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ORIGINAL ARTICLE

Phase I/II trial of combination therapy with S-1 and weekly paclitaxel in patients with unresectable or recurrent gastric cancer

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Abstract
Purpose We aimed to examine the safety and antitumor effects of a combination of S-1 and paclitaxel in patients with unresectable or recurrent gastric cancer in a phase I/II setting.
Patients and methods The study was designed as a phase I/II clinical trial. In phase I portion, the dose of paclitaxel was escalated to estimate the maximum-tolerated dose (MTD) and recommended dose (RD) of paclitaxel with fixed dose of S-1. S-1 (daily dose, 80 mg/m^2) was given orally on days 1–21 every 35-day cycle (rest on days 22–35). Paclitaxel was administered intravenously on days 1, 8 and 15, at an initial dose of 40 mg/m^2, stepping up to 70 mg/m^2 in 10-mg/m^2 increment. Dose-limiting toxicity (DLT) was defined as grade 4 hematological toxicity, grade 3 or higher nonhematological toxicity, and treatment discontinuation due to adverse reactions during the first course of treatment. In phase II portion, the efficacy and toxicity at the RD of paclitaxel with S-1 were assessed.
Results The MTD of paclitaxel was estimated to be 60 mg/m^2, because >33.3% of patients (2/3) developed DLTs. DLT included postponement of treatment due to grade 2 neutropenia, and grade 3 stomatitis, anorexia, and nausea. Therefore, the RD of paclitaxel was estimated to be 50 mg/m^2. In the phase II portion, 22 patients were evaluated with 50 mg/m^2 paclitaxel and 80 mg/m^2 S-1 in a 35-day cycle. The response rate was 54.5% (95% CI, 32.2–75.6%). The median survival time was 283 days (95% CI, 218–508 days). The median number of treatment courses was 4 (range 1–10), indicating that this regimen could be given repeatedly.
Conclusions This phase I/II trial of combination therapy with S-1 and paclitaxel in patients with unresectable or recurrent gastric cancer showed that this regimen has substantial antitumor activity and can be given safely.

Keywords S-1 · Paclitaxel · Advanced gastric cancer · Phase I/II

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Introduction

Many regimens for combination chemotherapy have been developed in the hope of improving outcomes in patients

with unresectable or recurrent gastric cancer, but standard treatment remains controversial.

S-1 is an oral 5-fluorouracil derivative approved in Japan for the treatment of gastric cancer. S-1 combines tegafur, a prodrug of 5-fluorouracil, with gimeracil, which reversibly inhibits dihydropyrimidine dehydrogenase (the rate-limiting enzyme catalyzing the degradation of 5-fluorouracil), and potassium oxonate, which reversibly inhibits the enzyme responsible for the phosphorylation of 5-fluorouracil (orotate phosphoribosyltransferase) and thereby reduces gastrointestinal toxicity. Tegafur, gimeracil, and potassium oxonate are combined at a molar ratio of 1:0.4:1. This combination of ingredients is designed to increase 5-fluorouracil concentrations in plasma and thereby enhance antitumor activity, while reducing the risk of associated gastrointestinal toxicity [6, 21, 22]. The response rate in patients with gastric cancer who received S-1 alone was 53.6% (15/28) in an early phase II clinical trial [23] and 44.6% (45/101) in a late phase II clinical trial [14, 19]. In most recent large phase III studies, the response rates of 28–31% have been provided [3, 15]. The major advantage of S-1 is that this drug is an oral preparation that can be used on an outpatient basis.

Paclitaxel is an antitumor agent isolated from the bark of the yew tree (*Taxus brevifolia*). Paclitaxel acts on microtubules during mitosis, resulting in antitumor activity. Its main action is the promotion and stabilization of microtubule synthesis and the inhibition of depolymerization. The response rate with a 3-hour intravenous infusion of paclitaxel (at 3-week intervals) was 20% (3/15) in early phase II trials [18] and 23% (14/60) in late phase II trials in patients with gastric cancer [26]. Of note, paclitaxel is characterized by a response rate of 27% (7/26) in previously treated patients, indicating the lack of cross-resistance to other anticancer agents, and a response rate of 29% (9/31) in diffuse-type gastric cancer [26]. In addition, paclitaxel given triweekly or weekly infusion is active, also in esophageal cancer [1, 10].

Kano et al. experimentally studied the antitumor activity of combined treatment with paclitaxel and 5-fluorouracil against various human cancer cell lines. After long-term (5 days) combined treatment, paclitaxel and 5-fluorouracil mainly had an addictive effect, even after simultaneous application [12].

In Japan, paclitaxel is usually given once weekly to reduce the risk of neutropenia and peripheral neuropathy, without compromising effectiveness [2, 20], also for gastric cancer patients [7, 13].

We therefore conducted a phase I/II clinical study of combination treatment of S-1 with weekly paclitaxel. The primary objectives of the phase I portion were to estimate the maximum-tolerated dose (MTD) of paclitaxel in combination with S-1 and to determine the recommended dose (RD) for phase II studies. In the phase II portion, we investigated the clinical activity and the feasibility of this chemotherapy regimen.

Patients and methods

Patient eligibility

Patients were eligible for this study if they had a histopathologically or cytologically confirmed diagnosis of unresectable or recurrent gastric cancer, irrespective of whether they had received previous treatment; if they were at least 20 and younger than 75 years; if they had a performance status of 0 to 1; and if they were expected to survive for at least 3 months. Other eligible criteria were no severe dysfunction of major organs such as the marrow, heart, lung, liver, and kidney; a leukocyte count of 4,000–12,000 per μL, a neutrophil count of $\geq$2,000 per μL, a platelet count of $\geq 100 \times 10^3$ per μL, a hemoglobin level of $\geq$8.0 g/dL, serum aspartate aminotransferase and alanine aminotransferase levels not exceeding twice the upper limits of normal, a serum total bilirubin level of $\leq$1.5 mg/dL, a serum creatinine level not exceeding the upper limit of normal, a creatinine clearance of at least 50 mL/min, a clinically normal electrocardiogram (clinically irrelevant abnormalities allowed); and the ability to take oral medications. All patients gave written informed consent to participate in the study.

In the phase I portion of this study, the presence or absence of measurable and assessable lesions was not specified. In phase II, patients had to have measurable or assessable lesions. The study was approved by the ethics committee of hospitals associated with the Chuetsu Gastrointestinal Cancer Study Group before enrollment was begun.

Treatment regimen and dose-escalation schedule

S-1 (80 mg/m^2 per day) was given on days 1–21 of a 35-day cycle, followed by 14 days of rest. This cycle was repeated unless disease progression or severe toxicity was observed. The daily dose of S-1 was calculated according to body surface area (BSA) as follows: BSA < 1.25 m^2, 80 mg/day; BSA $\geq$ 1.25 m^2 but <1.5 m^2, 100 mg/day; and BSA $\geq$ 1.5 m^2, 120 mg/day. Patients received their assigned dose of S-1 divided in two, after breakfast and dinner orally. Paclitaxel was given as an intravenous infusion for 60–90 min on days 1, 8, and 15.

In phase I, we studied cohorts of 3 patients each. MTD was defined as the dose level associated with DLT in 33% or more of the patients. The starting dose of paclitaxel was 40 mg/m^2. The dose was escalated to 70 mg/m^2 (level 4) in

10-mg/m^2 increments. Toxicity was evaluated according to the Common Toxicity Criteria of the National Cancer Institute version 2.0. DLT was defined as any of the following during the first course of treatment: grade 4 leukopenia; grade 4 neutropenia; fever (body temperature, ≥38°C) with grade 3 neutropenia; grade 3 or higher thrombocytopenia; grade 3 or higher nonhematologic toxicity, except for pigmentation and alopecia; more than 7 days of rest during the S-1 treatment period (days 1–21) because of adverse reactions; or treatment with paclitaxel skipped 2 or more times because of adverse reactions. In phase II, patients received the RD of paclitaxel as determined in phase I to confirm the response rate and safety.

Response evaluation and toxicity

Antitumor effects in patients with assessable and measurable lesions were evaluated according to "Response assessment of chemotherapy and radiotherapy for gastric carcinoma" of the Japanese Classification of Gastric Carcinoma (13th edition), which were established based on criteria established by the WHO. For gastric lesions, response was evaluated on the basis of the percent reduction in tumor volume and changes in lesion morphology on radiographic or endoscopic examination. Lesions other than primary gastric tumors, i.e., metastatic lesions, were assessed according to organ on the basis of computed tomographic and radiographic images.

End points and statistical analysis

In phase I, the end points were the estimated MTD and RD of paclitaxel in combination with S-1. In phase II, the primary end point was the response rate at the RD of paclitaxel as determined in phase I. The secondary end points were MST, time to treatment failure (TTF), and safety. Given an expected response rate of 60% and a threshold response rate of 30% for our regimen of S-1 plus paclitaxel, the sample size required to maintain an α error of 0.05 and a β error of 0.10 was 21 patients.

Results

From November 2002 through December 2005, a total of 31 patients were enrolled in the study. In phase I, 2 patients given the RD of paclitaxel were excluded: 1 patient was transferred to another hospital after enrollment, but before treatment; the other patient refused the study treatment. Consequently, data from 13 patients in phase I and 22 in phase II (including those who received the RD of paclitaxel in phase I) were included in analysis. The demographic characteristics of the patients are shown in Table 1. The median age was 64 years (range 47–75). Histopathologically, 18 patients had differentiated adenocarcinomas and 11 had poorly differentiated adenocarcinomas. Overall, 25 patients had a PS of 0, and 4 had a PS of 1. One patient had previously received postoperative adjuvant chemotherapy with S-1.

Results of phase I portion

Toxicity during the first course of treatment in phase I portion is summarized in Table 2. DLT occurred in 2 patients at level 3 (paclitaxel, 60 mg/m^2). One patient had grade 2 neutropenia, precluding further treatment. The other had grade 3 stomatitis, grade 3 anorexia, and grade 3 nausea. These two cases discontinued the treatment with S-1 plus paclitaxel in one course. Therefore, level 3 (paclitaxel, 60 mg/m^2) was considered the MTD, and level 2 (paclitaxel, 50 mg/m^2) was estimated to be the RD for phase II portion. The median number of treatment courses was 4 (range 1–12) in phase I portion.

Results of phase II portion

Primary lesions as well as metastatic lesions were evaluated to assess antitumor effects (Table 3). Of the 22 patients included in analysis, 12 responded to treatment,

Table 1 Patient characteristics

	Phase I portion			Phase II portion[a]
Level	1	2	3	
Paclitaxel (mg/m^2)	40	50	60	50
No. of patients	4	6	3	22
Age (years)				
Median	61.5	61.5	67	64
Range	45–69	54–74	59–69	47–75
Sex				
Female	0	1	2	6
Male	4	5	1	16
Pathology				
Intestinal	2	2	2	14
Diffuse	2	4	1	8
Gastrectomy	0	3	3	4
Metastatic sites				
Lymph node	1	3	1	15
Liver	2	5	0	12
Others[b]	2	3	2	6
Number of metastases				
1	1	2	1	8
>1	3	4	1	13

[a] Including six patients who received level 2 in the phase I portion

[b] Lung, peritoneum, ascites, portal vein embolism

Table 2 Incidences of toxicity

Course	Phase I portion First course						Phase II portion All courses	
Paclitaxel (mg/m^2)	40		50		60		50	
No. of patients	4		6		3		22	
Toxicity/grade	All events	Grade 3/4	All events	Grade 3/4	All events	Grade 3/4	All events	Grade 3/4
Hematological								
Leukopenia	3	0	3	1	2	0	9	1
Neutropenia	2	0	2	1	2	1	6	2
Anemia	3	0	2	1	0	0	10	2
Nonhematological								
Anorexia	1	0	1	0	0	1	7	1
Nausea	1	0	2	1	0	1	6	1
Vomiting	0	0	0	0	0	0	2	0
Diarrhea	0	0	1	0	0	0	4	2
Stomatitis	0	0	4	0	0	1	9	0
Pigmentation	0	0	1	0	0	0	3	0
Rash	0	0	1	0	0	0	1	0
Alopecia	0	0	1	0	0	0	7	0
Fatigue	1	0	1	0	0	0	7	1
Disorder of hepatic function	0	0	1	0	0	0	4	1
Increase of serum creatinine value	0	0	1	0	0	0	1	0
Decrease of serum potassium value	1	0	0	0	0	0	0	0

Table 3 Response rates

	n	CR	PR	NC	PD	NE	Response (%)
Phase II portion	22	1	11	4	6		54.5
Lymph nodes	15	1	8	5	1		60
Liver	12	1	4	3	4		41.7
Portal-vein embolism	1	1	0	0	0		100
Primary	18	1	6	5	2	4	38.9

CR complete response, *PR* partial response, *NC* no change, *PD* progressive disease, *NE* not evaluated; Response rate = number of CR and PR/total number (*n*)

including 1 patient with a complete response. The response rate was 54.5% (95% confidence interval, 32.2–75.6%). The response rate according to site was 38.9% (7/18) for primary lesions, 60.0% (9/15) for lymph-node metastases, and 41.7% (5/12) for liver metastases. One patient with portal embolism had a complete response. The MST was 283 days (95% confidence interval, 218–508) (Fig. 1). The median follow-up time for all 22 cases was 229.5 days (range 101–756). The median TTF was 140 days (95% confidence interval, 111–204) (Fig. 2). The median number of treatment courses was 4 (range 1–10) in phase II portion.

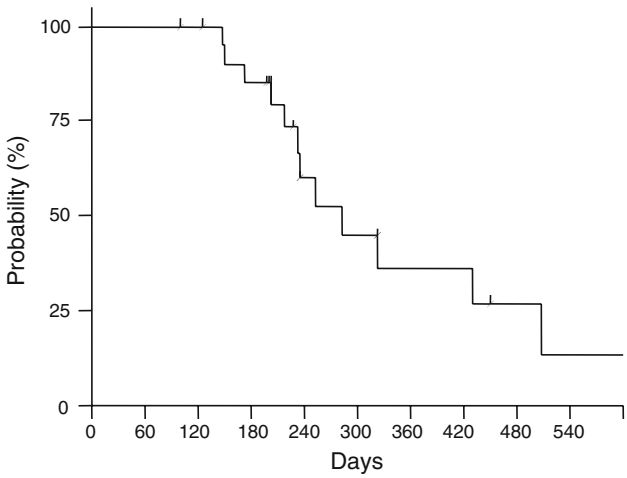

Fig. 1 Cumulative probability of overall survival as estimated by the Kaplan–Meier method in 22 patients. The median overall survival time was 283 days (95% confidence interval, 218–508)

The incidence of toxicity during all courses of treatment was low. Hematologic toxicity rated grade 3 was leukopenia (1 case, 4.5%) and neutropenia (2 cases, 9.1%). Nonhematologic toxicity rated grade 3 was diarrhea (2 cases, 9.1%), nausea (1 case, 4.5%), and anorexia (1 case, 4.5%) (Table 2). No grade 4 toxicities were observed throughout phase I and phase II studies.

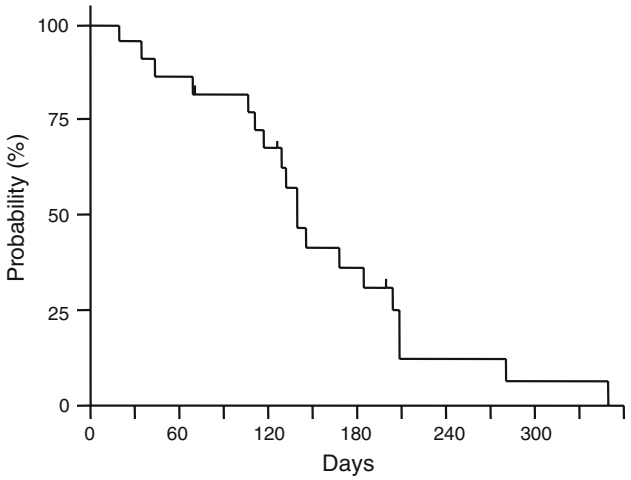

Fig. 2 Cumulative probability of time to treatment failure as estimated by the Kaplan–Meier method in 22 patients. The median time to treatment failure was 140 days (95% confidence interval, 111–204)

Discussion

We found that a combination of S-1 and paclitaxel was active in patients with advanced or recurrent gastric cancer; therapy could be continued according to the protocol. Results are encouraging and merit exploration in a larger clinical trial. Concomitant treatment with paclitaxel allowed chemotherapy to be administered on an outpatient basis, thereby avoiding the negative effects of hospital admission on patients' quality of life.

In Japan, S-1 is widely used for the chemotherapy of unresectable or recurrent gastric cancer and is acknowledged to be highly effective. Various regimens for combination chemotherapy have been studied in the hope of further enhancing antitumor efficacy and prolonging survival. Previous phase III studies have shown that cisplatin-based chemotherapy produces the best antitumor response. The results of a phase III trial performed by the Japan Clinical Oncology Group (JCOG9912), comparing 5-fluououracil (continuous intravenous infusion), S-1 alone, and cisplatin plus irinotecan in patients with unresectable or recurrent gastric cancer were reported at the 2007 meeting of the American Society of Clinical Oncology [3]. The results of the SPIRITS trial, comparing S-1 plus cisplatin with S-1 alone, were also reported [15]. The JCOG 9912 trial demonstrated that S-1 is not inferior to a continuous intravenous infusion of 5-fluorouracil, previously considered the standard treatment. The SPIRITS trial showed that survival in patients given a combination of S-1 and cisplatin was superior to that in patients given S-1 alone. These results will probably establish S-1 plus cisplatin to be one of the standard treatments for advanced gastric cancer. However, because treatment with cisplatin requires hydration and other precautions, patients have to be repeatedly admitted for short hospital stays. Moreover, repeated administration of cisplatin carries a risk of cumulative adverse effects, sometimes necessitating the withdrawal of treatment. Drawing on the experience of Koizumi et al. with S-1 plus cisplatin [16], we decided to administer S-1 in a 5-week cycle, consisting of 3 weeks of treatment followed by 2 weeks of rest, in combination with paclitaxel.

On the other hand, docetaxel, another taxane, has been already a key component of chemotherapy in the first-line gastric cancer treatment with DCF regimen [25]. However, substantial toxicities were also reported and fifty percent of patients receiving DCF were taken off therapy either because of adverse events from treatment or because of patient withdrawal of concent [9]. More safe and effective treatment strategy is clearly needed.

In phase I of our study, toxic effects were mild and included gastrointestinal symptoms such as diarrhea (7.7%) and stomatitis (38.5%) caused by S-1 and elevated serum potassium concentrations (7.7%) and nausea (23.1%) caused by paclitaxel. In phase II, liver dysfunction (18.2%) occurred in addition to the toxic effects occurring in phase I; however, treatment could be continued on an outpatient basis. In addition to the toxic effects confirmed in our study, several previous studies of combination therapy with S-1 and paclitaxel have reported hematologic toxicity and laboratory abnormalities such as neutropenia and hyperkalemia in patients who received high doses of paclitaxel [8, 24]. Pharmacokinetic studies of S-1 and paclitaxel have reported that the concurrent use of paclitaxel has a minimal effect on the area under the curve of 5-fluorouracil, suggesting no marked alteration of drug pharmacokinetics [5]. These pharmacokinetic data and our results showed that the combination of S-1 and paclitaxel is well tolerated, with no specific adverse effects.

In our study, primary lesions responded to treatment in 7 patients, including 1 with a complete response. High antitumor activity against primary lesions, which generally respond poorly to chemotherapy, was thus confirmed. Even though 18 of the 22 patients in phase II had advanced, unresectable, primary gastric cancer, 12 patients (54.5%) responded to the treatment in overall response. The response rate was higher than that obtained in phase II trials of S-1 monotherapy (44.2%). Concurrent treatment with paclitaxel thus enhanced antitumor activity. The overall survival and TTF, designated as secondary end points, were, respectively, 9.4 and 4.7 months, slightly longer than the reported values for S-1 alone. The median number of treatment courses was 4 (range 1–10), indicating that therapy can be continued. The observed TTF and overall survival are modest and at least not inferior to those reported from larger phase III trials of combination chemotherapy regimens in gastric cancer, although only

S-1 plus cisplatin regimen achieved 12 months or longer median overall survival [4, 11, 15, 25]. It will be necessary to examine a survival prolongation effect by randomized control trial.

Weekly paclitaxel is characterized by high activity for ascites and peritoneal dissemination in ovarian and gastric cancer with manageable toxicity [7, 17]. Phase II clinical trials showed that S-1 is also effective for diffuse type gastric tumors [14]. Therefore, combination therapy with S-1 and paclitaxel has two main objectives. The first is to perform phase III trials and establish this regimen as first-line chemotherapy on an outpatient basis. The second is to establish treatment regimens that take advantage of the characteristics of both drugs and define subgroups of patients that will maximally benefit from the therapy, such as those with peritoneal dissemination.

In conclusion, our phase I/II trial showed that S-1 combined with weekly paclitaxel is active and well tolerated with acceptable toxicity. This regimen could be one of the choices for an experimental arm in phase III trials in near future.

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