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ORIGINAL ARTICLE

Three-week combination chemotherapy with S-1 and cisplatin as first-line treatment in patients with advanced gastric cancer: a retrospective study with 159 patients

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Abstract
Background Doses and schedules of the combination of S-1 and cisplatin for the treatment of advanced gastric cancer (AGC) have not been standardized. We therefore evaluated the efficacy and feasibility of a 3-week schedule of S-1 and cisplatin in patients with AGC, as well as assessing factors prognostic of patient outcomes.
Methods A total of 159 patients with AGC were treated with S-1 (40 mg/m^2 bid on days 1–14) and cisplatin (60 mg/m^2 IV on day 1) between January 2004 and December 2008.
Results Median follow-up duration was 20.0 months (range, 11.4–48.5 months), during which time 129 patients (81.1%) died. Patients received a median 6 cycles of chemotherapy (range, 1–19 cycles). Among the 59 patients with measurable disease, 1 achieved a complete response (1.7%) and 24 (40.7%) had partial responses, giving an overall response rate of 42.4% (95% CI, 23.0–61.8%). The median progression-free survival (PFS) was 5.8 months (95% CI, 4.8–6.9 months), and the median overall survival (OS) was 11.3 months (95% CI, 9.6–13.0 months). Multivariate analysis showed that initial metastasis, bone metastasis, and liver metastasis were independent prognostic factors for reduced PFS, whereas poor performance status, initial metastasis, and bone metastasis were prognostic for reduced OS. Application of a previous prognostic model showed that observed PFS and OS survival curves for patients in various risk groups differed significantly ($P < 0.001$ each).
Conclusions A 3-week regimen of S-1 plus cisplatin was active and well tolerated as first-line treatment in patients with AGC. Disease status and bone metastasis were the most important prognostic factors.

Keywords Stomach neoplasms · S-1 · Cisplatin · Chemotherapy · Prognosis

Introduction

Gastric cancer is the second leading cause of cancer death worldwide, with patients who are diagnosed at an advanced stage having a median survival time of less than 1 year [1]. Several randomized clinical trials showed that, compared with best supportive care alone, chemotherapy plus best supportive care improved median patient survival, from 4–6 months to 9–11 months, and the quality of life in patients with advanced gastric cancer (AGC) [2, 3]. Moreover, a large meta-analysis showed that first-line treatment with combination chemotherapy resulted in a survival benefit compared with monotherapy [hazard ratio (HR), 0.82; 95% confidence interval (CI), 0.74–0.90] [4]. Most chemotherapy regimens for AGC are based on a fluoropyrimidine-plus-platinum backbone, with or without an anthracycline [5].

S-1 is a compound drug consisting of the oral fluoropyrimidine prodrug, tegafur; the dihydropyrimidine dehydrogenase (DPD) inhibitor, 5-chloro-2,4-dihydroxypyridine (CDHP, gimeracil); and the orotate phosphoribosyl transferase (OPRT) inhibitor, potassium oxonate (OXO, oteracil) [6]. Several studies in Japan showed that S-1 monotherapy or S-1 plus cisplatin had antitumor activity against AGC [7, 8].

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Two recent phase III trials in Japan showed that S-1 monotherapy was not inferior to the continuous infusion of 5-fluorouracil (5-FU) and that S-1 plus cisplatin was superior to S-1 monotherapy [9, 10]. Based on these results, the combination of S-1 with cisplatin became the new standard treatment for AGC in Japan.

Because a standardized schedule of S-1 and cisplatin in combination has not been established, several doses and schedules were evaluated [8, 11, 12]. Although a 5-week schedule (3 weeks on and 2 weeks off) has been used primarily in Japan [10], the dose of cisplatin was relatively lower in this schedule than in other phase III studies [13, 14]. A phase I/II study of S-1, consisting of 2 weeks of treatment followed by 1 week of rest with a fixed cisplatin dosage, as first-line chemotherapy for AGC showed encouraging results [15]. The recommended doses of S-1 and cisplatin were determined as 80 mg/m^2/day and 60 mg/m^2, respectively, and this 3-week schedule has been utilized in clinical practice in Korea. We have therefore evaluated the efficacy and safety of this 3-week schedule of S-1 plus cisplatin in patients with AGC. In addition, we analyzed factors prognostic of patient outcome and evaluated whether our previously reported prognostic model was applicable to these patients [16].

Materials and methods

Patients

We retrospectively reviewed the Asan Medical Center Stomach Cancer Registry to identify all patients who had been treated for AGC at the Asan Medical Center (Seoul, Korea) between January 2004 and December 2008. We included patients 18 years of age and older with histologically confirmed recurrent or metastatic adenocarcinoma of the stomach; with adequate bone marrow, renal, and hepatic function; who received at least one cycle of chemotherapy; and who had no history of other malignancies. A total of 1,925 patients with recurrent or metastatic gastric cancer received first-line chemotherapy, and 159 patients (8.3%) were identified to receive this 3-week schedule of S-1 with cisplatin chemotherapy as first-line treatment of AGC. The study protocol was approved by the Institutional Review Board of the Asan Medical Center.

Patients were grouped into three categories according to disease status at the time of chemotherapy initiation: those with initially metastatic disease (i.e., presenting with metastatic disease), those with recurrent disease (i.e., presenting with tumor recurrence after curative gastrectomy), and those with resected metastatic disease (i.e., presenting with residual disease after gastrectomy or with distant metastases who had gastrectomies) [17].

In addition, patients were grouped by our prognostic model for recurrent or metastatic AGC [16]. This model used a scoring system consisting of eight prognostic factors [Eastern Cooperative Oncology Group (ECOG) performance score (PS) $\geq$2 (2 points); no gastrectomy, peritoneal metastasis, or bone metastasis (2 points); and lung metastasis, alkaline phosphatase >120 IU/l, albumin <3.3 g/dl, or total bilirubin >1.2 mg/dl], with patients divided into good (0–1 points), moderate (2–3 points), and poor ($\geq$4 points) risk groups.

Treatment schedule

Before chemotherapy, all patients were evaluated with a complete history and physical examination, a complete blood count, serum chemistry evaluations (liver and renal function tests and electrolytes), ECG, chest radiograph, computed tomography (CT) scanning of the abdomen and pelvis, and, if indicated, CT scans of the chest and a bone scan. All patients were treated with 40 mg/m^2 S-1, administered orally twice daily on days 1–14; and 60 mg/m^2 cisplatin, administered intravenously over 60 min on day 1. Treatment courses were repeated every 3 weeks. Treatment was continued until disease progression or unacceptable toxicity occurred, or if the patient chose to discontinue treatment.

Dose modification for adverse events

S-1 and/or cisplatin doses were modified for hematological, gastrointestinal, or neurological toxicities, based on the most severe grade of toxicity occurring during the previous cycle. Patients were assessed before the beginning of each cycle, in accordance with the National Cancer Institute-Common Toxicity Criteria (NCI-CTC) version 3.0 (http://www.cancer.gov). When a grade 3 or 4 hematological toxicity occurred, except for anemia, or a grade 2 or 3 nonhematological toxicity occurred during a 2-week period of S-1 administration, S-1 was interrupted until the hematological toxicity subsided to grade 2 or the nonhematological toxicity subsided to grade 1, with S-1 subsequently resumed at the same dose or reduced by 25%, respectively. If there was a second occurrence of grade 4 hematological or grade 3 nonhematological toxicity after dose reduction, S-1 treatment was interrupted temporarily, and was resumed at 50% of the original dose. The subsequent chemotherapy cycle was started when absolute neutrophil count (ANC), platelet count, and nonhematological toxicities recovered. Cisplatin dose was modified according to renal toxicity and peripheral neuropathy. If serum creatinine before each cycle was <1.5 mg/dl, full-dose cisplatin was given; if serum creatinine was 1.5–2.5 mg/dl, 50% cisplatin was administered; if serum

creatinine was >2.5 mg/dl, chemotherapy was discontinued. If a grade 2 neurotoxicity occurred, cisplatin treatment was delayed up to 3 weeks until neuropathy recovered to grade 1 or better. If neuropathy persisted for more than 3 weeks or a grade 3 or higher neuropathy occurred, chemotherapy was discontinued.

Response evaluation

Physical examination, chest X-rays, complete blood counts, and biochemical tests were performed before each chemotherapy cycle. CT scans were performed every two or three cycles until the tumor progressed. Tumor response was classified according to the response evaluation criteria in solid tumors (RECIST) 1.0 guidelines. Confirmation of the response was not required for this study.

Statistical analysis

Overall survival (OS) was measured from the starting date of chemotherapy until death from any cause. Progression-free survival (PFS) was measured from the starting date of chemotherapy until tumor progression or death from any cause. Survival rates were estimated using the Kaplan–Meier method and compared using the log-rank test. Prognostic factors were analyzed by searching all clinical variables in univariate analysis, with all variables with a P value <0.10 in the univariate analysis entered into multivariate analysis using stepwise Cox proportional hazard regression models. A two-sided P value <0.05 was considered significant, and 95% confidential intervals (CIs) were calculated. All statistical analyses were performed using the SPSS software package (SPSS, Chicago, IL, USA).

Results

Patient characteristics

Median age was 54 years (range, 29–84 years); of these, 98 (61.6%) were men and 138 (86.8%) had ECOG PS of 0 to 1. Patients were followed up for a median 20.0 months (range, 11.4–48.5 months). Overall, 129 patients (81.1%) died, with a median survival time of 11.3 months (95% CI, 9.6–13.0 months). Patient characteristics are summarized in Table 1. Before the start of S-1 plus cisplatin chemotherapy, 24 patients (15.1%) underwent palliative gastrectomy (resected metastatic group), 40 (25.2%) had recurrent disease after curative gastrectomy (recurrent group), and 95 (59.7%) had distant metastases without gastrectomy (initially metastatic group).

Table 1 Patient characteristics

Characteristic	n = 159 (100%)
Age (years)	
Median (range)	54.0 (29–84)
Gender	
Male	98 (61.6)
Female	61 (38.4)
ECOG PS	
0/1	138 (86.8)
2/3	21 (13.2)
Histology	
WD/MD	30 (18.9)
PD/UD	106 (66.7)
NA	23 (14.5)
Disease status	
Resected metastatic	24 (15.1)
Recurrent	40 (25.2)
Metastatic	95 (59.7)
Tumor location	
Upper 1/3	6 (3.8)
Middle 1/3	52 (32.7)
Lower 1/3	32 (20.1)
Multiple	19 (11.9)
NA	50 (31.4)
Measurable lesion (presence)	59 (37.1)
Metastasis	
Peritoneum	93 (58.5)
Liver	30 (18.9)
Abdominal lymph nodes	48 (30.2)
Lung	5 (3.1)
Bone	9 (5.7)
Number of metastases	
1	115 (72.3)
≥2	44 (27.7)
Second-line chemotherapy (received)	85 (53.5)
Albumin (<3.3 g/dl)	52 (32.7)
Alkaline phosphatase (>120 IU/l)	26 (16.4)
Total bilirubin (>1.2 mg/dl)	11 (6.9)

ECOG PS Eastern Cooperative Oncology Group Performance Status, *WD* well differentiated, *MD* moderately differentiated, *PD* poorly differentiated, *UD* undifferentiated, *NA* not available

Tumor response

Of the 59 patients with measurable disease, 5 were not evaluable for tumor response because they were lost to follow-up after the first treatment cycle (Table 2). Twenty-four patients (40.7%) achieved a partial response (PR), with 1 achieving a complete response (CR, 1.7%), making the overall response rate (ORR) 42.4% (95% CI,

Table 2 Response rate

Response	Resected metastatic or recurrent ($n = 21$)	Initially metastatic ($n = 38$)	Total (%) ($n = 59$)
Complete response	0	1	1 (1.7)
Partial response	9	15	24 (40.7)
Stable disease	6	11	17 (28.8)
Disease progression	2	10	12 (20.3)
Not evaluable	4	1	5 (8.5)
Response rate (%)	42.9	42.1	42.4

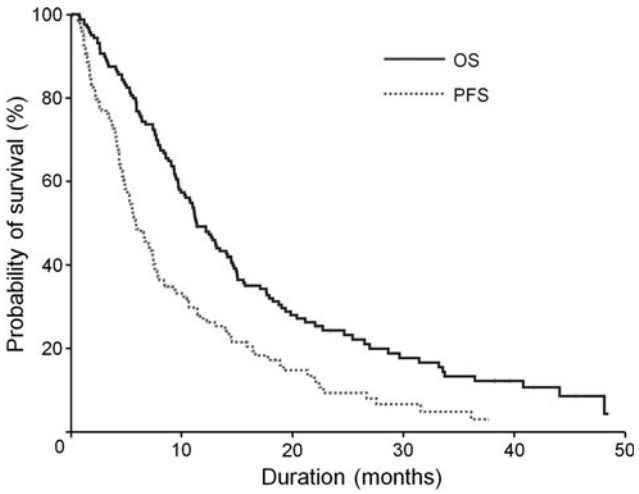

Fig. 1 Kaplan–Meier survival curves of progression-free survival (*PFS*) and overall survival (*OS*)

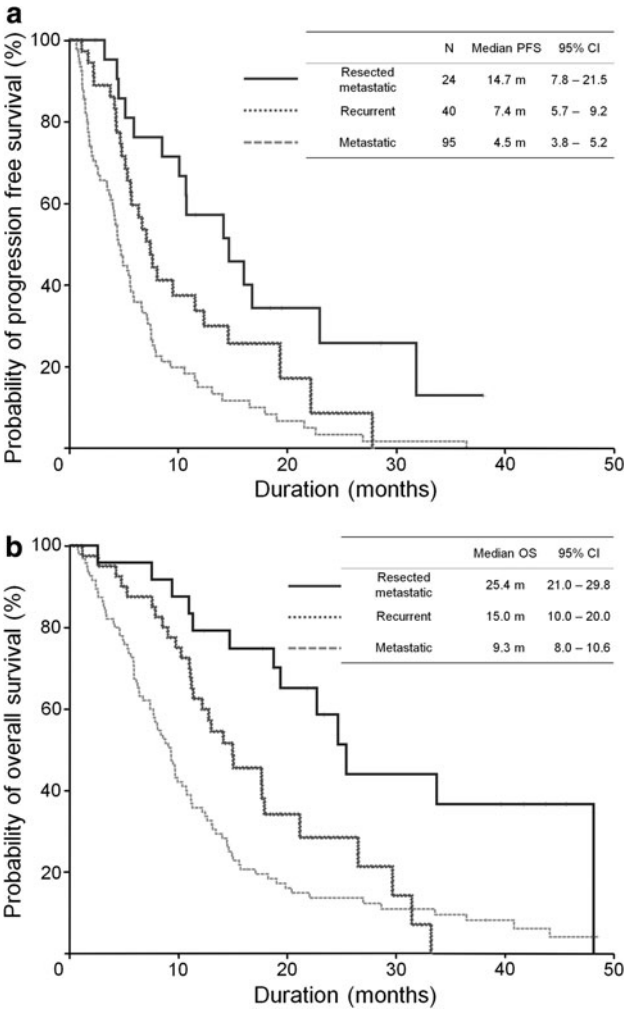

Fig. 2 Kaplan–Meier survival curves relative to disease status of progression-free survival (*PFS*) (**a**) and overall survival (*OS*) (**b**). *CI*, confidence interval

23.0–61.8%). The median duration of response in these 25 patients was 5.6 months (range, 3.4–7.9 months). There was no difference in response rate among the resected metastatic, recurrent, and initially metastatic groups (RR= 42.1, 42.1, and 50.0%, respectively; $P = 0.269$).

Survival outcome

The median PFS was 5.8 months (95% CI, 4.8–6.9 months) and the median OS was 11.3 months (95% CI, 9.6–13.0 months; Fig. 1). Both PFS and OS differed significantly among the three groups. The resected metastatic, recurrent, and initially metastatic groups had median PFS values of 14.7, 7.4, and 4.5 months, respectively ($P < 0.001$), and median OS values of 25.4, 15.0, and 9.3 months, respectively ($P < 0.001$; Fig. 2).

Adverse events

Patients received a median of 6 cycles of chemotherapy (range, 1–19 cycles). The most common treatment-related hematological adverse events were anemia (95.0%) and neutropenia (78.0%), with grades 3 and 4 anemia occurring in 18.9% and 1.3% of these patients, respectively, and grades 3 and 4 neutropenia occurring in 31.4 and 10.1%, respectively. Grade 3 thrombocytopenia was observed in 13 patients (8.2%), but none had grade 4 thrombocytopenia. Nausea and vomiting were relatively common (16.3%), but only 1 patient had grade 3 nausea and vomiting. Grade 3 diarrhea, stomatitis, anorexia, and fatigue were observed in 1.9, 1.3, 1.9, and 0.6% of patients, respectively. Drug dose was reduced in 49 patients (30.8%): in 41 (83.7%) for hematological toxicities, in 4 each (8.2%) for anorexia and fatigue, and in 1 (2.0%) for diarrhea. Treatment was delayed in 68 patients (42.8%): in 56 (82.1%) for hematological toxicities, in 2 (3.0%) for nausea or vomiting, and in 1 (1.5%) for infection. During the first to third cycle of chemotherapy, 19 patients (11.9%) required dose reductions and 35 (22.0%) required treatment delays. In addition, median relative dose intensity was 87.9% for scheduled cycles during the first 6 cycles.

Prognostic factors and prognostic model

Table 3 shows the results of univariate analysis of factors prognostic of patient survival. Performance status, disease status, number of metastases, peritoneal metastases, liver metastases, and bone metastases were significant or borderline prognostic factors for PFS or OS. Multivariate analysis showed that the initial metastatic group (vs. recurrent and resected metastatic group), bone metastasis, and liver metastasis were independent prognostic factors for reduced PFS (Table 4), and that poor PS, initial metastatic group, and bone metastasis were independent prognostic factors for reduced OS. After applying our prognostic model [16], we found that the survival curves of patients in various risk groups showed highly significant differences in both PFS and OS ($P < 0.001$ each; Fig. 3). The good, moderate, and poor risk groups had a median PFS of 7.6, 5.3, and 2.6 months, respectively, and a median OS of 19.8, 10.8, and 6.7 months, respectively.

Discussion

We evaluated the efficacy and safety of a 3-week combination of S-1 and cisplatin in AGC patients in the clinical practice setting. We also identified factors prognostic of patient survival, and we applied our prognostic model to categorize these patients into three risk groups.

Table 3 Univariate analysis of factors predictive of prognosis

	n	Median PFS (months)	95% CI	*P* value	Median OS (months)	95% CI	*P* value
Age (years)							
≤54	81	5.1	4.0–6.3	0.609	11.4	9.1–13.6	0.813
>54	78	7.2	5.1–9.2		11.2	7.9–14.6	
Gender							
Male	98	6.7	4.8–8.6	0.707	11.3	9.3–13.4	0.558
Female	61	5.6	4.1–7.2		11.3	7.4–15.2	
ECOG PS							
0/1	138	6.6	5.3–7.9	0.012	12.6	10.3–15.0	0.001
2/3	21	3.9	1.6–6.3		6.7	4.9–8.6	
Histology							
WD/MD	30	6.7	3.0–10.3	0.798	13.1	7.6–18.7	0.111
PD/UD	106	5.7	4.6–6.8		10.7	8.5–12.9	
Disease status							
Resected meta	24	14.7	7.8–21.5	<0.001	25.4	21.0–29.8	<0.001
Recurrent	40	7.4	5.7–9.2		15.0	10.0–20.0	
Metastatic	95	4.5	3.8–5.2		9.3	8.0–10.6	
No. of metastases							
1	115	7.1	5.4–8.8	0.028	13.4	10.5–16.4	0.002
≥2	44	4.9	3.7–6.1		9.3	8.3–10.4	
Peritoneum metastasis							
Yes	93	5.4	3.9–7.0	0.893	11.2	8.7–13.6	0.058
No	66	6.7	5.2–8.2		14.1	10.0–18.3	
Liver metastasis							
Yes	30	3.9	2.9–5.0	<0.001	10.3	7.7–13.0	0.316
No	129	6.6	5.1–8.1		12.2	10.2–14.1	
Lung metastasis							
Yes	5	7.6	0.0–16.0	0.905	17.6	7.3–28.0	0.203
No	154	5.8	4.8–6.9		11.3	9.3–13.3	
Abdominal LN metastasis							
Yes	48	5.6	4.9–6.2	0.096	9.8	7.9–11.6	0.225
No	111	6.6	4.9–8.3		12.6	10.8–14.5	
Bone metastasis							
Yes	9	2.0	0.0–5.7	0.004	9.7	9.1–10.3	0.013
No	150	5.9	4.5–7.3		12.2	10.0–14.4	

PFS progression-free survival, *OS* overall survival, *ECOG PS* Eastern Cooperative Oncology Group Performance Status, *WD* well differentiated, *MD* moderately differentiated, *PD* poorly differentiated, *UD* undifferentiated, *LN* lymph node

Table 4 Multivariate analysis of factors predictive of poor prognosis

		HR for PFS	95% CI	*P* value	HR for OS	95% CI	*P* value
ECOG PS	2/3	1.76	0.98–3.14	0.057	1.78	1.05–3.02	0.034
Initial status	Metastatic	2.05	1.39–3.02	<0.001	2.19	1.51–3.18	<0.001
Peritoneum metastasis	Yes	–	–	–	1.36	0.95–1.96	0.098
Bone metastasis	Yes	2.73	1.27–5.88	0.010	2.09	1.01–4.32	0.048
Liver metastasis	Yes	2.10	1.33–3.30	0.001	–	–	–

HR hazard ratio, *PFS* progression-free survival, *OS* overall survival, *ECOG PS* Eastern Cooperative Oncology Group Performance Status

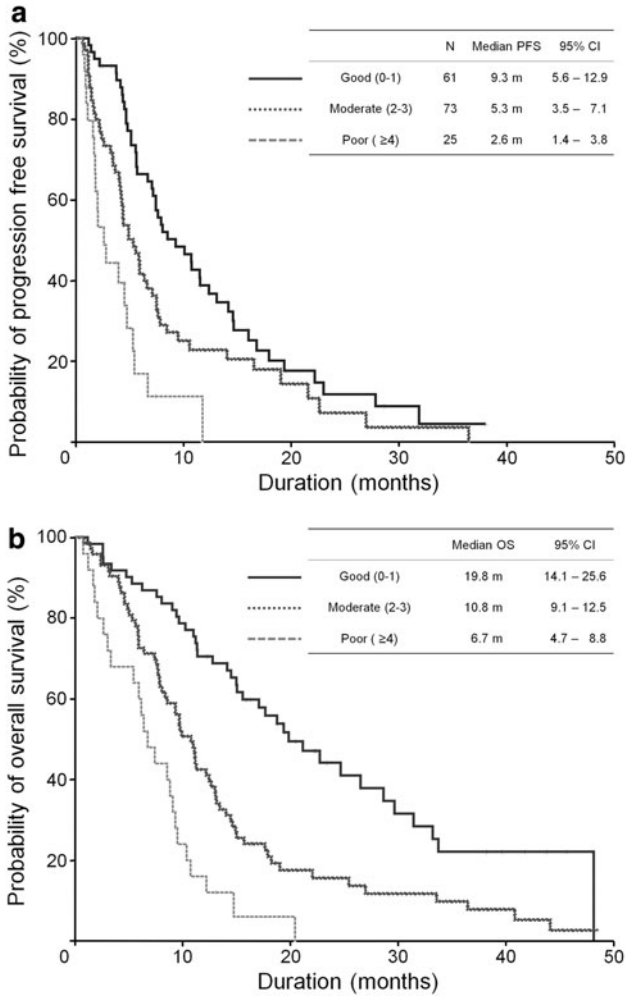

Fig. 3 Kaplan–Meier survival curves relative to our prognostic model of progression-free survival (*PFS*) (**a**) and overall survival (*OS*) (**b**)

We observed an ORR of 42.4%, a median PFS of 5.6 months, and a median OS of 11.4 months, similar to the results of our phase II study (confirmed RR, 47.6%; median PFS, 5.3 months; median OS, 10.0 months) [15] and within the range of those observed in recent phase 3 trials of fluoropyrimidine and platinum-based agents as first-line chemotherapy in AGC patients (RR, 25-45%; median PFS, 4–6 months; median OS, 8–11 months) [18–21]. Our median survival, however, was shorter than that observed with a 5-week schedule in the Japanese SPIRITS trial. It is difficult to compare these trials directly, although a higher percentage of our patients had poorer PS (ECOG PS 2/3; 13 vs. 3%) and fewer had received second-line chemotherapy (54 vs. 74%). In addition, the SPIRITS trial results require further confirmation. Our regimen resulted in generally acceptable safety and toxicity. Grade 1/2 hematological toxicities and nausea/vomiting were relatively common, but severe toxicities were rare, similar to results in our previous phase II study and SPIRITS trial [10, 15]. Thus, our findings indicate that the 3-week schedule of combination S-1 with cisplatin is effective and safe in the treatment of AGC, not only in a clinical trial setting but also in clinical practice.

We identified four factors independently prognostic of poor PFS and OS, all of which had previously been associated with poor prognosis in patients with AGC: poor PS [17], initial metastatic (no prior gastrectomy) [17], liver metastasis [22], and bone metastasis [23]. Because disease status, particularly initial metastatic (vs. recurrent or resected metastatic), and bone metastasis were independently significant factors for both PFS and OS, these two factors seemed to be most representative of tumor burden in this patient population. When our prognostic model was applied [16], we found that the three risk groups had highly significant differences in PFS and OS ($P < 0.001$ each), indicating the applicability of our model in this patient population.

To date, there have been many modified schedules for S-1 and cisplatin combination chemotherapy. Initially, S-1 was developed in Japan and usually administered in doses of 40–60 mg bid, depending on each patient's body surface area, in a 5-week cycle (3 weeks on and 2 weeks off), in combination with 60 mg/m^2 cisplatin on day 8 [8, 10]. However, a subsequent Japanese post-marketing survey of S-1 showed that this schedule resulted in median times to worst toxic events of 22 days for hematological toxicities and 15 days for diarrhea and stomatitis, with median recovery times of about 2 weeks from these toxicities [24]. These findings suggested that a 3-week cycle may have

some advantages. In Western studies, S-1 was given for 3 weeks followed by a 1-week rest; the maximal tolerated dose (MTD) of S-1 was 50 mg/m^2/day when given with cisplatin 75 mg/m^2 on day 1 of each 4-week cycle [19, 25, 26]. The development of late-onset diarrhea was a major concern in these studies. Because most toxicities occurred during the third week of administration in both Japanese and Western studies, a drug-free interval in the third week of each cycle may reduce the incidence of adverse reactions and improve efficacy. Indeed, S-1 showed better toxicity profiles and similar efficacy when given in 3-week rather than 6-week cycles to patients with head and neck cancer [27].

The Japanese 5-week schedule resulted in a lower dose of cisplatin (12 mg/m^2/week) [10] than with the reference dose (20–25 mg/m^2/week) for AGC in several phase III studies [13, 14]. The S-1 dose was much lower in Western (50 mg/m^2/day) than in Asian (70–80 mg/m^2/day) studies, which may be the result of differences in cytochrome P450 metabolism related to genetic polymorphisms in CYP2A6 [28]. Based on these findings, we conducted a phase I/II study of a 3-week schedule of S-1 (80 mg/m^2/day) plus cisplatin (60 mg/m^2) [15]. These different schedules and dosages of S-1 plus cisplatin make it difficult to compare the results of these clinical trials, to choose the optimal schedule in clinical practice, and to design global trials using S-1 plus cisplatin with or without targeted agents. A prospective phase III trial of a 3-week versus a 5-week schedule of S-1 with cisplatin (SOS study) is currently underway in Korea and Japan.

In conclusion, the 3-week combination of S-1 plus cisplatin was safe and effective as first-line treatment for patients with AGC in a clinical practice setting. Disease status and bone metastasis were the most important prognostic factors in these patients, and our prognostic model was able to classify patients into three groups with significantly different survival outcomes following treatment with S-1 plus cisplatin.

Conflict of interest None.

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