



Phase I study of S-1 and biweekly docetaxel combination chemotherapy for advanced and recurrent gastric cancer

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Abstract. A phase I study of S-1 and biweekly docetaxel (DOC) combination therapy was conducted to determine the maximum tolerated dose (MTD) and pharmacokinetic parameters. Fourteen patients with advanced or recurrent gastric cancer were analyzed. The treatment consisted of S-1 [body surface area (BSA) <1.25 m²:80 mg/day, 1.25≤BSA<1.50 m²:100 mg/day, 1.50 m²≤BSA; 120 mg/day, orally, day 1-14] and DOC (30-40 mg/m²/day, intravenously, day 1 and 15), which were repeated as often as possible every four weeks. Pharmacokinetic analysis was done at DOC 40 mg/m²/day. Initially, patients were administered S-1 and 40 mg/m²/day of DOC, and DOC 40 mg/m²/day was considered as MTD. In detail, one patient developed neutropenia (grade 4, G4), and two other patients had no day 15 DOC administration because of neutropenia (grade 3, G3). When S-1 and 35 mg/m²/day of DOC were administered to three patients, no adverse reactions were noted. In six patients treated with S-1 and 30 mg/m²/day of DOC, one patient developed neutropenia (G4), and another patient developed diarrhea (G3) and anorexia (G3). The rest of this cohort showed no adverse reactions. Although 5-fluorouracil and gimeracil concentrations remained high under impaired renal function, no pharmacokinetic interactions appeared between S-1 and DOC under normal renal function. The dose limiting toxicity of a combination of S-1 and biweekly DOC was leukopenia and neutropenia. The recommended dose for this combination in phase II study is DOC 35 mg/m²/day.

Introduction

S-1 is a novel oral anticancer drug, which was developed based on the biochemical modulation of tegafur (FT) by 5-chloro-

2,4-dihydropyridine (gimeracil, CDHP) and potassium oxonate (oteracil, oxo) in a molar ratio of 1:0.4:1 (1-3). FT is a prodrug of 5-fluorouracil (5-FU), an active drug against various forms of gastrointestinal malignancy. 5-FU is degraded to α -fluoro- β -alanine by dihydropyrimidine dehydrogenase (DPD), which is produced in various organs, including tumor tissue. CDHP strongly inhibits DPD, which results in a prolonged increased concentration of 5-FU in the plasma (4). Oxo inhibits phosphorylation of 5-FU to 5-fluorouridine-5'-monophosphate (5). As oxo is distributed in the gastrointestinal tract after oral administration, it possibly decreases 5-FU-induced gastrointestinal tract toxicity (5). Thus, S-1 was designed both to increase antitumor activity and to reduce drug-induced adverse gastrointestinal adverse reaction.

Independent phase II studies of S-1, including gastric cancer patients without prior chemotherapy, give an excellent response rate and survival (6-8). The response rate using S-1 alone is comparable to or better than the response rate in combination studies such as FAMTX or ECF, which has been mainly used in Europe or the United States (9-12). S-1 has been in common use in clinical practice since March 1999 in Japan against advanced and recurrent gastric cancer. Clinical information on this drug has accumulated. We previously summarized recent clinical data of 29 patients with advanced or recurrent gastric cancer and, as expected, a high response rate and good survival were confirmed in patients without prior chemotherapy (13). However, in patients who had received chemotherapy, the response rate was 12.5%. Today, S-1 is a main drug for the treatment of advanced or recurrent gastric cancer, especially in first-line chemotherapy. However, the questions arise as to which is the best chemotherapy regimen for second-line chemotherapy, and whether combination therapy of S-1 is superior to S-1 monotherapy. Thus, a new combination therapy of S-1 is worth exploring.

Docetaxel (DOC) is a semi-synthetic taxane prepared from a non-cytotoxic precursor extracted from the needles of the European yew tree *Taxus baccata*. Docetaxel accelerates microtubule assembly from tubulin, and blocks depolymerization of microtubules. Stable microtubules result in cell death. As a single agent, taxanes are currently the most widely administered agents for metastatic breast cancer after anthracycline treatment (14). DOC is also active against gastric cancer. Independent

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Table I. Patient characteristics (n=14).

Covariate	No. of patients	
Gender		
Male	13	
Female	1	
Age (years old)	58 (41-72)	
Performance status		
0	10	
1	4	
Type of disease		
Recurrence	7	
Inoperable	3	
Postoperation with residual tumor	4	
Histological type		
Differentiated	6	
Undifferentiated	8	
Treatment course	24 courses	[1-4 courses for each pt]
Level 1 (n=5)	9 courses	[1-4 courses for each pt]
Level 0 (n=3)	7 courses	[1-4 courses for each pt]
Level -1 (n=6)	8 courses	[1-2 courses for each pt]
Calculated creatinine clearance (ml/min)	81.3	(33.9-129.8)

pt, patient.

phase II studies in Japan showed that the response rate is 23.7% (15,16).

Recent reports of docetaxel-based combination therapy showed high response rates as a first line for gastric cancer patients (17,18). We focused on DOC as a candidate for combination therapy with S-1, and we made a phase I study of S-1 and biweekly DOC combination therapy, to find the maximum tolerated dose (MTD) and recommended dose in a phase II clinical trial.

Patients and methods

Eligibility. Patients with advanced or recurrent gastric cancer were eligible for this study. This study started after obtaining approval from the institutional review board. Disease characteristics included the following criteria: i) histologically or cytologically proved gastric cancer, ii) measurable or evaluable lesions, iii) no prior chemotherapy (history of postoperative adjuvant chemotherapy was allowed), and iv) adjuvant therapy (including chemotherapy and immunotherapy) must be finished at least four weeks before the combination therapy starts. Patient characteristics included the following criteria: i) age of ≥ 20 and < 75 years, ii) an Eastern Cooperative Oncology Group performance status of ≤ 2 , iii) adequate hematopoietic function ($4000/\text{mm}^3 \leq$ white blood cell

Table II. Hematological toxicity.

	NCI-CTC grade				
	1	2	3	4	% grade ≥ 3
Level 1 (n=5)					
Leukopenia	1	1	1	1	40
Neutropenia			2	1	60
Anemia		3	1		20
Thrombocytopenia	1				0
Level 0 (n=3)					
Leukopenia		1			0
Neutropenia		1			0
Anemia		1			0
Thrombocytopenia					0
Level -1 (n=6)					
Leukopenia	1	1	3		50
Neutropenia		1	2	1	50
Anemia		4			0
Thrombocytopenia					0

NCI-CTC grade, National Cancer Institute-Common Toxicity Criteria grade.

$\leq 12000/\text{mm}^3$, neutrocyte, $\geq 2000/\text{mm}^3$, platelet $\geq 10 \times 10^4/\text{mm}^3$, hemoglobin ≥ 9.0 g/dl), iv) adequate hepatic function [total bilirubin ≤ 1.5 mg/dl, transaminase ≤ 2 times institutional normal upper limit (if caused by liver metastases, transaminase ≥ 2 times may be allowed based on the doctor's judgement)], v) serum creatinine \leq institutional normal upper limit, blood urea nitrogen ≤ 25 mg/dl, vi) adequate cardiac function, vii) neither brain metastases nor history of brain metastases, and viii) before treatment, written informed consent must be obtained from the patients. As complimentary data about renal function, creatinine clearance was calculated based on a formula described elsewhere (19).

From March 2001 to June 2003, 17 patients were enrolled in this study. Three patients were excluded because 1 of them showed marked disease progression before initiation of the treatment and 2 of them took half of the indicated dose of S-1 during the treatment. Thus, a total of 14 patients were evaluated.

Dose and drug administration. S-1 was administered orally in the morning and evening on days 1-14 according to the body surface area (BSA); BSA < 1.25 m²; 80 mg/day, $1.25 \leq$ BSA < 1.50 m²; 100 mg/day, $1.50 \leq$ BSA; 120 mg/day). DOC was diluted in normal saline and was administered with an infusion pump for 1 h on days 1 and 15. As a premedication, 8 mg of dexamethasone was administered intravenously, 0.5 h before; and 4 mg orally, 12, 24, 36 and 48 h after the start of DOC administration. One course was 28 days, and was repeated as often as possible. Treatment continued unless disease progressed, unacceptable toxicity occurred or the patient refused further treatment. The dose of DOC started at

	NCI-CTC grade				
	1	2	3	4	% grade ≥ 3
Level 1 (n=5)					
Anorexia	1		1		20
Diarrhea			1		20
General fatigue	1				0
Skin eruption	1				0
Level 0 (n=3)					
Anorexia	1				0
Nausea, vomiting	1				0
Stomatitis	1				0
General fatigue	1				0
Alopecia	1				0
Level -1 (n=6)					
Anorexia	2		1		16.7
Diarrhea	1	1		1	16.7
Stomatitis	1				0
General fatigue	2	1			0
Alopecia	4				-
Headache	2				0
Abdominal pain		1			0

NCI-CTC grade, National Cancer Institute-Common Toxicity Criteria grade.

40 mg/m² (Level 1). Doses of 35 mg/m² (Level 0) and 30 mg/m² (Level -1) were also evaluated because the dose limiting toxicity (DLT) was at Level 1.

DLT, MTD and dose escalation schedule. Toxicity was evaluated according to the National Cancer Institute (NCI) common toxicity criteria. The DLT was defined as: i) grade 4 leukopenia or neutropenia lasting longer than three days despite the use of granulocyte-colony stimulating factor (G-CSF), ii) grade 3 neutropenia with a fever of $>38^{\circ}\text{C}$ lasting longer than three days despite the use of G-CSF, iii) grade 4 thrombocytopenia or grade 3 thrombocytopenia with bleeding tendency, and iv) grade 3-4 non-hematological toxicity except nausea, vomiting or alopecia.

In an initial study, three patients at one dose level were evaluated: i) the dose was defined as MTD when all patients developed DLT; ii) when one or two of three patients developed DLT, three other patients were enrolled; iii) when more than three of six patients developed DLT, the dose was defined as MTD; iv) when fewer than two of six patients developed DLT, the dose was increased to the next step.

Pharmacokinetic study design. Pharmacokinetic study was conducted for three patients on the first day of treatment at dose level 1 (S-1 at the fixed dose described above, and DOC 40 mg/m²). S-1 and DOC administration started simult-

aneously, and heparinized blood samples to test for 5-FU, FT, CDHP and oxo were taken from the patients before and 1, 2, 4 and 8 h after administration. Heparinized blood samples to test for DOC were taken before and 0.5, 1, 1.5, 2, 3, 4, 5 and 8 h after administration. Immediately, the blood samples were cooled in ice and then centrifuged at 3000 round per minute for 15 min, and the separated serums were stored at -80°C until assay. The plasma levels of FT, 5-FU, CDHP, oxo and DOC concentration were measured as described elsewhere (20,21). WinNonlin ver.3.0 (Phasight Co.) software was used to calculate the pharmacokinetic parameters such as maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), area under the plasma concentration-versus-time curve from time zero to infinity (AUC 0- ∞), and plasma elimination half-life (T_{1/2}).

Independently from this phase I study, three patients with advanced or recurrent gastric cancer were treated with docetaxel monotherapy biweekly (40 mg/m²). After informed consent was obtained, blood samples were taken at the same times as used in the phase I study. The plasma docetaxel concentration was measured by using the same method.

Results

Patients characteristics, toxicity and DLT. Table I lists patient characteristics. The performance status was 0 in 10 patients, and the median age was 58 years old. Twenty four courses were conducted, with a mean of 1.7 courses for each patient (range 1-4 courses). The creatinine clearance was >50 ml/min except for patient 1 in the pharmacokinetic study. Tables II and III list hematological and non-hematological toxicity profiles.

This study started with a cohort of three patients at DOC dose 40 mg/m² (Level I). Leukopenia and neutropenia were found as DLT, and Level 1 (40 mg/m²) as MTD. In detail, one patient developed grade 4 neutropenia and another patient could not receive day 15 DOC administration due to prolonged grade 3 leukopenia and neutropenia; the third patient developed no adverse reactions. Two additional patients were enrolled in Level 1; one of these patients also could not receive day 15 DOC administration because of grade 3 neutropenia.

In the second step, we evaluated the DOC dose at 30 mg/m² (Level -1) as the safety of the registered patients was the highest priority. Among the first three patients in this cohort, one patient completed two courses of treatment, one patient developed grade 4 leukopenia and neutropenia and the third patient discontinued treatment because this patient developed grade 3 anorexia and grade 3 diarrhea. As the latter two patients were considered to show DLT, an additional three patients were enrolled in this cohort. Two of these patients developed grade 3 leukopenia and neutropenia, and the third patient developed grade 2 diarrhea, abdominal pain and grade 1 headache: no DLT appeared during the treatment. Thus, 30 mg/m² (Level -1) was not considered as DLT.

In the third step, three patients received S-1 and DOC 35 mg/m² (Level 0), to confirm if DOC at 30 mg/m² (Level -1) or DOC at 35 mg/m² (Level 0) can be a recommended dose. Although grade 2 leukopenia, neutropenia and anemia developed in 1 patient, grade 3 and 4 hematological toxicity were not noted. When considering non-hematological toxicity, only grade 1 anorexia, nausea, vomiting, stomatitis, general

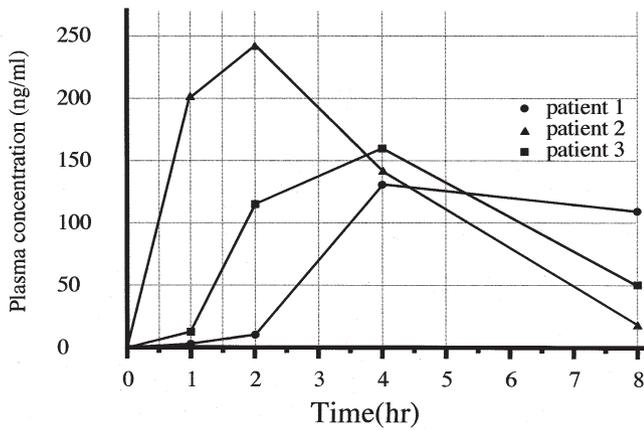


Figure 1. Plasma 5-fluorouracil concentration after administration of combined S-1 and docetaxel (DOC) (S-1, 50 mg/body, orally; DOC, 40 mg/m², 1 h infusion, intravenously).

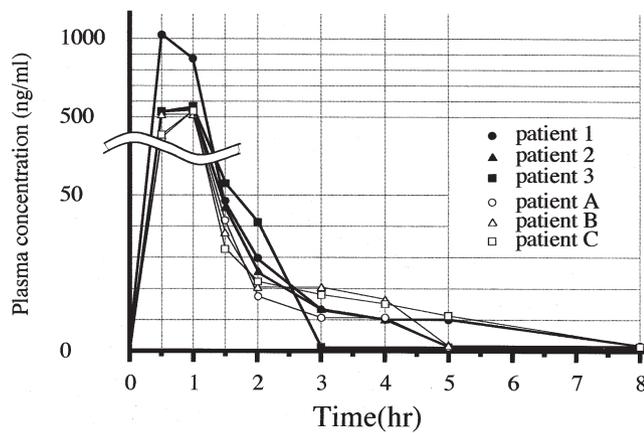


Figure 2. Plasma docetaxel (DOC) concentration after administration of DOC alone or DOC and S-1 combination. (S-1, 50 mg/body, orally; DOC, 40 mg/m², 1 h infusion, intravenously). Patients 1-3 were treated with a combination of S-1 and DOC, whereas patients A-C were treated with DOC monotherapy.

fatigue and alopecia were noted. Thus, DOC at 35 mg/m² (Level 0) was considered a recommended dose.

Pharmacokinetics. A pharmacokinetic study was conducted with three patients on the first day of treatment at dose level 1 (S-1 orally at the dose stated in the Patients and methods section, and DOC at 40 mg/m² intravenously for 1 h). Fig. 1 shows 5-FU concentrations in combined therapy (patients 1-3). Fig. 2 shows DOC concentrations in patients treated with combined therapy (patients 1-3), as well as in patients treated with DOC at 40 mg/m² monotherapy (patients A-C). Table IV shows the C_{max}, T_{max}, AUC_{0-∞} and T_{1/2}. Although the C_{max} of 5-FU was from 132.6 to 244.4 ng/ml, the 5-FU concentration was maximum at 2-4 h after administration. One patient with impaired renal function (patient 1) showed a prolonged 5-FU concentration plateau and a longer half-life of 5-FU.

In terms of DOC pharmacokinetics, plasma DOC concentration in the Level 1 combination therapy group was maximum at 0.5-1 h after the start of administration (i.e., 0.5 h before or

Table IV. Pharmacokinetic parameters after administration of S-1 and DOC (40 mg/m²) combination therapy (patients 1-3) and DOC monotherapy (patients A-C).

	C _{max} (ng/ml)	T _{max} (h)	AUC _{0-∞} (ng. h/ml)	T _{1/2} (h)
5-FU				
Patient 1	132.6	4	2737	13.6
Patient 2	244.4	2	1072	1.31
Patient 3	158.0	4	941	2.42
FT				
Patient 1	3235.1	4	33295	5.99
Patient 2	2008.6	1	10610	3.91
Patient 3	1859.8	2	16658	6.88
CDHP				
Patient 1	294.3	4	2054	3.89
Patient 2	428.6	1	1380	2.10
Patient 3	259.4	2	1559	3.30
Oxo				
Patient 1	71.7	4	506	3.59
Patient 2	112.8	1	495	2.50
Patient 3	38.3	2	771	13.6
DOC				
Patient 1	1030	0.5	1055.6	1.87
Patient 2	554	1	625.4	1.53
Patient 3	569	1	660.0	1.18
DOC				
Patient A	544	1	490.7	1.85
Patient B	510	0.5	655.3	3.22
Patient C	517	1	533.2	2.99

C_{max}, maximum plasma concentration; T_{max}, time to maximum plasma concentration; AUC_{0-∞}, area under the plasma concentration-versus-time curve from time zero to infinity; T_{1/2}, plasma elimination half-life.

at the end of administration), and then decreased rapidly. The change in plasma DOC concentration in the DOC monotherapy group showed the same pharmacokinetic profile.

Discussion

In Japan, gastric cancer still remains most frequent malignancy. Despite of the advance in early detection of this disease and surgical improvement, the survival of patients with recurrent and advanced gastric cancer is unsatisfactory. The Japan Gastric Cancer Association issued the first edition of gastric cancer treatment guidelines in March 2001 to provide a common basis of understanding of the extent of disease and selection of proper treatment (22). This guideline did not mention particular regimen of chemotherapy for advanced and recurrent gastric cancer, but it stated that 5-FU and cisplatin may be important drugs. Thus, the standard regimen has not been established.

 SPANDIDOS synthesized in Japan and has been a key drug in the of advanced and recurrent gastric cancer in Japan

because of a high response rate (7,8,13). In this study, we investigated the safety and pharmacokinetic profiles of a combination therapy of S-1 and biweekly DOC. As a monotherapy, the DLT of DOC is leukopenia and neutropenia (15,16). Although, in patients in Europe and in the United States, the DLT of S-1 is diarrhea (23), the DLT of S-1 in Japanese patients is mainly haematological and stomatitis and diarrhea is mild (6-8). As expected, in the S-1 and biweekly DOC regimen, the DLT was leukopenia and neutropenia in this study. Although the toxicity profile of both drugs is similar in Japanese patients, we thought it rational to examine this combination for the following reasons: i) the mechanism of antitumor activity of S-1 and DOC is completely different, ii) DOC is beneficial for gastric cancer patients who have been previously treated and for patients as a first-line therapy (15,16), and iii) the resistance of 5-FU is overcome by DOC *in vitro* (24). Our previous *in vivo* therapeutic experiment that used gastric cancer xenografts showed that S-1 (day 1-14 administration) and DOC (day 1 or day 8 intravenous administration) were synergistic (25), although schedule dependency between paclitaxel and 5-fluorouracil *in vitro* has been reported (26). Thus, we scheduled days 1-14 of administration with S-1 with days 1 and 15 of administration with DOC.

The combination therapy of DOC and continuous 5-FU has showed no pharmacokinetic interaction between the two drugs (27,28). As the pharmacokinetics of S-1 is similar to that of continuous 5-FU intravenous infusion (29), S-1 may not interact with DOC unless the 5-FU concentration remains the same as expected. One study showed that pharmacokinetic parameters of 5-FU in Japanese patients were C_{max}, 128.5 ng/ml; T_{max}, 3.5 h; AUC 0-14, 724 ng.h/ml; and T_{1/2}, 1.9 h (29). In our study, the AUC of 5-FU in patients 2 and 3 were similar to these data. Patient 1, which developed grade 4 leukopenia and neutropenia, showed a larger AUC 0-∞ of 5-FU and CDHP. The calculated creatinine clearance was 33.9 ml/min. The different pharmacokinetic profile may be partly explained by impaired renal function. CDHP, excreted in the kidney, inhibits DPD, the catabolic enzyme of 5-FU, and results in a prolonged and higher 5-FU concentration in the plasma. Impaired renal function is directly connected to an elevated level of CDHP, which results in a prolonged plasma 5-FU plateau level. The results of a postmarketing survey of S-1 in Japan support this hypothesis (30). This survey monitored the toxicity profile and estimated creatinine clearance and showed that patients with a lower creatinine clearance frequently experience severe adverse reactions. In terms of DOC, hepatic metabolism and biliary excretion is the major pathway of DOC elimination (31). Our data showed that the plasma concentration of DOC is maximum just after drug administration, and the same pharmacokinetic profiles were confirmed with or without combination with S-1.

In conclusion, patients should be strictly screened for impaired renal function based on creatinine clearance. Although careful blood count monitoring should be used, a combination therapy of S-1 and biweekly DOC is worth investigating. The recommended dose for this combination is 35 mg/m²/day DOC on days 1 and 15.

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