Cancer Chemother Pharmacol (2009) 63:1083–1090
DOI 10.1007/s00280-008-0818-3

ORIGINAL ARTICLE

A multi-center phase II study of S-1 plus paclitaxel as first-line therapy for patients with advanced or recurrent unresectable gastric cancer

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Received: 24 April 2008 / Accepted: 28 July 2008 / Published online: 24 September 2008

Abstract
Purpose This study was conducted to evaluate the safety and efficacy of S-1 and paclitaxel combination therapy for patients with advanced gastric cancer.
Methods Eligible patients had previously untreated advanced or relapsed gastric cancer with measurable lesion(s) and an ECOG PS of 0-2. Treatment consisted of S-1 35 mg/m^2 p.o. b.i.d. on days 1–14 followed by a 7-day off plus paclitaxel 70 mg/m^2 i.v. on days 1 and 8 of a 21-day cycle.
Results Fifty-six patients (M/F = 37/19) were enrolled. The median age was 59 years. The median number of cycles administered was six (range 1–18). Out of the 53 patients evaluated, there was 1 (1.9%) CR, 20 (37.7%) confirmed PRs, 5 (9.4%) unconfirmed PRs, 21 (39.6%) SDs, and 6 (11.3%) PDs. The objective tumor response was 39.6%. The median time to progression was 29 weeks. The median survival was 51 weeks. All 56 patients were assessed for treatment safety. The treatment was well tolerated with grade 3/4 neutropenia in 20%/13%, grade 3 febrile neutropenia in 7%, grade 2/3 diarrhea in 9%/4%, vomiting in 11%/0%, stomatitis in 4%/4%, and neuropathy in 4%/0% of patients.

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Conclusions S-1 and paclitaxel combination treatment is an effective regimen with a favorable toxicity profile in patients with advanced gastric cancer.

Keywords Advanced gastric cancer · Chemotherapy · First line · Paclitaxel · Phase II · S-1

Introduction

Adenocarcinoma of the stomach has been the leading cause of cancer-related death worldwide. The incidence and mortality of gastric cancer are high in Asian countries [16]. Although the overall incidence of gastric cancer has decreased in Western countries, that of proximal gastric cancer has increased [10]. Gastric cancer recurs in approximately 40% of patients after curative gastrectomy [5] and the median survival for relapsed patients is 6–9 months [24]. For several decades, many chemotherapeutic agents have been tried to improve survival, response rate and quality of life in patients with advanced gastric cancer. Combination regimens including several agents, e.g., 5-fluorouracil, cisplatin, doxorubicin, epirubicin, and methotrexate, have had better response rates than single agents. However, these treatments have the modest increase of the overall patient survival but have not been satisfactory [15]. Recently, the development of new chemotherapeutic agents has led to many clinical trials to find novel therapeutic strategies to improve the outcome of patients with advanced gastric cancer.

S-1 is an oral pyrimidine fluoride-derived new anticancer agent in which 5-fluoro-1-(tetrahydro-2-furanyl)-2,4(1H, 3H)-pyrimidinedione is combined with two classes of modulators, 5-chloro-2,4-dihydroxypyridine and oteracil potassium, to enhance antitumor effects and decrease gastrointestinal toxicity [4, 8]. In five clinical trials, including three Japanese trials, the response rate after treatment with S-1 was 20–50% in patients with advanced gastric cancer as a single agent, when it was administered for 4 weeks with 2 weeks off [3, 11, 14, 21, 22]. The main side effects of S-1 treatment were diarrhea, fatigue, anemia, and neutropenia.

Paclitaxel has been reported as a promising novel agent for the treatment of gastric cancer. The response rate for paclitaxel has been reported to be about 20% as a single agent. The side effects include neutropenia, peripheral neuropathy and arthralgia [1]. Paclitaxel has synergistic antitumor effects with 5-fluorouracil (5-FU) according to clinical trials as well as preclinical studies, and a different spectrum of side effects [12, 18]. Several clinical trials of S-1 and paclitaxel combination therapy have been conducted in Japan [6, 7, 9, 13, 17, 20, 23]. The response rate has been reported to be 40–60% with the schedule of S-1 80 mg/m^2 for 14 days plus weekly paclitaxel 50–60 mg/m^2 on days 1 and 8.

Based on this data, a multi-center phase II study was conducted by the Korean Cancer Study Group in order to assess the efficacy of S-1 and weekly paclitaxel administered every 3 weeks as first-line treatment for patients with advanced or metastatic gastric cancer.

Materials and methods

Study population

The eligible patients were required to have histologically confirmed adenocarcinomas of the stomach, unresectable advanced or recurrent gastric cancer with an age from 18 to 75. Patients with a history of prior chemotherapy were excluded. However, those with one adjuvant chemotherapy regimen, without taxane or S-1 and an interval of 6 months between treatment and study entry were included. In addition, no enrolled patient had prior radiotherapy for treatment of the primary site or measurable lesions. At least one measurable lesion existed and was assessed by Response Evaluation Criteria in Solid Tumors (RECIST) criteria. The measurable lesions were defined as more than 20 mm of the longest diameter on physical examination, X-ray or computer tomography of metastatic or locally advanced lesions or more than 10 mm of the longest diameter on spiral computer tomography of metastatic or locally advanced lesions. Others lesion, i.e., bone lesions, leptomeningeal disease, ascites, pleural or pericardial effusion were defined as non-measurable or evaluable lesion. An ECOG performance status (PS) of 0–2 was required, as was adequate bone marrow function (WBC $\geq$ 4,000/mm^3, hemoglobin $\geq$ 10.0 g/dL and platelet count of $\geq 100 \times 10^9$ cells/L). As well, hepatic (total bilirubin $\leq$ 1.5 times the upper limit of normal, serum transaminase $\leq$ 2.5 times the upper limit of normal) and renal function (serum creatinine level $\leq$ 1.5 times the upper limit of normal, creatinine clearance $\geq$ 60 mL/min, 24 h proteinuria < 300 mg/day), were required. The life expectancy of patients was estimated to be at least 12 weeks.

The exclusion criteria included a prior history of malignancy, with the exception of basal cell carcinoma of the skin or a carcinoma in situ of the cervix, an active infection or other serious underlying medical conditions, and prior adjuvant chemotherapy with S-1 or taxane. We also excluded patients with a history of drug-induced hypersensitivity with Cremophor EL®, cyclosporine and vitamin K and who were taking medicines that could affect the pharmacodynamic activity of S-1. All patients signed written informed consent to participate in the study. This study

protocol was approved by the institutional review board at each center.

Treatment plan and dose modification

Chemotherapy was given on an outpatient basis. Paclitaxel 70 mg/m^2 was administered as a 1-h intravenous infusion on days 1 and 8 of each 3-week cycle along with S-1 35 mg/m^2 p.o. b.i.d. on days 1–14. S-1 was administered between 7–10 am and 7–10 pm, within 1 h after a meal (breakfast and dinner). Paclitaxel was prepared according to the manufacturer's directions in 250 mL 5% dextrose in water or 0.9% normal saline or 5% dextrose saline. For premedication for paclitaxel, dexamethasone 20 mg IV, diphenhydramine 50 mg IV and ranitidine 50 mg or cimetidine 300 mg IV were administered 30 min before the paclitaxel.

The next course of treatment was to begin only when the absolute neutrophil count recovered above 1,500/mm^3 and the platelet count was above 100,000/mm^3. In addition, any treatment-related toxicity had to resolve to grade 1 or lower. If the toxicity had not resolved to grade 0–1 at the end of this period, treatment could be delayed for a maximum of 3 weeks. Granulocyte-colony stimulating factor could be available for grade 3 or 4 neutropenia but should not be administered for prophylaxis.

For hematological toxicity, a dose modification for the next cycle was determined according to the nadir of the previous cycle. S-1 or paclitaxel were alternatively reduced by 10 mg/m^2/day and paclitaxel was the first to be reduced for a grade 4 neutropenia, grade 3/4 thrombocytopenia, neutropenic fever, or grade 3/4 hemorrhage. On day 8, both drugs were withheld for a grade 4 neutropenia, grade 3/4 thrombocytopenia, neutropenic fever, or grade 3/4 hemorrhage. On day 8, for grade 3 neutropenia or grade 2 or thrombocytopenia with counts less than 100,000/mm^3, paclitaxel treatment was reduced by 10 mg/m^2/day without the reduction of S-1. The dose of S-1 was not reduced in the same cycle.

For the non-hematological toxicity, S-1 for the next cycle was reduced by 10 mg/m^2/day for grade 2 diarrhea or grade 3/4 abdominal pain and was discontinued for grade 3 diarrhea. Paclitaxel was reduced by 10 mg/m^2/day for a grade 2 peripheral neuropathy and was withheld for a grade 3 peripheral neuropathy. Both drugs were reduced by 10 mg/m^2 per day for a grade 2 hyperbilirubinemia, grade 3 liver dysfunction and a grade 3 non-hematological toxicity except alopecia, nausea, vomiting, myalgia, and arthralgia. Both drugs were withheld for grade 3 hyperbilirubinemia, grade 4 liver dysfunction and grade 4 other non-hematologic toxicity except alopecia, nausea, vomiting, myalgia, and arthralgia. The dose of S-1 was not reduced in the same cycle. The treatment could be administered for a maximum of 6 cycles, unless there was documented disease progression or unacceptable toxicity.

Assessment of patients

All patients had a medical history and physical examination. Assessments including complete blood cell count, renal and liver function tests, urinalysis, electrocardiogram, performance status evaluation, height and weight determination were conducted within 1 week prior to study entry. The 24-h urine protein and creatinine clearance were evaluated within 2 weeks before study enrollment. Chest X-rays, endoscopy, abdominal computed tomography (CT) scans, and radionuclide bone scans were conducted within 3 weeks prior to study enrollment.

Before each treatment course, height, weight, physical examination, performance status, complete blood cell count, blood chemistry and toxicity evaluations were repeated. The complete blood cell count was repeated on days 8 and 15 after the first cycle or when the dose was modified by hematological toxicity. The blood chemistry was repeated on days 8 and 15 of the first cycle. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria (version 3.0).

Assessment of response

The primary endpoint of this trial was the response rate. Response assessment was performed every two cycles and whenever clinically indicated. The responses were documented and confirmed following two cycles. After six cycles of chemotherapy were completed, response assessment was performed every 3 months until disease progression. The responses were assessed according to the RECIST guidelines.

Statistical analysis

This trial was designed as a prospective, multi-center, phase II study. The primary objectives of this study were to evaluate the safety and efficacy of S-1 and paclitaxel combination therapy for advanced gastric cancer. The secondary objectives were to evaluate the duration of the response, time to disease progression, progression free survival, and overall survival. The sample size was calculated according to the Fleming's single-stage formula. The study was designed to reject a response rate of less than 20% (p0) and provide a statistical power of 90% for assessing an efficacy of 40% for the regimen (p1) ($p1 - p0 = 20\%$) with an alpha error of less than 0.05. Therefore, 56 patients were required with the inclusion of a 10% follow-up loss.

The survival rates were estimated using the Kaplan–Meier method. The confidence intervals (CI) were constructed

around the Kaplan–Meier estimates, using Greenwood's variance formula. The overall survival was measured from the date of the first chemotherapy administration to the date of death or the last follow-up. The progression free survival was measured from the date of first administration of the chemotherapy to the date of disease progression, the date of the last follow-up, the date of receiving another chemotherapy regimen, or death from any cause. The time to disease progression was measured from the date of the first administration of the chemotherapy to the date of disease progression, the date of the last follow-up or the date of receiving another chemotherapy regimen. All patients alive at the time of the analysis were censored at the date of the last follow-up. The duration of response was calculated from the day the response was first noted to the day of disease progression. In addition, we analyzed the time to response; it was calculated from the date of the first chemotherapy administration to the date when the response was first noted.

Results

Patient characteristics

Fifty-six patients were accrued from October 2005 to July 2006. The characteristics of the 56 eligible patients are listed in Table 1. Three patients were not available to evaluate their response; two patients had treatment-unrelated early deaths, i.e., unknown cause at second day and gastric tumor bleeding at eighth day in the course of the first cycle, and one patient stopped treatment early because of a grade 4 hyperbilirubinemia. All other patients were eligible for the toxicity evaluation. The median age was 59 years, ranging from 29 to 74 years; 37 (66%) patients were male. Most of the patients had a good performance status. Forty-three patients had advanced stage disease at diagnosis and 13 (23%) patients had disease relapse after curative surgery. Nine patients received adjuvant chemotherapy. The common metastatic lesions were abdominal lymph nodes (71%), liver (39%) and peritoneum (21%).

Tumor response and survival

Fifty-three patients of the 56 eligible patients were available for evaluation of the response to treatment. There was one (1.9%) complete response (CR), 20 (37.7%) confirmed partial responses (PR), 5 (9.4%) unconfirmed PRs, 21 (39.6%) patients with stable disease (SD), and 6 (11.3%) patients with disease progression (PD) (Table 2). The confirmed objective response rate was 39.6% (95% confidence interval, 26.5–52.8%). The overall objective response rate including the unconfirmed PR was 49.0% (95% confidence interval, 35.6–62.5%).

The median time to response, of 21 patients showing a confirmed response, was by the 12th week (95% confidence interval, 12th–14th week). The median duration of the response in the 21 patients, showing a confirmed response, was 17 weeks (95% confidence interval, 15–27 weeks).

The median follow-up duration was 52 weeks. The median progression free survival of 53 patients was 28 weeks (95% confidence interval, 23–33 weeks) and median time to progression of 53 patients was 29 weeks (95% confidence interval, 26–36 weeks) (Fig. 1). The

Table 1 Patient characteristics

Characteristic	No. of patients (%)
Total no.	56 (100)
Assessable for response	53[a]
Assessable for toxicity	56
Sex	
Male	37 (66)
Female	19 (34)
Age (years)	
Median (range)	59 (29–74)
Performance status by ECOG	
0	17 (30)
1	35 (63)
2	4 (7)
Disease status	
Advanced	43 (77)
Relapsed	13 (23)
Prior therapy	
Surgery	19 (34)
Adjuvant chemotherapy	9 (16)
Radiotherapy	0 (0)

[a] Three patients were not evaluable. There were two treatment-unrelated early deaths and an early termination because of grade 4 hyperbilirubinemia

Table 2 Response assessment

	Overall	
	$N = 53$	(%)
Complete response	1	(1.9)
Partial response (confirmed)	20	(37.7)
Partial response (unconfirmed)	5	(9.4)
Stable disease	21	(39.6)
Progressive disease	6	(11.3)

The confirmed objective response rate was 39.6% (95% confidence interval, 26.5–52.8%) and overall response rate including unconfirmed partial response was 49.0% (95% confidence interval, 35.6–62.5%)

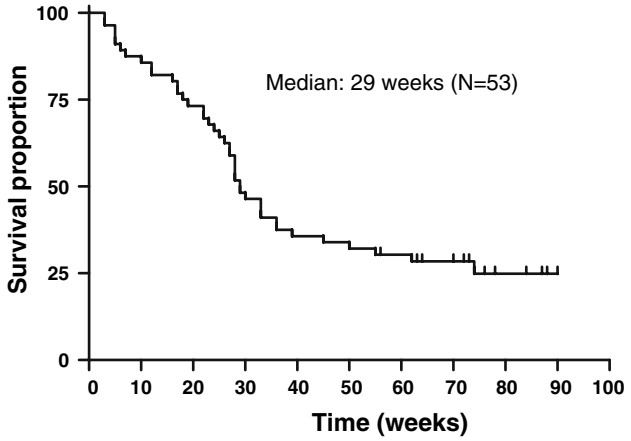

Fig. 1 The time to progression. The median time to progression of 53 patients was 29 weeks (95% confidence interval, 26–36 weeks)

median overall survival of the 56 patients was 51 weeks (95% confidence interval, 38–84 weeks) (Fig. 2).

Treatment delivery

Three hundred and thirty-six cycles were administered with a median number of six cycles (range, 1–18 cycles). The number of cycles with S-1 administered, without any delay or dose reduction, was 267 (79.5%) and for paclitaxel it was 271 (80.7%). Treatment of S-1 was delayed for a median of 7 days in 56 (16.7%) out of 336 cycles, mainly due to neutropenia (32 cycles). Dose reduction or discontinuation of S-1 was necessary in 17 cycles (5.1%), mainly due to diarrhea (5 cycles) and neutropenia (3 cycles). Treatment of S-1 was needed for the delay and dose reduction in 4 cycles (1.2%). Treatment of paclitaxel was delayed for a median of 7 days in 50 (14.9%) out of 336 cycles, mainly due to neutropenia (29 cycles). Dose reduction or discontinuation of paclitaxel was necessary in 18 cycles (5.4%), because of neutropenia (5 cycles) and hepatic dysfunction (3 cycles). Treatment of paclitaxel was needed for the delay and dose reduction in 3 cycles (0.8%). The mean dose-intensity (DI) was 316.9 mg/m^2 per week (93.3% of planned dose) for S-1, and 45.1 mg/m^{2}per week (93.1% of planned dose) for paclitaxel.

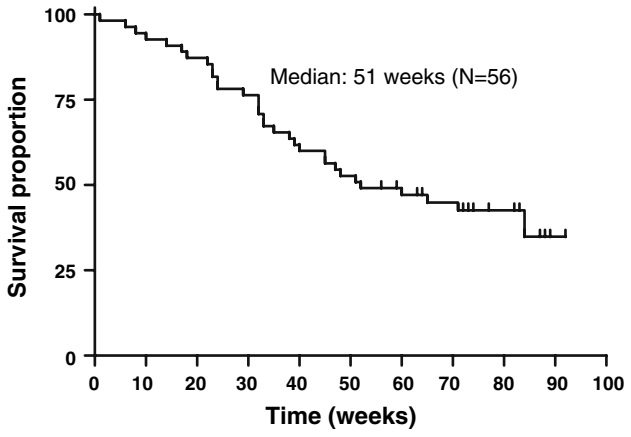

Fig. 2 The overall survival. The median overall survival of all patients was 51 weeks (95% confidence interval, 38–84 weeks) with a median follow-up duration of 52 weeks

Toxicities

Fifty-six patients were included in the toxicity evaluation (Table 3). For hematological toxicity, grade 3/4 neutropenia was present in 20%/13% of all patients. Febrile neutropenia developed in 4 (7%) patients. Grade 3/4 anemia was present in 7%/4% of all patients. For non-hematological toxicity, gastrointestinal toxicities, such as nausea, vomiting, diarrhea, and stomatitis, were very mild. Grade 3 diarrhea and stomatitis developed in 4% of all patients. Grade 3 AST and ALT abnormalities developed in 4% and 2% of all patients, respectively. Grade 4 hyperbilirubinemia developed in one patient. There was no grade 3 or 4 peripheral neuropathy and a grade 2 peripheral neuropathy developed in 4% of patients. Treatment-related deaths occurred in two (4%) patients who had sepsis associated with pneumonia and diarrhea.

Discussion

For patients with advanced gastric cancer, palliative chemotherapy has been associated with improved survival compared to the best supportive care. This benefit has been confirmed by four randomized trials that demonstrated a median survival of 9–11 months and a 1-year-survival rate of 35–40% for patients receiving chemotherapy compared to the median survival of 3–5 months and the 1-year-survival rate of 10% for patients receiving the best supportive care [24]. Although, over the past several decades investigators have tried to identify improved chemotherapeutic agents there has not been any standard regimen identified to date for effective treatment of advanced gastric cancer.

S-1, as a prodrug of 5-FU, has been developed to increase the efficacy and decrease the gastrointestinal toxicities of 5-FU [4, 8]. In several phase II studies, S-1 alone has had modest antitumor activity in advanced gastric cancer [3, 11, 14, 21, 22]. A phase III trial of comparing S-1 with 5-FU was reported that of S-1 showed not inferior to 5-FU in overall survival (S-1 vs. 5-FU; 11.4 month vs. 10.8 month) [19]. Paclitaxel stabilizes microtubules by preventing depolymerization and interferes with the process of cell division. S-1 and paclitaxel have different antitumor mechanisms and both used together for the treatment of

Table 3 Hematologic and non-hematologic toxicities, by patient

	NCI-CTC ($N = 56$)[a], N (%)					
	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 3–4
Hematologic toxicities						
Neutropenia	17 (29)	11 (20)	10 (18)	11 (20)	7 (13)	18 (33)
Anemia	23 (41)	9 (16)	18 (32)	4 (7)	2 (4)	6 (11)
Thrombocytopenia	53 (94)	1 (2)	0 (0)	0 (0)	2 (4)	2 (4)
Febrile neutropenia	52 (93)	0 (0)	0 (0)	4 (7)	0 (0)	4 (7)
Non-hematologic toxicities						
Abdominal pain	36 (64)	18 (32)	2 (4)	0 (0)	0 (0)	0 (0)
Alopecia	34 (60)	7 (13)	14 (25)	1 (2)	0 (0)	1 (2)
Anorexia	25 (44)	18 (32)	11 (20)	2 (4)	0 (0)	2 (4)
ALT	53 (94)	1 (2)	0 (0)	2 (4)	0 (0)	2 (4)
AST	55 (98)	0 (0)	0 (0)	1 (2)	0 (0)	1 (2)
Diarrhea	40 (71)	9 (16)	5 (9)	2 (4)	0 (0)	2 (4)
Dizziness	47 (83)	7 (13)	1 (2)	1 (2)	0 (0)	1 (2)
Fatigue	37 (65)	16 (29)	2 (4)	1 (2)	0 (0)	1 (2)
Infection	50 (89)	5 (9)	0 (0)	0 (0)	1 (2)	1 (2)
Nausea	28 (50)	19 (34)	9 (16)	0 (0)	0 (0)	0 (0)
Peripheral neuropathy	33 (58)	21 (38)	2 (4)	0 (0)	0 (0)	0 (0)
Stomatitis	43 (76)	9 (16)	2 (4)	2 (4)	0 (0)	2 (4)
Vomiting	40 (71)	10 (18)	6 (11)	0 (0)	0 (0)	0 (0)

ALT alanine aminotransferase, *AST* aspartate aminotransferase

[a] Grading according to the National Cancer Institute Common Toxicity Criteria (version 3.0)

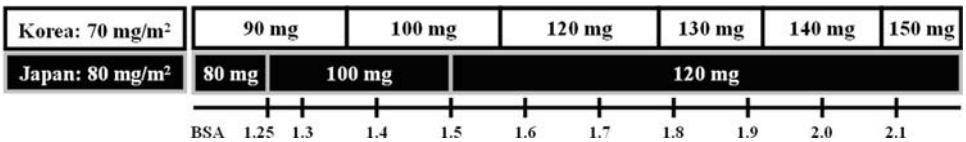

Fig. 3 A comparison of the S-1 dose between Japan and Korea The dose level of S-1 was different between two nations. In Korean trial, the dose was finely adjusted compared with Japanese trials in which S-1 dose by body surface area (BSA) was roughly divided into three levels. The actual dose was nearly same in patients with BSA between 1.4–1.7 m^2 of two nations

gastric cancer may provide improved treatment outcomes for advanced cases.

The most common grade 3/4 hematological toxicities identified were neutropenia and anemia in several Japanese phase II trials of S-1 monotherapy [14, 21, 22]. In the early Japanese phase II trials, the dose of S-1 was 100 mg/day or 150 mg/day and the common toxicities were diarrhea and myelosuppression [22]. In the late phase II trials, the dose of S-1 was 80 mg/m^2 and the incidence of grade 3/4 neutropenia was reduced to less than 20% [21]. The standard dose of S-1 is currently 80 mg/m^2 in Japan. However, the actual administered dose is 80 mg for a body surface area (BSA) <1.25 m^2, 100 mg for BSA 1.25–1.50 m^2, 120 mg for BSA $\geq$ 1.50 m^2 and the maximal limiting dose is 120 mg (Fig. 3).

In a Korean and European phase II trial of S-1 monotherapy, 70 and 80 mg/m^2 doses of S-1 were evaluated [3, 11]. In the Korean study, the common toxicities were anemia and abdominal pain, and the incidence of toxicities tended to increase at a dose of 80 mg/m^2 [3, 11]. In the European study, the common toxicities were diarrhea and hand-foot syndrome rather than hematological toxicity and the toxicities were decreased at the 70 mg/m^2 dose [3]. The differences in the toxicity profiles might be caused by genetic differences between Asian and Caucasian populations. For the Korean and European trials, S-1 at a dose of 70 mg/m^2 was suggested as a safe and effective dose.

The response rates with S-1 monotherapy, in patients with advanced gastric cancer, as the first-line therapy were variable, 44–49% in Japan, 16.1% in Korea and 26.1% in Europe [3, 11, 14, 21, 22]. The response rates reported from the Japanese trials were higher than those from the Korean and European trials were. This difference can be explained by the criteria used for the response assessment. The Japanese trials used the criteria established by the Japanese Research Society for Gastric Cancer, which includes assessment of the primary gastric lesion. However, the RECIST criteria were used for the Korean and European trials.

In several Japanese phase I/II clinical trials of combination S-1 and paclitaxel, S-1 was administered 80 mg/m^2 and

paclitaxel 50–60 mg/m^2, weekly [6, 7, 9, 13, 17, 20, 23]. The most common dose limiting toxicities were grade 3 diarrhea or grade 4 neutropenia. In those studies, the response rate was 45–64% (Table 4). Mochiki et al. [17] have conducted the phase I/II study of paclitaxel 40–70 mg/m^2 weekly with S-1 80 mg/m^2. The dose limiting toxicity of the study was grade 3 diarrhea at paclitaxel 70 mg/m^2 weekly with S-1 80 mg/m^2. The dose schedule of the current study was defined as the combination of S-1 70 mg/m^2 and paclitaxel 70 mg/m^2 weekly on the basis of Korean phase II trial and Japanese clinical trial [11, 17]. In the current trial, the most common grade 3/4 toxicity was also neutropenia, but non-hematological toxicities including adverse gastrointestinal events were mild. The maximum response rate of the current trial was approximately 49%.

The dose of S-1 used for this study was based on the results of the Korean phase II study of S-1 monotherapy [11]. The dose of S-1 was planned to be more accurately adjusted by the body surface area (BSA) compared to the dose used in the Japanese trials. The actual dose of S-1 was nearly the same as the Japanese dose, in patients with a BSA between 1.4–1.7 m^2 (Fig. 3). The gastrointestinal toxicities of the current regimen were tolerable, with less than 5% of cases with grade 3 diarrhea and stomatitis. In the Japanese phase I/II trial, reported by Ueda et al. [23], febrile neutropenia developed in one (17%) patient with 40.0 mg/m^2 per week of paclitaxel and in one (11%) patient with 33.3 mg/m^2 per week of paclitaxel . In the current study, febrile neutropenia developed in four (7%) patients with 46.7 mg/m^2 per week of paclitaxel. Two patients had treatment-related mortality due to sepsis associated with pneumonia and diarrhea. One patient was treated through the fifth cycle of chemotherapy and showed a partial response after the fourth cycle. He had a grade 3 neutropenia during the third cycle of chemotherapy and the dose of paclitaxel was reduced for the subsequent cycle. However, severe pneumonia developed with a grade 4 neutropenia during the fifth cycle of chemotherapy. The other patient had a grade 3 diarrhea after the completion of the second course of chemotherapy; the dose of S-1 for the second cycle was reduced because of the grade 3 diarrhea during the first cycle.

Many clinical trials of S-1 and other chemotherapeutic agents such as cisplatin and docetaxel have been carried out in patients with gastric cancer [2, 15, 25]. Some promising results have been reported with a response rate of 40–70% and a median survival of 11–14 months with these combination regimens. In recent studies of S-1 and cisplatin combination therapy including SIRITS trial, although promising results were reported, grade 3–4 gastrointestinal toxicities significantly occurred [2, 15]. In the current study, S-1 and weekly paclitaxel combination therapy had very tolerable gastrointestinal toxicities as well as active antitumor effects. Grade 3–4 anorexia, diarrhea and stomatitis

Table 4 Clinical trials of S-1 in combination with paclitaxel for advanced gastric cancer

Author [reference]	Phase	No. of patients	Dose schedule			Response rate	Remarks	
			S-1 (S)	Paclitaxel (T)	Interval (weeks)		Dose limiting toxicity	Recommended dose
Fujiwara et al. [7]	I	9	40 mg/m^2 po bid, d1-14	50–60 mg/m^2 iv d1, 8, 15	Q 4	NA	G3 Diarrhea G4 Neutropenia	T 50 d1, 8, 15 + S 40 bid 14 days
Hokita et al. [9]	I	15	40 mg/m^2 po bid, d1-14	100–130 mg/m^2 iv d1, 15	Q 4	53%	G3 Diarrhea G4 Neutropenia	T 120 d1, 15 + S 40 bid 14 days
Ueda et al. [23]	I	23	40 mg/m^2 po bid, d1-14	50–60 mg/m^2 iv d1, 8, 15	Q 4	51%	G4 Neutropenia G3 Diarrhea	T 50 d1, 8, 15 + S 40 bid 14 days
Fujitani et al. [6]	I	12	40 mg/m^2 po bid, d1-14	50–80 mg/m^2 iv d1, 8	Q 3	62.5%	G3 Anorexia	T 50 d1, 8 + S 40 bid 14 days
Mochiki et al. [17]	I/II	17/24	40 mg/m^2 po bid, d1-14	40–70 mg/m^2 iv d1, 8, 15	Q 4	54.1%	G3 Anorexia G3 diarrhea	T 60 d1, 8, 15 + S 40 bid 14 days
Kawabata et al. [13]	I/II	18	40 mg/m^2 po bid, d1-14	50–60 mg/m^2 iv d1, 8, 15	Q 4	64.7%	G3 Neutropenia/Anemia G4 Diarrhea/Stomatitis	T 50 d1, 8, 15 + S 40 bid 14 days
Nakajo et al. [20]	II	39	40 mg/m^2 po bid, d1-14	120 mg/m^2 iv d1, 15	Q 4	43.6%	G3/4 Neutropenia (38%) G3/4 Anorexia (5%), G3/4 Diarrhea (5%)	
Lee et al. [current study]	II	56	35 mg/m^2 po bid, d1-14	70 mg/m^2 iv d1, 8	Q 3	39.6%	G3/4 Neutropenia (33%), FN (7%) G3 Stomatitis (4%), G3 Diarrhea (4%), TRD (2)	

All of phase I or I/II clinical trials were conducted in Japan except this current study

NA not available, *FN* febrile neutropenia, *TRD* treatment-related death (the number of patients)

developed only in less than 5% and no grade 3–4 nausea and vomiting was observed. Future studies are needed to determine what combination with S-1 would be better on the basis of treatment efficacy and toxicity.

In conclusion, the results of this phase II study demonstrated that the combination of S-1 and paclitaxel was safe and effective with a favorable toxicity profile. This combination is a novel option for initial treatment of patients with advanced or metastatic gastric cancer. Further investigation with comparative trials is needed for confirmation.

Acknowledgments This study was partially supported by a grant of the Korea Health 21 R&D Project, Ministry of Health & Welfare, Republic of Korea (0412-CR01-0704-0001)

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