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ORIGINAL ARTICLE

Phase II study of biweekly docetaxel and S-1 combination chemotherapy as first-line treatment for advanced gastric cancer

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Abstract
Purpose We evaluated the efficacy and toxicity of biweekly S-1 and docetaxel combination therapy in patients with advanced gastric cancer.
Methods Patients with histologically proven, unresectable advanced or recurrent gastric cancer, a performance status (PS) of 0–2 and no prior chemotherapy history were eligible for inclusion ($n = 45$). Patients received a total of 215 treatment courses (median, 4; range, 2–12) of S-1 oral administration twice daily for 1 week followed by a drug-free interval of 1 week. Docetaxel (40 mg/m^2) was administered intravenously on days 1 and 15.
Results We observed 25 partial responses (55.6%) and one complete response (2.2%), resulting in an overall response rate of 57.8%. Twenty-four patients (53.3%) received second-line chemotherapy. Five patients (11.1%) underwent R0 gastrectomy during the course of the study. The median overall survival time was 15.3 months, the median time to progression was 6.9 months, and the median duration of response in 26 patients was 8.0 months. Neutropenia was the most frequently observed (40.4%) haematological toxicity at grades 3 and 4 and leucopenia was the second most common (29.8%). There were no treatment-related deaths.
Conclusions S-1 plus docetaxel combination therapy in an outpatient setting provided promising activity with acceptable adverse toxicities.

Keywords Docetaxel · Gastric cancer · Phase II · S-1

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Introduction

Although the incidence of gastric cancer has recently declined in Japan, it remains one of the most prevalent causes of cancer-related deaths [1]. Surgical resection is a promising treatment for advanced gastric cancer, but is limited in its ability to improve prognosis. It is therefore essential to establish an effective chemotherapeutic regimen for advanced gastric cancer.

The oral anticancer drug S-1 was developed by biochemical modulation of tegafur (FT) to inhibit dihydropyrimidine dehydrogenase (DPD) by gimeracil and by prevention of phosphorylation of 5-fluorouracil in the gastrointestinal tract by oteracil potassium (TS-1; Taiho Pharmaceutical Co. Ltd., Tokyo, Japan) [2]. These dual actions reinforce antitumour activity and reduce gastrointestinal toxicity.

Recently, the therapeutic results for S-1 either alone or in combination with other chemotherapeutic agents in patients with advanced gastric cancer showed satisfactory outcomes [3–5]. Docetaxel (Taxotere, Sanofi-aventis, Paris, France) is a semi-synthetic taxoid derived from the European yew tree, *Taxus baccata*. Docetaxel also showed acceptable outcomes in patient trials both as a single agent and in combination with fluoropyrimidines or other agents [6–8]. Enhanced antitumour activity was reported in a laboratory study of human gastric cancer xenografts treated with S-1 and docetaxel [9]. Although some phase I and II studies of S-1 and docetaxel therapy for advanced gastric cancer have been carried out previously [10, 11], they involved relatively small mean numbers of treatment cycles. In our previous phase I study, the dose-limiting toxicity was assessed over two courses in order to establish a safe and long-lasting regimen with docetaxel and S-1 in an outpatient clinic [12]. In the present study, we conducted a multicenter phase II study to assess further the efficacy and toxicity profile of biweekly docetaxel and S-1 combination chemotherapy for advanced gastric cancer in an outpatient setting.

Patients and methods

Eligibility

Patients with histologically proven advanced (inoperable or recurrent) gastric cancer were enrolled in this study. The inclusion criteria were as follows: at least one measurable lesion; no prior chemotherapy; 20–80 years of age; Eastern Cooperative Oncology Group performance status (PS) <2; estimated life expectancy ≥3 months; adequate liver function (total serum bilirubin <1.5 mg/dl and transaminase no more than twice the normal upper limit for our institution); adequate renal function (serum creatinine within the normal upper limit for our institution, blood urea nitrogen ≤25 mg/dl and 24-h creatinine clearance >50 ml/min); adequate haematopoietic function ($4{,}000/mm^3 \leq$ WBC count $\leq 12{,}000/mm^3$, absolute neutrophil count $>2{,}000/mm^3$, platelet count $\geq 10 \times 10^4/mm^3$ and haemoglobin level ≥9.5 g/dl) and adequate cardiac and pulmonary function. All subjects provided written informed consent.

The major exclusion criteria were as follows: brain metastasis, symptomatic infectious disease, history of drug allergy, symptomatic peripheral neuropathy or oedema, other active malignancies, pregnancy or breast feeding, uncontrolled diabetes mellitus, uncontrolled mental illness and gastrointestinal haemorrhage.

This study was approved by the institutional review board of each institution.

Study design and treatment

The primary end point of this study was the objective response rate after two courses of treatment. Assuming a null hypothesis of a 35% overall response rate and an alternative hypothesis of a 55% overall response rate with one-sided $\alpha = 0.05$ and 80% power, it was necessary to enrol a minimum of 41 evaluable patients. Considering a 10% drop-out rate, 45 patients were needed for this trial.

S-1 was administered orally twice daily for 1 week according to the body surface area (BSA) as follows: BSA $<1.25\ m^2$, 80 mg/day; $1.25 \leq$ BSA $<1.50\ m^2$, 100 mg/day; $1.50\ m^2 \leq$ BSA, 120 mg/day. This was followed by a drug-free interval of 1 week. Docetaxel (40 mg/m^2) was administered intravenously on days 1 and 15. Docetaxel was diluted in 100 ml normal saline and infused for 1 h. Dexamethasone (8 mg) was infused 1 h prior to the administration of docetaxel, and a further 4 mg dexamethasone was administered orally for 2 days to reduce the risk of a hypersensitivity reaction. Each course lasted for 1 month. Treatment was continued until disease progression, patient refusal or unacceptable toxicity occurred.

Dose modification

Toxicity was graded for each cycle according to the National Cancer Institute Common Toxicity Criteria (version 3). Treatment was discontinued if recovery did not occur within days.

Treatment was continued at the same dose of docetaxel if patients experienced grade 1 toxicities or other non-serious toxicities. For all other treatment-related toxicities of grade 2 intensity or higher, dose modification of docetaxel was implemented as follows: no dose reduction was made after the first appearance of grade 2 toxicity, but administration was interrupted until the toxicity recovered to grade 0 or 1. Interruption was allowed twice (2 weeks) within a course. Dose reduction (of 5 mg/m^2) was necessary after dose-limiting toxicity (DLT) appeared (grade 4 haematological toxicity, grade 3 neutropenia with fever, grade 4 thrombocytopenia and grade 3 or 4 non-haematological toxicities). Moreover, dose reduction was required after the previous interruption. If adverse events did not improve to grade 0 or 1 after three interruptions (3 weeks), the patient was excluded from the study.

The use of granulocyte colony-stimulating factor (G-CSF) was permitted if a patient developed grade 4 neutropenia. Antiemetic treatment was also permitted under the direction of the physician.

The tumour response was assessed according to the Response Evaluation Criteria in Solid Tumours version 1.0 (RECIST) after two courses of treatment [13]. The response status of measurable lesions during treatment was evaluated

by a barium-meal study, endoscopy, ultrasonography, computed tomography or magnetic resonance imaging. These evaluations were repeated after one course if there was a partial response (PR). Responses were not evaluated in the primary gastric tumour to avoid measurement bias. Cytology or diagnostic laparoscopy was additionally employed to assess non-measurable lesions, such as ascites.

Statistical analysis

Time to progression (TTP) and overall survival were calculated using the Kaplan–Meier method. The duration of response was defined as the interval from the onset of complete response (CR) or PR until evidence of progression of disease (PD) was found. The TTP was calculated from the initiation of chemotherapy to the date of disease progression, and overall survival was measured from the initiation of chemotherapy to the time of death.

Statistical data were obtained using an SPSS 10.0 software package (SPSS, Chicago, IL).

Results

Patient characteristics

In total, 47 patients with advanced gastric cancer were enrolled in this study between July 2007 and March 2009. Two patients were excluded because of a lack of objective measurable lesions by RECIST, and so the analysis was performed on 45 patients. The patient characteristics are listed in Table 1. All patients had locally advanced or metastatic lesions, with the lymph nodes, peritoneum, liver and other organs as the predominant sites of metastases. The median age was 68 years (range, 37–80), and most patients had a PS of 0/1. Histologically, 16 patients had differentiated-type adenocarcinoma, and 29 had undifferentiated adenocarcinoma. Thirty-eight patients had lymph-node metastasis; of these, 10 had distant lymph-node metastasis, 12 (26.7%) had peritoneal metastases, and eight (15.6%) had liver metastases. Most patients (95.6%) had multiple sites of metastasis. The mean ± standard deviation (SD) follow-up period was 13.2 ± 5.8 months.

Table 1 Patient characteristics

Characteristics	No. of patients $n = 45$ (%)
Age (years)	
Median	68
Range	37–80
Gender	
Male	32 (71.1)
Female	13 (28.9)
ECOG	
0	40 (88.9)
1	5 (11.1)
Disease status	
Newly diagnosed	42 (93.3)
Recurrent	3 (6.7)
Locally advanced disease	15 (33.3)
Metastatic disease	30 (66.7)
Histological type	
Differentiated	16 (35.6)
Undifferentiated	29 (64.4)
Site of primary tumour	
Upper third	21 (46.7)
Middle third	4 (8.8)
Lower third	12 (26.7)
Entire	8 (17.8)
Metastatic sites	
Lymph nodes	38 (84.4)
Peritoneum	12 (26.7)
Liver	8 (15.6)
Others	3 (6.7)
No. of involved organs	
1	2 (4.4)
2	29 (64.5)
3	14 (31.1)
Prior treatment	
None	41 (91.1)
Gastrectomy	4 (8.9)

ECOG Eastern Cooperative Oncology Group, *Others* adrenal gland, lung and bone

Treatment administration

The 45 patients were administered a total of 215 courses, with a median of 4 (range, 2–12). The docetaxel dose was reduced to 35 mg/m^2 in eight patients (17.7%), and stepwise to 30 mg/m^2 in four patients (8.8%) according to the dose-reduction criteria (four patients had grade 4 neutropenia, three patients had repeating grade 3 neutropenia, one patient had grade 3 neutropenia with fever, and four patients had grade 3 anorexia). Treatment administration was delayed in 43 (20.0%) of the 215 courses, with 40 (18.6%) of the course intervals being delayed for >7 days. The major causes of delayed administration were treatment-related toxicity, including neutropenia for 33/215 (15.3%) courses and anorexia for 8/215 (3.7%) courses, as well as personal convenience for 2/215 (0.9%) courses. The reasons for treatment discontinuations were tumour progression (39 patients, 86.7%), surgery with curative intent (five patients, 11.1%) and personal convenience (one patient, 2.2%).

Response and survival analysis

Of the 45 patients who were assessable for tumour response and survival, 25 (55.6%) showed a PR and one (2.2%) showed a CR, resulting in an overall response rate of 57.8% (95% confidence interval [CI], 43.3–72.2%). The disease was stable in 12 patients (26.7%) and progressive in seven (15.6%) at the end of the two courses. The overall response rates according to metastatic site were as follows: 8/12 (66.7%) for peritoneal metastasis, 5/8 (62.5%) for liver metastasis and 21/38 (55.3%) for lymph-node metastases. A CR was observed in one patient with multiple lung metastases after curative gastrectomy.

The overall response rates according to histological type were as follows: 11/16 (68.8%) for differentiated-type adenocarcinoma and 15/29 (51.7%) for undifferentiated-type adenocarcinoma. The overall response rates were in accordance with the number of organs involved: 1/2 (50.0%), 15/29 (51.7%) and 10/14 (71.6%) in patients with one, two and three involved organs, respectively.

A total of 24 patients (53.3%) received second-line chemotherapies: 22 irinotecan-based and seven S-1-based regimens. Three of these patients also received third-line chemotherapies, all of which were taxane-based regimens. Of the 45 patients, five (11.1%) underwent R0 gastrectomy during the study.

The median overall survival time for all patients was 15.3 months (95% CI, 10.4—20.3 months) with a 1-year survival of 60.8% (Fig. 1). The median TTP for the 45 patients was 6.9 months (95% CI, 5.5–8.4 months) (Fig. 1). The median duration of response for 26 patients was 8.0 months (95% CI, 3.4–12.6 months) (Fig. 1).

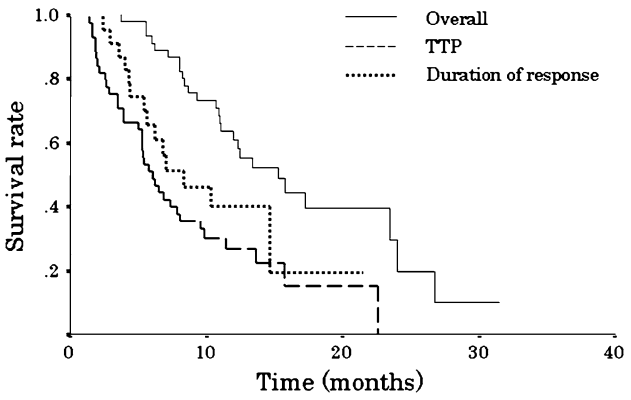

Fig. 1 Overall survival rate, TTP and duration of response. The median overall survival rate in 45 registered patients was 15.3 (95% CI, 10.4–20.3) months with a 1-year survival rate of 60.8% (*solid line*). The median TTP in 45 registered patients was 6.9 (95% CI, 5.4–8.4) months (*dashed line*). The median duration of response in 26 patients was 8.0 (95% CI, 3.4–12.6) months (*dotted line*)

Table 2 Toxicity

Toxicity	No. of patients (%)	
	Grades 1–2	Grades 3–4
Haematological		
Leucopenia	14 (29.8)	14 (29.8)
Neutropenia	15 (31.9)	19 (40.4)
Anaemia	7 (15.6)	0
Thrombocytopenia	1 (2.2)	0
Non-haematological		
Alopecia	35 (74.5)	–
Anorexia	28 (59.6)	4 (8.8)
Nausea	23 (48.9)	0
General fatigue	21 (44.7)	0
Skin	12 (26.6)	0
Vomiting	7 (14.9)	0
Diarrhoea	6 (13.3)	0
Liver dysfunction	2 (4.4)	0
Neuropathy:sensory	2 (4.4)	0

Toxicity

All the 47 patients, who were initially included in this study, were assessable for toxicity. Among the haematological toxicities at grades 3 and 4, neutropenia was most frequently observed (19 patients, 40.4%), followed by leucopenia (14 patients, 29.8%). Three patients were classed as grade 4 neutropenia although we did not encounter any patient with febrile neutropenia. All of the patients were manageable by administering G-CSF followed by dose reduction according to the criteria described earlier. Most non-haematological toxicities were at grades 1 and 2, with the exception of four patients who had grade 3 anorexia. The most common non-haematological toxicities were alopecia (35 patients, 74.5%), anorexia (28, 59.6%), nausea (23, 48.9%) and general fatigue (21, 44.7%). Other non-haematological toxicities were less frequent (Table 2). All non-haematological toxicities were controllable with optimal treatments. There were no treatment-related deaths.

Pharmacokinetics

The serum concentration of docetaxel was measured in six patients. The mean concentrations at 1, 2, 3 and 8 h after the administration of docetaxel were $1{,}058.6 \pm 226.4$, 67.4 ± 32.2, 36.2 ± 17.6 and 12.6 ± 2.9 ng/ml, respectively. The serum concentration of docetaxel drastically decreased at 2 h after docetaxel administration (Fig. 2a).

The serum concentration of fluorouracil (5-FU) was measured in six patients. The mean concentrations at 1, 2, 3 and 8 h after the administration of S-1 were 51.8 ± 50.4,

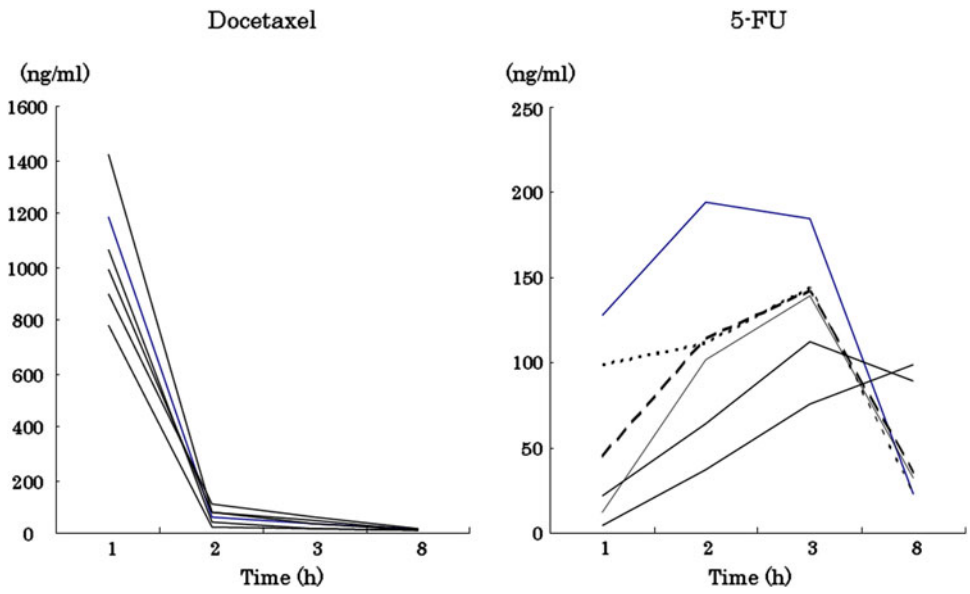

Fig. 2 Serum concentration of docetaxel (**a**) and 5-FU (**b**) after simultaneous administration of S-1 and docetaxel

104.1 ± 53.7, 133.3 ± 36.4 and 50.4 ± 34.4 ng/ml, respectively. The highest serum concentration of 5-FU was obtained at 3 h after S-1 administration (Fig. 2b).

Discussion

The current study showed that biweekly docetaxel and S-1 combination chemotherapy offered high antitumour effects and had an acceptable and manageable toxicity profile for advanced gastric cancer in an outpatient setting.

Previously, several phase I and II studies reported satisfactory outcomes and acceptable toxicities for combination therapy with S-1 and docetaxel in patients with advanced gastric cancer [10, 11, 14, 15]. Furthermore, we previously conducted a phase I study of biweekly combination treatments in order to develop a more effective and safe therapy for advanced gastric cancer in an outpatient setting [12]; we assessed the toxicities during the first and second courses to develop a safety regimen, whereas they were assessed during the first course of treatment in other studies.

In our previous phase I study, the recommended docetaxel dose was identified as 40 mg/m^2, and the response rate was 57.1%. In the current phase II study, the response rate was similar, at 57.8%. The dose intensities of S-1 and docetaxel in our study were 280 and 20.0 mg/m^2/week, respectively. In two previous phase II studies, the respective dose intensities of S-1 and docetaxel were found to be 373.3 and 13.3 mg/m^2/week [14], and 280 and 10.0 mg/m^2/week [15]. The dose intensity of docetaxel in the present study was therefore higher than that in the previous studies. The mean numbers of courses for each patient in previous studies were 4.0 and 3.0, which were comparable to the current study in which the number was 4.0. This regimen might thus be acceptable for advanced gastric cancer.

The two previous phase II studies reported overall response rates of 56.3 and 46.0%, and median overall survival times of 14.3 and 14.0 months, respectively [14, 15]. As the overall response rate and median survival time in the present study were 57.8% and 15.3 months, respectively, the current regimen appeared to be satisfactorily active for advanced gastric cancer. This regimen provided favourable response rates for peritoneal metastasis induced by histologically undifferentiated-type advanced gastric cancer. Synergistic action of these drugs has also previously been reported [16].

A noteworthy advantage of the current regimen was the reduced toxicity. In the current study, the incidence of grade 3 or more neutropenia and that of leucopenia were less frequent, and most non-haematological toxicities were at grades 1–2 and were controllable in an outpatient setting. The incidences of dose reduction and delayed administration of docetaxel were acceptable. Moreover, this regimen could be continued safely after dose reduction.

A randomized phase III study recently showed that the therapeutic outcomes of S-1 plus cisplatin treatment were superior to those of S-1 monotherapy for advanced gastric cancer. Therefore, this combination therapy is regarded as a standard treatment for unresectable advanced gastric cancer in Japan [17]. A randomized phase III trial comparing the efficacy of S-1 plus docetaxel combination therapy and S-1 monotherapy is currently in progress and might identify a candidate regimen with synergistic effects for advanced gastric cancer.

In conclusion, biweekly docetaxel and S-1 combination chemotherapy in an outpatient setting offered favourable survival benefits with controllable tolerance against

advanced gastric cancer. It will be necessary to conduct a well-designed randomized phase III study to compare this regimen with S-1-based combination treatments such as S-1 plus cisplatin.

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