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Phase II Study of a Combination of S-1 and Paclitaxel in Patients with Unresectable or Metastatic Gastric Cancer

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Key Words
Gastric cancer, unresectable and/or metastatic · Combination chemotherapy · Paclitaxel · Phase II study · S-1

Abstract
Objectives: A phase II study of weekly paclitaxel combined with S-1, a novel oral fluoropyrimidine, was performed to evaluate the efficacy and tolerability in unresectable or metastatic gastric cancer. ***Patients and Methods:*** Twenty-nine patients with unresectable and/or metastatic gastric cancer were enrolled in the study. Paclitaxel 50 mg/m^2 was administered on days 1 and 8. S-1 was administered orally at 40 mg/m^2 b.i.d. for 14 consecutive days, followed by a 1-week rest. The primary endpoint was the response rate. Secondary endpoints were safety and overall survival. ***Results:*** The overall response rate in 29 patients was 48.3%, differentiated 36.4% and undifferentiated 55.6%. The median survival time was 13.9 months. Grade 3 or higher toxicity was observed in neutropenia (3.4%), diarrhea (3.4%), bilirubin (3.4%) and neuropathy (3.4%). ***Conclusions:*** Combination chemotherapy of weekly paclitaxel and S-1 demonstrated tolerable toxicity and efficacy. This regimen will be one of the initial treatment options for unresectable or metastatic gastric cancer.

Introduction

Clinically, 5-fluorouracil (5-FU)-based chemotherapy is regarded as first-line therapy for the treatment of unresectable or metastatic gastric cancer. However, the clinical outcome remained poor for such patients. Recently, a gastrointestinal oncology group from the Japan Clinical Oncology Group reported a 3-arm comparative study of 5-FU, CPT-11 (irinotecan)/cisplatin (CDDP) and S-1, in which the results verified the efficacy of S-1 with regard to overall survival and safety [1]. Furthermore, Narahara et al. [2] reported a phase III randomized study (SPIRITS trial) in unresectable/metastatic gastric cancer. S-1 + CDDP combination therapy showed significantly prolonged survival [median survival time (MST) 13 months] compared with S-1 monotherapy.

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The antineoplastic agent S-1, an oral derivative of 5-FU newly developed in Japan, combines tegafur, gimeracil and oteracil at a molar ratio of 1:0.4:1. Gimeracil is a reversible competitive inhibitor of the 5-FU degrading enzyme (dihydropyrimidine dehydrogenase), resulting in prolonged maintenance of a high 5-FU concentration in both blood and tumor [3]; oteracil potassium is a competitive inhibitor of 5-FU phosphorylation (orotate phosphoribosyltransferase) [4]. Designed to enhance the antitumor effect by elevating 5-FU levels in the blood and reduce gastrointestinal toxicity enhanced by being distributed primarily to the gastrointestinal tract [5, 6], orally active S-1 has the advantage of being more convenient for patients receiving chemotherapy. The response rate for S-1 was reported at more than 40% for advanced gastric cancer.

Meanwhile, paclitaxel (Taxol, TXL) was approved as an indication for gastric cancer and has been clinically used in Japan since May 2001. The response rate for Taxol every 3 weeks for gastric cancer is 20–24.3% [7, 8]. Recently, the response rate in a study of weekly Taxol administration was reported to be 16–40% [9–11].

On the other hand, the combination of TXL and 5-FU showed superior antitumor activity of 32–65% and a MST of 6.5–14 months against advanced gastric cancer [12–16]. In an effort to obtain favorable therapeutic results combining S-1 and TXL, we conducted a phase I study and reported the results [17]. After that, we designed a phase II study of combination therapy with S-1 and weekly TXL considering the feasibility of outpatient treatment.

Patients and Methods

Patients

Patients in this study had histologically proven unresectable or metastatic gastric cancer with measurable lesions. If patients underwent pretreatment, it was completed 4 weeks before this study. Other eligibility criteria included ages of 20–75 years; Eastern Cooperative Oncology Group Performance Status of 0–2; adequate hematological baseline function (white blood cell count >4,000/mm^3, absolute neutrophil count >2,000/mm^3, hemoglobin >8.0 g/dl, platelet count >100,000/mm^3), hepatic function (total bilirubin <1.5 mg/dl, AST and ALT <100 U/l), and renal function (serum creatinine normal upper limit); no active cancer in other organs, and a life expectancy >3 months. All patients provided written informed consent. This study was approved by the Institutional Review Board at the participating sites.

Treatment Schedule

TXL 50 mg/m^2 was mixed with 5% glucose solution 250 ml and administered intravenously over the course of 1 h on days 1 and 8. To prevent reactions due to hypersensitivity, premedication consisting of dexamethasone 20 mg (i.v.), diphenhydramine 50 mg (p.o.) and ranitidine 50 mg (i.v.) was administered 30 min before each TXL administration. When no hypersensitivity symptoms occurred after the first dose, the treating physician was allowed to reduce the dose of dexamethasone to 10 mg in subsequent courses. S-1 was orally administered at a daily dose of 40 mg/m^2 b.i.d. for 14 consecutive days.

When any one of the criteria (white blood cell count ≥3,000/mm^3, absolute neutrophil count ≥1,500/mm^3, platelets ≥75,000/mm^3, creatinine normal upper limit, non-hematologic toxicities ≤grade 2 or infection) for initiation of a new treatment course was not met on examination after 1 week of withdrawal (on the day of initiation of the second course), the second course was delayed up to 14 days after the scheduled end of the first course of treatment.

Evaluation of Toxicity and Tumor Response

The primary endpoint was the response rate, and the secondary endpoint was toxicity. The clinical response was assessed according to the response evaluation criteria in solid tumors (RECIST) after at least 2 courses of chemotherapy. Toxicity was assessed according to the Japanese version of the National Cancer Institute Common Toxicity Criteria, version 2.0, issued by the Japan Clinical Oncology Group.

Statistics

The expected response rate for combination therapy with TXL was set at 60%, 10% higher than the 95% confidence parameter of the response rate for S-1 monotherapy, and the threshold response rate was set at 35 of the 95% confidence level for S-1 alone. With a power of 95% and a one-sided significance level of 5%, a total of 29 patients was required.

The survival period was calculated from the start of treatment to death or the latest follow-up day. The Kaplan-Meier method was used to plot the overall survival curve.

Results

From June 2002 to August 2003, a total of 29 patients with unresectable or metastatic gastric cancer was enrolled in the study. Patient characteristics are listed in table 1. All 29 patients were fully evaluated for adverse reactions. The median number of cycles administered was 6 (range 1–21).

Fourteen patients had a partial response, 12 patients had stable disease and 3 patients had progressive disease (table 2). The overall response rate was 48.3% (14/29; 95% CI 30.1–66.5). The response rate in patients with differentiated cancer was 36.4% (4/11) and in patients with undifferentiated cancer 55.6% (10/18). The MST was 13.9 months. The 1-year survival rate was 57.6% (fig. 1).

Toxicities associated with treatment are listed in table 3. Leukopenia, neutropenia, anemia and thrombocytopenia were observed in 17.2, 34.5, 75.9 and 10.3%. He-

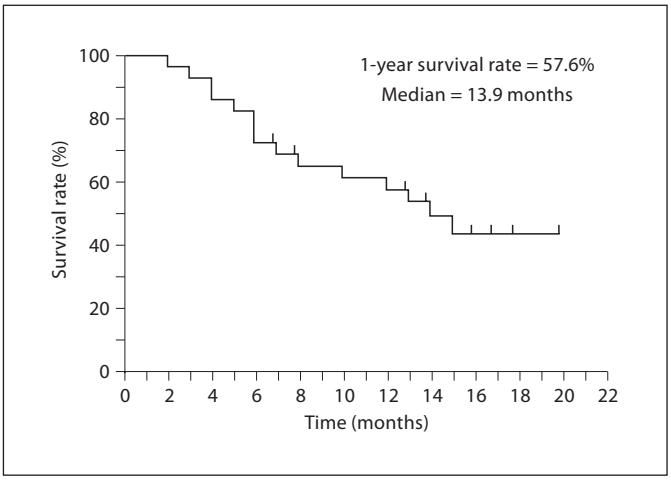

Fig. 1. Overall survival (n = 29).

Table 1. Patient characteristics

		Patients (n = 29)
Age, years	Median	61.0
	Range	22–73
Gender	Male	23
	Female	6
ECOG PS	0	13
	1	15
	2	1
Prior chemotherapy	Yes	5
	Fluorouracil + CDDP	3
	Fluorouracil	1
	CPT-11 + CDDP	1
	No	24
Primary site	Yes	10
	No	19
Histology	Differentiated	11
	Undifferentiated	18

ECOG PS = Eastern Cooperative Oncology Group performance status; CPT-11 = irinotecan.

matologic toxicity of grade 3 or higher was neutropenia (3.4%) only. Non-hematologic toxicities included abdominal pain (10.3%), diarrhea (17.2%), anorexia (44.8%), nausea and vomiting (27.6%), fatigue (24.1%), alopecia (44.8%), mucositis (13.8%), hot flashes (3.4%), hand-foot skin reactions (17.2%), bilirubin (10.3%) and neuropathy (20.7%). Of these, grade 3 or 4 events included diarrhea (3.4%), abnormal bilirubin levels (3.4%) and neuropathy (3.4%).

Table 2. Response rates

	CR	PR	SD	PD	RR, %
Total	0	14	12	3	48.3
Histology					
Differentiated	0	4	4	3	36.4
Undifferentiated	0	10	8	0	55.6

CR = Complete response; PR = partial response; SD = stable disease; PD = progressive disease; RR = response rate.

Table 3. Toxicities

	Grade (NCI-CTC version 2.0)				
	G1	G2	G3	G4	≥G3, %
Leukopenia	2	3		0	
Neutropenia	4	5	1	0	3.4
Anemia	13	9		0	
Thrombocytopenia	3			0	
Abdominal pain	3			0	
Diarrhea	3	1	1	0	3.4
Anorexia	11	2		0	
Nausea/vomiting	5	3		0	
Fatigue	5	2		0	
Alopecia	10	3		0	
Mucositis	4			0	
Hot flash	1			0	
Bilirubin	0	2	1	0	3.4
Neuropathy-sensory	5		1	0	3.4
Hand-foot skin reaction	1	4		0	

NCI-CTC = National cancer institute common toxicity criteria.

Discussion

Fluoropyrimidine is still the standard therapy for unresectable/metastatic gastric cancer. The results of the SPIRITS study (S-1 vs. S-1 + CDDP) were recently reported and proved the superiority of the S-1 + CDDP combination therapy to S-1 monotherapy [2]. The response rate from combination therapy versus monotherapy was 54.0 versus 31% (p = 0.0018), and the MST was 13.0 versus 11.0 months (median follow-up time 34.6 months; hazard ratio 0.774; p = 0.0366).

Recently reported clinical phase II studies of S-1 combination therapy are summarized in table 4. Although differences in study subjects preclude direct compari-

Table 4. Combination chemotherapy (phase II)

Author	Regimen	Patients	DI, mg/m^2/week		RR %	MST
Current study	TXL (50) days 1, 8 + S-1 (80) days 1–14 q 3 weeks	29	TXL 33.3	S-1 53.3	48.3	13.9 months
Mochiki et al. [18]	TXL (60) days 1, 8, 15 + S-1 (80) days 1–14 q 4 weeks	24	TXL 45.0	S-1 40.0	44	15.5 months
Hokita et al. [19]	TXL (120) days 1, 15 + S-1 (80) days 1–14 q 4 weeks	15	TXL 60.0	S-1 40.0	53	428 days
Inokuchi et al. [20]	CPT-11 (80) days 1, 8 + S-1 (80) days 1–14 q 4 weeks	35	CPT-11 40.0	S-1 40.0	62	444 days
Koizumi et al. [21]	CDDP (60) day 8 + S-1 (80) day 1–21 q 5 weeks	19	CDDP 12.0	S-1 48.0	74	383 days
Iwase et al. [22]	CDDP (70) day 8 + S-1 (80) days 1–14 q 4 weeks	42	CDDP 17.5	S-1 40.0	50	344 days
Koizumi et al. [23]	CPT-11 (30) days 1, 8 + CDDP (60) days 1, 8 q 4 weeks	40	CPT-11 15.0	CDDP 30.0	33	288 days

DI = Dose; RR = response rate; CPT-11 = irinotecan.

sons, nearly 50% of patients in each study responded to therapy. With respect to survival, these studies reported an MST of about 400 days. The best drug to be combined with S-1 is still unclear. Also, the combination schedules vary among drugs. Fluoropyrimidine should be the key drug and investigated in combination with S-1 and TXL. We investigated the combination with TXL and found favorable outcomes with a response rate of 62.5%, a time to progression of 179 days and minimal toxicity [17]. Favorable response rates and MST were observed in the present phase II study: 48.3% and 13.9 months, respectively. These results were considered comparable with the SPIRITS trial. Nukatsuka et al. [24] reported that a synergistic antitumor effect was observed with a combination of S-1 and TXL in a mouse model. Dose intensity in our present study was sufficiently high, suggesting that the combination schedule of S-1 + TXL resulted in a favorable response rate and MST.

Treatment methods for patients with non-target lesions have not yet been established. In our study, the non-progressive disease rate was as high as 89.7%. In addition, the evaluation of hematologic toxicity revealed that the incidence of grade 3 neutropenia was 3.4%, which was lower than the incidence of grade 3 neutropenia or greater reported with S-1 + CDDP in the SPIRITS study (40%) [2]. In our study, other toxicities were also generally mild, suggesting that the treatment was very safe.

Combination therapy with S-1 and TXL will be one of the initial treatment options for unresectable or metastatic gastric cancer. Further randomized phase II trials of S-1 + TXL and S-1 + CDDP will be needed in the future to verify the best drug to combine with S-1.

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