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ORIGINAL ARTICLE

Phase II study of S-1 monotherapy in paclitaxel- and cisplatin-refractory gastric cancer

Sung-Ji Lee · Sang-Hee Cho · Ju-Young Yoon · Jun-Eul Hwang · Woo-Kyun Bae · Hyun-Jeong Shim · Ik-Joo Chung

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Abstract
Purpose S-1 is a fourth-generation oral fluoropyrimidine that was developed to mimic the effects achieved with protracted continuous infusion of 5-fluorouracil (5-FU). This phase II study evaluated the efficacy and safety of S-1 salvage chemotherapy in patients with paclitaxel- and cisplatin-refractory gastric cancer. The primary end point was progression-free survival; secondary end points were overall survival, safety, and clinical benefit.
Methods Patients were eligible for the study if they had histologically documented gastric adenocarcinoma previously treated with paclitaxel and cisplatin, age ≥ 18 years, Eastern Clinical Oncology Group performance status ≤2, adequate organ function, and no evidence of gastrointestinal obstruction or passage disturbance. Patients were treated with a dose of S-1 based on body surface area (BSA) as follows: BSA < 1.25 m^2, 80 mg/day; 1.25 ≤ BSA < 1.5 m^2, 100 mg/day; BSA ≥ 1.5 m^2, 120 mg/day. The total dose was divided in two and administered twice daily for 4 weeks followed by a 2-week rest period.
Results Of the 53 patients enrolled in this study, 49 were evaluable. A total of 190 chemotherapy cycles were administered, and the median number of cycles was 2. Five patients (9.4%) had a partial response, and 18 (34%) had stable disease. Median progression-free survival and overall survival were 4.9 and 10.4 months, respectively. Grade 3/4 hematological toxicities included neutropenia in six patients (11%) but no cases of febrile neutropenia were found. Most of the non-hematological toxicities were diarrhea, asthenia, and mucositis, but none reached grade 3 or grade 4 in severity. Improvement of pain was observed in 17 patients (32.1%).
Conclusions S-1 monotherapy provides active and safe salvage chemotherapy for patients with advanced gastric cancer who have been previously treated with paclitaxel and cisplatin.

Keywords S-1 · Gastric cancer · Salvage therapy

S.-J. Lee · S.-H. Cho · J.-Y. Yoon · J.-E. Hwang · W.-K. Bae · H.-J. Shim · I.-J. Chung
Division of Hemato-Oncology, Department of Internal Medicine, Center for Biomedical Human Resources, Chonnam National University Medical School, Kwangju, Korea

I.-J. Chung
The Brain Korea 21 Project,
Center for Biomedical Human Resources,
Chonnam National University Medical School, Kwangju, Korea

I.-J. Chung (✉)
Department of Internal Medicine,
Chonnam National University Hwasun Hospital,
Jeollanamdo 519-809, Korea
e-mail: shcho@chonnam.ac.kr

Introduction

Gastric cancer is a leading cause of cancer deaths worldwide, ranking second after lung cancer in global cancer mortality [1]. According to a report by the Korean Cancer Registry, gastric cancer is not only the most common cancer in Korea, but also the second leading cause of cancer deaths in the country [2]. Although improvements in early diagnosis have increased the number of curative resections (the main curative treatment), most of the patients present either with locally advanced unresectable disease or have a distant metastasis when first diagnosed [3].

During the past decade, new chemotherapeutic agents, including taxanes (paclitaxel, docetaxel), irinotecan, oxaliplatin, and oral 5-fluouracil (5-FU), have been intensively

investigated throughout the world. Several clinical trials examining these new drugs showed prolonged survival compared to the results achieved with the older chemotherapeutic agents such as cisplatin, 5-FU, doxurubicin, and mitomycin C [4–7]. In a randomized phase III trial, the combination of docetaxel, cisplatin, and 5-FU (DCF) showed promising results when compared with CF [7]. Also, several phase II studies with paclitaxel have shown modest antitumor activity, manageable toxicities [8–10] and comparable efficacy to docetaxel without diminution in gastric cancer [11].

Thus, taxane and cisplatin, with or without 5-FU, have been commonly used as an effective regimen in the treatment of advanced gastric cancer. A major limitation of this approach, however, is that a complete response is rare, and the time to progression is not satisfactory after only a single regimen. An additional consideration is that some patients who are refractory to first-line chemotherapy tolerate relatively well to subsequent chemotherapy, emphasizing the need to more closely evaluate second- and even third-line salvage chemotherapy. Also, advanced gastric cancer is not a curable disease, and the main aim of treatment is palliation. Thus, not only the response rate but also the clinical benefits and patient tolerance are important in assessing the efficacy of second-line chemotherapy.

The fourth-generation oral fluoropyrimidine S-1 was developed to mimic protracted continuous infusion of 5-FU. In phase II trials conducted in Japan, S-1 monotherapy demonstrated excellent activity against gastric cancer, with a mild toxicity profile [12, 13].

Several studies have examined S-1 monotherapy as salvage chemotherapy [14, 15]; however, they included patients whose prior chemotherapy consisted of heterogeneous regimens, with S-1 administered as second- or third-line therapy. The present study was conducted to evaluate the efficacy and tolerability of S-1 as a second-line chemotherapy agent in patients with advanced gastric cancer who were previously treated with paclitaxel and cisplatin.

Materials and methods

Patients

Patients were eligible if they had histologically documented gastric adenocarcioma that progressed during or within 6 months after discontinuation of prior paclitaxel- and cisplatin-based chemotherapy; age $\geq$ 18; Eastern Clinical Oncology Group (ECOG) performance status $\leq$2; adequate bone marrow and organ function (absolute neutrophil count $\geq$ 1,500/μL, platelets $\geq$ 100,000/μL, serum bilirubin $<$ 2.0 mg/dL, and serum transaminase levels less than twice the upper normal limit), serum creatinine $<$ 1.5 mg/dL; and no past or concurrent history of malignancy other than stomach cancer. Patients with significant gastrointestinal obstruction or uncontrolled significant comorbid conditions were excluded from the study.

Written informed consent was obtained from all patients and the study was approved by the Chonnam National University Hwasun Hospital institutional review board.

Treatment schedule and dose modification

The initial doses of S-1 were assigned on the basis of body surface area (BSA). Accordingly, the patients received one of the following oral doses divided into two and administered daily after meals: 80 mg for patients with BSA $<$ 1.25 m^2, 100 mg for BSA $\geq$ 1.25 and $<$ 1.50 m^2, and 120 mg for BSA $\geq$ 1.50 m^2. One therapy cycle comprised the administration of single-agent S-1 for 28 consecutive days followed by 14 days of no treatment. This schedule was repeated every 6 weeks until the occurrence of disease progression, unacceptable toxicities, or patient refusal. In the absence of evidence of disease progression, patients were allowed to continue S-1 treatment. A dose reduction of 20 mg/day was recommended if $\geq$grade 3 hematological or non-hematological toxicity was shown in the previous cycle; dose re-escalation was not allowed. Patients who required more than 4 weeks of rest for recovery from any toxicity other than nausea, vomiting, or anemia, or who required a dose reduction >20 mg/day, were withdrawn from the study.

Evaluation of response and toxicity

Baseline evaluations of each patient consisted of a complete medical history, including physical examination, complete blood count, serum chemistry, urine analysis, and electrocardiography. Computed tomography scans of measurable or non-measurable lesions were carried out within 4 weeks before the start of treatment and were repeated after every two cycles. Tumor responses were classified according to the guidelines of the Response Evaluation Criteria in Solid Tumors (RECIST) [16]. Toxicity was evaluated before each treatment cycle according to National Cancer Institute Common Toxicity Criteria, version 3.0. Clinical benefit was assessed by pain intensity which determined at baseline and then checked again before every chemotherapy cycle. Pain intensity was evaluated and graded based on analgesic use: grade 0, pain absent; grade 1, pain controlled with occasional administration of non-opioid analgesics; grade 2, controlled with regular administration of non-opioid analgesics; grade 3, controlled with occasional administration of opioid analgesics; grade 4, controlled with regular administration of opioid analgesics; grade 5, controlled with continuous infusion

of opioid analgesics. Clinical benefit was defined as an improvement in pain intensity, and pain improvement as a decrease in pain of one grade or more from baseline for at least 4 weeks duration.

Study design and statistics

The primary aim of the study was progression-free survival (PFS), with secondary end points of improved OS, decreased toxicity, and clinical benefit. The hypothesis was that the S-1 regimen would improve 1-year survival compared with the historical control. The design of this study resulted in an 85% power to show an improvement in 1-year survival of 35% from a historical control of 15% [14, 17, 18], with a 5% type I error. According to Minimax phase II design, a sample size of 46 patients was required. Thus, the 53 patients enrolled in the study allowed for the expected 15% drop-out rate. All enrolled patients were included in the intention-to-treat analysis. PFS was measured from the first day of S-1 treatment until disease progression was noted; OS was measured from the first day of S-1 treatment until death from any cause. Kaplan–Meier estimates were used in the analysis of all time–event variables. The difference in response compared to previous therapy was evaluated by Fisher's exact test and Chi-square analysis. Statistical significance was established as $P < 0.05$. Exact 95% confidence interval (CI) is provided for proportions. Statistical analyses were carried out with SPSS for Windows (SPSS Inc., Chicago, IL, USA), version 16.0.

Results

Patient characteristics

A total of 53 patients were enrolled between February 2005 and January 2008. Of the 53 patients, 49 could be evaluated for treatment response. The remaining four patients left the study at an early phase: two were lost to follow-up after one cycle of treatment, the general condition of one was too poor to allow treatment to continue, and one refused further treatment. Characteristics of patients are listed in Table 1.

Table 1 Baseline characteristics of patients

	Number patient	Percentage (%)
Total number	53	100
Evaluable	49	92.5
Age (years) (median, range)	58 (28–74)	
Gender		
Male	40	75.5
Female	13	24.5
ECOG performance status		
0	4	7.5
1	24	45.3
2	25	47.2
Histology		
Well/moderately differentiated	16	30.2
Poorly differentiated or signet ring cell type	26	49
Unknown	11	20.8
Prior gastrectomy		
Yes	29	54.7
No	24	45.3
Metastatic site		
Distant abdominal lymph nodes	18	27.7
Liver	16	24.6
Peritoneum	12	18.5
Ovary	4	6.2
Cervical LN	3	4.6
Bone	3	4.6
Lung/pleura	2	3.1
Adrenal gland	1	1.5
Others	6	9.2
Number of metastatic sites		
1	37	62.3
2	14	26.4
3	2	3.8
Disease status		
Initially metastatic	38	71.7
Recurrent	15	28.3
Prior chemotherapy		
Paclitaxel/Cisplatin (PC)	23	43.4
Paclitaxel/Cisplatin/5-FU (PCF)	30	56.6

ECOG Eastern Clinical Oncology Group, *LN* lymph node

Drug delivery

A total of 190 treatment cycles were delivered, with a median number of 2 cycles per patient (range 1–12). One patient received 12 cycles of chemotherapy; 3 patients (5.7%) received 10 cycles. Treatment was delayed in 4 cycles (2.1%), and dose reduction from the initial dose was necessary in 5 cycles (2.6%) of four patients (7.5%). The reasons for the dose reduction were severe asthenia in two patients, with grade 3 diarrhea and thrombocytopenia, respectively. The median relative dose intensity of S-1 for the entire study population was 97.6%, indicating that patient compliance with S-1 chemotherapy was good.

Efficacy

A total of 49 patients were evaluable for response. Five patients achieved PR, resulting in an overall response rate

Table 2 Evaluation of tumor response

	Patients (*n*)	CR (*n*, %)	PR (*n*, %)	SD (*n*, %)	PD (*n*, %)	NE (*n*, %)	RR (%)	DCR (%)
Overall (95% CI)	53	–	5 (9.4)	18 (34)	26 (49.1)	4 (7.5)	9.4 (1.5–17.3)	43.4 (30.1–56.7)
Measurable	40	–	5 (12.5)	12 (30)	20 (50)	3 (7.5)	12	42.5
Non-measurable	13	–	–	6 (46.2)	6 (46.2)	1 (7.7)	0	46.2

CI confidence interval, *CR* complete response, *DCR* disease control rate, *NE* not evaluable, *PD* progressive disease, *PR* partial response, *RR* response rate, *SD* stable disease

of 9.4% (95% CI, 1.5–17.3%) in the intention-to-treat analysis. Another 18 patients had stable disease, making the overall disease control rate 43.4% (95% CI, 30.1–56.7%; Table 2). The overall response and disease control rates were evaluated separately from the previous first-line chemotherapy. Four of the 23 patients in the PC group (17.4%) and 1 of the 30 in the PCF group (3.3%) responded to second-line chemotherapy ($P = 0.15$), with overall disease control rates of 56.5% (95% CI, 36.2–76.8%) and 33.3% (95% CI, 16.4–50.2%), respectively ($P = 0.069$; Table 3).

Improvement of pain was observed in 17 patients (32.1%); 2 in PR (33.1%), 8 in SD (47.1%), and 7 in PD (26.9%). Two patients improved the pain intensity by more than two grade and the others improved 1 grade. However, there were no statistical difference according to each response groups ($P = 0.409$). The median time to clinical benefit was 6 weeks (95% CI, 4.7–7.3), and the median duration of clinical benefit was 12 weeks (95% CI, 7.4–16.6).

With the median follow-up period of 17.9 months (range 5.2–39.7), the median PFS and OS were 4.9 months (95% CI, 2.4–7.4) and 10.4 months (95% CI, 7.4–14.4; Fig. 1) respectively for intention-to-treat population. 1-year OS was 45.3% (95% CI, 24-53). A comparison between the outcomes of previous chemotherapy (PC group vs. PCF group) and those obtained with the second-line S-1 chemotherapy of this study showed that the median PFS was 5.4 months (95% CI, 5.0–5.8) versus 2.8 months (95% CI, 2.1–3.5), and the median OS 12.2 months (95% CI, 8.3–16.1) versus 9.6 months (95% CI, 4.6–14.6). However, these differences were not statistically significant ($P = 0.663$ and $P = 0.647$, respectively; Fig. 2). Of the 53 patients, 4 (7.5%) were alive at a median follow-up of 24.5 months. Median survival from the date of diagnosis of recurrent or metastatic cancer was 20 months (95% CI, 16.5–23.5).

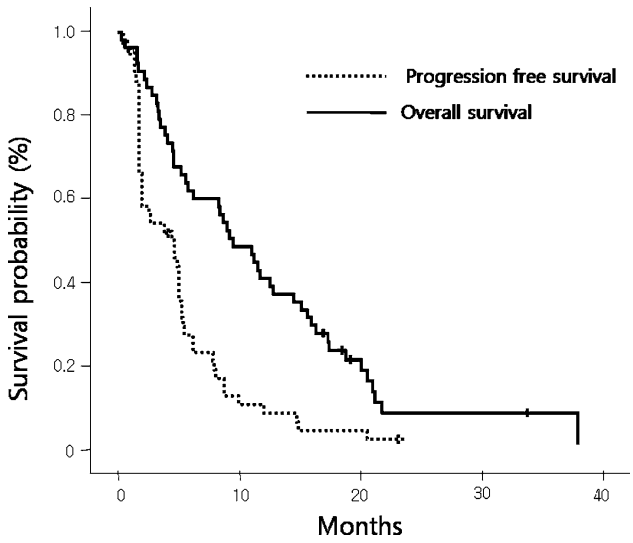

Fig. 1 Progression-free survival and overall survival curves. Progression-free survival and overall survival in the 53 patients with advanced gastric cancer treated with S-1 monotherapy after the failure of paclitaxel and cisplatin chemotherapy

Table 3 Tumor response according to previous chemotherapy

	PC group	PCF group	*P* value
Number of enrolled patients	23	30	
CR (*n*, %)	–	–	
PR (*n*, %)	4 (17.4)	1 (3.3)	
SD (*n*, %)	9 (39.1)	9 (30)	
PD (*n*, %)	8 (34.8)	18 (60)	
NE (*n*, %)	2 (8.7)	2 (6.7)	
RR (95% CI)	17.4 (1.9–32.9)	3.3 (0–9.7)	0.15
DCR (95% CI)	56.5 (36.2–76.8)	33.3 (16.4–50.2)	0.069

CI confidence interval, *CR* complete response, *DCR* disease control rate, *NE* not evaluable, *PD* progressive disease, *PR* partial response, *RR* response rate, *SD* stable disease, *PC* Paclitaxel and Cisplatin, *PCF* Paclitaxel and Cisplatin, 5-FU

Toxicity

Table 4 lists the patient distribution of the highest observed toxicity grade and the incidence of adverse events per chemotherapy cycle for each form of toxicity. The most common hematological toxicity was mild or moderate anemia. Neutropenia of grade 3 or worse occurred in six patients (11%), but none of them showed febrile neutropenia. Neutropenia was successfully treated without the administration of G-CSF. There were no episodes of thrombocytopenia

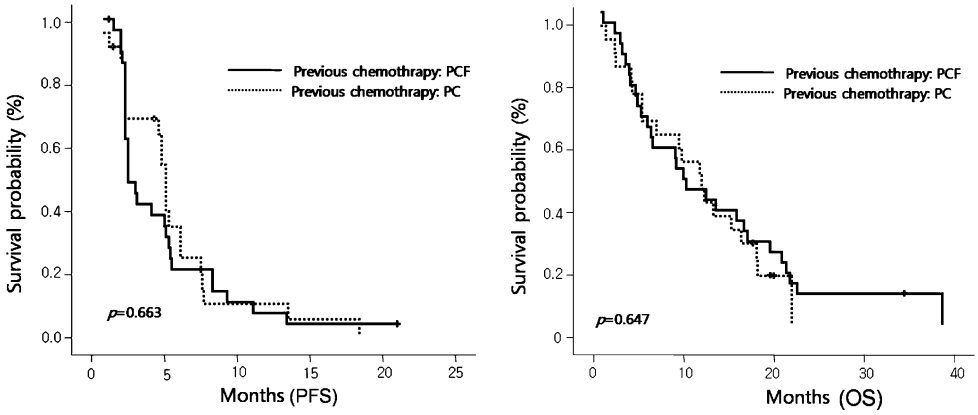

Fig. 2 Progression-free survival and overall survival curves according to previous chemotherapy. Progression-free survival and overall survival after S-1 salvage treatment according to previous chemotherapy (*PC* Paclitaxel and Cisplatin, *PCF* Paclitaxel and Cisplatin, 5-FU)

Table 4 Toxicities

Toxicity	Number of patients (%, $n = 53$)				
	0	1	2	3	4
Hemotologic					
Leukopenia	34 (64)	15 (28)	3 (6)	1 (2)	0
Neutropenia	28 (53)	14 (26)	5 (9)	4 (8)	2 (4)
Anemia	11 (21)	19 (36)	21 (40)	0	2 (4)
Thrombocytopenia	45 (85)	5 (9)	3 (6)	0	0
Non-hematological					
Asthenia	50 (94)	0	2 (4)	1 (2)	0
Anorexia	49 (92)	3 (6)	1 (2)	0	0
Mucositis	47 (89)	4 (8)	2 (4)	0	0
Diarrhea	47 (89)	5 (9)	0	1 (2)	0
Nausea	52 (98)	1 (2)	0	0	0
Peripheral neuropathy	39 (74)	9 (17)	5 (9)	0	0

of grade 3 or worse. Non-hematological toxicities consisted of diarrhea (11%), mucositis (11%), anorexia (8%), and asthenia (6%). Peripheral neuropathy developed in 14 patients (26%) but was mild and probably due to previous paclitaxel and cisplatin chemotherapy. The few clinically relevant non-hematological adverse events of grade 3 or worse were limited to diarrhea (1 patient, 2%) and asthenia (1 patient, 2%). There were no treatment-related deaths directly attributable to S-1 chemotherapy.

Discussion

Gastric cancer is the second leading cause of cancer death worldwide [19]. Chemotherapy is associated with a significant survival advantage in gastric cancer patients and an improved quality of life compared with the best supportive care [20–22]. However, most of the patients receiving first-line chemotherapy eventually develop progressive disease, and there is no established second-line regimen. There has not been yet proven of the role about second line chemotherapy, some randomized controlled trial data supporting a benefit of second line chemotherapy has been reported. Some studies have suggested that patients who respond to second-line chemotherapy survive longer than non-responders and that symptomatic benefit is obtained from second-line therapy [23, 24], whereas other studies have failed to demonstrate the effectiveness of second-line treatment [25, 26]. These discrepancies concerning the benefits of second-line chemotherapy in gastric cancer may be attributable to patients' variable responses to first-line chemotherapy and to the chemotherapeutics used previously. However, a randomized clinical trial to verify the efficacy of second-line chemotherapy is difficult to perform in the clinical setting, as it must be meticulously designed and controlled.

Of the currently available second-line regimens, those based on docetaxel have shown modest activity [27], but the value of these regimens as palliative treatment is reduced because the regimens are inevitably accompanied by substantial toxicities. In a recent phase II study, docetaxel (75 mg/m^2) was given every 3 weeks as second-line chemotherapy to patients who did not respond adequately to first-line fluoropyrimidine and platinum [28]. The median time to disease progression was 2.5 months (95% CI, 2.3–2.7), and the median OS 8.3 months (95% CI, 6.7–9.8). However, grade 3/4 neutropenia and febrile neutropenia occurred in 18.4% of the patients, and the incidence of non-hematological toxicity of grade 3 or worse was as follows: asthenia 32.7%, diarrhea 10.2%, and peripheral sensory neuropathy 8.2%. Also, Sym et al. [29] assessed the combination of biweekly irinotecan and 5-FU, with leucovorin as salvage chemotherapy, in patients previously treated with fluoropyrimidine, platinum, and taxane. The results showed that this regimen was associated with reasonable toxicity, but the median time to progression was 2.2 months (95% CI, 1.9–2.6) and the median overall survival 6.2 months (95% CI, 5.6–6.9).

S-1 is a fourth-generation oral fluoropyrimidine based on the combination of tegafur with two biochemical modulators: 5-chloro-2,4-dihydroxypyridine and potassium oxonate.

The drug mimics protracted continuous infusion of 5-FU but with enhanced efficacy, safety, and activity in the treatment of advanced gastric cancer [30, 31].

In early and late phase II trials in Japan, S-1 achieved promising efficacies of 54 and 45%, respectively [12, 13, 32, 33]. A Japanese nationwide post-marketing survey of S-1 for safety monitoring, consisting of more than 3,000 evaluable patients, confirmed that the safety profile of S-1 was similar to that demonstrated in two prior phase II trials [34]. In addition, S-1 was reported to be potentially effective at prolonging the survival of patients with gastric cancer involving peritoneal dissemination [35–37]. An experimental study to assess the effect of S-1 on peritoneal dissemination of gastric cancer confirmed that a high concentration of 5-FU is maintained in intraperitoneal tumors after S-1 administration and that survival time is prolonged, without any decrease in oral food intake or body weight [38]. These findings point to the benefit of S-1 for gastric cancer patients with carcinomatosis peritonei, which is a frequent and difficult problem in those with advanced disease.

Regarding the clinical benefits of S-1 therapy, Osugi et al. reported that the survival of an S-1-treated group was longer than that of a control group treated mostly with other oral fluoropyrimidines or intravenous FP. Median survival was 257 versus 118 days, although patients were not randomized in this study [37].

A recent study examined S-1 as salvage chemotherapy in gastric cancer patients with poor performance status. It showed an overall response rate of 12% (95% CI, 3–21) and stable disease in 35% of patients, resulting in a disease control rate of 47% (95% CI, 32–60). However, this study comprised patients with prior heterogeneous chemotherapy regimens, with S-1 administered as either second- or third-line therapy [14].

Ours is the first phase II study of S-1 treatment as salvage chemotherapy in gastric cancer patients pretreated with paclitaxel and cisplatin. The results show that second-line S-1 treatment has several benefits, including convenience, as patients were not frequently required to come to the hospital; greater tolerability than that achieved with intravenous chemotherapeutics; and the avoidance of cross-resistance and cumulative toxicities such as peripheral neuropathy. Median PFS and OS were 4.9 and 10.4 months, respectively, and these results were comparable to other studies [14, 28, 39–43]. Together with the OS time achieved with the first line of chemotherapy, the median OS was shown as 20 months (95% CI, 16.5–23.5). In a comparison of PFS and OS values in our study with those reported in previous treatment regimens (PC vs. PCF), neither PFS nor OS was affected by previous exposure to 5-FU. Therefore, the S-1 regimen is also an acceptable option in patients previously treated with 5-FU. Most of the toxicities were of mild intensity, with toxicities of grade 3 or worse reported in 10 (18.9%) patients only. The most common hematological toxicity was mild or moderate anemia. Neutropenia of grade 3 or worse occurred in six patients (11%), but no patient experienced febrile neutropenia. Common non-hematological toxicities were mucositis (11%), diarrhea (11%), anorexia (8%), and asthenia (6%). There were no treatment-related deaths directly attributable to S-1 chemotherapy. The toxicity profile of S-1, as evaluated in this study, was more favorable than reported in other, established studies of second-line chemotherapy. Although more than half of the patients had an ECOG PS of 2, compliance was relatively good.

Only a few studies have examined the symptomatic benefits obtained from second-line chemotherapy in advanced gastric cancer patients [23, 44]. Although clinical benefit, determined by assessing pain intensity, was observed in just 17 patients (32.1%), S-1 monotherapy in the second-line treatment setting was beneficial not only with respect to tumor regression but also to improvement of quality of life.

In conclusion, S-1 monotherapy is an active and safe salvage chemotherapy for patients with advanced gastric cancer treated with paclitaxel- and cisplatin-based first-line chemotherapy. The convenience and efficacy of S-1 is expected not only to improve the survival of patients with refractory gastric cancer but also to enhance their quality of life.

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