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ORIGINAL ARTICLE

Phase I/II trial with docetaxel and S-1 for patients with advanced or recurrent gastric cancer with consideration to age

Dae Young Zang · Dae Hyun Yang · Hae Wan Lee · Se Won Hwang · Hun Ho Song · Joo Young Jung · Jung Hye Kwon · Hyo Jung Kim · Jung Han Kim · Sa Rah Park · Min-Jeong Kim · Kyung Mi Jang · Choong Kee Park · Jong Hyeok Kim · Bong Hwa Lee

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Abstract
Purpose To determine the dose-limiting toxicity (DLT) and activity of combination with docetaxel and S-1 on unresectable gastric cancer.
Patients and methods Docetaxel was administered intravenously on day 1 and S-1 was administered orally on days 1–14, every 3 weeks. Doses of each drug in phase I study were docetaxel 60–75 mg/m^2 and S-1 60–80 mg/m^2. A phase II study was conducted with the recommended dose (RD) based on phase I.
Results Sixty-five patients (median age 54 years) were enrolled. The DLTs were neutropenia with fever or stomatitis. The RD was docetaxel 75 mg/m^2 and S-1 60 mg/m^2. Two patients (aged 66 and 64 years) developed septic shock during the initial part of phase II study. A phase I study at lower dose (docetaxel 60 mg/m^2 and S-1 80 mg/m^2) was conducted for patients older than 60 years, and this dose was determined as the RD for these patients. In the phase II study, frequent grade 3/4 toxicities were neutropenia (47%) and febrile neutropenia (26%). The overall response rate was 50% (95% CI, 35–66%) and median survival was 15.3 months (95% CI, 10.0–20.6 months).
Conclusions Combination with docetaxel and S-1 was active against advanced gastric cancer and gave manageable toxicities.

Keywords Docetaxel · S 1 (combination) · Stomach neoplasm · Clinical trial

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D. Y. Zang · S. W. Hwang · H. H. Song · J. Y. Jung · J. H. Kwon · H. J. Kim · J. H. Kim · S. R. Park · C. K. Park · J. H. Kim
Department of Internal Medicine,
Hallym University Medical Center and Hallym University College of Medicine, Anyang, South Korea

D. H. Yang · H. W. Lee · B. H. Lee
Department of Surgery, Hallym University Medical Center and Hallym University College of Medicine, Anyang, South Korea

M.-J. Kim · K. M. Jang
Department of Radiology, Hallym University Medical Center and Hallym University College of Medicine, Anyang, South Korea

D. Y. Zang (✉)
Department of Internal Medicine,
Hallym University Sacred Heart Hospital, 896 Pyeongchon-dong, Dongan-gu, Anyang, Gyeonggi-do 431-070, South Korea
e-mail: fhdzang@hallym.or.kr

Introduction

Although gastric cancer is the fourth most common cancer worldwide and the second leading cause of cancer death, the prognosis for patients with advanced gastric cancer remains poor and there is no established standard frontline chemotherapy for the advanced stage [4]. However, many clinical trials have been developed to improve the response rate (RR) and survival for patients with advanced gastric cancer. Several combination chemotherapeutic regimens show high RRs; however, toxicities limit the survival benefit. Therefore, new chemotherapeutic regimens to achieve survival benefit with low toxicities are needed.

Docetaxel is an anti-microtubule agent that enhances polymerization of tubulin monomers into stable microtubules and inhibits microtubule depolymerization. This disrupts the microtubule system of the epithelium and

ultimately leads to cell death [3]. Docetaxel is an active agent for treating patients with gastric cancer, with RRs of 20–24% as a single agent [6, 7, 13] and RRs of 37–40% when used in a combination therapy with 5-fluorouracil and/or cisplatin [1, 8].

S-1 is a new oral dihydropyrimidine dehydrogenase (DPD) inhibitory fluoropyrimidine (DIF) and consists of tegafur (FT), 5-chloro-2,4-dihydroxypyridine (CDHP) and potassium oxonate (Oxo) at a molar ratio of 1:0.4:1. It achieved high efficacy without increasing gastrointestinal toxicity, based on biochemical modulation theory [10]. In two late phase II studies of S-1 for advanced gastric cancer it gave a RR of 44.6%, with very low (2.0%) incidence of grade 3 toxicities [5, 9].

The rationales for combination of docetaxel and S-1 are as follows. First, as single agents, both agents have activity in patients with gastric cancer. Second, the two drugs have distinct mechanism of actions. Third, the principal toxicities of these two agents are different: neutropenia is the principal toxicity of docetaxel, whereas gastrointestinal toxicity is the main side effect of S-1. Finally, the preclinical and clinical studies listed above have shown the synergistic efficacy of docetaxel with fluoropyrimidine. With these strong rationales for the combination of two drugs, we defined the maximum tolerated dose (MTD) and recommended dose (RD) in a phase I study and determined the anti-tumor effect and safety profile of the RD in a phase II study.

Patients and methods

Eligibility

Patients were eligible if they met all the following criteria: presence of unresectable, locally advanced or metastatic, 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 white blood cell count $\geq 4.0 \times 10^9$ per L or absolute granulocyte count $\geq 1.5 \times 10^9$ per L, platelet count $\geq 100 \times 10^9$ per L, hemoglobin level ≥ 9.0 g/dL, serum creatinine level $\leq$ 1.4 mg/dL, serum bilirubin level ≤ 1.8 mg/dL and AST/ALT $\leq$ two times the upper limit of normal. The presence of measurable lesion was required for phase II study. Patients were excluded if they had previous history of chemotherapy (but adjuvant chemotherapy was allowed), central nervous system metastasis, obvious bowel obstruction, serous gastrointestinal bleeding or serious comorbid conditions. Each patient gave written informed consent before entering the study.

Pretreatment evaluations

The baseline evaluations included history, physical examination, ECOG performance status, CBC, serum chemistry and electrolytes, urine analysis, chest X-ray and three-dimensional computed tomography.

Treatment scheme

The dose-limiting toxicity (DLT) was defined, according to the National Cancer Institute Common Toxicity Criteria Version 3.0, as grade 4 neutropenia or thrombocytopenia lasting more than 7 days; febrile neutropenia or grade 3–4 nonhematological toxicities (excluding controlled anorexia, nausea, vomiting and diarrhea) during the first two cycles. To determine the MTD in the phase I study, docetaxel and/or S-1 were escalated according to toxicities from dose level I to dose level III (Fig. 1). Doses of each drug in the phase I study were as follows: level I, docetaxel 60 mg/m^2 and S-1 60 mg/m^2; level IIA, docetaxel 60 mg/m^2 and S-1 80 mg/m^2; level IIB, docetaxel 75 mg/m^2 and S-1 60 mg/m^2 and level III, docetaxel 75 mg/m^2 and S-1 80 mg/m^2. At least three patients were treated at each dose level. If more than two patients in a given cohort experienced a DLT, this dose level was determined as the MTD. If one patient experienced a DLT, the cohort was expanded to six patients, with the MTD determined if two or more patients experienced a DLT. Thus, the MTD was defined as the highest dose level at which less than 33% of the patients experienced a DLT. The RD for phase II study was defined as one level below the MTD.

Docetaxel was administered intravenously over 1 h on day 1 and S-1 orally twice daily from day 1 to day 14 of each 21-day cycle. Therapy was continued until there was occurrence of progression, development of unacceptable toxicity, or if the patient withdrew consent.

Dose modifications

Dose adjustments were made for each agent if a distinction in toxicity could be made. If both agents were believed to be causing the toxicity, dose reductions were performed for both. The dose of docetaxel was 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. Doses of drugs were never increased.

Response and toxicity evaluation

Criteria of the Response Evaluation Criteria in Solid Tumors Group were used to assess tumor responses and the National Cancer Institute Common Toxicity Criteria

		Docetaxel (mg/m²)	S-1 (mg/day)		
			BSA		
			< 1.25	1.25–1.50	> 1.50
Level (n = 3–6, each level)	I	60	60	80	100
	IIA	60	80	100	120
	IIB	75	60	80	100
	III	75	80	100	120

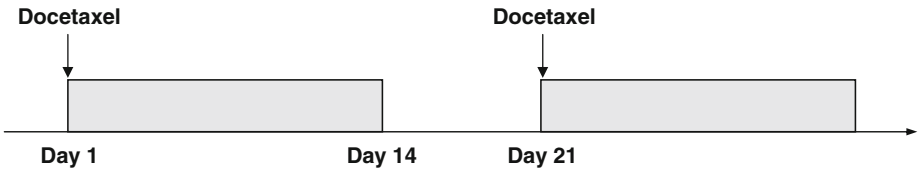

Fig. 1 Treatment schedule of docetaxel and S-1 combination therapy

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.

Statistical analysis

The primary aim of the phase II study was to assess the RR. Simon's MinMax two-stage design was used to calculate the sample size [11]. The first stage required at least seven or more patients out of 19 to have a confirmed response assuming $p_1 = 0.50$, $p_0 = 0.30$, $\alpha = 0.05$ and $\beta = 0.20$ before proceeding to the second stage. In the second stage, 20 additional patients needed to be entered to achieve a target sample size of 39 assessable patients. Assuming a dropout rate of 10%, 44 enrolled patients were needed for the phase II study. Duration of response, time to progression and survival time were estimated via the Kaplan–Meier method.

Results

Patient characteristics

Sixty-five patients were enrolled in this study: 15 in the phase I study and 44 in phase II. Six patients older than 60 years were enrolled in the additional phase I study because of the increased toxicity rate (febrile neutropenia) in older patients observed during the phase I study ($n = 15$) and the initial part of the phase II study ($n = 7$). All patients except one (who was relocated to another hospital after the first cycle) were evaluated for safety, and all patients were assessed for survival. Sixty-one patients were assessable for response. Four patients were not assessable for response because one withdrew consent after two cycles and gave up treatment; one patient was lost to follow-up after the first cycle; one patient died as a result of a neutropenic infection on day 21 of the first cycle; and one patient was relocated to another hospital after the first cycle. Patient characteristics are listed in Table 1. Forty-nine patients were men, and the median age was 54 years (range 29–69). The median age of patients in the phase I study for the elderly was 66 years (range 61–69). Twenty-seven patients (42%) had recurrent gastric cancers that relapsed after adjuvant chemotherapy. Poorly differentiated cancers were most commonly observed, and the most common metastatic sites were the distant lymph nodes, peritoneum and liver.

MTD in the phase I study

All 15 patients in the phase I study were assessed for safety, and the toxicities are summarized in Table 2. None of nine patients given dose levels I, IIA and IIB showed a DLT during the first two cycles. At dose level III, one of three patients developed grade 4 neutropenia with fever and another patient developed grade 4 neutropenia with grade 3 stomatitis. Three more patients were treated with dose level IIB, but none had a DLT. There was no severe nonhematological toxicity except for grade 3 stomatitis at dose level III. From these results, dose level III was determined as the MTD and level IIB was determined as the RD for the phase II study.

After finishing the phase I study, we conducted a phase II study using the established RD (docetaxel 75 mg/m^2 and S-1 60 mg/m^2). Two of the seven patients developed fatal

Table 1 Patient characteristics

	Total	Phase I	Phase I for >60 years	Phase II
Number of patients	65	15	6	44
Sex				
Female	16	3	1	12
Male	49	12	5	32
Median age in years (range)	54 (29–69)	52 (30–69)	66 (61–69)	54 (29–69)
ECOG performance status				
0	39	5	3	31
1	26	10	3	13
2	0	0	0	0
Gastrectomy				
None	38	8	4	26
With chemotherapy	27	7	2	18
Differentiation				
Well	4	2	1	1
Moderate	18	3	3	12
Poor	35	6	2	27
Unknown	8	4	0	4
Metastatic sites				
Liver	23	6	4	13
Lung	11	2	0	9
Lymph nodes	30	3	5	22
Peritoneum	30	8	1	21
Bone	4	1	0	3
Others	19	5	0	14

ECOG Eastern Cooperative Oncology Group

Table 2 Toxicities observed per patient at various dose levels of docetaxel plus S-1 during the initial two cycles in the phase I study ($n = 15$)

Dose levels	Level I ($n = 3$)					Level IIA ($n = 3$)					Level IIB ($n = 6$)					Level III ($n = 3$)				
NCI-CTC grade	I	II	III	IV	≥III (%)	I	II	III	IV	≥III (%)	I	II	III	IV	≥III (%)	I	II	III	IV	≥III (%)
Leukopenia	0	0	1	0	33	1	1	0	0	0	1	0	0	0	0	0	0	1	1	67
Neutropenia	0	0	0	1	33	0	1	0	0	0	1	0	0	0	0	0	0	0	2[a]	67
Anemia	0	2	0	0	0	0	1	0	0	0	2	4	0	0	0	1	1	0	0	0
Thrombocytopenia	1	0	0	0	0	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Anorexia	2	0	0	0	0	1	0	0	0	0	0	0	0	0	0	3	0	0	0	0
Nausea	1	1	0	0	0	1	0	0	0	0	2	0	0	0	0	2	1	0	0	0
Vomiting	1	1	0	0	0	0	0	0	0	0	0	0	0	0	0	2	1	0	0	0
Diarrhea	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Stomatitis	0	0	0	0	0	0	0	0	0	0	1	0	0	0	0	1	0	1[a]	0	33

NCI-CTC National Cancer Institute Common Toxicity Criteria

[a] Dose-limiting toxicity

febrile neutropenia; one patient (male, 66 years) developed febrile neutropenia with shock at day 12 of third cycle and another (male, 64 years) developed febrile neutropenia with shock at day 20 of first cycle. We found that patients older than 60 years experienced grade 4 neutropenia exclusively (5/9 patients, 56%) or febrile neutropenia (4/9 patients, 44%) from the phase I and the early part of phase II studies. By contrast, no patient younger than 60 years developed grade 4 neutropenia or febrile neutropenia (0/13 patients) in initial cycles of the phase I and the early part of phase II studies.

We performed an additional phase I study for patients older than 60 years with level IIA (docetaxel 60 mg/m^2 and S-1 80 mg/m^2): a lower dose than the RD, level IIB. One DLT, grade 3 neutropenia with fever, developed in one patient among six patients during the initial two cycles. According to these results, we decided that the dose level IIA could be assumed as the RD for elderly patients.

Efficacy in phase I and phase II studies

A total of 402 treatment cycles were administered to 65 patients, with a median of six cycles (range 1–17) per patients; a median of six cycles in the phase II study (n = 44, 293 cycles); a median of six cycles (range 2–8) in the phase I study (n = 15, 78 cycles) and a median of four cycles (range 2–9) in the phase I study for older than 60 years of age (n = 6, 31 total cycles).

Tumor response data of the phase I and II studies are listed in Table 3. The confirmed overall RR was 33% at dose level IIA and 67% at level IIB in the phase I study. The confirmed RR was 50% (95% CI, 35–66%) in the phase II study. At dose level IIA of phase I and II studies, the confirmed RR was 37% (95% CI, 15–59%) and 56% (95% CI, 40–72%) at dose level IIB of the phase I and II studies. The median time to response in phase I and II studies was 1.4 months (range 1.1–4.6). The median duration of response in phase I and II studies was 7.4 months (95% CI, 1.9–13.0). The disease control rate was 88% in the phase II study and 89% in 61 assessable patients.

The median time to progression was 6.1 months (95% CI, 4.0–8.1; Fig. 2) in 40 assessable patients of the phase II study and 6.3 months (95% CI, 4.2–8.4) in a total of 61 assessable patients. The median survival time was 15.3 months (95% CI, 10.0–20.6; Fig. 2) in all 44 patients of the phase II study and 12.3 months (95% CI, 8.7–16.0) in all 65 patients, with a median follow-up time of 26.2 months (95% CI, 24.2–28.2 months). One-year and 2-year survival rates were 58 and 28% in the phase II study, respectively, and 52 and 27% in all 65 patients, respectively.

Safety in the phase II study

Forty-three patients receiving 292 cycles of the phase II study were assessed for safety. Toxicities are listed in Table 4. Neutropenia was the most common severe toxicity. Grades 3 or 4 neutropenia developed in 47% of patients and 11% of cycles. Febrile neutropenia was observed in 26% of patients and 5% of cycles. Nonhematological toxicities were usually mild and presented infrequently.

The median relative dose intensities of docetaxel and S-1 in phase II study were 100% for both, ranging from 75 to 100%. The doses of docetaxel and S-1 were reduced in 51 (17.4%) cycles, mainly because of neutropenia. Five (1.7%) cycles were delayed for the following reasons: three when patients developed neutropenia; one for a personal economic reason and one for an insertion of gastric stent.

Discussion

Although the treatment of patients with advanced gastric cancer has achieved considerable progress during recent years, the prognosis is still poor. New combinations with active agents (taxanes, irrinotecan, platinum compounds, and oral fluoropyrimidines) have been trialed. Among the new combinations, docetaxel and S-1 have appealing rationales in term of activity, adverse effect, and convenient administration.

In the phase I study, we determined docetaxel at 75 mg/m^2 on day 1 and S-1 at 60 mg/m^2 on days 1–14 every 3 weeks to be the RD for the phase II study. Through the initial phase II study, we found that these doses might not be tolerated in patients older than 60 years because of higher incidences of severe neutropenia and febrile neutropenia. This finding is consistent with the American Society of Clinical Oncology (ASCO) recommendations for the use of neutrophil growth factor [12]. After conducting an additional phase I study for the older patients, we determined a lower dose of docetaxel (60 mg/m^2) with S-1 at 80 mg/m^2

Table 3 Objective responses in the phase I and II studies

	CR	PR	SD	PD	RR (%)	DCR (%)
Phase I, level I (n^a = 3/3)	0	0	3	0	0	100
Phase I, level IIA (n^a = 3/3)	0	1	2	0	33	100
Phase I, level IIA for patients >60 years (n^a = 6/6)	0	2	3	1	33	83
Phase I, level IIB (n^a = 6/6)	1	3	1	1	67	83
Phase I, level III (n^a = 3/3)	0	2	1	0	67	100
Phase II (n^a = 40/44)	5	15	15	5	50	88
Level IIA, phase I + II (n^a = 19/20)	1	6	9	3	37	84
Level IIB, phase I + II (n^a = 36/39)	5	15	12	4	56	89
Total (n^a = 61/65)	6	23	25	7	48	89

CR complete response, *PR* partial response, *SD* stable disease, *PD* progression, *RR* response rate, *DCR* disease control rate

[a] n = evaluable/total patients

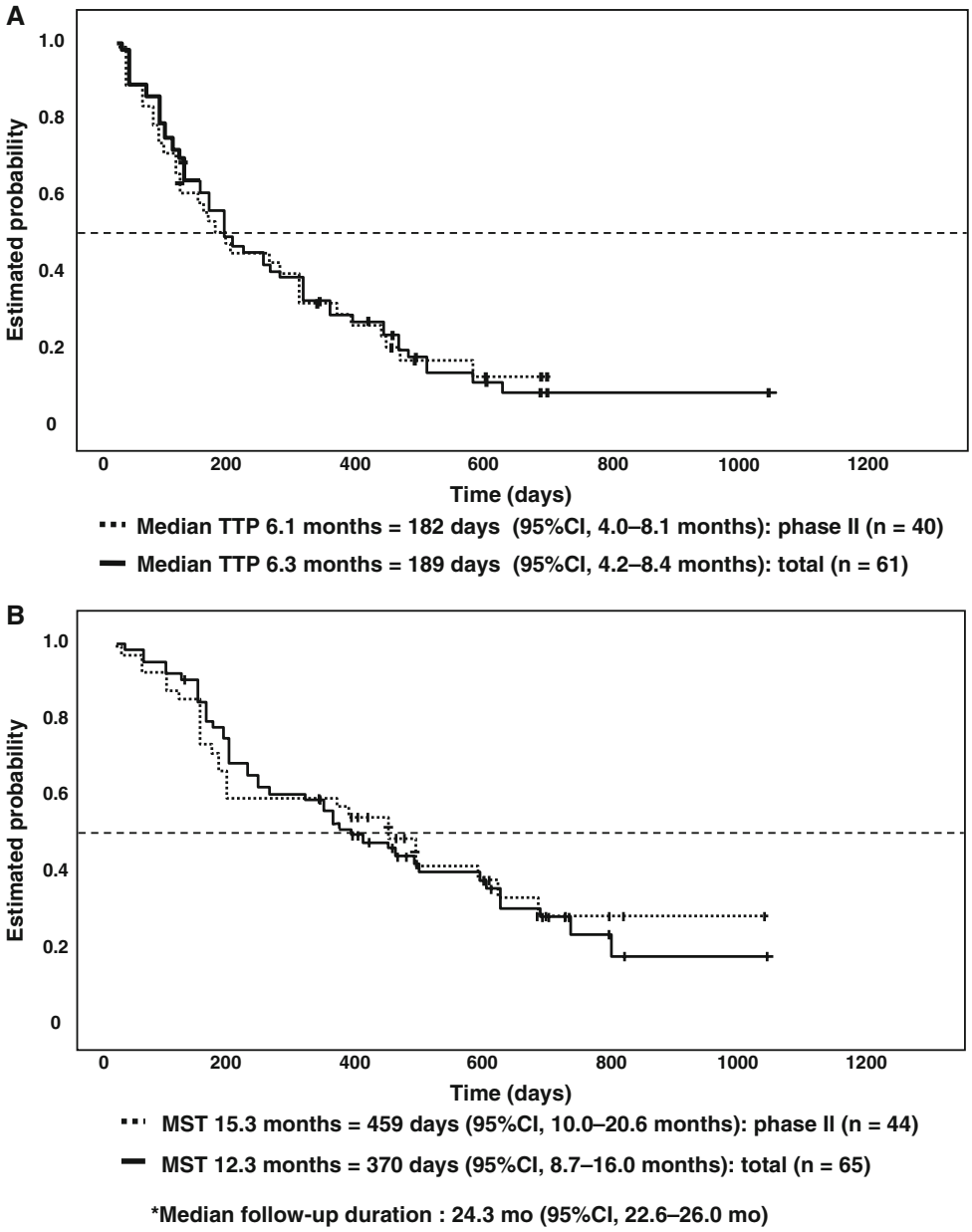

Fig. 2 Kaplan–Meier estimates of **a** progression-free survival and **b** overall survival

as the RD for older patients in the phase II study. These doses of docetaxel, 60 or 75 mg/m^2, are higher than those used in two Japanese studies of the combination of docetaxel and S-1 in advanced gastric cancer [14, 15]. In those two studies, the RD was docetaxel at 40 mg/m^2 on day 1 and S-1 at 80 mg/m^2 on days 1–14 every 3 or 4 weeks. The median age of patients in our study was 54 years (range 29–69) and all patients were younger than 70 years. In contrast, the median age of patients in the two Japanese studies were 65 (range 42–79) and 65 (range 25–75) years, respectively [14, 15]. Therefore, we speculate that a lower dose of docetaxel was administered in these studies because of a larger proportion of elderly patients. Based on these results, the dosage of docetaxel should be graded according to the age group of the patients.

In the phase II study, the primary end point was RR and the RR was 50%. This result is consistent with the two Japanese studies (46 and 56%) [14, 15]. The RRs were different in the two patient groups: 56% in patients younger than 60 years treated with dose level IIB (docetaxel 75 mg/m^2 and S-1 60 mg/m^2) and 37% in patients older than 60 years treated with dose level IIA (docetaxel 60 mg/m^2 and S-1 80 mg/m^2). The disease control rates were similar between the two patient groups: 89 and 84%, respectively. In agreement with the two Japanese phase II reports (14.0 and 14.3 months), we showed an excellent median survival time of 15.3 months in the phase II study. Conceivably, the favorable RR and good disease control rate could provide excellent median survival time.

The major DLT was febrile neutropenia. Although the incidence of febrile neutropenia was relatively high (26%

Table 4 Toxicities observed per patient and cycle during the phase II study

	Per patient (43 evaluable patients)					Per cycle (292 evaluable cycles)				
	NCI-CTC grade, version 3					NCI-CTC grade, version 3				
	I	II	III	IV	≥III (%)	I	II	III	IV	≥III (%)
Leukopenia	3	7	7	9	37.2	9	9	14	12	8.9
Neutropenia[a]	2	4	3	17	46.5	4	8	9	24	11.3
Anemia	20	19	2	2	9.3	187	89	3	2	1.7
Thrombocytopenia	2	0	0	0	0	2	0	0	0	0
Anorexia	29	8	0	0	0	95	10	0	0	0
Nausea	25	4	0	0	0	59	4	0	0	0
Vomiting	12	1	1	0	2.3	18	1	2	0	0.7
Diarrhea	13	2	1	0	2.3	17	2	1	0	0.3
Stomatitis	12	3	0	0	0	33	4	0	0	0
Myalgia	7	0	0	0	0	9	0	0	0	0
Neuropathy	11	0	0	0	0	54	0	0	0	0
Abnormal AST/ALT	10	1	1	0	2.3	19	1	1	0	0.3
Hand–foot syndrome	3	0	0	0	0	3	0	0	0	0
Asthenia	22	2	0	0	0	67	2	0	0	0
Edema	3	3	0	0	0	8	4	0	0	0
Deep vein thrombosis	1	0	1	0	2.3	7	0	3	0	1.0

[a] Febrile neutropenia, 11 patients (26%); 14 cycles (4.8%)

of the patients in the phase II study), the patients generally tolerated treatment well without sequelae through careful monitoring, education, proper management and appropriate dose reduction in subsequent cycles. Thus, the incidence of febrile neutropenia was decreased to 5% of the administered cycles. Prophylactic granulocyte colony-stimulating factor could be considered as an option in the future trial containing docetaxel as recommended by ASCO and the European Society of Medical Oncology [2, 12].

In conclusion, the combination of docetaxel and S-1, if used with appropriate dosage according to patient age, can be an active, well-tolerated, and convenient therapeutic strategy in patients with advanced gastric cancer. Comparative clinical trials with an acceptable reference regimen are warranted.

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