Combination Chemotherapy of S-1 and Low-dose Twice-Weekly Cisplatin for Advanced and Recurrent Gastric Cancer in an Outpatient Setting: A Retrospective Study

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Abstract. *Background: We have reported the efficacy and safety of S-1 combined with low-dose consecutive cisplatin therapy for advanced and recurrent gastric cancer, but the regimen was difficult because daily cisplatin administration was necessary. We have already confirmed that cisplatin of 6 mg/m^2 twice-weekly maintained the same protein-bound Pt concentration as that of 3 mg/m^2 of cisplatin daily. In the present study, the efficacy and safety of a combination of S-1 and low-dose twice-weekly cisplatin were investigated. Patients and Methods: The participants were 32 patients treated at our hospital, and all were admitted for the first 2 weeks of therapy. S-1 at 80 mg/m^2 daily was administered orally in two divided doses. Cisplatin at 6 mg/m^2 was administered by intravenous drip infusion over 30 minutes on 2 days each week, day 1 and day 4. Each treatment cycle consisted of 4 weeks of drug administration followed by a 2-week drug-free period (6 weeks in total). Results: A total of 146 cycles were administered, with a median of three cycles (range: 1-24) per patient. The results were rated as a complete response in 1 case, partial response in 24 cases and stable disease in 5 cases. The response rate was 78.1% (25/32) and the median survival time was 12.0 months (95% confidence interval (CI) 8.9-15.1 months). The response rate did not differ between previously treated and untreated patients. The one-year survival rate was 48.2% (95% CI 30.3-66.0%). The major adverse reactions were myelosuppression and gastrointestinal symptoms. The total incidence of grade 3 or greater adverse reactions was 15.6% (5/32). Conclusion: The combination of S-1 and low-dose twice-weekly cisplatin therapy appears to be highly efficacious and safe and shows promise as a useful treatment strategy, even in outpatient clinics.*

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5-Fluorouracil (5-FU) has been used worldwide for the treatment of solid cancers for many years since its development by Heidelberger in 1957 (1), and it is considered one of the key drugs for the treatment of gastrointestinal cancer. However, insufficient evidence has been collected to establish its effectiveness against gastric cancer. The guidelines for the treatment of gastric cancer published in April 2004 by the Japanese Gastric Cancer Association (2) state that although regimens containing cisplatin or 5-FU are very promising as standard regimens for the chemotherapy of gastric cancer, no particular regimen can be recommended.

Cisplatin and 5-FU therapy (FP therapy) are popular treatments for gastric cancer in Japan. In particular, a combination of low-dose cisplatin and 5-FU therapy (low-dose FP therapy), in which cisplatin is used as a modulator of 5-FU and administered in divided doses to reduce the single dose level to avoid the need for hydration, has frequently been used. Low-dose FP therapy has also been used in advanced and recurrent gastrointestinal cancer (3-5) at our institution with excellent results and it has yielded a response rate of 65.4% (68/104) and median survival time (MST) of 8.2 months (6).

A succession of chemotherapeutic agents that are effective against gastric cancer has recently been developed. Shirasaka *et al.* reported S-1, a dihydropyrimidine dehydrogenase inhibitor fluoropyrimidine (DIF), as a novel 5-FU-based preparation for oral administration. S-1 consists of tegafur (a prodrug of 5-FU) and two modulators, 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate, at a molar

ratio of 1:0.4:1. Since CDHP is a reversible competitive inhibitor of dihydropyrimidine dehydrogenase (DPD), an enzyme that degrades 5-FU, CDHP with tegafur was expected to yield prolonged high 5-FU concentrations in plasma and tumor tissue (7). Oxonate is a reversible competitive inhibitor of orotate phosphoribosyltransferase, an enzyme that catalyzes 5-FU phosphoribosylation in the gastrointestinal mucosa (8). Oxonate has been reported to selectively concentrate in gastrointestinal tissue after oral administration and suppress gastrointestinal toxicity caused by phosphoribosylation of 5-FU in the gastrointestinal tract without decreasing its antitumor activity (9). S-1 administered as a single agent for advanced gastric cancer yielded more favorable results than other agents in a late phase II clinical study. The response rate was 46.5% with on MST of 8.3 months (10). Because it is an oral preparation and its adverse effects are relatively mild, S-1 is gradually replacing continuous 5-FU infusion therapy in the treatment of gastric cancer (11). The Japan Clinical Oncology Group is currently conducting a phase III clinical study comparing S-1 with continuous 5-FU infusion.

We have already reported the efficacy and safety of S-1 combined with low-dose consecutive cisplatin therapy for advanced and recurrent gastric cancer (12). However, this regimen is difficult because cisplatin is administered daily. We confirmed that cisplatin of 6 mg/m^2 twice-weekly maintained the same protein-bounded Pt concentration as that of 3 mg/m^2 of cisplatin daily (13). The present study was undertaken to evaluate the efficacy and safety of S-1 combined with low-dose twice-weekly cisplatin therapy (S-1/low-dose P therapy) in advanced and recurrent gastric cancer patients in an outpatient setting.

Patients and Methods

Eligibility criteria. The study protocol was approved by the Kochi Health Science Center and written informed consent was obtained from all the patients. The eligibility criteria were: (i) histologically or cytologically confirmed gastric cancer; (ii) measurable disease; (iii) age 18 years or more; (iv) Eastern Cooperative Oncology Group (ECOG) performance status of 2 or less; (v) estimated life expectancy of 3 months or more; (vi) adequate bone marrow function (leukocyte count >3500/μl, neutrophil count >1500/μl and platelet count >100,000/μl); (vii) transaminases <3 times the upper limit of normal and normal renal function tests (creatine level <1.5 mg/dl, or creatinine clearance >30 ml/min). Patients with a concomitant malignancy or serious concomitant disease were excluded from the study.

Treatment schedule. All patients were admitted to the hospital for the first 2 weeks of therapy. During the first two weeks, cisplatin (3 mg/m^2) dissolved in 100 mL of physiological saline was administered by intravenous drip infusion over 30 minutes daily on 5 consecutive days of each week (days 1-5) and, after discharge, cisplatin (6 mg/m^2) dissolved in 100 mL of physiological saline was administered by intravenous drip infusion over 30 minutes on 2 days of the week (day 1 and day 4). S-1 was administered orally daily at a daily dose level of 80 mg/m^2 in two divided doses. Each treatment cycle consisted of 4 weeks of drug administration followed by a 2-week drug-free period (6 weeks in total). Cycles of treatment were repeated unless exacerbation of symptoms was observed. As a rule, the first cycle of treatment was administered in the hospital and the second and subsequent cycles were administered in the outpatient clinic.

Study evaluation and statistical methods. The primary endpoint of this study was the tumor response rate to the treatment protocol. Tumor response was evaluated according to the Japanese Research Society for Gastric Cancer (14). The primary lesion was estimated by roentgenophotographic and endoscopic findings and, for metastatic lesions, CT scanning was used. Adverse events were evaluated using the National Cancer Institute Common Toxicity Criteria version 2.0 (NCI-CTC) (15). Survival time was counted from the day combined S-1/low-dose P therapy was started. The survival curve began on the day when the combined S-1/low-dose P therapy was started and the survival rate was calculated by the Kaplan-Meier method. The *U*-test was used for comparisons of antitumor efficacy.

Results

Patient characteristics. Between June 2000 and July 2005, a total of 32 patients were enrolled in this study. Table I shows the background characteristics of the patients. There were 25 males and 7 females, with a median age of 60 years (range: 30-74 years). Twenty patients had received no prior treatment, and the other 12 had received some prior treatment consisting of 5-FU therapy in 1 case; low-dose FP therapy in 3; low- dose FP therapy (1st line) followed by paclitaxel therapy (2nd line) in 2; low-dose FP therapy (1st line), S-1 therapy (2nd line) followed by paclitaxel therapy (3rd line) in 1; S-1 therapy (1st line) followed by paclitaxel therapy (2nd line) in 1; CPT-11 and cisplatin therapy in 1; and UFT therapy (postoperative adjuvant therapy) in 3 cases.

The median follow-up period for the entire population was 13 months. Ambulatory treatment from the third week onward was possible in 31 (96.8%) of the 32 patients.

Antitumor efficacy. A total of 146 cycles of combined S-1/low-dose P therapy were administered, with a median of three cycles (range: 1-24) per patient. The results were rated as a complete response in 1 case, partial response in 24 and stable disease in 5. As shown in Table II, the response rate was 78.1% (95% confidence interval (CI): 61.2-89.0%). The median response duration was 5.0 months (range: 1.7-32.9 months). Analysis of the response rate according to whether previous treatment had been received, showed no difference between the previously untreated group (75.0%, 9/12) and the group that had received prior treatment (80.0%, 16/20) (*U*-test). Analysis of the response rate according to tumor site (Table III) showed that it was 100% effective (5/5) for primary gastric lesions, 80.0% (12/15) for intraperitoneal lymph node metastases, 66.7% (8/12) for

Table I. *Patient characteristics (n=32).*

Characteristic	Number of patients (%)
Gender	
Male	25 (78)
Female	7 (22)
Age (years): Median (range)	60 (30-74)
ECOG PS	
0	19 (59)
1	9 (28)
2	4 (13)
Type of lesion	
Unresectable	12 (38)
Recurrence	10 (31)
Residual	10 (31)
Histology	
Intestinal	12 (38)
Diffuse	20 (63)
Prior chemotherapy	
None	20 (63)
1 regimen	8 (25)
2 regimens	3 (9)
3 regimens	1 (3)

ECOG PS: Eastern Cooperative Oncology Group performance status.

Table II. *Response to S-1/low-dose P therapy.*

	CR	PR	SD	PD	Response rate	95% C.I.
All Patients	1	24	5	2	78.1% (25/32)	61.2-89.0
Prior chemotherapy						
No	1	15	3	1	80.0% (16/20)	58.4-91.9
Yes	0	9	2	1	75.0% (9/12)	46.8-91.1

CR: Complete response, PR: partial response, SD: stable disease, PD: progressive disease; C.I.: confidence interval.

Table III. *Response to S-1/low-dose P therapy by evaluable lesions.*

Site of lesion	CR	PR	NC	PD	Response rate	
Primary	0	5	0	0	100.0%	(5/5)
Intraperitoneal lymph nodes	1	11	3	0	80.0%	(12/15)
Liver	1	7	4	0	66.7%	(8/12)
Lung	0	3	2	0	60.0%	(3/5)
Peritoneum	0	11	2	2	73.3%	(11/15)
Bone	0	1	3	0	25.0%	(1/4)
Other	0	5	1	0	83.3%	(5/6)

CR: Complete response, PR: partial response, NC: no change, PD: progressive disease.

hepatic metastases, 60.9% (3/5) for lung metastases and 73.3% (11/15) for peritoneal lesions.

Survival time. The MST after combined S-1/low-dose P therapy was 12.0 months (95% CI 8.9-15.1 months) and the one-year survival rate was 48.2% (95% CI 30.3-66.0%) (Figure 1).

Adverse events. The incidence of adverse events for the entire population was 56.3% (18/32). Grade 3 or greater adverse events were seen in 5 (15.6%) of the 32 patients. The major grade 3 or greater adverse events were thrombocytopenia (12.5%) and renal dysfunction (3.1%), as shown in Table IV.

Table IV. *Adverse events associated with S-1/low-dose P therapy.*

Adverse event	Grade*				Incidence of grade 3-4	
	1	2	3	4	n	Percentage
Hematological						
Leukocytopenia	0	1	0	0	0	0%
Anemia	0	3	0	0	0	0%
Thrombocytopenia	0	1	4	0	4	12.5%
Non-hematological						
Nausea/vomiting	4	3	0	0	0	0%
Diarrhea	0	2	0	0	0	0%
Liver dysfunction	0	0	0	0	0	0%
Renal dysfunction	0	0	1	0	1	3.1%
Fatigue	2	1	0	0	0	0%

*National Cancer Institute common toxicity criteria version 2.0.

Discussion

We treated 32 patients with S-1/low-dose P therapy to evaluate its usefulness against advanced and recurrent gastric cancer, and the results showed a better response rate (78.1%) and MST (12.0 months) than with conventional FP therapy. The conventional low-dose FP therapy requires continuous 24-hour infusion of 5-FU, and this requirement can be eliminated by S-1/low-dose P therapy, in which 5-FU is replaced by an oral preparation (S-1). This regimen is simple and there are fewer complications than with the conventional method. Patients' compliance with therapy is improved by substituting S-1/low-dose P therapy for low-dose FP therapy.

Koizumi *et al*. (16) recommended the following dosing regimen for S-1 combined with cisplatin therapy for advanced gastric cancer based on the results of phase I and II clinical studies: S-1 for 3 weeks (80 mg/m^2/day) followed by a 2-week drug-free period, and cisplatin on day 8 at a dose level of 60 mg/m^2. They obtained a high response rate of 73.7% (14/19) with this regimen. Hyodo *et al*. (17) reported a regimen suitable for use in outpatient clinics in which S-1 is administered for 2 weeks at a dose level of 70 mg/m^2/day,

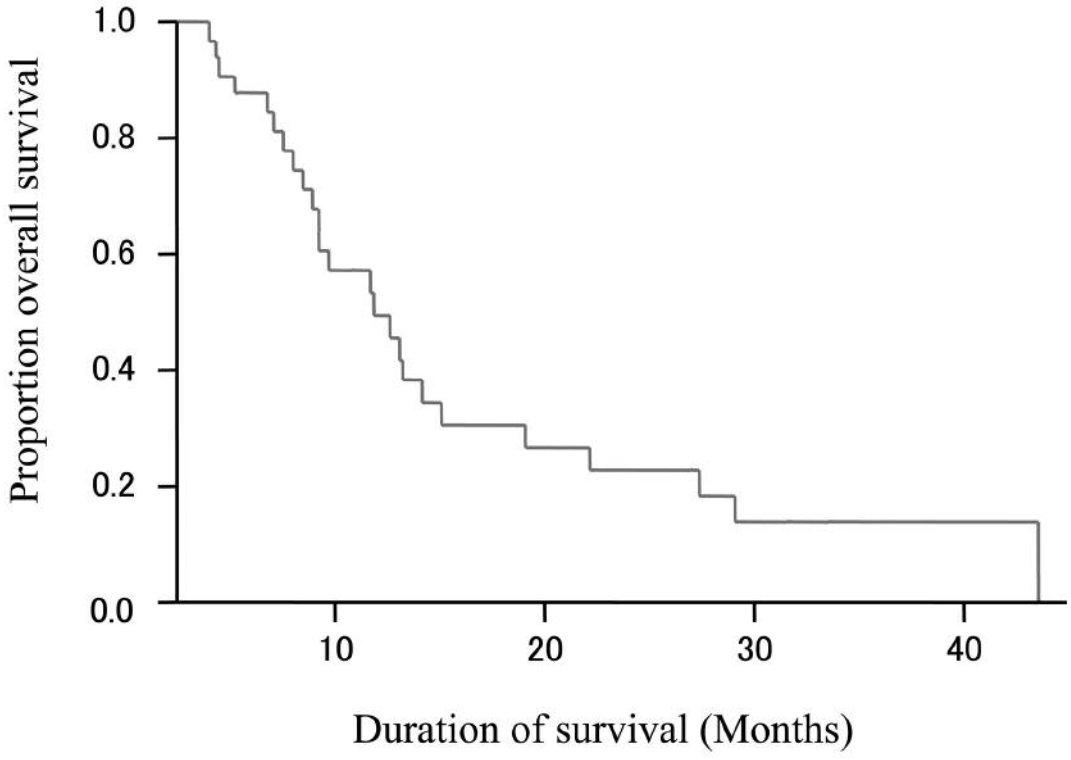

Figure 1. *Overall survival of patients following S-1/low-dose P therapy.*

followed by a one week drug-free period, and cisplatin is administered on day 1 and day 8 at a dose level of 20 mg/m^2; they reported a response rate of 61.1% with this regimen. Iwase *et al*., in an attempt to reduce nausea and vomiting caused by cisplatin, also developed a regimen including 24-hour continuous infusion of this agent, but reported a response rate of 50% with a 10% incidence of grade 3 or greater nausea and vomiting (18).

The combined regimen of S-1 daily and low-dose twice-weekly cisplatin in the present study enabled highly effective and safe therapy that is suitable for use in outpatient clinics. Although phase I and II clinical studies of S-1 combined with taxane (19) or CPT-11 (20) have also been conducted, their results were no better than those yielded by S-1 plus cisplatin therapy. The favorable results of S-1 combined with cisplatin seem to be explained by the synergistic activity between 5-FU and cisplatin based on the theory of biochemical modulation (21, 22). The antitumor activity of 5-FU has been reported to be reinforced particularly markedly when combined with frequent low-dose cisplatin (23). This may explain the fact that the response rate in the previously treated cases was comparable to that in the cases that had never been treated. Furthermore, based on the results of a study comparing the pharmacokinetics of 5-FU in S-1 therapy (80 mg/m^2/day) and continuous intravenous infusion of 5-FU (250 mg/m^2/day) it was reported that the $AUC_{0\text{-}10h}$ for oral S-1 was 1.9 times higher than that of 5-FU administered by intravenous infusion (9). This may explain why S-1/low-dose P therapy had much greater antitumor activity than low-dose FP therapy. This greater antitumor activity may have contributed to the present high response rate in the previously treated cases.

Koizumi *et al*. (16) reported finding that grade 3 or greater adverse events following S-1 combined with high-dose cisplatin therapy consisted of hematological adverse reactions in 16.0% of all patients, anorexia in 26.0% and nausea in 16.0%. Comparison of the results reported by Koizumi *et al*. and the results of the present study shows that the toxicological profile of high-dose cisplatin therapy seems to differ slightly from that of S-1/low-dose P therapy because gastrointestinal toxicities were observed less frequently in our study.

The problems associated with outpatient chemotherapy with oral anticancer agents include variable patient compliance with the dosing instructions, the development of adverse events, and frequent difficulty in completing therapy as scheduled. Outpatient drug therapy was possible in 31 (96.9%) of the 32 patients in the present study and it was possible to complete therapy without the development of any adverse events in all but one patient. In this last

patient, the serum creatinine level increased to 1.4 mg/dl, suggesting mild compromise of renal function immediately prior to the start of the 5th cycle of treatment, and was accompanied by grade 4 thrombocytopenia and grade 3 renal and hepatic dysfunction. Combined S-1 and cisplatin therapy seems to be associated with a rise in the blood 5-FU level and an elevated risk of 5-FU toxicity for the following reasons: (i) cisplatin is a nephrotoxic drug; (ii) CDHP, a component of S-1, is excreted by the kidneys; and (iii) the serum concentration of CDHP (a DPD inhibitor) may increase. In this light, greater caution should be exercised when using combined S-1 and cisplatin therapy in renally compromised patients.

Reflecting recent phase III results in unresectable advanced and recurrent gastric cancer (24, 25), the standard regimen in Japan is shifting toward combined S-1 and cisplatin therapy.

In the S-1 and cisplatin regimen used in this study, cisplatin was administered in divided doses at a low dose level. When administered in this way, hydration is unnecessary, and even if renal function does become compromised during treatment, it is easy to reduce the dose level of cisplatin or discontinue it altogether. In this respect, this regimen is more favorable from the viewpoint of preventing adverse events than regimens involving the administration of high dose levels of cisplatin.

Conclusion

In conclusion, based on the high response rate, possibility of administration on an outpatient basis and the high quality of life of the patients, combined S-1/low-dose P therapy is considered to offer promise for the treatment of advanced and recurrent gastric cancer. The therapy deserves further evaluation, including its usefulness as second-line therapy for gastric cancer patients.

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