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CLINICAL TRIAL REPORT

A multicenter phase II study of biweekly paclitaxel and S-1 combination chemotherapy for unresectable or recurrent gastric cancer

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Abstract
Purpose This Phase II study assessed the activity and safety of biweekly paclitaxel and oral S-1 as treatment for unresectable and recurrent gastric cancer. The maximum tolerated dose for this regimen had been established previously in a Phase I study performed in Japanese patients.
Patients and methods Chemotherapy was performed using two anticancer agents, S-1 and paclitaxel. Oral S-1 (80 mg/m^2) was administered twice a day after meals for two consecutive weeks from Day 1 to 14, followed by a 2 week recovery period; paclitaxel (120 mg/m^2) was administered intravenously, biweekly, on Days 1 and 15. The patient received cycles of this regimen every 4 weeks (q 28-day cycles). The primary end point was the response rate according to the Response Evaluation Criteria in Solid Tumors.
Results A total of 39 patients (median age, 65 years) were enrolled; 13 other patients were screened, but found to be ineligible. All patients had unresectable and recurrent gastric cancer. The most common treatment-related Grade 3/4 adverse events were neutropenia (37.5%), appetite loss, diarrhea, decreased sodium (each 5%), and anemia, increased alanine aminotransferase, general fatigue, and dizziness (each 2.5%). Almost all the patients experienced alopecia. Intent-to-treat analysis showed a response rate of 43.6%. With a median follow-up of 14 months (range 8–21 months), median survival was 256 days and the median time to progression was 4 months.
Conclusion A combination regimen of biweekly paclitaxel and oral S-1 was well tolerated and showed promising activity against unresectable and recurrent gastric cancer.

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Introduction

Gastric cancer is still one of the most common malignancies and a major leading cause of cancer-related death worldwide [1, 2]. Although patients in the early stages of gastric cancer have a good prognosis, those with advanced or unresectable disease are incurable, and for this group of patients the prognosis is poor.

Recently, some new regimens of combination chemotherapy have shown promising efficacy in advanced gastric cancer [3–5]. Several randomized studies have shown that these new combination chemotherapies have improved the quality of life and overall survival compared with the best supportive care [6–8]. Nevertheless, even with these promising regimens, the number of patients who benefit from treatment remains limited. In addition, because of interpatient differences with respect to efficacy and toxicity, there is no one regimen that stands out as better than the rest. Therefore, by designing new combination regimens and investigating their efficacy and safety in the clinical trial setting, it is hoped that a protocol with a clear clinical benefit may emerge.

Among these new anticancer agents, S-1 (Taiho Pharmaceutical Co Ltd, Tokyo, Japan) based combination chemotherapies have been popular in Japan. S-1 is a novel fluoropyrimidine derivative, which is composed of tegafur (FT); a prodrug of 5-fluorouracil (5-FU)), and two modulators, gimeracil (CDHP) and oteracil potassium (Oxo). Following the oral administration of S-1, the antitumor effect is achieved by the gradual conversion of FT to 5-FU. S-1 was designed to enhance the clinical utility of an oral fluoropyrimidine, but at the same time to be associated with reduced gastrointestinal toxicity [9–11]. S-1 monotherapy showed an overall response rate of 44% in the Phase II study [12]. Combination of S-1 and CDDP showed high activity and the response rate of this regimen was reportedly as high as 60%.

Paclitaxel (Bristol-Myers Squibb Co., Tokyo, Japan) is a taxane which is extracted from the bark of the Pacific yew and the needles of the English yew. It binds with high affinity to microtubules and enhances tubulin polymerization. This action inhibits the normal dynamic process of the cell's microtubule network resulting in the inhibition of mitosis and cell division [13, 14]. Paclitaxel's antitumor effect is derived from this inhibitory action. Monotherapy with paclitaxel is associated with an overall response rate of 28% in advanced gastric cancer patients [15]. Biweekly administration of paclitaxel has also succeeded in breast, lung and head and neck cancer, the merit of biweekly administration reportedly weakening the toxicity of paclitaxel while preserving its activity.

Therefore, it can be seen that S-1 and paclitaxel have different mechanisms behind their function and resistance, as well as non-overlapping toxicities. We developed this combination chemotherapy of S-1 and biweekly paclitaxel, and determined the maximum tolerated dose (MTD) in a Phase I study in Japanese patients with advanced gastric cancer [16]. We report here the results of a subsequent multicenter Phase II study with biweekly paclitaxel and oral S-1 combination chemotherapy as first-line treatment for recurrent and unresectable gastric cancer.

Patients and methods

Patients' eligibility

To be eligible for the study, patients had to have unresectable, histologically confirmed adenocarcinoma of the stomach. The extent of the tumor was evaluated with computed tomography (CT) or magnetic resonance imaging (MRI). The presence of at least one measurable lesion by the response evaluation criteria in solid tumors (RECIST) was required [17]. Patients were excluded if they had brain metastasis, large ascites or pleural effusion. Prior treatment for advanced gastric cancer, including the administration of paclitaxel, was an exclusion criterion, although patients who had received adjuvant therapy with fluorouracil were eligible provided more than 4 months had elapsed between the end of adjuvant therapy and registration on this study. All patients had to be aged between 20 and 80 years, with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 to 2, and life expectancy of 12 weeks; in addition, they had to be able to swallow tablets.

Pretreatment evaluation included complete medical history and physical examination, electrocardiography (ECG), complete blood count (CBC), serum chemistries and electrolytes, urinalysis, chest X-ray, and recording of concomitant medications. Patients were required to have adequate bone marrow, renal and hepatic function, defined as an absolute neutrophil count (ANC) of 2,000 μL^{-1}, a platelet count of 100,000 μL^{-1}, hemoglobin of 8.0 g/dL, serum creatinine of 1.5 mg/dL, and total bilirubin of 1.5 mg/dL. Patients were also required to have serum alanine aminotransferase (ALT) and serum aspartate aminotransferase (AST) levels of 2.5× the upper limit of normal (ULN) (3.0× the ULN in the presence of liver metastasis). Patients with serious arrhythmia or ischemic changes on the ECG were excluded. All patients gave written informed consent before enrolment and the study was approved by the ethics committees in each institution. The study conformed to the

principles of the Declaration of Helsinki and its subsequent amendments.

Chemotherapy

Chemotherapy was performed using two anticancer agents, S-1 and paclitaxel. The MTD and DLT of this combination of biweekly paclitaxel and S-1 in advanced gastric cancer had been established previously in a Phase I study performed in Japanese patients [16]. Based on the findings from this earlier study, the recommended doses for this Phase II study with paclitaxel and S-1 were set at 120 and 80 mg/m^2, respectively [13]. Oral S-1 was administered twice a day, after meals, for two consecutive weeks from Day 1 to 14, followed by a 14-day recovery period. Paclitaxel was administered intravenously, biweekly on Days 1 and 15. Cycles were repeated every 28 days. The patient continued to receive cycles of this regimen until there was evidence of disease progression, the development of unacceptable toxicity in the investigator's opinion, or if the patient withdrew consent. Patients going off study were allowed to receive any second-line treatment.

Evaluations of toxicity

Patients were monitored for CBC and serum chemistries every week during the first cycle. After the second cycle, they were monitored every 2 weeks. All adverse events were graded using the National Cancer Institute Common Toxicity Criteria (NCI-CTC, version 2.0). Dose modifications and treatment delays were performed as necessary according to the extent of hematological and organ toxicity. When a Grade 4 hematotoxicity or febrile neutropenia, or a Grade 3 non-hematotoxicity except alopecia, occurred during therapy, S-1 and paclitaxel were withheld and resumed at a reduced dose once the toxicity had resolved; all subsequent cycles were administered at the reduced dose. If treatment-related Grade 3 stomatitis or diarrhea occurred, only the S-1 dose was reduced. In cases of severe peripheral neuropathy, only the dose of paclitaxel was reduced. Treatment could be delayed for up to 2 weeks for hematological toxicities and/or other severe non-hematologic toxicities. If these toxicities had not resolved within 2 weeks after dose reduction, the administration of the study drugs was discontinued.

Evaluation of response

Baseline CT or MRI scans of measurable lesions were carried out within 4 weeks of the start of study treatment. After every cycle of chemotherapy, patients received follow-up CT or MRI scans for assessment of response according to RECIST definitions [14]. The tumor size of all measurable lesions had to have been assessed by the first day of the next cycle. Complete response (CR) and partial response (PR) had to be confirmed at least 4 weeks after the first assessment. Imaging films of all assessable patients were also reviewed externally by an independent-review panel to confirm investigator-designed responses.

Statistical considerations

The primary end point of this study was the overall response rate (ORR = CR + PR). Secondary end points were progression-free survival (PFS), overall survival (OS) and adverse events. The required number of patients for this trial was 34, calculated according to Fleming's single-stage design with a power of 80% and a significance level of 5%. In anticipation of 10% of patients being ineligible, we planned to enrol 38 patients. All eligible patients were included in the response, safety and survival analyses. Time to progression (TTP), defined as the time from study entry until documented tumor progression, and OS, defined as the time from study entry until death, were analyzed according to the Kaplan–Meier method.

Results

Patient characteristics

A total of 52 patients were registered at 20 centers between July 2003 and December 2005. Thirteen patients did not meet the entry requirements and therefore, 39 patients (33 males, 6 females) were finally enrolled into the study. Baseline characteristics are listed in Table 1. The median age was 65 years (range 37–79 years); 37 (95%) patients had ECOG PS 0 to 1, and 26 (65%) had multiple metastatic lesions involving two or more organ systems. Histological types of primary lesion were: tubular adenocarcinoma (52.5%), papillary adenocarcinoma (2.5%), poorly differentiated adenocarcinoma (35%), signet-ring cell carcinoma (7.5%) and mucinous adenocarcinoma (2.5%) (Table 1). Abdominal lymph nodes and the liver were the most common metastatic sites.

Treatment administered

A total of 144 cycles of paclitaxel-S1 were administered, with a median of 3.7 per patient (range 2–8). Four patients (10%) had a dose reduction, for Grade 4 leucopenia (1 patient) and Grade 3 non-hematologic toxicity, diarrhea (1 patient), dizziness (1 patient) and decreased sodium (1 patient). Treatment administration was delayed for a median of 7 days (range 4–14 days) in 5 patients, mainly for neutropenia (4 patients) and decrease of ALT (1 patient). The reasons for treatment discontinuations were tumor progression (37 patients) and adverse event without recovery

Table 1 Baseline characteristics and patient demographics

Characteristic	No. of patients	(%)
Age (years)		
Median	65	
Range	37–79	
Sex		
Male	33	85
Female	6	15
Performance status (ECOG)		
0	30	75
1	7	20
2	2	5
Total no. of cycles		
Median	3	
Range	2–8	
Prior therapy		
None	32	
Surgery only	3	
Surgery + adjuvant chemotherapy	4	
Metastatic site		
Abdominal lymph node	26	
Liver	23	
Peritoneum	5	
Cervical lymph node	5	
Lung	3	
Histological types of primary tumor		
Intestinal	21	55
Diffuse	18	45

within 14 days (2 patients). There were no patients with chemotherapy-related death (Tables 2, 3).

Efficacy

Tumor response was evaluable according to RECIST in 40 patients. Eighteen patients (45%) achieved a confirmed PR, 11 (27.5%) had stable disease (SD), and 11 (27.5%) progressive disease (PD), as judged by an independent review panel. This resulted, in an ORR of 45% [95% confidence intervals (Cis), 29.4–60.6%]. Median survival time (MST) was

Table 2 Tumor response

Characteristic	No. of patients	(%)
Confirmed response		
Complete response	0	0
Partial response	17	45
Stable disease	11	28
Progressive disease	11	28
95% CI: 29.4–60.6%	N = 39	

Table 3 Treatment-related adverse events

Adverse events	Grade 1, 2 No. of patients (%)	Grade 3, 4 No. of patients (%)
Hematological		
Anemia	36 (90)	1 (2.5)
Leucopenia	23 (58)	4 (10)
Neutropenia	12 (30)	15 (37.5)
Thrombocytopenia	2 (5)	0 (0)
Non-hematological		
Nausea/Vomiting	3 (60)	0 (0)
Anorexia	1 (2.5)	2 (5)
Fatigue	3 (8)	1 (2.5)
Dizziness	1 (2.5)	1 (2.5)
Fever	4 (10)	0 (0)
Alopecia	39 (100)	
Stomatitis	4 (10)	0 (0)
Diarrhea	2 (5)	2 (5)
AST↑	13 (33)	0 (0)
ALT↑	7 (18)	1 (2.5)
Neuropathy	13 (33)	0 (0)
Hyponatremia	5 (13)	2 (2)
Duodenal ulcer		1 (2.5)

ALT alanine aminotransferase, *AST* aspartate aminotransferase

8.5 months (95% CIs, 8.0–14.9 months, Fig. 1), median TTP was 4.0 months (95% CIs, 2.9–6.2 months, Fig. 2). One- and 2-year OS rates were 35.9 and 14.4%, respectively.

Following completion of this study regimen, a total of 32 (82%) patients received second- and third-line chemotherapies, with 56% receiving CPT-11 (irinotecan) and cisplatin (CDDP) combinations.

Toxicity

The median number of completed cycles was 3 (range 2–8). The most common treatment-related Grade 3/4 hematological

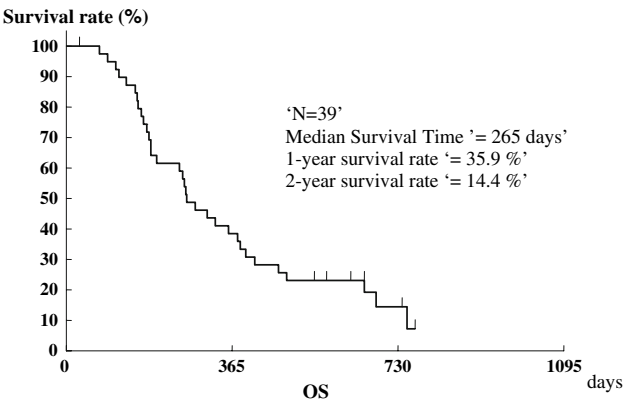

Fig. 1 Kaplan–Meier curve for overall survival

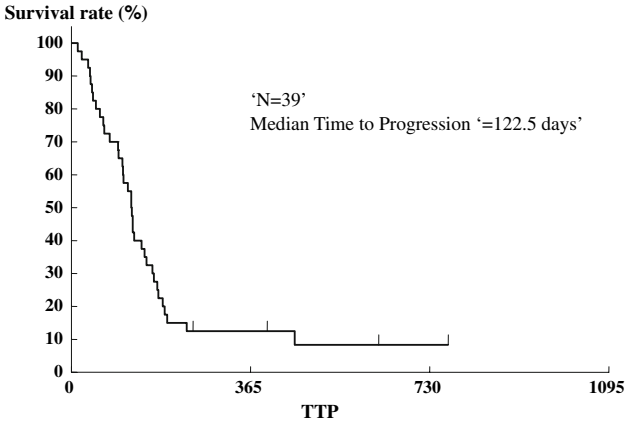

Fig. 2 Kaplan–Meier curve for time to disease progression. The median time to progression and median overall survival was 122 and 265 days respectively

toxicity was neutropenia (37.5% of patients). All of these patients were successfully treated with granulocyte-colony-stimulating factor (G-CSF) and antibiotics. Grade 3/4 anemia was seen in one patient (2.5%); no Grade 3/4 thrombocytopenia was reported. With non-hematological toxicity, there were very few Grade 3/4 adverse events. Appetite loss, diarrhea, and decreased sodium were each seen in two patients (5%), and dizziness, decrease of ALT, general fatigue and duodenal ulcer were each seen in one patient (2.5%), respectively. The most common Grade 1/2 non-hematological toxicities were alopecia (75% of patients), peripheral neuropathy (32.5%) and elevation of AST (32.5%).

Discussion

In this current multicenter Phase II study, we have shown that a combination of biweekly paclitaxel and oral S-1, given as first-line chemotherapy for far advanced gastric cancer such as unresectable and recurrent disease has acceptable antitumor activity (in terms of response rate) and a safe toxicity profile. We achieved an ORR of 45%, a median TTP of 123 days, and an MST of 256 days, and we consider these to be clinically meaningful data. We have reported previously the results of Phase I study with this paclitaxel plus S-1 combination regimen, where the response rate was 53% and the MST was 428 days [17]. Mochiki et al. [18] reported on the combination regimen of weekly paclitaxel and S-1 for advanced gastric cancer, and showed a response rate of 54.1% and an MST of over 15.5 months. Moreover, our feasibility study of paclitaxel and S-1 in 52 advanced gastric cancer patients in a single institute reported an MST of 17.0 months (data was not shown). The shorter MST in the current study is possibly due to the inclusion of many patients with very advanced and terminal disease.

Interestingly, we have already reported on 14 cases where we improved long-term survival by giving this regimen after performing radical salvage surgery to reduce the tumor burden [19]. However, unfortunately, there was no case in this current study where a radical operation was associated with clinical CR. Nevertheless, it seems to be a promising regimen to use as a follow-on from salvage gastrectomy in advanced gastric cancer patients.

Compared with some other S-1-based combination regimens, the clinical benefits achieved in this current study were associated with an acceptable and low toxicity profile, as well as good drug compliance. The most common, treatment-related Grade 3/4 hematological toxicity was neutropenia (37.5%), which was manageable and reversible with appropriate treatment with G-CSF and antibiotics. With respect to other hematological and non-hematological toxicities, few led to withdrawal of the patient from the study. Another advantage of this regimen was that patients could receive this combination chemotherapy as outpatients without a restriction on their time for admission; this may depend on the lower percentage of digestive adverse effects such as nausea and anorexia.

It is considered that following-up first-line therapy with second- or third-line combination chemotherapies is important for extending MST and OS. In this study, a CPT-11 plus /CDDP combination was the most popular regimen for second-line chemotherapy. However, we found that there were some cases where the administered dosage was insufficient; both of CPT-11 and CDDP were used with dosage of less than 30 mg/m^2 in these cases, and did not reach an effective plasma concentration. Takiuchi et al. [20] have pointed out the importance of second-line chemotherapy in the treatment of gastric cancer. A randomized, controlled trial (RCT), which was conducted as first-line chemotherapy for advanced gastric cancer patients by the Japan Clinical Oncology Group (JCOG 9205), and compared 5-FU alone with 5FU+CDDP, showed that both regimens have almost the same clinical benefit, not only in terms of MST but also in 1- and 2-year survival rates. Seven years later, the JCOG carried out another RCT (JCOG 9912) that compared 5-FU alone versus CPT-11+CDDP versus S-1 alone. In that study, there was no difference in the efficacy results in the three arms. Surprisingly, compared with the earlier JCOG 9205 trial, MST was prolonged by over 4 months in the JCOG 9912 trial. Many new chemotherapeutic agents (e.g., S-1, CPT-11, docetaxel and paclitaxel) were administered in the JCOG 9912 trial, which were not available at the time of the earlier JCOG 9205 study. The improvement in MST may have been linked to these newer, more effective drugs. In the future, it will be important to run clinical trials that investigate the

benefits of second- or third-line regimens as a means of improving the effect of chemotherapy in patients with advanced-stage gastric cancer. We are now running a randomized Phase II trial with a second-line regimen using CPT-11, CDDP and S-1 following a combination of paclitaxel and S-1, as a means of improving the effect of chemotherapy in patients with advanced-stage gastric cancer.

In conclusion, taken together with the results of previous reports of the same regimens, we found that a combination of biweekly paclitaxel and oral S-1 was well tolerated and effective, and propose that it can be considered as another first-line chemotherapy option to patients with advanced gastric cancer.

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