Clinical Medicine Insights: Oncology

ORIGINAL RESEARCH

A Phase II Study of S-1 Monotherapy as a First-line Combination Therapy of S-1 Plus Cisplatin as a Second-line Therapy, and Weekly Paclitaxel Monotherapy as a Third-line Therapy in Patients with Advanced Gastric Carcinoma: A Second Report

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Abstract

Background: We have previousy reported on a Phase II study of S-1 monotherapy as a first line, combination therapy of S-1 plus cisplatin as a second line, and weekly paclitaxel monotherapy as a third line therapy in patients with advanced gastric carcinomas. The median survival time (MST) of patients over the whole course of treatment was not previously calculated because 12 out of 19 patients had not yet succumbed. Since then, we have calculated the MST for this study and herein report our findings.

Patients and Methods: Between 2002 and 2005, 19 patients were enrolled in this study. Chemotherapy consisted of either 60 mg/m^2 of S-1 for 4 weeks at 6-week intervals, a combination of 60 mg/m^2 S-1 for 3 weeks and 60 mg/m^2 cisplatin on day 8 at 5-week intervals, or 60 mg/m^2 paclitaxel at days 1, 8, and 15, at 4-week intervals. The regimens were repeated until the occurrence of unacceptable toxicities, disease progression, or patient noncompliance. The primary end point was the overall survival.

Results: The median survival time was 774 days. The response rates were 33.3% (3/9), 12.5% (1/8), and 0% (0/4) after the first, second, and third line chemotherapies, respectively. The major adverse hematological toxicity was leukopenia, which reached grades 3–4 in all lines of chemotherapy investigated. In addition, the major adverse non-hematological toxicity was anorexia, which reached grade 3–4 in second line chemotherapy, and no deaths were attributable to the adverse effects of the drugs.

Conclusion: This sequential therapy was an effective treatment for advanced gastric cancer with acceptable toxic side-effects. We considered this therapy to be effective because of the smooth transition to the next regimen.

Keywords: advanced gastric cancer, recurrent gastric cancer, S-1, cisplatin, paclitaxel, phase II study, first line chemotherapy, second line chemotherapy, third line chemotherapy

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Introduction

S-1 is a novel oral fluorouracil antitumor drug that contains a combination of 3 pharmacological agents: tegafur (FT), a 5-Fluorouracil (5-FU) prodrug; 5-chloro-2,4-dihydroxypyridine (CDHP), which inhibits the activity of dihydropyrimidine dehydrogenase (DPD); and potassium oxonate (Oxo), which reduces the gastrointestinal toxicity of 5-FU.[1] A phase II study of S-1 showed a 44%–53.6% response rate to the drug and a median survival time (MST) of 207–298 days.[2,3] This drug has gradually been accepted as the front-line chemotherapy in Japan for the treatment of unresectable, resected but uncured, and recurrent gastric cancers.

In 2008, Koizumi et al described the results from the SPIRITS trial[4] and noted that the median overall survival was significantly longer in patients assigned to S-1 plus cisplatin than in those treated with S-1 alone. Since this report, many institutions in Japan have chosen to use S-1 plus cisplatin as the first line chemotherapy for advanced and recurrent gastric cancer.

In our previous report,[5] we evaluated S-1, S-1 plus cisplatin, and paclitaxel as chemotherapeutic regimens for treatment of advanced gastric cancer by measuring the objective response rate (RR), overall survival, and the safety profile, for the use of these therapies as first, second, and third line chemotherapeutic regimens. In this previous report, MST was not calculated because more than half of the patients were alive. In this study, we evaluated MST for the 19 patients.

Patients and Methods

Patient eligibility

A total of 19 patients were enrolled in this study between June 2002 and December 2005. To be eligible for inclusion, the patients had to have histologically or cytologically confirmed gastric adenocarcinoma that was either unresectable (n = 3), palliatively resected (n = 10), or recurrent (n = 6) (Table1). The patients had received no prior chemotherapy and were able to take S-1 orally. Patients with recurrent gastric cancers were included if 3 or more months had elapsed after the last post-operative adjuvant chemotherapy. After informed consents were received from patients, one group of patients received S-1, which was administered daily for two 4-week periods, separated by a 2-week interval for the first line chemotherapy.

Table 1. Characteristics of enrolled patients.

Characteristcs	Number of patients	(%)
Total number of patients	19	
Age (years)		
Mean ± SD (range)	61.3 ± 1.4 (38–75)	
Sex		
Male	12	63.2
Female	7	36.8
Karnofsky performance status		
80–100	19	100
Histological type (Japanese classification)		
Differntiated	6	31.6
Undifferentiated	13	68.4
Primary treatment		
Curative gastrectomy (recurrent cases)	6	31.6
Palliative gastrectomy	10	52.6
Without gastrectomy	3	15.8
Target lesions		
Primary	3	15.8
Peritoneal dissemination	14	73.3
Lymph node metastasis	5	26.3
Liver metastasis	2	10.5

A dose reduction was not allowed; however, the treatment schedule was changed in some cases to 5 consecutive days of treatment followed by 2 days of rest per week. This treatment schedule was repeated for 4 weeks, followed by 2 weeks of rest. The regimen was changed upon patient presentation of grade 3 toxicity, progressed disease, or elevated tumor markers. However, if grade 3–4 toxicity was observed after the first line chemotherapy, then a second line chemotherapy was administered after the patient recovered from the toxicity. If the second-line chemotherapy was refused by the patient who originally received S-1, then weekly Paclitaxel was given as the second line chemotherapy. The patients were also required to meet the following criteria: age of 75 years or less, amenable to oral administration of drugs, a Karnofsky performance score of 60, a life expectancy of at least 3 months, and an adequate hematological status (defined as having a total leukocyte count greater than 3,500 per mm^3, neutrophil count of greater than 1,500 per mm^3, platelet count greater than 100,000 per mm^3, serum creatinine levels under 1.5 mg/dl, total serum bilirubin

under 1.5 mg/dl, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels less than 2 times the upper limit of the normal range). Patients were excluded from the study if they had any other current or prior malignancies, active uncontrolled infections or other diseases, or a neurological or mental disease that prevented adequate comprehension of information. The pretreatment evaluation consisted of a complete history and physical examination, blood count, serum biochemistry, and computed tomography (CT) of the chest and abdomen. All patients gave informed consent before the initiation of treatment.

Study design (Fig. 1)

First line chemotherapy

S-1 was administered orally twice daily after breakfast or dinner, at 80 mg/m^2/day for 4 weeks, followed by 2 weeks of rest. During the course of the treatment, the patients were evaluated for complete blood counts (CBC), biochemical and physical examinations every 2 weeks, and for the presence of tumor markers (CEA, CA19-9, STn and SLX) on every 4 weeks. The treatment response was then evaluated by CT every 2 months.

Second line chemotherapy

S-1 was administered at the same dosage as the first line chemotherapy. S-1 was administered for 3 weeks followed by 2 weeks of rest. On day 8, S-1 was combined with cisplatin at 60 mg/m^2. The patients were pretreated with 8 mg dexamethasone and 10 mg azasetron hydrochrolide diluted in 50 ml of saline given intravenously 30 minutes prior to treatment. Chemotherapy was then administered by intravenous infusion, consisting of 60 mg/m^2 cisplatin administered over 120 minutes. During the course

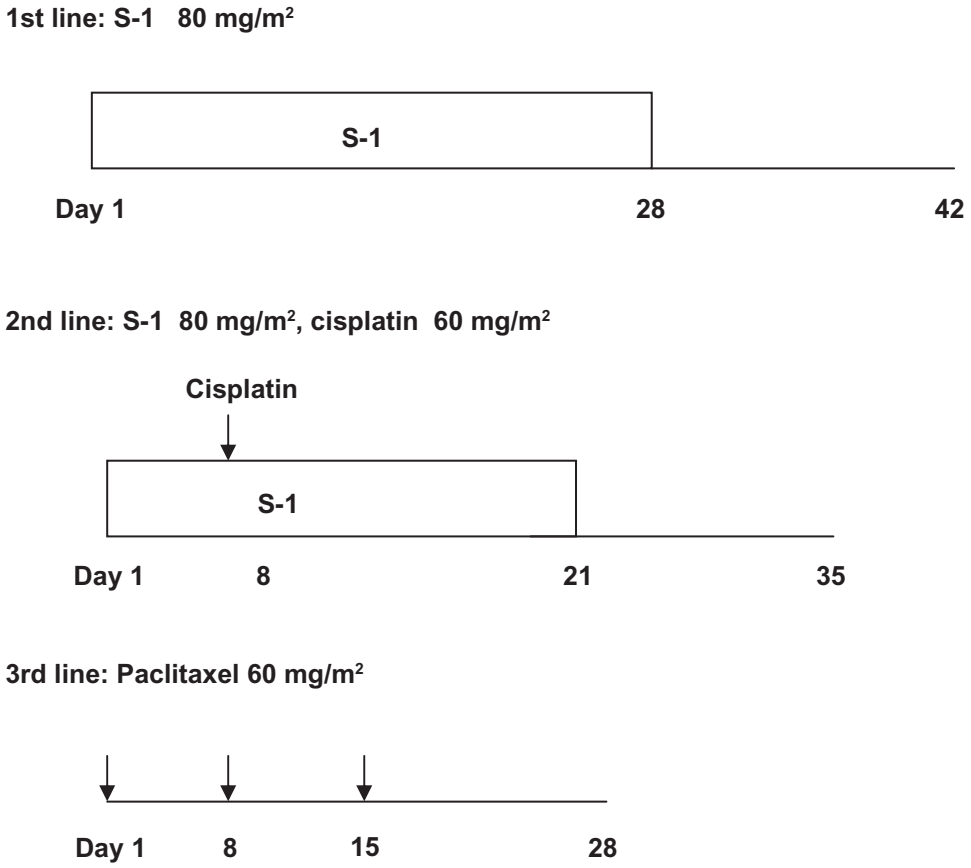

Figure 1. Protocols of First, Second, and Third line chemotherapy regimens.
First line chemotherapy: S-1 was administered orally twice daily after breakfast or dinner, at 80 mg/m^2/day for 4 weeks, followed by 2 weeks of rest.
Second line chemotherapy: S-1 was administered at the same dosage as the first line chemotherapy. S-1 was administered for 3 weeks followed by 2 weeks of rest. On day 8, S-1 was combined with cisplatin at 60 mg/m^2.
Third line chemotherapy: Paclitaxel was administered at 60 mg/m^2 on days 1, 8, and 15 of a 4-week treatment cycle.

of the treatment, the patients were evaluated for CBC values, biochemical and physical examinations every 2–3 weeks, and for expression of tumor markers (CEA, CA19-9, STn and SLX) every 4 weeks. The treatment response was evaluated every 2 months by CT.

Third line chemotherapy

Paclitaxel was administered at 60 mg/m^2 on days 1, 8, and 15 of a 4-week treatment cycle. Prior to paclitaxel administration, patients were given 50 mg oral diphenhydramine and 20 mg intravenous dexamethasone with 50 ml saline over 30 min, 50 mg intravenous ranitidine hydrochloride with 50 ml saline over 30 min, and 10 mg intravenous azasetron hydrochrolide with 50 ml saline over 30 min. Paclitaxel was administered by intravenous infusion and consisted of 60 mg/m^2 over 60 minutes.

All patients were admitted to the hospital for the first intravenous treatment of the second and third line chemotherapies. Subsequent intravenous treatments were performed on an outpatient basis. If hematological or non-hematological toxicities of grade 3 or higher occurred, or if the patient so requested, the treatment was halted.

Study evaluations

All responses were assessed by physical examination, direct visualization, examination of the upper gastrointestinal tract after barium ingestion, gastrofibroscopy, and CT. Tumor evaluation was performed every two months according to the Response Evaluation Criteria In Solid Tumors (RECIST), and the responses were confirmed by radiography within 2 weeks. All adverse events were graded using the National Cancer Institute Common Toxicity Criteria (NCI-CTC, versions 2.0 and 3.0) at each treatment cycle. In the event of toxicity, chemotherapy was postponed until the symptoms had resolved.

Survival analysis

The length of survival was measured from the time of treatment initiation up until patient death. The Kaplan-Meier method was used to calculate the survival rate. The difference between the curves was assessed using the log-rank test. Differences with probability (p) values less than 0.05 were considered to be statistically significant. Statistical calculations were conducted using the Dr. SPSS II for Windows software program.

Results

Patient characteristics

The demographic features of the 19 patients enrolled in this study are shown in Table 1. All patients were assessed for response and toxicity. The median patient age was 61.3 years (range: 38–75 years); 12 patients were male (63.2%) and 7 were female (36.8%), with all patients being in good general health (Karnofsky performance status: 80–100). All patients had histologically confirmed adenocarcinomas, with a total of 6 differentiated and 13 undifferentiated adenocarcinomas. The most frequently observed sites of tumors were peritoneal dissemination in 14 patients, lymph nodes metastases in 5 patients, followed by the primary tumor site in 3 patients and liver metastases in 2 patients.

The first line therapy was performed in 19 cases, and on average 6.2 courses of administration could be performed (range: 0–20, median: 5). The treatment schedule was changed to 5 consecutive days in three cases (range: 9–15, median: 10). The second line therapy was performed in 13 cases, with 2.8 courses performed on average (range: 1–7, median: 2). Third line therapy was performed in 13 cases with 6.2 courses on average (range: 0–24, median: 4). Cases with 0 courses in the first line and third line treatments were the result of patient noncompliance due to side effects, as well as rapidly increasing lesions. The fourth line and subsequent treatments were performed in 10 cases. None of the patients underwent any subsequent surgery.

For the tumor markers, we used CEA and CA19-9. Even if PD was not observed in CT, etc., the regimen was changed from first line to second line chemotherapy in cases in which the CEA level increased from 2.7 to 4.6 or from 19.2 to 24.9, or in which the CA19-9 level increased from 48 to 113.

Efficacy

There were measurable lesions in 9 patients who underwent first line therapy, 8 patients in second line therapy, and 4 patients who underwent third line therapy. In first line therapy, one case of CR (Fig. 2) and 2 cases of PR were identified; in second line therapy, there was one case of PR, but in third line therapy neither PR nor CR were found. The RR were 33.3%, 12.5%, and 0% for each therapy. In CR for first line therapy, there were episodes of lymph node

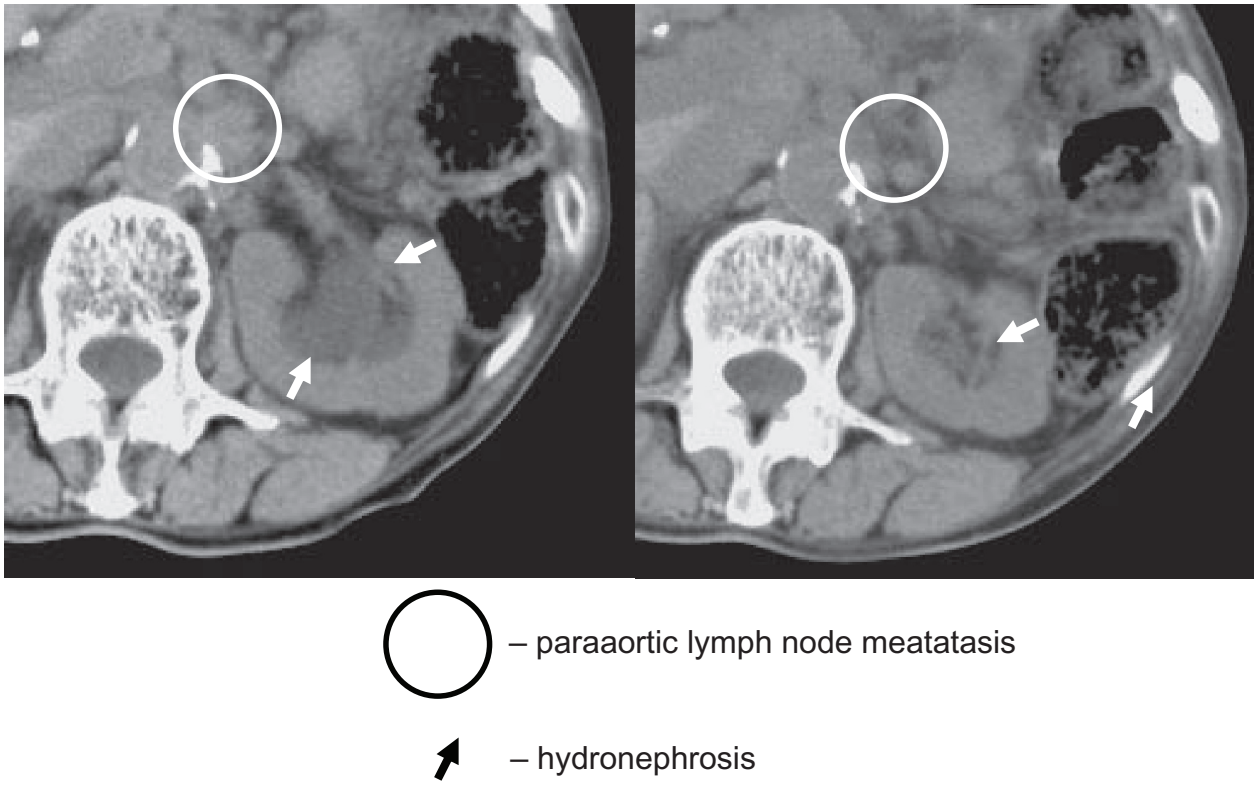

Figure 2. Lymph node metastasis and hydronephrosis. Left figure shows paraaortic lymph node metastasis and hydronephrosis. S-1 treatment alone was started for the patient. After 2 months, there was no lymph node swelling or hydronephrosis, as shown in the right figure.

metastasis, while in PR there were liver metastases, peritoneal dissemination, and primary tumors. There was liver metastasis in PR after second line therapy.

Survival

The mean follow-up time was 952.6 days with a range of 44 to 2295 days. The MST was 774 days (Fig. 3). In patients with non-curative resection (n = 10), the MST was 853 days. In patients without resection (n = 3), the MST was 522 days. In patients with recurrent cancers (n = 6), the MST was 376 days. There were no significant differences between the non-curative resection, non-resection, and recurrent patients (Fig. 4).

Toxicity

Leucopenia followed by anemia was the most frequent hematological toxicity, and was a side-effect of at least grade 3 severity. In first line therapy, 1 case of leucopenia and 1 case of neutropenia (10.5%) were observed; in second line therapy, 3 cases of leucopenia and 2 cases of anemia (23.1%); and in third line therapy, 2 cases of leucopenia and 1 case of anemia (23.1%) were observed. Loss of appetite was the most frequently observed non-hematological toxicity. In first line therapy, 1 case of stomatitis, 1 case of lachrymation, and 1 case of limb numbness (10.5%); in second line treatments, 1 case of nausea, 4 cases with a loss of appetite, 2 cases of diarrhea, 1 case of fatigue, and 1 case of abdominal pain (46.2%); and in third line therapy, not a single case was found to have severe toxicities (Table 2).

Discussion

S-1 has been the most widely used anti-cancer drug for advanced or recurrent gastric cancer in Japan for several years. S-1 inhibits tumors and disseminated peritoneal metastases in gastric carcinoma patients as confirmed by Mori et al[6] in a mouse model of gastric cancer. A high concentration of 5-FU was detected in intraperitoneal tumor lesions of the S-1 treatment group, and prolonged survival rates were also observed. However, the mechanism by which

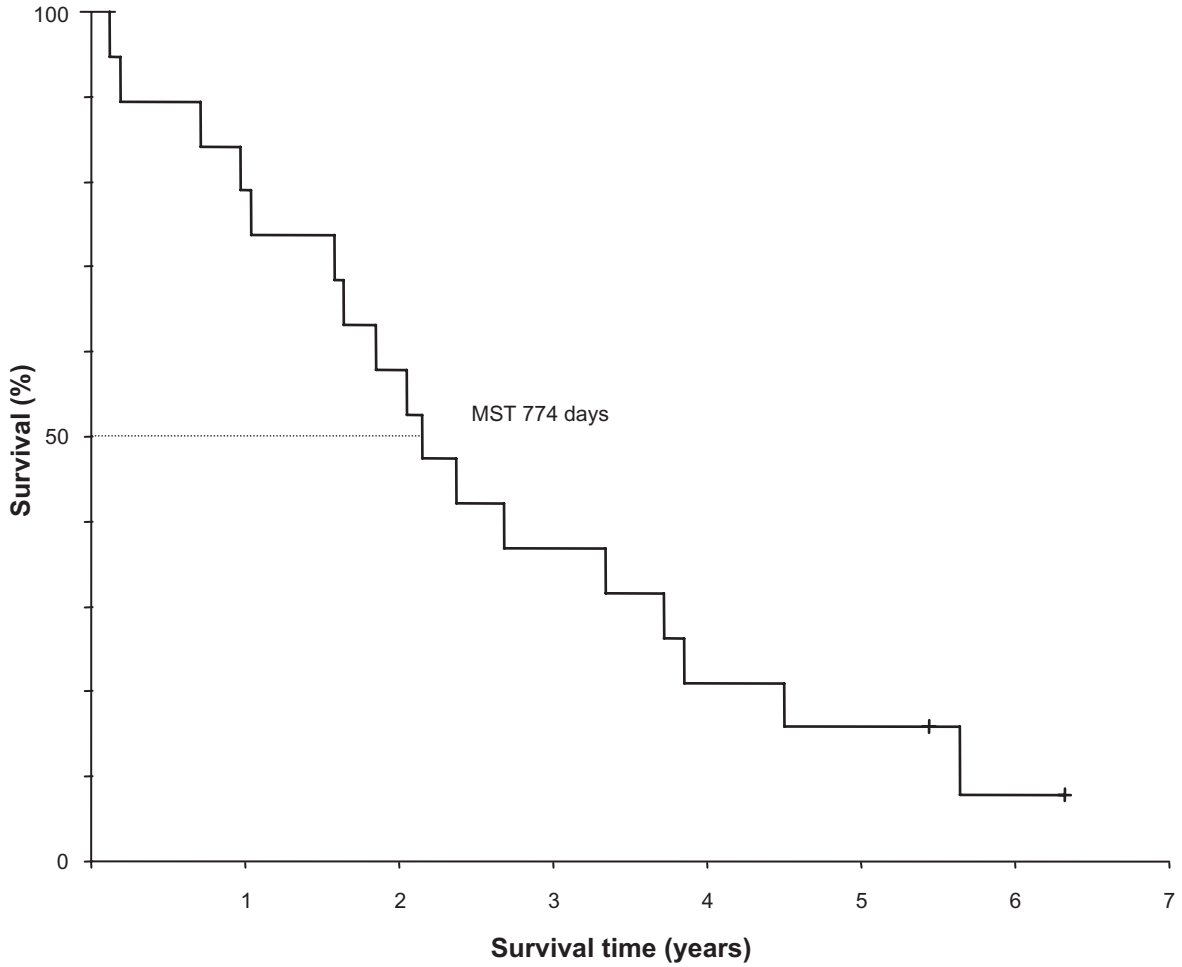

Figure 3. Over all Survival curve (n = 19). The median survival time was 774 days.

5-FU concentrations are maintained in the peritoneal cavity is not yet known.

In more than 4,000 patients administered S-1 for gastric cancer, 25% have experienced grade 3 or higher toxicities, and their MST was 8.3 months.[7] We herein observed an occurrence of grade 3 or higher toxicities in 9.4% of patients, a response rate of 38.4%, and a median survival rate of 343 days in the patients who received S-1 monotherapy for advanced or recurrent gastric cancer.[8]

In a report comparing S-1 plus cisplatin administration to S-1 administration alone, the frequency of patients with side-effects of grade 3 or higher severity were 43.5% and 22.5%, respectively, for each administration, and in combined therapy, side-effects were approximately twice as frequent as in single therapy, with 36.8% and 25.9% of RR, respectively, which is markedly higher with combined therapy. However, MST was 319 days and 322 days, respectively, which indicates that the therapies did not contribute in any way to the extension of survival time.[9]

In 2008, Koizumi et al reported the SPIRITS trial[4] that median overall survival was significantly longer in patients treated with S-1 plus cisplatin (13.0 months, IQR 7.6–21.9) than in those assigned to S-1 alone (11.0 months, 5.6–19.8; hazard ratio for death, 0.77; 95% CI 0.61–0.98; $P = 0.04$). Progression-free survival was significantly longer in patients assigned to S-1 plus cisplatin than in those assigned to S-1 alone (median progression free survival 6.0 months [3.3–12.9] versus 4.0 months [2.1–6.8]; $P < 0.0001$). They reported a higher frequency of grade 3 or 4 adverse events including leucopenia, neutropenia, anemia, nausea, and

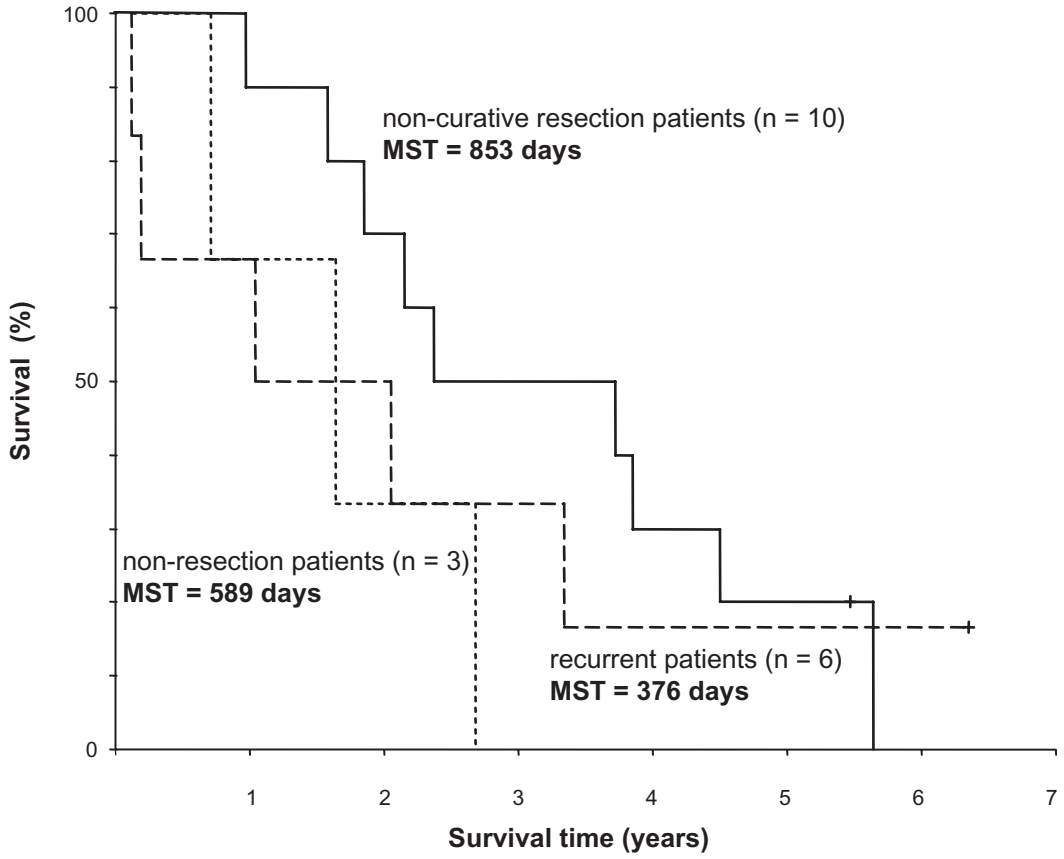

Figure 4. Survival curves for all primary treatments. In the non-curative resection patients (n = 10), the median survival time (MST) was 853 days. In the non-resection patients (n = 3), the MST was 522 days. In the recurrent patients (n = 6), the MST was 376 days. There were no significant differences among the non-curative resection, non- resection and recurrent patients.

anorexia in the group assigned to S-1 plus cisplatin than in the group assigned to S-1 alone. For example, grade 3 or 4 neutropenia accounted for 11% and 40%, respectively, in S-1 and S-1 plus cisplatin, and grade 3 or 4 anorexia was 6% and 30%, respectively.

Since this report, many institutions in Japan have implemented S-1 plus cisplatin as first line chemotherapy for advanced and recurrent gastric cancer. However, we chose to use S-1 alone as first line chemotherapy. With the additional results from the SPIRITS trial, therapeutic regimens may be more carefully selected for the treatment of gastric cancer. In this study, patients with this report, side-effects with at least grade 3 toxicities consisted of non-hematological toxicities in 10.5% and 46.2% and hematological toxicities in 10.5% and 23.1%, of S-1 and S-1 plus cisplatin treatment groups, respectively. S-1 plus cisplatin treatment administration following S-1 treatment did not significantly increase the number of side-effects.

The median treatment regimen for each patient was five cycles (range 0–20), in our study or three cycles (range 1–12) of S-1 treatment alone in the SPIRITS trial. The median for each patient was two cycles (range 1–7), four cycles (range 1–11) of S-1 plus cisplatin treatment, respectively. The cycles of S-1 plus cisplatin treatment in our study were fewer in number than those used in the SPIRITS trial. The RR in our study was lower than in the SPIRITS trial. Although a comparison cannot be made because non-curative resection patients were not included in the subjects of the SPIRITS trial, the MST in our study was longer than in the SPIRITS trial.[4] At our institute, we implement the S-1 plus cisplatin regimen on an outpatient basis.[10] However, at many institutes in Japan, the S-1 plus cisplatin regimen is implemented on an inpatient basis. Furthermore, because side effects occur more frequently in the S-1 plus cisplatin regimen than in a regimen using S-1 alone, there are cases in which the

Table 2. Adverse events, according to regimen group.

Regimen	Type	Grade				
		1	2	3	4	% 3 and 4
S-1 (n = 19)						
	diarrhea	2	3	0	0	0
	constipation	1	0	0	0	0
	nausea	2	1	0	0	0
	anorexia	1	5	0	0	0
	vomiting	1	1	1	0	5.3
	headache	2	0	0	0	0
	fatigue	7	2	0	0	0
	stomatitis	0	5	1	0	5.3
	dizziness	1	1	0	0	0
	AST,ALT	2	1	0	0	0
	lachrymation	3	1	0	0	0
	photophobia	3	0	1	0	5.3
	dysgeusia	1	1	0	0	0
	alopecia	1	0	0	0	0
	pigmentation	3	1	0	0	0
	nail changes	1	1	0	0	0
	conjunctivitis	1	0	0	0	0
	numbness of limbs	2	0	1	0	5.3
	abdominal pain	1	0	0	0	0
	edema	1	1	0	0	0
	allergic rhinitis	1	1	0	0	0
	anemia	0	1	0	0	0
	leukopenia	0	1	1	0	5.3
	neutropenia	0	0	1	0	5.3
S-1 + CDDP (n = 13)						
	diarrhea	2	0	2	0	15.4
	nausea	0	0	1	0	7.7
	anorexia	2	1	4	0	30.8
	fatigue	2	2	1	0	0
	AST,ALT	0	1	0	0	0
	pigmentation	2	0	0	0	0
	alopecia	1	0	0	0	0
	abdominal pain	0	1	1	0	7.7
	edema	0	1	0	0	0
	hypotension	1	0	0	0	0
	epistaxis	1	0	0	0	0
	rash	1	0	0	0	0
	anemia	0	1	2	0	15.4
	leukopenia	0	1	3	1	30.8
	neutropenia	0	0	2	0	15.4
	lymphopenia	0	0	0	1	7.7
Weekly paclitaxel (n = 13)						
	diarrhea	2	1	0	0	0
	constipation	0	1	0	0	0
	nausea	3	0	0	0	0
	anorexia	1	0	0	0	0
	fatigue	3	0	0	0	0
	dizziness	0	1	0	0	0
	AST, ALT	1	1	0	0	0
	lachrymation	1	0	0	0	0
	dysgeusia	1	0	0	0	0
	numbness of limbs	2	1	0	0	0

(*Continued*)

Table 2. (*Continued*)

Regimen	Type	Grade				
		1	2	3	4	% 3 and 4
	edema	0	1	0	0	0
	insomnia	1	0	0	0	0
	anemia	0	0	1	0	7.7
	leukopenia	0	1	2	0	15.4
	neutropenia	0	1	2	0	15.4

S-1 plus cisplatin regimen cannot be selected as the first line chemotherapy. We therefore believe that our regimen would be useful in such cases.

We adopted this approach because the paclitaxel used in this regimen showed no cross-resistance and had a completely different side-effect profile.[11] At the beginning of this therapy, weekly paclitaxel therapy for gastric cancer had not been established, and we determined a dose based on the reports for other types of cancer and tumors. In ovary cancers, 80 mg/m^2 of paclitaxel is the maximum tolerable dose, but it has been reported that the incidence of neuropathy is frequently found with 60 mg/m^2 of paclitaxel.[12] In breast and lung cancers, 60 mg/m^2 of paclitaxel was effective.[13,14] From these reports, we decided to perform weekly paclitaxel therapy with 60 mg/m^2 as the subsequent chemotherapy following S-1 plus cisplatin. In recent reports of weekly paclitaxel therapy for gastric cancers, the dose of paclitaxel is 80 mg/m^2, and we also provided weekly paclitaxel therapy as the second line chemotherapy, following S-1 in pretreatment, with a dose of 80 mg/m^2. In this therapy, the RR was 0%, MST was 495 days, and 11.8% hematological toxicity with at least grade 3 in severity was recognized.[15] In this therapy, the dose of paclitaxel was 60 mg/m^2, and after treatment with S-1 and S-1 plus cisplatin, neither CR nor PR developed. However, non-hematological toxicity was not found, and hematological toxicity was reported in only 23.1% of patients. The average number of cycles performed was 6.2, with a median value of 4. As the third line therapy, following S-1 and S-1 plus cisplatin (protocols with a relatively high frequency of side-effects), a dose of 80 mg/m^2 may be achievable, but this will require further study.

Therefore, in this study the response rate was low, but survival time was excellent. The MST was approximately 2.1 years (774 days). We believe that this was caused by the smooth transition between regimens. It is difficult to switch from one type of chemotherapy to another regimen if there is no obvious PD, but even in cases of peritoneal dissemination in which PD is difficult to determine, we switched regimens upon increased tumor markers and palpation of the Douglas cavity. Therefore, we were able to switch to the next regimen without any hesitation, because the next regimen had already been determined.

In conclusion, this report is of the results from the first line chemotherapy with S-1 alone, second line therapy with S-1 plus cisplatin, and third line therapy with weekly paclitaxel. In this therapy, direct curative effects for tumors were not universally successful, but improved survival rates were observed, and the side-effects were minor. Considering the possibility for adverse events and toxicities, S-1 plus cisplatin should not be the first line chemotherapy administered to gastric cancer patients.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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