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ORIGINAL ARTICLE

Multicenter phase II trial of S-1, paclitaxel and cisplatin triplet combination chemotherapy in patients with advanced gastric cancer

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Abstract
Objective The present study was conducted to evaluate the efficacy and safety of a combination regimen of S-1, paclitaxel plus cisplatin in patients with advanced gastric cancer.
Methods Patients with previously untreated metastatic or recurrent, measurable gastric cancer received intravenous paclitaxel 80 mg/m^2 plus cisplatin 30 mg/m^2 on days 1, 8 and S-1 35 mg/m^2 orally twice daily on days 1–14 based on a 3-week cycle.
Results Forty-four patients were enrolled in the current study, among whom 38 were assessable for efficacy and all assessable for toxicity. Two complete response and 24 partial responses were confirmed, giving an overall response rate of 59.1%. At a median follow-up of 11.4 months, the median time to progression and median overall survival was 9.4 (95% CI 6.8–12.1) months and 11.2 (95% CI 7.6–14.8) months, respectively. Grade 3/4 neutropenia occurred in 45 events (20.9%) and febrile neutropenia was observed in five events (2.3%). The common non-hematologic toxicity was nausea (grade 1/2, 27.2%) and diarrhea (grade 1/2, 9.0%).
Conclusion The combination of S-1, paclitaxel and cisplatin was found to be well tolerated and effective in patients with advanced gastric cancer.

Keywords S-1 · Paclitaxel · Cisplatin · Chemotherapy · Gastric cancer

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Introduction

The incidence of gastric cancer (GC) has been declining over the past few decades, but gastric cancer is still one of the most frequent causes of cancer-related deaths [1]. Despite poor prognosis of advanced gastric cancer, systemic chemotherapy improves the quality of life and overall survival compared with the best supportive care alone [2–4].

S-1 is a novel oral fluoropyrimidine consisting of a 5-fluorouracil (FU) prodrug, tegafur, and the dihydropyrimidine dehydrogenase inhibitor, 5-chloro-2,4-dihydropyrimidine and the orotate phosphoribosyl transferase inhibitor, potassium oxonate, which suppress the gastrointestinal toxicity of tegafur [5]. S-1 already demonstrated significant activity in advanced gastric cancer, achieving response rates of 26–49% with tolerable safety profile in several phase II trials [6–8].

Paclitaxel is an antitumor agent isolated from the bark of yew tree (*Taxus brevifolia*) and acts on microtubules during mitosis, resulting in antitumor activity. The response rate of 3-week intervals of intravenous paclitaxel was 20–23%

[9, 10]. In addition, weekly infusion of paclitaxel is also active in gastric cancer [11, 12]. Several phase II studies have shown that paclitaxel, alone or in combination with cisplatin or 5-fluorouracil, is active against advanced gastric cancer [13–15]. And also S-1, paclitaxel combination chemotherapy has good efficacy and favorable toxicity profile [16, 17]. However, there is no published data on the efficacy of a combination of weekly S-1, paclitaxel and cisplatin for the treatment of advanced gastric cancer.

Therefore, this phase II study was conducted to evaluate the response rate, time to progression, and safety of a combination regimen of weekly S-1/paclitaxel plus cisplatin in patients with advanced gastric cancer.

Patients and methods

Eligibility

All the patients involved in this study had histologically confirmed metastatic or recurrent gastric adenocarcinoma with at least one unidimensionally measurable lesion. The patients were 18–70 years of age with a performance status of 0–2 on the Eastern Cooperative Oncology Group (ECOG) scale. Other eligible criteria were adequate haematological (absolute neutrophil count $\geq 1.5 \times 10^9\,L^{-1}$, platelet count $\geq 100 \times 10^9\,L^{-1}$), renal (serum creatinine ≤ 1.5 mg/dL and creatinine clearance ≥ 60 mL/min), and hepatic (total bilirubin ≤ 1.5 mg/dL and serum transaminase level $\leq$ three times the upper limit of the normal range) functions. Patients who had received adjuvant chemotherapy completed 1 year before entry were eligible. Patients were ineligible if they had previously received paclitaxel and S-1 chemotherapy or radiation therapy, or had other severe comorbid conditions, CNS metastasis, and another active malignancy. Patients were excluded if they receive drugs with potential interactions with S-1 (allopurinol, phenytoin, and warfarin), or inability to comply with the requirements of the protocol. The institutional review board of each author's institution approved the protocol, and all patients provided written informed consent.

Treatment dose and schedule

S-1 (70 mg/m^2 per day) was administered on days 1–14 of 21-day cycle. Patients received their assigned oral dose of S-1 divided in two, within 1 h after meal. Paclitaxel 80 mg/m^2 and cisplatin 30 mg/m^2 were given as intravenous infusion for 1 h on days 1 and 8. All patients were premedicated with a dexamethasone to prevent hypersensitivity reactions of paclitaxel. Antiemetic treatment was routinely given before each cycle of chemotherapy. The prophylactic use of a colony stimulating factor (CSF) was not allowed but in the case of neutropenic fever we allowed to use of CSF. Treatment was continued until disease progression, patient refusal, or an unacceptable toxicity for a maximum nine cycles.

Dose modification

The next cycle of treatment began only when the absolute neutrophil count was $\geq 1.5 \times 10^9\,L^{-1}$, the platelet count was $\geq 100 \times 10^9\,L^{-1}$, and any other treatment-related toxicities were less than or equal to grade 1; otherwise, treatment was withheld for up to 2 weeks. If adverse events did not improve to grade 0 or 1 after 2 weeks, the patients were excluded from the study. Granulocyte-CSF could be available for grade 3 or 4 neutropenia.

For hematological toxicity, a dose modification for the next cycle was decided by the nadir count of the previous cycle. S-1 or paclitaxel was alternatively reduced by 5 or 10 mg/m^2/day, respectively. Paclitaxel was the first to be reduced for a grade 4 neutropenia, grade 3/4 thrombocytopenia, or neutropenic fever. On day 8, both drugs omitted in case of grade 4 neutropenia, grade 3/4 thrombocytopenia, neutropenic fever, or severe hemorrhage. On day 8, for grade 3 neutropenia or grade 2 thrombocytopenia or platelet counts less than $100 \times 10^9\,L^{-1}$, paclitaxel dose was reduced by 10 mg/m^2/day without the reduction of S-1. The dose of S-1 was not reduced in the same cycle. We permitted to use G-CSF in the case of febrile neutropenia.

For the non-hematological toxicity, S-1 for the next cycle was reduced by 5 mg/m^2/day for grade 2 diarrhea or grade 3/4 abdominal pain and was withheld for grade 3 diarrhea. Paclitaxel was reduced by 10 mg/m^2/day for a grade 2 peripheral neuropathy and was discontinued for grade 3 peripheral neuropathy. Both drugs were reduced by grade 2 hyperbilirubinemia, grade 3 liver dysfunction and grade 3 non-hematological toxicity except alopecia, nausea, vomiting, myalgia, and arthralgia. Both drugs were omitted for grade 3 hyperbilirubinemia, grade 4 liver dysfunction and grade 4 other non-hematological toxicity. The dose of S-1 was not changed in the same cycle. If the patients needs dose modification due to toxicities, the dose can be reduced to the 50% of initially planned dose.

Study assessments

A screening assessment, including a medical history, physical examination, ECG, chest X-ray, and tumor assessment, was conducted within 2 weeks before starting treatment. Other baseline evaluations conducted within 7 days before starting treatment included vital signs, an ECOG performance status, and laboratory tests. Complete blood counts were performed weekly during the first cycle and every cycle thereafter, and biochemical tests performed before each cycle. Response assessment was performed every two

cycles until the tumor progressed. The tumor responses were classified according to the response evaluation criteria in solid tumors (RECIST) guidelines [18]. Patients with a complete response (CR) or partial response (PR) required a confirmatory disease assessment at least 4 weeks later. Adverse events were graded according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0. Dose intensity was defined as the total amount of drug given (mg/m^2) divided by the number of weeks.

Statistical analysis

This trial was designed as a prospective, multi-center, phase II study. Primary end point of this trial was objective response rate and the secondary end points were time to progression, overall survival and safety. A two-stage optimal design proposed by Simon was used to decide the sample size of phase II study [19]. Assuming $P_0 = 0.2$, $P_1 = 0.4$, with $\alpha = 0.05$ and $\beta = 0.2$, the first stage needed at least 4 out of 16 patients to have a response before proceeding to the second stage. Therefore, 44 patients were required with the inclusion of a 10% follow-up loss. All enrolled patients were included in the intention-to-treat analysis of efficacy. The parameters time to progression and overall survival were estimated using the Kaplan–Meier method.

Results

Patient characteristics

From May 2007 to April 2008, a total of 44 patients were enrolled in this study from six centers. The characteristics of the patients are summarized in Table 1. The median age was 51 (range 29–70) years, with 31 males and 13 females. Most of the patients (86.4%) had a good performance status (ECOG 0 or 1). All patients had a metastatic disease; distant lymph nodes and the liver were the most common sites of the metastases. No patients had received prior palliative chemotherapy or radiotherapy.

Efficacy

Thirty-eight (86.4%) of the 44 patients were available for the evaluation of the response, with the remaining six being lost to follow-up or patient refusal. All efficacy data are reported using the intent-to-treat patient population. Two cases of complete remission and 24 cases of partial remission were confirmed, giving an overall response rate of 59.1%. The response characteristics are shown in Table 2. The median duration of response in the 26 responding patients was 8.3 (95% CI 6.5–10.1) months, while the median TTP for all patients was 9.4 (95% CI 6.8–12.1) (Fig. 1). Sixteen patients (64%) received a second-line therapy, such as Folfox4, docetaxel and cisplatin, folfiri, capecitabine, taxol. Thirty-two patients had died at the time of the present evaluation.

Table 1 Patient characteristics

Characteristic	Number of patients (n = 44) (%)
Age (years)	
Median (range)	51 (29–70)
Male/female	31 (70.5)/13 (29.5)
ECOG performance status	
0	7 (15.9)
1	31 (70.5)
2	6 (13.6)
Metastatic sites	
Lymph node	34 (77.3)
Liver	19 (43.2)
Peritoneum	7 (15.9)
Pancreas	3 (6.8)
Lung	2 (4.5)
Others	1 (2.3)
Number of metastatic sites	
1	20 (45.4)
2	20 (45.5)
≥3	4 (9.1)

Table 2 Tumor response (intention-to-treat analysis)

Response	Number (n = 44) (%)
Confirmed response	26 (59.1)
Complete response	2 (4.5)
Partial response	24 (54.6)
Stable disease	10 (22.7)
Progressive disease	2 (4.5)
Not assessable	6 (13.6)

Toxicity

The haematologic and non-haematologic adverse events that occurred during this study are summarized in Table 3. A total of 215 cycles (median 4.9, range 1–8 cycles) were administrated in 44 patients assessable for toxicity. For haematological toxicity, grade 3/4 neutropenia occurred in 31 events (14.4%)/14 events (6.5%) in all 215 cycles. Febrile neutropenia developed in four patients (9.1%). However, all cases were successfully treated with antibiotics and G-CSF. Non-haematological toxicities were generally mild and manageable. Nausea was the most common non-haematologic toxicities. Grade 2 nausea was observed in 27.2% of patients. Four patients (9.1%) experienced

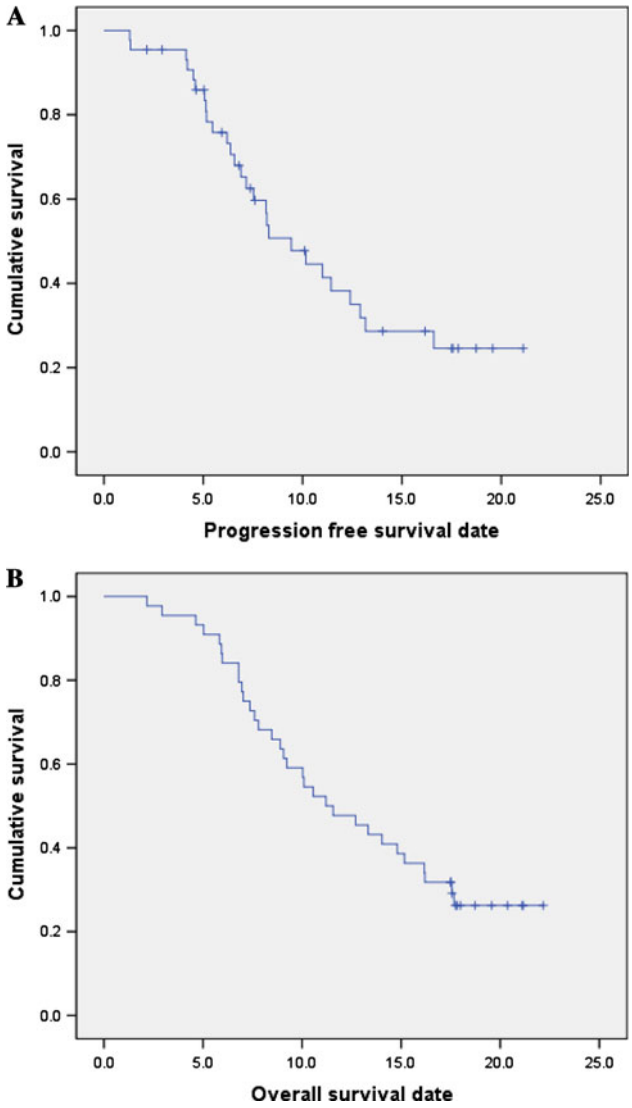

Fig. 1 Kaplan–Meier curves for time to disease progression (**a**) and overall survival (**b**) for intention-to-treat population ($n = 44$). The median time to progression and median overall survival was 9.4 and 11.2 months, respectively

grade 2 diarrhea. Yet, no grade 4 non-haematologic toxicity was observed. Eighteen patients were hospitalized due to treatment toxicities (nine due to febrile neutropenia, seven due to general weakness, two due to nausea and vomiting).

A total of 228 cycles were delivered to patients. Median cycle was 6.0 (range 1–8). The mean doses of taxol, cisplatin and S-1 were 77.2, 29. 2 and 68.0 mg/m^2/cycle which were 96.5, 97.3 and 97.2%, respectively, of planned dose-intensity of protocol.

Discussion

For patients with advanced gastric cancer, palliative chemotherapy has been associated with improved survival compared to the best supportive care. This benefit has been confirmed by four randomized trials that demonstrated a median survival of 9–11 months and a 1-year-survival rate of 35–40% for patients receiving chemotherapy compared to the median survival of 3–5 months and the 1-year survival rate of 10% for patients receiving the best supportive care [20]. Although, over the past several decades investigators have tried to identify improved chemotherapeutic agents there has not been any standard regimen identified to date for effective treatment of advanced gastric cancer.

This is the first report of S-1, paclitaxel and cisplatin combination chemotherapy in advanced gastric cancer. The overall response rate (56.8%), median time to progression (9.4 months), and median overall survival 11.2 months following treatment with the present regimen were promising. This trial confirmed that a combination of these three chemotherapeutic agents were active in advanced gastric cancer. The results are encouraging and merit exploration in larger clinical trial. Treatment schedule and dose allowed chemotherapy to be administered on an outpatient basis.

S-1 and paclitaxel have different antitumor mechanism and both agents were used together for the treatment of gastric cancer. In several Japanese phase I/II trials of combination S-1 and paclitaxel, S-1 was given 80 mg/m^2 and paclitaxel 40–60 mg/m^2, weekly [21–23]. The most common dose limiting toxicities were grade 3 diarrhea or grade 4 neutropenia. The responses of these studies were 45–64%. In this trial, grade 3/4 neutropenia were the most common toxicities, but non-hematological toxicities were mild.

Clinical trials of S-1 and other chemotherapeutic agents such as cisplatin and docetaxel have been performed in advanced gastric cancer patients [24–26]. These combination regimens showed promising results with a response rate of 40–70% and median survival 11–14 months. Ajani et al. treated patients with untreated advanced gastric or gastroesophageal junction adenocarcinoma with cisplatin intravenously at 75 mg/m^2 on day 1 and S-1 orally at 25 mg/m^2/dose bid on days 1–21 every 4 weeks [24]. This study showed overall response rate of 51%, a median survival of 10.9 months and a median progression-free survival of 4.4 months. Grade 3 or 4 neutropenia was recorded in 26% of patients. The most frequent non-hematologic toxicities were fatigue (26%), vomiting (17%), diarrhea (15%), and nausea (15%).

In recent trial of S-1 and cisplatin combination therapy including S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRIT trial), median overall survival and progression free survival was 13.0 and 6.0 months in patients assigned to S-1 plus cisplatin [25]. Although promising results were reported, grade 3–4 gastrointestinal toxicities significantly occurred. Treatment

Table 3 Adverse reactions

	Grade[a] (% of patients, $n = 44$)		Grade[a] (% of cycles, $n = 215$)	
	3	4	3	4
Hematologic				
Anemia	4.8		5.1	1.9
Leukopenia	7.1	4.8	4.8	1.6
Neutropenia	7.1	19.0	14.4	6.5
Thrombocytopenia	2.4		0.5	
Non-hematologic				
Nausea	2.4			
Vomiting	4.8			
Fatigue				
Stomatitis	2.4		0.5	
Diarrhea	4.8		1.1	
Peripheral neuropathy			2.3	
Febrile neutropenia	9.1		2.3	

[a] National Cancer Institute Common Toxicity Criteria version 3.0

with cisplatin requires hydration and other precaution, patients need to be repeatedly admitted for short hospital stay. In our study, the dose of cisplatin does not need long prehydration, so patient can receive chemotherapy in outpatient basis.

Docetaxel has been used as a key component of chemotherapy in first-line gastric cancer treatment with cisplatin and fluorouracil (DCF) regimen [27]. Time to progression, primary end point of this report, was 5.6 months and overall survival was 9.2 months and overall response rate was 37%. However, toxicities were quite substantial, 50% of patients receiving DCF regimen were taken off treatment either because of adverse events from chemotherapy or patient withdrawal of consent [28]. More safe and convenient and effective treatment strategy is clearly needed. In the current study, S-1, paclitaxel and cisplatin combination regimen had tolerable gastrointestinal toxicities as well as active antitumor effects. Grade 3/4 stomatitis and diarrhea were not observed. There were no report about grade 3/4 nausea and vomiting. Grade 3/4 neutropenia (20.9%) was comparable to weekly docetaxel regimen [26] but less frequent when compared to docetaxel, cisplatin and 5-fluorouracil regimen [27].

In conclusion, S-1, paclitaxel and cisplatin combination chemotherapy was found to be well tolerated and effective in patients with advanced gastric cancer. However, further studies are warranted to clarify the role of this regimen compared to other doublet or triplet regimens in the first-line treatment for advanced gastric cancer.

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