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ORIGINAL ARTICLE

Dose-finding study of docetaxel, oxaliplatin, and S-1 for patients with advanced gastric cancer

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Abstract
Purpose To determine the maximum tolerated dose (MTD), recommended dose (RD), and activity of combined docetaxel, oxaliplatin, and S-1 (DOS) chemotherapy on metastatic gastric cancer.
Patients and methods Docetaxel and oxaliplatin were administered intravenously on day 1 and S-1 was administered orally on days 1–14 of every 21-day cycle. The doses of docetaxel/oxaliplatin/S-1 in the phase I study were level −1A, 52.5/80/60 mg/m^2; level −1B, 52.5/80/80 mg/m^2; level 1A, 52.5/105/80 mg/m^2; level 1B, 52.5/130/80 mg/m^2; level 2A, 60/105/80 mg/m^2; level 2B, 60/130/80 mg/m^2; level 3A, 67.5/105/80 mg/m^2; level 3B, 67.5/130/80 mg/m^2; level 4A, 75/105/80 mg/m^2; level 4B, 75/130/80 mg/m^2.
Results Nine patients were enrolled. One of six patients at level 1A and two of three patients at level 1B developed dose-limiting toxicity (febrile neutropenia) during the initial two cycles. Therefore, the doses used at levels 1B and 1A were defined as the MTD and RD, respectively. All patients were evaluated for toxicity and response. Six partial responses were noted, and the overall response rate was 67%.
Conclusion The RD of the DOS regimen in patients with advanced gastric cancer was docetaxel 52.5 mg/m^2 and oxaliplatin 105 mg/m^2 on day 1 and S-1 80 mg/m^2 on days 1–14 of every 21-day cycle. A phase II study using the RD is currently underway.

Keywords Docetaxel · Oxaliplatin · S1 (combination) · Stomach neoplasm

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Introduction

To date, there is no established standard front-line chemotherapy for advanced gastric cancer. Compared with the reference cisplatin and 5-fluorouracil (CF) regimen, the docetaxel, cisplatin, and fluorouracil (DCF) regimen results in a significantly longer time to progression (3.7 vs. 5.6 months, respectively), improved survival (8.6 vs. 9.2 months), and increased response rate (RR; 25 vs. 37%) in advanced gastric cancer [20]. Nevertheless, the increased incidence of severe adverse events such as febrile neutropenia (29%) and the inconvenience of continuous intravenous fluorouracil infusion limit the use of this therapy worldwide as a standard chemotherapeutic regimen in advanced gastric cancer.

Docetaxel (Taxotere, Sanofi-Aventis, Paris, France), an anti-microtubule agent, is an active agent for treating patients with gastric cancer, with RRs of 16–24% as a single agent [4, 13, 18] and 19–37% when used in combination with 5-fluorouracil and/or cisplatin [14, 15, 20]. Oxaliplatin (Eloxatin, Sanofi-Aventis, Paris, France) is a third-generation platinum analog with less nephrotoxicity but greater neurotoxicity than cisplatin [5, 7]. Although oxaliplatin is inactive as a single agent in patients with gastric cancer, phase II and III trials for combination therapy with fluorouracil and leucovorin [3, 10, 11], or with fluoropyrimidines and epirubicin [6] produced significant results with minimal toxicities in gastric cancer. Oxaliplatin seems to be at least as active, and relatively less toxic, than cisplatin in combination regimens for gastric cancer and can therefore replace cisplatin [3, 6]. S-1 (TS-1, Taiho, Tokyo, Japan) is an oral dihydropyrimidine dehydrogenase inhibitory fluoropyrimidine and is active for advanced gastric cancer as a single agent with minimal toxicities [8, 16]. Recently, S-1 combined with docetaxel [21–23] or cisplatin [2, 9] showed favorable efficacy in advanced gastric cancer. In addition, it appears that S-1 can be used to replace continuous intravenous fluorouracil infusion in the treatment of advanced gastric cancer.

The rationale for combined docetaxel, oxaliplatin, and S-1 (DOS) therapy is as follows. First, these agents have activity in patients with gastric cancer. Second, each drug has a distinct mechanism of action. Third, the principal toxicities of these three agents are different: neutropenia is the principal toxicity of docetaxel, neuropathy is the major toxicity of oxaliplatin, and gastrointestinal toxicity is the main side effect of S-1. As mentioned, clinical studies have shown a synergistic effect of docetaxel or oxaliplatin with fluoropyrimidine. Thus, the DOS regimen is expected to be more effective, better tolerated, and more convenient than previously employed therapies. In this study, we identified the maximum tolerated dose (MTD) and recommended dose (RD) of DOS combination therapy in advanced gastric cancer.

Patients and methods

Eligibility

Patients were eligible if they met all of the following criteria: presence of unresectable, locally advanced or metastatic, and histologically confirmed adenocarcinoma of the stomach; age range, 18–70 years; Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; estimated life expectancy of more than 3 months; and adequate hematological, renal, and hepatic functions as defined by a white blood cell count $\geq 4.0 \times 10^9$/L or an absolute granulocyte count $\geq 1.5 \times 10^9$/L, a platelet count $\geq 100 \times 10^9$/L, hemoglobin level ≥ 9.0 g/dL, serum creatinine level ≤ 1.4 mg/dL, serum bilirubin level ≤ 1.8 mg/dL, and aspartate transaminase/alanine transaminase (AST/ALT) levels less than or equal to twofold the upper limit of normal. Patients were excluded if they had a previous history of chemotherapy (excluding adjuvant chemotherapy), central nervous system metastasis, obvious bowel obstruction, serous gastrointestinal bleeding, or other serious comorbid condition. Each patient provided written informed consent before entering the study. The protocol was approved by the institutional review board of Hallym University Medical Center, Anyang, South Korea.

Pretreatment evaluations

The baseline evaluations included a medical history, physical examination, ECOG performance status, complete blood count, serum chemistry and electrolytes, urine analysis, chest X-ray, and three-dimensional computed tomography (CT).

Treatment scheme

Dose-limiting toxicities (DLTs) were defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0 (http://www.cancer.gov) and included the following: grade 4 neutropenia lasting more than 7 days, grade 4 thrombocytopenia, febrile neutropenia, and grade 3–4 non-hematological toxicities during the first two cycles. To determine MTD, the doses of docetaxel, oxaliplatin, and/or S-1 were increased (in the absence of dose-limiting toxicities) from dose level 1A to dose level 4B. The doses of each drug (docetaxel/oxaliplatin/S-1) were as follows: level 1A, 52.5/105/80 mg/m^2; level 1B, 52.5/130/80 mg/m^2; level 2A, 60/105/80 mg/m^2; level 2B, 60/130/80 mg/m^2; level 3A, 67.5/105/80 mg/m^2; level 3B, 67.5/130/80 mg/m^2; level 4A, 75/105/80 mg/m^2; and level 4B, 75/130/80 mg/m^2.

This phase I trial was carried out using the classical 3 ± 3 design. At least three patients were treated at each dose level. If none of the three patients in a given cohort experienced DLTs, the dose was increased to the next dose level in a new cohort of patients. If one of the three patients experienced a DLT, the cohort was expanded to a total of six patients. If no further DLTs occurred, escalation to the next dose level began in a new cohort of patients. If one or more additional DLTs were seen (i.e., two or more of the six patients), this dose level was defined as the MTD. If two of three patients in a given cohort experienced DLTs, this dose level was defined as the MTD. Therefore, the MTD was defined as the dose at which two of three or two of six patients experienced DLTs. The RD for the phase II study

was defined as one dose level below the MTD. If more than two DLTs were observed in three to six patients at dose level 1A, the administered dose level was to be reduced to level −1B (docetaxel 52.5 mg/m^2, oxaliplatin 80 mg/m^2, and S-1 80 mg/m^2). At dose level −1B, if more than two DLTs were still observed in three to six patients, the administered dose level was to be reduced to level −1A (docetaxel 52.5 mg/m^2, oxaliplatin 80 mg/m^2, and S-1 60 mg/m^2).

Docetaxel and oxaliplatin were administered intravenously over 1 and 2 h, respectively, on day 1, and S-1 was administered orally twice daily from day 1 to day 14 of each 21-day cycle. Therapy was continued until disease progression or unacceptable toxicity occurred, or until the patient withdrew consent.

Dose modifications

Dose adjustments were made for each agent if a distinction in toxicity could be made. If all three agents were thought to be causing the toxicity, dose reductions were performed for all three agents. The doses of docetaxel and oxaliplatin were reduced by 20% for the subsequent cycle if related grade 3 or 4 toxicity occurred. The dose of S-1 was reduced by 20 mg/day if related grade 3 or 4 toxicity occurred. This dose modification scheme was not applied to the first two cycles unless DLTs occurred during the first cycle. No dose increase was allowed. Treatment was initiated only when the absolute granulocyte count was $\geq 1.5 \times 10^9$/L, platelet count was $\geq 100 \times 10^9$/L, and all toxicities were resolved to grade ≤ 1.

Response and toxicity evaluation

The Response Evaluation Criteria in Solid Tumors (RECIST) guidelines [19] were used to assess tumor responses, and the NCI-CTCAE version 3.0 was used to assess toxicity. Response was evaluated every two cycles. All partial and complete responses were confirmed for a minimum of 4 weeks. Toxicity was evaluated every week during the first two cycles and then every 3 weeks after the first two cycles or any time a patient complained of symptoms.

Statistical analysis

The primary aim of the study was to determine the MTD and RD for DOS combination therapy. The secondary purpose of the study was to assess the efficacy of the regimen. The duration of response, progression-free survival (PFS), and survival time were estimated via the Kaplan–Meier method. PFS was defined as the interval between the initiation of treatment to the first evidence of disease progression documented by the investigators, or death from any cause.

Results

Patient characteristics

Nine patients were enrolled in this study. All patients were evaluated for safety and assessed for response and survival. Patient characteristics are listed in Table 1. Five of the nine patients (56%) had recurrent gastric cancers that relapsed after adjuvant chemotherapy. All patients had more than two metastatic lesions.

MTD

All nine patients in the study were assessed for safety, and the toxicities during the initial two cycles are summarized

Table 1 Patient characteristics

Characteristic	No. of patients
Total number of patients	9
Gender	
Male	6
Female	3
Age, years	
Median	52
Range	39–67
Eastern Cooperative Oncology Group performance status	
0	8
1	1
Gastrectomy	
None	4
With adjuvant chemotherapy	5
Primary disease sites	
Antrum	2
Body	7
Cardia	0
Differentiation	
Well	1
Moderate	2
Poor	6
Metastatic sites	
Peritoneum	8
Lymph nodes	7
Liver	5
Bone	1
Ovary	1
Skin	1
Number of metastatic organs	
2	5
≥3	4

Table 2 Toxicities observed per patient at various dose levels of docetaxel, oxaliplatin, and S-1 during the initial two cycles in the phase I study

	Level 1A ($n = 6$)					Level 1B ($n = 3$)				
	NCI-CTCAE grade, version 3					NCI-CTCAE grade, version 3				
	1	2	3	4	3/4 (%)	1	2	3	4	3/4 (%)
Leukopenia	1	2	2	1	50	0	0	2	1	100
Neutropenia	0	1	1	4[a]	83	0	0	1	2[a]	100
Anemia	1	5	0	0	0	2	1	0	0	0
Thrombocytopenia	2	0	0	0	0	0	0	0	0	0
Anorexia	2	2	0	0	0	1	2	0	0	0
Nausea	3	0	0	0	0	1	0	0	0	0
Diarrhea	2	0	0	0	0	1	1	0	0	0
Stomatitis	1	0	0	0	0	1	0	0	0	0
Fatigue	2	0	0	0	0	2	0	0	0	0

NCI-CTCAE National Cancer Institute Common Terminology Criteria for Adverse Events

[a] One of 6 (level 1A) and 2 of 3 (level 1B) patients experienced dose-limiting toxicity (febrile neutropenia)

in Table 2. At dose level 1A, one of three patients developed grade 4 neutropenia with fever. Three more patients were treated with the same dose level 1A, but none showed a DLT. At dose level 1B, two of three patients developed grade 4 neutropenia with fever. No severe non-hematological toxicity was observed at dose level 1A or 1B during the initial two cycles. From these results, dose level 1B was defined as the MTD and level 1A was defined as the RD for the future phase II study.

Efficacy

In total, 105 treatment cycles were administered to nine patients, with a median of ten cycles (range, 1–22 cycles) per patient.

The tumor response data are presented in Table 3. The confirmed externally reviewed overall RR (ORR) was 67% [95% confidence interval (CI), 36–98%] and the disease control rate was 89% (95% CI, 69–100%) in all nine patients. Among six responders, the DOS regimen was effective for distant lesions in four patients and was effective for distant and primary lesions in two patients.

The median PFS was 9.6 months (95% CI, 6.5–12.8 months) and the median survival time was 11.3 months (95% CI, 6.5–16.0 months) in nine patients, with a median follow-up time of 18.4 months. The 1-year survival rate was 44%.

Safety

Nine patients receiving 105 cycles of DOS combination therapy were assessed for safety. The toxicities throughout the entire course of treatment are listed in Table 4. Neutropenia was the most common severe toxicity. Grade 3/4 neutropenia developed in 100% of patients and in 30% of cycles. Febrile neutropenia was observed in 56% of the patients and in 11% of the cycles. Non-hematological toxicities were generally mild (grade 1/2) and manageable. The most common non-hematological toxicities were anorexia, diarrhea, neuropathy, and fatigue.

Table 3 Analysis of responses in the phase I study, as assessed by an independent response review committee

	CR	PR	SD	PD	ORR	DCR
Level 1A ($n = 6$)	1	3	1	1	67%	83%
Level 1B ($n = 3$)	0	2	1	0	67%	100%
Total ($n = 9$)	1	5	2	1	67%	89%
Median time to response ($n = 6$)	1.5 (95% CI, 0.8–2.1) months					
Median response duration ($n = 6$)	9.5 (95% CI, 1.0–18.1) months					
Median PFS ($n = 9$)	9.6 (95% CI, 6.5–12.8) months					
Median overall survival ($n = 9$)	11.3 (95% CI, 6.5–16.0) months					

CR complete response, *PR* partial response, *SD* stable disease, *PD* Progression, O*RR* overall response rate, *DCR* disease control rate, *PFS* progression-free survival

Table 4 Toxicities observed per patient and per cycle throughout the course of treatment

	Per patient (nine evaluable patients)					Per cycle (105 evaluable cycles)				
	NCI-CTCAE, version 3.0					NCI-CTCAE, version 3.0				
	1	2	3	4	3/4 (%)	1	2	3	4	3/4 (%)
Leukopenia	1	1	2	5	78	5	5	14	12	25
Neutropenia[a]	0	0	2	7	100	6	2	7	24	30
Anemia	1	5	3	0	33	49	47	4	0	4
Thrombocytopenia	2	1	0	0	0	4	1	0	0	0
Anorexia	0	8	1	0	11	43	35	1	0	1
Nausea	4	4	0	0	0	43	5	0	0	0
Vomiting	4	1	0	0	0	14	1	0	0	0
Diarrhea	3	2	1	0	11	31	8	1	0	1
Stomatitis	3	3	0	0	0	50	8	0	0	0
Bilirubin	2	0	0	0	0	5	0	0	0	0
Abnormal AST/ALT	3	1	0	0	0	8	1	0	0	0
Abnormal ALP	4	0	0	0	0	9	0	0	0	0
Neuropathy	1	5	1	0	11	34	43	1	0	1
Fatigue	4	4	1	0	11	48	27	3	0	3
Edema	2	2	0	0	0	25	8	0	0	0

NCI-CTCAE National Cancer Institute Common Terminology Criteria for Adverse Events, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase

[a] Febrile neutropenia, 5/9 patients (56%); 12/105 cycles (11%)

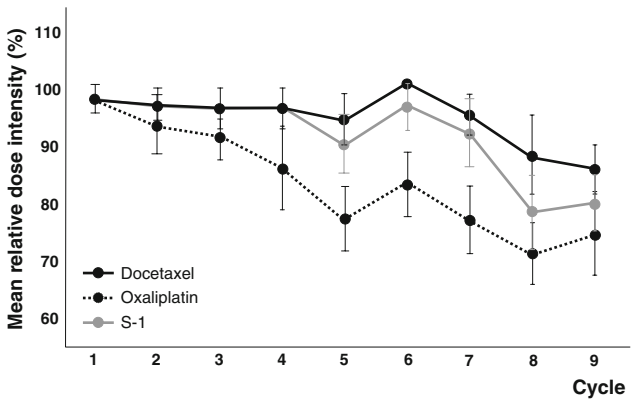

Fig. 1 Mean relative dose intensities of docetaxel, oxaliplatin, and S-1 (DOS) in each cycle between the first and ninth treatment cycles

The mean relative dose intensities of docetaxel, oxaliplatin, and S-1 in the first nine cycles of nine patients were 96, 87, and 93%, respectively (Fig. 1). Five of six patients (83%) received the RD for more than nine cycles of therapy (range, 9–22 cycles), with the exception being one patient who showed disease progression after the second cycle. The doses of docetaxel, oxaliplatin, and S-1 were reduced at seven cycles (6.7%), 21 cycles (20%), and five cycles (4.8%), respectively. The main reasons for dose reduction were as follows: neutropenia (7 cycles) and thrombocytopenia (3 cycles) for docetaxel; neuropathy (17 cycles), neutropenia (4 cycles), and thrombocytopenia (2 cycles) for oxaliplatin; and neutropenia (4 cycles) and neuropathy with fatigue (1 cycle) for S-1. Ten cycles (9.5%) were delayed due to neutropenia (6 cycles), neuropathy (2 cycles), thrombocytopenia (1 cycle), and hemorrhoid surgery (1 cycle).

Discussion

In this phase I study, we identified the RDs for docetaxel (52.5 mg/m^2 on day 1), oxaliplatin (105 mg/m^2 on day 1), and S-1 (80 mg/m^2 on days 1–14) when administered as a combined chemotherapy regimen every 3 weeks. These doses will next be examined in a phase II study. The major DLT was febrile neutropenia. Although the incidence of febrile neutropenia was high (50% of patients receiving the RD and 56% of all patients), the patients tolerated the therapy well and did not experience sequelae. The incidence of febrile neutropenia was higher than with the DCF combination of the V325 study [20]. However, the more frequent assessment of toxicities (every 3 weeks in DCF vs. every week in DOS) and longer administration of the treatment (median 6 cycles, range 1–16 cycles in DCF vs. median 10 cycles, range 1–22 cycles in DOS) likely led to the higher incidence of febrile neutropenia in our study. Through careful monitoring, patient education, proper management, and appropriate dose reduction in subsequent cycles, the

Table 5 The duration of grade 3/4 neutropenia during the initial two cycles in seven patients

UPN	1	2	3	6	7	8	9
Cycle 1	D 10–13	D 8	D 7–9	D 8–12	D 8–13	D 6–8	D 7–9
Cycle 2	D 7–11		D 6–9	D 6–9		D 8	D 11

UPN unique patient number

incidence of febrile neutropenia was decreased to 11% of administered cycles. Most patients (83% of patients receiving the RD) tolerated prolonged treatment (>9 cycles). To decrease the incidence of febrile neutropenia, we analyzed the patterns of grade 3/4 neutropenia development in the initial two cycles in seven patients. Our analysis revealed that grade 3/4 neutropenia typically developed from days 6 to 10 (Table 5). For this reason, we suggest prophylactic treatment with granulocyte colony-stimulating factor (G-CSF) from days 6 to 10, as recommended by the American Society of Clinical Oncology and the European Society of Medical Oncology [1, 17], in future trials examining docetaxel. After nine cycles, the incidence of oxaliplatin-induced neuropathy appeared to increase. In two patients, oxaliplatin was omitted after the 12th cycle because of prolonged grade 2 neurologic toxicity. All of the patients, except for two patients who progressed early, received more than nine cycles and a cumulative oxaliplatin dose of more than 820 mg/m^2. After nine cycles, six among these seven patients experienced transient or prolonged, greater than grade 2 peripheral neuropathy, and we had to decide whether to stop or continue administering of oxaliplatin. To prevent chronic oxaliplatin-induced neuropathy, a Stop-and-Go strategy, the so-called OPTIMOX concept [12], may be applied in the next phase II study, especially after six to nine cycles. In addition, several neuromodulatory agents have been tested in attempts to treat oxaliplatin-induced neuropathy, and these drugs may be used after their effect is proven [7].

The confirmed ORR was 67% (95% CI, 36–98%) in all patients. Although ORR was not the primary endpoint in this study and the number of the patients was small, this result is promising. In addition, the observed median response duration and PFS (9.5 and 9.6 months, respectively) were excellent. Although this was a phase I study with a small number of patients, these results compare favorably to an ORR of 37% (95% CI, 30–43%), a time to progression of 5.6 months (95% CI, 4.9–5.9 months), and a median survival time of 9.2 months (95% CI, 8.4–10.6 months) for DCF as a first-line chemotherapy for advanced gastric cancer [20].

The DOS regimen requires only a 1 h infusion of docetaxel, a 2 h infusion of oxaliplatin, and twice daily oral administration of S-1 for 14 days every 3 weeks, making this therapy much more convenient for patients than the DCF regimen, which requires a 5-day, continuous infusion of 5-FU and pre- and post-hydration for cisplatin. Thus, the DOS regimen was more feasible for patients receiving treatment through an outpatient clinic.

In conclusion, the RD of combined DOS chemotherapy in patients with advanced gastric cancer was docetaxel 52.5 mg/m^2 and oxaliplatin 105 mg/m^2 on day 1 and S-1 80 mg/m^2 on days 1–14 of every 21-day cycle. This regimen, if used with the appropriate precautions for febrile neutropenia, is a tolerable, convenient therapeutic strategy for patients with advanced gastric cancer. A phase II study using this DOS regimen with primary prevention for neutropenia using G-CSF is currently underway at our institute.

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Conflict of interest statement None.

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