicity

	All Grades (%)	Grade 3 or 4 (%)
Hematologic toxicity		
Leukopenia	50.0	6.1
Neutropenia	46.9	24.5
Anemia	71.4	20.4
Thrombocytopenia	24.5	4.1
Nonhematologic toxicity		
ALT/AST	8.2	4.1
Total bilirubin	4.1	2.0
Anorexia	73.5	20.4
Nausea	51.0	10.2
Vomiting	32.7	4.1
Diarrhea	34.7	4.1
Fatigue	14.3	2.0
Stomatitis	4.1	0
Rash	8.2	0

Toxicity was assessed according to the Common Terminology Criteria of Adverse Events (CTC-AE), version 3.0

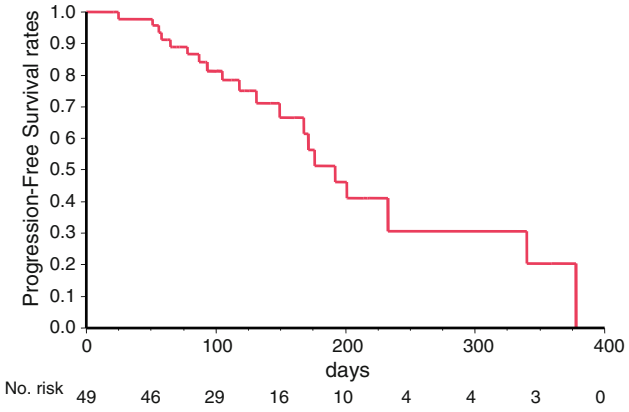

Fig. 1 Kaplan–Meier plots of progression-free survival in all patients

218–660) in patients with measurable lesions and 402 days (13.4 months, 95% CI 247–660; Fig. 2) in all patients.

Discussion

Recent clinical studies have shown that combination chemotherapy with S-1 plus cisplatin is an effective and feasible frontline therapy for advanced and recurrent gastric cancer. Previously, several studies of combined treatment with these agents reported a response rate of 40–70%, a median PFS and time to progression or time to treatment failure of 4.5–6.5 months, and an MST of 11–13 months (Table 3a). In our study, the response rate was 40.8% (95% CI: 27.0–55.8%) in the study group as a whole and 44.7% (95% CI: 28.6–61.7%) in patients with measurable lesions

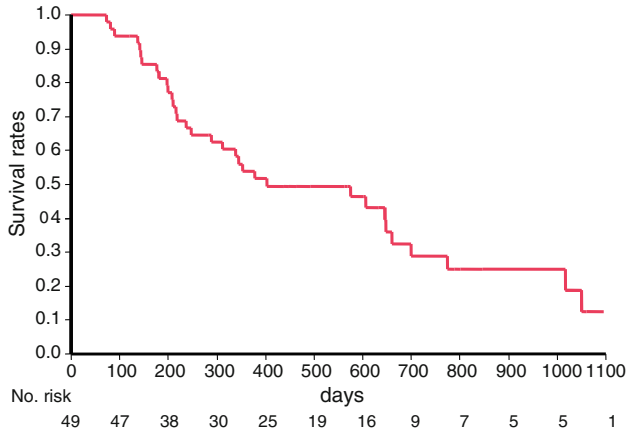

Fig. 2 Kaplan–Meier plots of overall survival in all patients

and primary endpoint was not met. However, in all patients or in those with measurable lesions, the median PFS was 6.4 and 7.8 months and the median MST was 13.4 and 19.0 months, respectively. These findings strongly suggested that sequential therapy with S-1 plus cisplatin was effective against advanced and recurrent gastric cancer. Although other recent studies of S-1 plus cisplatin (Table 3a), excluding one Phase III study, enrolled only patients with measurable lesions, the present series of 38 patients with measurable lesions generated a superior PFS and OS. Several factors most likely contributed to these good outcomes. First, although the protocol allowed patients with a PS of 2 to be enrolled, only 1 such patient participated in the trial, suggesting that patients in relatively good physical condition were preferentially enrolled. Second, the dose intensities of S-1 and cisplatin were slightly high and the incidence of skipping treatment with cisplatin was low. It is also conceivable that preceding treatment with S-1 synergistically enhanced the effect of cisplatin by means of biochemical modification.

Second-line chemotherapy with irinotecan-based regimens may contribute to prolonged survival in patients with advanced gastric cancer [14]. In our study, the MST after terminating the protocol therapy was 11.2 months in patients with measurable lesions and 6.9 months overall. As compared with the MST of 7 months in the SPIRITS study, our findings suggest that patients with measurable lesions may in particular derive a greater survival benefit from our regimen for first-line chemotherapy. In addition, a possibility that extending survival after failure of the first-line treatment may depend on the subsequent treatments should be concerned.

As for safety, although protocol treatment was terminated in more than half patients due to other reasons than disease progression, the median number of treatment cycles was equivalent to that of all patients (data not shown). In addition, profile of adverse events including neutropenia,

Table 3 Recent S-1/cisplatin studies

	Regimen	Phase	*N*	RR (%)	DCR (%)	PFS (M)	OS (M)
a. Efficacy in recent S-1/cisplatin studies							
Present study	q5w	II	49	40.8	79.6	6.4	13.4
			38 (with measurable lesions)	44.7	89.5	7.8	19.0
SPIRITS [9]	q5w	III	148	54	70.0	6.0	13.0
Koizumi et al. [8]	q5w	II	25	76.0	92.0	5.3 (TTP)	12.6
Iwase et al. [17]	q4w	II	42	50.0	85.7	NA	11.2
Abe et al. [18]	q4w	II	51	40.6	87.5	4.4	13.5
FLAGS [10]	q4w	III	527	29.1	NA	4.8	8.6
Lee et al. [15]	q3w	II	62	48	84.0	5.3	10.0

	Regimen	Phase	*N*	Adverse events of grade 3 or higher			
				Neutropenia (%)	Anemia (%)	Nausea (%)	Anorexia (%)
b. Safety profiles of recent S-1/cisplatin studies							
Present study	q5w	II	49	24.5	20.4	10.2	20.4
SPIRITS [9]	q5w	III	148	40	26	11	30
Koizumi et al. [8]	q5w	II	25	15.8	15.8	15.8	26.3
Iwase et al. [17]	q4w	II	42	–	7	10	–
Abe et al. [18]	q4w	II	51	29	17	21	31
FLAGS [10]	q4w	III	527	32.3	20.7	7.5	6.0
Lee et al. [15]	q3w	II	62	33.4	31.0	2.4	23.8

RR response rate; *DCR* disease control rate; *PFS* progression-free survival; *OS* overall survival; *M* month; *TTP* time to progression; *NA* not available

anemia, anorexia, and nausea was similar to the results of previous studies (Table 3b). Therefore, we thought that the protocol regimen could be resulted to be feasible.

A 5-week regimen of S-1 plus cisplatin was established as a standard chemotherapeutic regimen for advanced gastric cancer on the basis of the phase III SPIRITS study [9]. However, alternative regimens of S-1 and cisplatin have also been reported. Kan and colleagues used a 3-week regimen in which S-1 was administered for 14 days followed by 7 days' rest, and cisplatin was administered on day 1; that study reported a response rate of 48% and an overall survival of 10.0 months [15]. In Western countries, a 4-week regimen in which S-1 is administered for 21 days and cisplatin is given on day 1 has been used [10]. A randomized phase III study of capecitabine plus cisplatin with or without trastuzumab showed that the inclusion of trastuzumab enhanced overall response and survival in patients with Her-2-positive advanced gastric cancer (ToGA study) [16]. A 3-week regimen of 80 mg/m^2 cisplatin was shown to be safe in the ToGA study, which used a higher dose intensity of cisplatin than other studies. To evaluate the effectiveness of higher dose intensity, a randomized phase III trial comparing a 3-week regimen with a 5-week regimen of S-1 plus cisplatin is now underway. The higher dose intensity of cisplatin employed in the present study will probably be shown to be feasible and effective. Sequential treatment with S-1 followed by cisplatin, evaluated in the present study, is expected to become a major option for chemotherapy in patients with advanced gastric cancer.

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