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ORIGINAL ARTICLE

Phase I dose escalation study of docetaxel with a fixed dose of S-1 in combination chemotherapy for advanced gastric cancer

Yeul Hong Kim · Hee Yeon Seo · Yoon Tae Jeen · Hoon-Kyo Kim · Byoung Yong Shim · Jinmo Yang

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Abstract
Background The primary objectives of this study were to estimate the maximum-tolerated dose (MTD) of docetaxel in combination with a fixed dose of S-1 and to determine the recommended dose (RD).
Patients and methods Patients with histologically proven gastric carcinoma with metastatic or locally advanced inoperable disease were eligible. Patients received intravenous docetaxel starting at 40 mg/m^2 (dose level 1), and stepwise dose increases to 50, 60, and 70 mg/m^2 were planned for successive patient cohorts (dose levels 2, 3, and 4, respectively) over 1 h on day 1 and oral S-1 administered at a fixed dose of 40 mg/m^2 twice daily on days 1–14, both drugs every 21 days.
Results A total of 13 patients were enrolled into this trial. All three patients at dose level 3 developed dose-limiting toxicities (DLT), and this level was declared to be the MTD. Hence, level 2 (docetaxel 50 mg/m^2) was declared to be the RD for the next study. As 9 of the 13 enrolled patients responded to treatment, the overall objective response rate was 69.2% (95% CI, 44.1–94.3%). The median time to progression was 8.38 months (range 1.44–8.51) and the overall survival duration was 9.9 months (range 0.62–11.57). The most common grade 3/4 toxicity of docetaxel plus S-1 was neutropenia, which was tolerable and manageable.
Conclusion This regimen showed encouraging activity and a manageable safety profile in advanced gastric carcinoma and could be used in further randomized studies.

Keywords Gastric neoplasm · Docetaxel · S-1 · Combination chemotherapy · Phase I · Clinical trial

Y. H. Kim · H. Y. Seo · Y. T. Jeen
Department of Internal Medicine, Korea University, College of Medicine, Seoul, South Korea

H.-K. Kim (✉) · B. Y. Shim · J. Yang
Department of Internal Medicine, St. Vincent's Hospital, The Catholic University of Korea, 93-6, Ji-dong, Paldal-Gu, Suwon, South Korea
e-mail: kimhoonkyo@yahoo.co.kr

Introduction

Although the incidence of gastric carcinoma has decreased in most Western countries, it remains a significant problem in terms of global health and is the second most common cause of cancer mortality worldwide [1]. Surgical resection is the only therapeutic modality capable of cure and improvements in early diagnosis, preoperative assessment, and surgical techniques have increased the number of potentially curative resections over the last 20 years. However, despite these improvements, prognosis remains poor with the overall 5-year relative survival rates approximating 20% in most areas of the world, except in Japan [1].

The reasons for this grim outlook are that both local and distant relapse, even after an apparently complete resection, are common, and that many patients present inoperable disease at the time of diagnosis. In such patients, chemotherapy is one of the main treatment strategies employed.

Docetaxel (*Taxotere*®, sanofi-aventis, Paris, France) is a semisynthetic taxoid derived from the European yew tree, *Taxus baccata* [2]. Docetaxel has more potent activity than natural taxane paclitaxel in the stabilization/hyperplasia of microtubules, by facilitating microtubule protein polymerization; thereby it inhibits mitosis and displays anti-tumor effects [3]. Docetaxel has shown encouraging activity in gastric cancer, as a single agent response rate ranged from 17 to 24%, with a mean of 19.1% (95% confidence interval;

14.3–23.8%) [4]. The Phase III TAX 325 study enabled the registration of docetaxel in Europe and the US, in combination with cisplatin and intravenous 5-FU, and demonstrated a superior response rate, time to progression, overall survival, clinical benefit and quality of life over cisplatin and intravenous 5-FU, and thus clearly demonstrated both the activity of docetaxel in this disease, and also the proof of principle of the benefit of adding docetaxel to standard regimens [5].

S-1 (*TS-1*®; Taiho Pharmaceutical Co. Ltd, Tokyo, Japan) is an oral fluoropyrimidine derivative that combines tegafur with two modulators of 5-FU metabolism, 5-chloro-2,4-dihydroxy pyridine (gimeracil) and potassium oxonate (oteracil), in a molar ratio of 1:0.4:1. Tegafur, an oral prodrug of 5-FU, is gradually converted to 5-FU and rapidly catabolized by dihydropyrimidine dehydrogenase (DPD) in the liver. Gimeracil inhibits the degradation of 5-FU by inhibition of DPD. Oteracil is an orotate phosphoribosyl transferase (OPRT) inhibitor, which preferentially localizes in the digestive tract. This component of S-1 decreases the phosphorylation of 5-FU in the gastrointestinal mucosa and reduces the incidence and severity of diarrhea [6]. Phase II studies of S-1 monotherapy in patients with advanced gastric cancer showed an overall response rate of 26–49% with the most relevant adverse effects being diarrhea in a European study and neutropenia in two Japanese studies [7–9]. Two recent randomized trials have shown the noninferiority of S-1 monotherapy to the continuous infusion of 5-FU and the activity of S-1 in combination with cisplatin in advanced gastric cancer patients [10, 11]. Also, according to recently published data, adjuvant S-1 treatment improved overall survival in stage II–III gastric cancer patients. As shown in these phase III studies, S-1 is a new pivotal chemotherapeutic agent for the treatment of gastric cancer [12].

Docetaxel and S-1 have different modes of action and are highly synergistic in gastric cancer xenografts [13]. Also, the synergistic effects of docetaxel and S-1 were evident both in vivo and in vitro and could be explained by docetaxel's biochemical modulation of the expression and activity of the thymidylate synthase (TS), DPD, and OPRT enzymes, which play key roles in the functional activities of 5-FU or S-1 [14]. The combination was active and well tolerated in phase I studies, a phase I/II study, and a phase II study in advanced gastric cancer, although the treatment schedule was slightly different [15–19]. Since the result of the recent phase II study in advanced gastric cancer was highly promising (a response rate of 56.3% with a median survival time of 14.3 months) and tolerable with docetaxel 40 mg/m^2 administered intravenously over 1 h on day 1 and oral S-1 administered at a fixed dose of 40 mg/m^2 twice daily on days 1–14 of each 3-week cycle, a multinational randomized phase III study comparing S-1 alone versus docetaxel plus S-1 was planned at this dose and schedule. The relatively low dose of docetaxel recommended in that study, possibly as a result of the conservative definitions used for dose-limiting-toxicities (DLT) in a previous phase I study was mild, compared with other phase I studies [18] and resulted in the need to conduct a further dose-finding phase I trial of the docetaxel and S-1 combination.

The primary objectives of this study were to estimate the maximum-tolerated dose (MTD) of docetaxel in combination with a fixed dose of S-1 and to determine the recommended dose (RD) for a multinational phase III study.

Patients and methods

Study design

This study was a prospective, multicenter, open-label, single arm, non-blinded, sequential cohort dose escalation phase I study in patients with advanced gastric cancer. The primary end point of this study was the determination of 3-weekly docetaxel dose feasibility in the combination of docetaxel and oral S-1 administered at a fixed dose of 40 mg/m^2 twice daily on days 1–14 of each 3-week cycle in patients with advanced gastric cancer. A docetaxel dose was considered feasible if at least 2/3 (3 out of 3; 4 or 5 out of 6) patients do not experience dose-limiting toxicity during the first cycle. The secondary end points were (1) time to tumor progression, which was defined as time from inclusion in the study to date of first documentation of progressive disease and (2) clinical response rate, which was defined as the sum of complete responses and partial responses according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria.

Eligibility

Patients with histologically proven metastatic or locally advanced inoperable gastric carcinoma were eligible. Patients were required to be older than 20 years with a life expectancy of >3 months and to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1. All patients were required to have at least one target lesion according to RECIST criteria and/or assessable metastatic disease according to World Health Organization criteria [20, 21]. Failure of one line of prior palliative chemotherapy was allowed except for prior taxane or S-1 (considering that patients receive one palliative chemotherapy if recurrence occurs within 6 months of adjuvant chemotherapy), and patients should not be under the influence of the effects or side effects of previous treatments; at least 4 weeks must have passed since the last drug administration. All eligible patients were also required to have adequate hematologic

counts [a white blood cell count of ≥4,000/μl, an absolute neutrophil count (ANC) of ≥2,000/μl, a platelet count of ≥100,000/μl, and hemoglobin ≥8.0 g/dl], laboratory results within the following limits [serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase <2.5 × UNL, serum bilirubin ≤1.5 mg/dl], and renal function within the following limits (creatinine <1.25 × UNL or ≤120 μmol/L).

Exclusion criteria were as follows: pregnant or nursing women; sexually active males/females unwilling to use contraception during the study; gastric cancer other than adenocarcinoma; within the previous 5 years, malignancies other than gastric carcinoma except for adequately treated in situ carcinoma of the cervix, or non-melanoma skin cancer; known brain or leptomeningeal metastasis; a history of hypersensitivity to the treatment drugs or preparations containing polysorvate 80, taxotere, or fluoropyrimidine derivatives; obvious corticosteroid contraindication; simultaneous administration of other anticancer drug; peripheral sensory neuropathy of ≥Grade 2 according to National Cancer Institute—Common Toxicity Criteria Adverse Event (NCI-CTCAE) version 3.0; or other medically important illnesses or medical conditions as determined by the treating physician. Finally, all patients provided informed consent and this study was approved by the institutional review boards at each institute.

Treatment

Patients received variable doses of intravenous docetaxel administered intravenously over 1 h on day 1 and 40 mg/m^2 of oral S-1 twice daily on days 1–14 of each 3-week cycle. Treatment was continued up to 12 cycles unless disease progression, unacceptable toxicity, or of the patient requested to withdraw.

The initial starting dose of docetaxel was 40 mg/m^2 (dose level 1), and stepwise dose increases to 50, 60, and 70 mg/m^2 were planned for successive patient cohorts (dose levels 2, 3, and 4, respectively). Initially, only three patients were to be recruited to receive dose level 1. If none of the three patients developed any DLT at the first cycle, the dose of docetaxel were to be escalated to the next level and then three patients were to be enrolled for level 2 (50 mg/m^2), and in the same manner for level 3 (60 mg/m^2) and the final level 4 (70 mg/m^2). If one or two out of three patients developed any DLT in the first cycle, three more patients were to be treated at the same dose level. If two or less out of six patients developed any DLT, the dose of docetaxel were to be escalated to the next level and three patients were to be recruited at level two and in the same manner to level 3 and 4. If three patients out of three, or three or more patients out of six patients develop any DLT in the first cycle, the dose level would be regarded as not feasible.

DLTs were defined as follows; (1) grade 3 febrile neutropenia (ANC < 1,000/μl with fever ≥38.5°C); (2) grade 4 neutropenia lasting for 7 days or longer; (3) grade 4 thrombocytopenia or thrombocytopenic bleeding; (4) grade 3/4 nonhematological toxicities other than nausea/vomiting and alopecia.

S-1 was administered orally at 40 mg/m^2 twice daily within 1 h after the morning and evening meals for 2 weeks followed by a drug-free interval of 1 week. Three doses of S-1 were established according to body surface area (BSA) as follows; BSA < 1.25 m^2; 80 mg/day; 1.25 m^2 ≤ BSA < 1.5 m^2, 100 mg/day; and 1.5 m^2 ≤ BSA, 120 mg/day. S-1 treatment was replaced in cases of vomiting intact capsules.

Patients treated with docetaxel received six doses of oral dexamethasone 4 mg starting the night before docetaxel infusion. Prophylactic use of granulocyte colony-stimulating factor (G-CSF) administration was not allowed during the first cycle in this study.

Subsequent treatment cycles were started only when neutrophil count ≥1,500/μl, platelet count ≥100,000/μl, AST or ALT ≤ 100 IU/l, and total bilirubin ≤1.5 mg/dl. Planned treatment was withheld until recovery in cases with: a fever of 38°C or higher, an ECOG performance status of 2 or higher, grade 2 or higher of diarrhea, grade 2 or higher of sensory neuropathy, or grade 2 or higher of edema. When drugs could not be administered due to adverse events even after a 2-week postponement from the planned day of the next administration, treatment was stopped. If infection with grade 3 or 4 neutropenia (ANC < 1,000/μl), grade 3 or 4 febrile neutropenia, grade 4 thrombocytopenia, nonhematologic toxicity ≥grade 3 except alopecia and nausea/vomiting or reappearance of peripheral neuropathy/edema ≥grade 2 occurred during the previous treatment, the dose of docetaxel was reduced by 20% for the following treatment. A second episode required another 20% dose reduction of docetaxel on subsequent treatments. If grade 4 sensory neuropathy or grade 4 nonhematologic toxicity occurred, treatment was stopped.

If nonhematologic toxicity ≥grade 2 except alopecia and nausea/vomiting, neutrophil count <500/μl, platelet count <50,000/μl, febrile neutropenia, or infection with grade 3 or 4 neutropenia (ANC < 1,000/μl) occurred during the planned administration period of S-1 in the cycle, S-1 administration was interrupted. S-1 treatment was restarted after recovery to nonhematologic toxicity ≤grade 1, neutrophil count ≥500/μl, and platelet count ≥50,000/μl. If grade 2/3 nonhematologic toxicities redeveloped with resumed S-1 administration, in the subsequent treatment S-1 dosage was reduced by 20%. If infection with grade 3 or 4 neutropenia (ANC < 1,000/μl), febrile neutropenia, or grade 4 thrombocytopenia occurred during the previous treatment, the dose of S-1 was reduced by 20 mg/day from

previous dosage for the following treatment. Dose escalation after dose reduction was not permitted.

Response to treatment and adverse effects

Before entering the study, all patients received a physical examination, and full blood count, serum chemistry analyses, urinalysis, creatinine clearance, and EKG at least 8 days before enrollment. Chest X-ray, abdominal computer tomographic (CT) scans, and other appropriate procedures were also performed within 2 weeks of registration. During the first cycle, full blood count test was done four times (between days 4–5, days 7–9, days 11–12, and days 14–16, respectively) and serum chemistries were checked every week. From second cycle, patients were checked for full blood count and serum chemistries two times per cycle (between days 6–10 and before next treatment). After every two cycles of treatment, response was evaluated using RECIST criteria. In cases of partial or complete response, a confirmative CT scan was performed 4 weeks later and this was followed by a CT scan after every two treatment cycles. Toxicity was reported using an NCI-CTCAE version 3.0.

Results

Patient characteristics

A total of 13 patients were enrolled into this trial from November 2004 to May 2005. Patient characteristics are listed in Table 1. A total of 12 patients had metastatic diseases at the time of enrollment. Metastatic sites were in the abdominal lymph nodes ($n = 12$), liver ($n = 1$), ovary ($n = 1$), and pancreas ($n = 1$). Eight patients were male, and four patients (30.8%) had previously received palliative chemotherapy. The palliative chemotherapy regimens were pemetrexed (*Alimta*®; Eli Lilly and Company, Indianapolis, IN) + cisplatin in two patients, 5-FU + cisplatin in one patient and 5-FU + mitomycin in one patient, respectively. Three patients had undergone surgery for the treatment of gastric cancer before entry (one patient with curative intent, two patients with palliative intent).

Determination of MTD

All 13 patients were fully evaluated for toxicity. Initially, four patients were allocated dose level 1. However, one patient was dropped after the first cycle of treatment due to violation of eligibility criteria (A 47-year-old female patient, whose biloma was diagnosed by the radiologist's interpretation of baseline CT scan after the first cycle of docetaxel infusion, was excluded from the study. However, this patient was included in toxicity evaluation). Other three patients at dose level 1 did not experience DLT. Therefore, the dose of docetaxel was increased, and the initial three patients at dose level 2 (first cohort of level 2) were enrolled. One patient in this cohort developed grade 3 elevation of alkaline phosphatase and another patient had prolonged grade 4 neutropenia. To evaluate toxicity in a larger group at dose level 2, three additional patients were enrolled (second cohort of level 2). No patient in this cohort developed DLT. Thus, two out of six patients at dose level 2 developed DLT and the initial three patients at dose level 3 were enrolled. All three patients at this dose level developed DLT (one with grade 4 metabolic acidosis;one with grade 3 gastrointestinal hemorrhage; one with grade 3 febrile neutropenia, grade 3 mucositis, and grade 3 diarrhea), and this level was declared to be the MTD. Hence, level 2 (docetaxel 50 mg/m^2) was declared to be the RD for the next study.

Table 1 Patient characteristics

No. of patients	13
Male/female	8/5
ECOG performance status (0/1)	2/11
Age (years)	
Median	58
Range	43–79
Histology	
Well-differentiated adenocarcinoma	0
Moderately differentiated adenocarcinoma	4
Poorly differentiated adenocarcinoma	8
Signet ring cell carcinoma	1
Mucinous adnocarcinoma	0
Previous treatment	
None	8
Surgery	3
Palliative chemotherapy	4
Metastatic sites	
Abdominal lymph nodes	12
Liver	1
Ovary	1
Pancreas	1
No. of metastatic sites	
1	9
≥2	3

Response to chemotherapy

A total of 83 treatment courses were administered to the 13 patients. Three patients received only one cycle of treatment, three patients had 6 cycles, three patients had 12 cycles, and one patient had 2, 5, 8, and 11 cycles, respectively. Among

Table 2 Response rate

	Dose level			
	1 ($n = 4$)	2 ($n = 6$)	3 ($n = 3$)	Total (%)
Partial response	3	5	1	9 (69.2)
Stable disease	0	0	0	0 (0)
Progressive disease	0	1	1	2 (15.4)
Not evaluable	1	0	1	2 (15.4)
Response rate	3/4 (75.0)	5/6 (83.3)	1/3 (33.3)	9/13 (69.2)

the three patients, who had one cycle of treatment, one went off the study due to ineligibility, one went off due to early death, and one because of progressive disease. Among the three patients, who had six cycles of treatment, one refused further treatment, one went off due to delayed bone marrow recovery, and one showed progressive disease. The patients, who went off the study after 2, 5, and 8 cycles had progressive disease, respectively, and one patient went off after 11 cycles due to repeated nonhematologic toxicity. Three patients finished the planned 12 cycles of treatment. Among 13 patients, 11 patients were evaluable for efficacy (one patient dropped out after one cycle of treatment due to violation of eligibility, one patient died after one cycle of treatment due to metabolic acidosis). All three evaluable patients in the first cohort of level 1 achieved a partial response. Five out of six patients treated with docetaxel 50 mg/m^2 achieved a partial response. Among the two evaluable patients treated with docetaxel 60 mg/m^2, one patient achieved a partial response and one patient achieved stable disease, although these patients had DLT in the first cycle and were treated with docetaxel 50 mg/m^2 from the second cycle. The median number of treatment cycles per patient was 6 with a range from 1 to 12. As 9 of the 13 enrolled patients responded to treatment, the overall objective response rate was 69.2% (95% CI, 44.1–94.3%) (per protocol analysis; 9/11, 81.8%) (Table 2). As 6 of the 11 evaluable patients had disease progression, the median time to progression was 8.38 months (range 1.44–8.51). The overall survival duration of the 13 enrolled patients was 9.9 months (range 0.62–11.57).

Toxicity

Toxicity was assessed for all treated patients. Grade 4 neutropenia occurred in two of four patients with docetaxel 40 mg/m^2, in four of six patients with docetaxel 50 mg/m^2, and in one of three patients with docetaxel 60 mg/m^2 (Table 3). Grade 3 and 4 thrombocytopenia was developed in one patient at 40 and 60 mg/m^2 of docetaxel, respectively.

Most nonhematologic toxicities were of mild to moderate intensity (Table 4). Grade 3 nonhematologic toxicities were observed in five patients (diarrhea and infection without neutropenia in two patients, respectively, and one patient with nausea/vomiting). In three patients, treatment was discontinued due to the following adverse events; grade 4 metabolic acidosis, grade 3 diarrhea associated with grade 3 mucositis, and delayed recovery of myelosuppression.

With the docetaxel 40 mg/m^2 starting dose, one patient received up to five cycles, but required dose reduction due to nonhematologic toxicity from the third cycle. Two patients received up to 12 cycles without dose modification. One patient was excluded due to violation of eligibility. At the docetaxel 50 mg/m^2 starting dose, three patients received up to 6 cycles and one patient received up to 8 and 12 cycles, respectively. One patient showed progressive disease after one cycle of treatment. In total, 39 cycles were given to six patients in this dose level without dose modification. With the docetaxel 60 mg/m^2 starting dose, one patient received up to 11 cycles and had a dose reduction to docetaxel 50 mg/m^2 dose level from the second cycle due to occurrence of DLT. One patient received up to two cycles with dose reduction to docetaxel 50 mg/m^2 dose level from the second cycle due to occurrence of DLT. One patient died after the first cycle of treatment due to an adverse event.

Discussion

The aim of this study was to estimate the MTD of docetaxel in combination with a fixed dose of S-1 and to determine

Table 3 Hematologic toxicities

Adverse events	Dose level					
	1 ($n = 4$)		2 ($n = 6$)		3 ($n = 3$)	
	Grade 1 or 2	Grade 3/4	Grade 1 or 2	Grade 3/4	Grade 1 or 2	Grade 3/4
Leukopenia	1	2/0	1	4/0	1	2/0
Neutropenia	0	0/2	1	1/4	0	2/1
Anemia	1	2/0	6	0/0	1	1/1
Thrombocytopenia	0	1/0	1	0/0	0	0/1

Table 4 Non-hematologic toxicities

Adverse events	Dose level					
	1 (n = 4)		2 (n = 6)		3 (n = 3)	
	Grade 1 or 2	Grade 3/4	Grade 1 or 2	Grade 3/4	Grade 1 or 2	Grade 3/4
Anorexia	3	0/0	6	0/0	2	0/0
Abdominal pain	2	0/0	3	0/0	2	0/0
Diarrhea	0	1/0	4	0/0	1	1/0
Nausea	1	0/0	4	0/0	1	1/0
Vomiting	1	0/0	1	0/0	1	1/0
Fatigue	1	0/0	4	0/0	2	0/0
Hepatic function abnormal	3	0/0	3	0/0	3	0/0
Infection without neutropenia	2	1/0	1	0/0	2	1/0
Sensory neuropathy	0	0/0	2	0/0	1	0/0
Myalgia	2	0/0	3	0/0	0	0/0
Edema	1	0/0	2	0/0	0	0/0

the RD for the treatment of advanced gastric cancer. The study demonstrates that the dose level 3 (docetaxel 60 mg/m^2) was the MTD and level 2 (docetaxel 50 mg/m^2) was declared to be the RD for the next study.

5-FU is the mainstay of treatment for gastric cancer. S-1, a newly developed oral 5-FU prodrug, contains 5-chloro-2,4-dihydroxypyridine (CDHP), which transiently, but strongly, inhibits DPD. The presence of this enzyme in the formulation allows the plasma concentration of 5-FU to be maintained at a high level. Also, the presence of oteracil reduces gastrointestinal toxicity, which was one of the main dose-limiting toxicities observed with prolonged 5-FU infusion [6, 22]. In addition, oral administration of S-1 is an attractive modality, since it is easy to administer and can be given in outpatient clinics, while maintaining the serum level of 5-FU, which mimics that of continuous intravenous infusion [22].

Docetaxel has shown an activity against gastric cancer as monotherapy and in combination with other agents. Several studies from Europe, the USA, Japan, and Korea have assessed docetaxel monotherapy in the treatment of advanced gastric cancer with generally consistent results. While four studies from Europe and the USA administered docetaxel at 100 mg/m^2 dosage [23–26], Japanese studies used docetaxel 60 mg/m^2 [27, 28] and a Korean phase II study used 75 mg/m^2 [29] and reported a narrow range of response rate that varied from 17 to 24%, despite variable dosage.

Two phase I studies of combination therapy with docetaxel and S-1 were conducted in Japan. One study adopted an every 3 week schedule with S-1 administration for 2 weeks [18] and the other study used an every 4-week schedule with 2 weeks on and 2 weeks off of S-1 [17]. In both studies, RD of docetaxel was 40 mg/m^2 every 3 or 4 weeks in combination with a fixed dose of S-1 administered at a fixed dose of 40 mg/m^2 twice daily on days 1–14. In a phase I study with every 3-week schedule, DLTs were defined as grade 4 neutropenia, grade 4 thrombocytopenia, or any grade 3 nonhematological toxicity, except general fatigue, emesis/nausea and alopecia [18]. Although the duration of neutropenia was brief and the incidence of complicated neutropenia was infrequent in phase II studies of docetaxel monotherapy, the incidence of grade 4 neutropenia was over 50% [23, 24, 29]. Considering the definition of DLTs in Yoshida et al.'s study, there was a possibility that the reported RD might be a suboptimal one, since most of grade 4 neutropenia lasting less than 7 days are considered to be manageable. Actually, Yoshida et al. reported that the MTD was reached at level 2 (docetaxel 50 mg/m^2 plus oral S-1 administered at a fixed dose of 40 mg/m^2 twice daily on days 1–14 of each 3-week cycle) in three patients out of six and the grade 4 neutropenia was DLT in two patients. In another phase I study of docetaxel plus S-1, DLTs were defined as grade 4 neutropenia lasting for 5 days or longer, grade 4 neutropenia with fever, grade 4 thrombocytopenia, grade 3/4 nonhematological toxicities other than nausea/vomiting, anorexia, and general fatigue, and any grade 4 hematological toxicity during S-1 administration. DLTs in this study were one patient with grade 3 infection associated with grade 3 neutropenia and two patients with grade 4 neutropenia during S-1 administration at dose level 1 (docetaxel 50 mg/m^2 plus oral S-1 administered at a fixed dose of 40 mg/m^2 twice daily on days 1–14 of each 4-week cycle). The results from those two phase I studies suggested that development of grade 4 neutropenia were frequent at dose level of docetaxel 50 mg/m^2 plus oral S-1 administered at a fixed dose of 40 mg/m^2 twice daily on days 1–14 of 3 or 4-week cycle, but the duration of severe neutropenia was not specified.

In this study, we defined that docetaxel 50 mg/m^2 on day 1 plus oral S-1 administered at a fixed dose of 40 mg/m^2

twice daily on days 1–14 of each 3-week cycle would be an RD for further study. Out of five patients with DLT, only two patients had DLT related with significant neutropenia (one patient with grade 4 neutropenia more than 7 days, one patient with grade 3 febrile neutropenia). Also, six patients, who were enrolled at the dose level of docetaxel 50 mg/m^2 plus S-1 40 mg/m^2 twice daily on days 1–14 of each 3-week cycle, tolerated 39 cycles of treatment without dose modification. The mean dose intensity of docetaxel was 15.5 mg/m^2 per week, which supports that docetaxel 50 mg/m^2 plus S-1 40 mg/m^2 twice daily on days 1–14 of each 3-week cycle would be a tolerable dosage in this patient group. However, grade 4 neutropenia still developed in two of the four patients at the dose level of docetaxel 40 mg/m^2 plus S-1 40 mg/m^2 twice daily on days 1–14 of each 3-week cycle and clinical efficacy was also noted from this dose level. Hence, Korean investigators agreed to adopt docetaxel 40 mg/m^2 on day 1 plus S-1 40 mg/m^2 twice daily on days 1–14 of each 3-week cycle, as an experimental arm for a phase III study to be compared with S-1 40 mg/m^2 twice daily monotreatment on days 1–28, every 6 weeks.

Although the efficacy was not the primary purpose of this study and the number of patient was small, it is highly notable that the response rate of docetaxel plus S-1 combination chemotherapy was impressively high. As 9 of the 13 enrolled patients responded to treatment, the overall objective response rate by intention-to-treat analysis was 69.2%. Yoshida et al. also reported 56.3% (27/48) response rate with docetaxel 40 mg/m^2 on day 1 plus S-1 40 mg/m^2 twice daily on days 1–14 of each 3-week cycle, which was similar to our study [19]. In a phase I/II study using docetaxel 40 mg/m^2 on day 1 plus S-1 40 mg/m^2 twice daily on days 1–14 of each 4-week cycle, the response rate was 46% (21/46) with two complete responses [17]. These response rates are the most favorable that have been reported in the treatment of advanced gastric cancer.

The main toxicity of docetaxel plus S-1 was neutropenia. Ten out of 13 patients showed grade 3/4 neutropenia during treatment; however, most cases were tolerable and manageable. The incidence of grade 3 or higher diarrhea, nausea/vomiting, or mucositis was low. This toxicity profile is different from that of docetaxel plus capecitabine. Although the incidence of grade 3/4 neutropenia was not so high, docetaxel plus capecitabine had a high incidence of hand–foot syndrome/onycholysis, nausea, or stomatitis with different doses of capecitabine and schedules of docetaxel administration [30–32]. Since nonhematologic toxicities are more difficult to manage than uncomplicated neutropenia, the combination of docetaxel and S-1 seems more tolerable than docetaxel plus capcitabine. Also, eight patients tolerated more than six cycles of docetaxel plus S-1, which suggests the absence of cumulative toxicity in this regimen.

As demonstrated in this phase I study, the RD of docetaxel is 50 mg/m^2 every 3 weeks in combination with a fixed dose of S-1 40 mg/m^2 twice daily on days 1–14 of each 3-week cycle. This combination regimen showed a significant activity in advanced gastric carcinoma and was characterized by a favorable toxicity pattern. We are awaiting the final result of a large phase III study comparing S-1 alone to docetaxel plus S-1 in patients with advanced gastric cancer, which is ongoing in Japan and Korea, to confirm docetaxel advantage in terms of response and survival, as suggested in this study.

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