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ORIGINAL ARTICLE

Phase I/II study of 3-week combination of S-1 and cisplatin chemotherapy for metastatic or recurrent gastric cancer

Jae-Lyun Lee · Hye Jin Kang · Yoon-Koo Kang · Min-Hee Ryu · Heung Moon Chang · Tae-Won Kim · Hee Jung Sohn · Hawk Kim · Jung Shin Lee

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Abstract
Purpose To define the maximum-tolerated dose (MTD) of S-1, given daily for 2 weeks followed by a 1-week rest, with a fixed dose of cisplatin on the initial day, and to determine the activity and safety of this regimen at the recommended dose (RD) when used as first line treatment of advanced gastric cancer (AGC).
Patients and methods Cisplatin was fixed at a dose of 60 mg/m^2 on day 1 (D1) and the starting dose of S-1 was 60 mg/m^2/day (30 mg/m^2 bid) (level I) on D1 to D14, every 3 weeks. The dose of S-1 was increased by 5 mg/m^2 bid up to 100 mg/m^2/day (level V) unless the MTD was achieved.
Results Sixty-two eligible patients were enrolled. MTD was set at level V with two of three patients developing grade 3 diarrhea or febrile neutropenia. The RD was determined at level IV (90 mg/m^2/day). After the first 20 patients were enrolled in phase II, the protocol was amended; the S-1 dose was reduced to 80 mg/m^2/day ($N = 23$) because of poor bone marrow recovery. The objective response was observed in 20 of 42 evaluable patients (48%). SD was achieved in 15 (36%). The median PFS was 5.3 months (95% CI, 4.6–6.0 months) with a median OS of 10.0 months (95% CI, 5.1–14.8 months). Grade 3–4 toxicities included neutropenia (33%), anemia (31%), and anorexia (24%).
Conclusions The 3-week combination of cisplatin plus S-1 is active against AGC with favorable toxicitiy profiles. The phase II schedule or doses may need further refinements.

J.-L. Lee · H. J. Kang · Y.-K. Kang (✉) · M.-H. Ryu · H. M. Chang · T.-W. Kim · H. J. Sohn · H. Kim · J. S. Lee
Division of Oncology, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, 388-1 Poongnap-dong, Songpa-gu, Seoul 138-736, South Korea
e-mail: ykkang@amc.seoul.kr

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Introduction

Despite a sharp decline in incidence and reduction of mortality in the last 40 years, gastric cancer is the fourth most common cancer and the second most common cause of cancer deaths world wide [20]. Although, improvements in early diagnosis have increased the number of curative resections, many patients present with locally advanced or metastatic disease when first diagnosed, and local or distant relapse are common even after complete resection. For these patients the main therapeutic option is a palliative chemotherapy.

A 5-day infusion of 5-fluorouracil (5-FU) in combination with cisplatin every 3–4 weeks has been adopted as a reference regimen for the treatment of advanced gastric cancer (AGC) [12, 27, 29]. However, 5-FU infusion is cumbersome and inconvenient requiring hospital admission or central venous catheters with portable infusion pumps. Newer orally available fluoropyrimides, which avoid these limitations, have been emerging in the clinical area of oncology [13, 15, 22].

S-1 is an oral fluoropyrimidine, consisting of tegafur, and dihydropyrimidine dehydrogenase inhibitor, 5-chloro-2,4-dihydroxypyridine and orotate phosphoribosyl transferase inhibitor, potassium oxonate [15]. In phase II studies for AGC conducted in Japan, 80 mg/m^2/day S-1 daily for 4 weeks followed by a 2-week rest, showed high response rates (RR) of 44–49% [15, 22]. Based on synergism between S-1 and cisplatin seen in preclinical studies [3], several phase I/II studies of these two drugs were performed [4, 10, 16]. In the study conducted by Koizumi et al. [16], S-1 was administered for 3 weeks followed by a 2-week rest, and cisplatin (60 mg/m^2) was given on day 8.

The overall RR was 76% in 19 eligible patients. Using the same treatment schedule, Baba et al. [4] also reported a RR of 67% in 12 patients.

Although, they demonstrated high activity, the dose intensity (DI) of cisplatin (a single 60 mg/m^2 done in a 5-week period, i.e. 12 mg/m^2/week) was much lower than those of the regimens which have been accepted as reference for AGC (20–25 mg/m^2/week) [12, 27, 29, 30]. In addition, a new S-1 regimen consisting of a 2-week treatment followed by 1-week rest has been shown to reduce the adverse events and increase patient compliance, which may increase the efficacy [14]. We conducted a phase I/II study to confirm the efficacy and safety of the new treatment schedule of S-1 with a fixed cisplatin dosage in AGC.

Patients and methods

Patients

All patients with advanced, histologically confirmed adenocarcinoma of stomach were eligible if they met the following inclusion criteria: age 18–70 years; ECOG performance status 0–2; no previous palliative chemotherapy or radiotherapy; ability for sufficient oral intake; adequate bone marrow, renal, and hepatic function; and written informed consent. The presence of measurable lesions by the response evaluation criteria in solid tumors group (RECIST) criteria was required for enrollment in the phase II study. Patients were excluded if they had brain metastases, significant gastrointestinal bleeding, had serious comorbid condition, or the use of concomitant drugs which have potential interaction with S-1. This study was approved by the institutional review board of Asan Medical Center (Approval No. 2004-0021).

Phase I: treatment and dose escalation scheme

The dose of cisplatin was fixed at 60 mg/m^2 and administered intravenously over 60 min on day 1. S-1 was given orally twice a day within 1 h after a meal from day 1 to day 14. The single S-1 dose was calculated in milligrams per square meter of body surface area (BSA) and rounded down or up to the nearest 5 mg. The starting dose of S-1 was 60 mg/m^2/day (level 1). At level 2, the dose of S-1 was 35 mg/m^2/dose (70 mg/m^2/day), and subsequently, the dose of S-1 was escalated by 5 mg/m^2/dose up to 100 mg/m^2/day (level 5). The treatment was repeated every 3 weeks. The next course was started when ANC $\geq$ 1,500/μL and platelet count $\geq$100,000/μL and all the non-hematologic toxicities had to recover to $\leq$grade 1. Dose limiting toxicities (DLTs) were defined as: (1) ANC <500/μL for $\geq$5 days; (2) febrile neutropenia; (3) grade 4 thrombocytopenia; (4) any other non-hematological grade 3–4 toxicities, (excluding alopecia) that do not improve to at least grade 1 within 2 days after the institution of appropriate therapy, or (5) delay of treatment for more than 2 weeks. A minimum of three patients were treated at each dose level. If one of three patients experienced a DLT, three additional patients were entered at that dose level. The first two treatment cycles were assessed for determination of the MTD. Dose escalation was continued until DLTs were experienced in two or more out of six patients, and that level was defined as the MTD. No intra-cyclic dose reduction of S-1 was allowed for the first two cycles unless DLT was observed.

Phase II: treatment and dose modification scheme

The RD for the phase II study was defined as the one dose level below MTD. When a grade 3 or 4 hematologic toxicity with the exception of anemia or grade 2 or 3 non-hematologic toxicity occurred during a 2-week period of S-1 administration, S-1 was interrupted until the toxicity subsided to $\leq$grade 2 for hematologic toxicity or $\leq$grade 1 for non-hematologic toxicity, and then S-1 was resumed at the same dose or reduced by 25%, respectively. If there was a second occurrence of grade 4 hematologic or grade 3 non-hematologic toxicity despite dose reduction, S-1 treatment was interrupted temporarily, and was resumed at 50% of the original dose. The subsequent chemotherapy cycle was started when ANC, platelet count and non-hematologic toxicities recovered as described above. A treatment delay of up to 2 weeks was permitted without dose reduction. If the ANC $\geq$1,000/μL but <1,500/μL and platelet count $\geq$75,000/μL but <100,000/μL on the scheduled day 1 of subsequent cycle after a 1-week delay, treatment could be started with a 25% reduced dose of S-1. If the ANC and platelet count did not recover to $\geq$1,500 and $\geq$100,000/μL after a 2-week delay, the patient was taken off-study. In addition, when grade 4 non-hematologic toxicities occurred, or grade 4 hematologic toxicities or grade 3 non-hematologic toxicities recurred despite dose reduction by 50% of original dose, the patient was taken off-study. Cisplatin dose was modified according to the renal toxicity and peripheral neuropathy. If serum creatinine prior to 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, the patient was excluded from the study. If grade 2 neurotoxicity occurred, treatment was delayed up to 3 weeks until neuropathy recovered grade 1 or better. If neuropathy persisted for more than 3 weeks or grade 3 or worse neuropathy occurred, patient was taken off-study. Treatment was continued until the occurrence of disease progression, appearance of unacceptable toxicities, or consent withdrawal, for a maximum of 12 cycles.

Pretreatment and on-treatment evaluation

Within 2 weeks before entry into the study, patients underwent the following evaluations: medical history; complete physical examination; CBC, serum chemistry with electrolyte and coagulation battery; urinalysis; chest X-ray; electrocardiogram; and computed tomography (CT) of abdomen pelvis (CT of chest or neck if indicated). All patients were reviewed prior to the commencement of each cycle of chemotherapy. CBCs were performed weekly, and serum chemistry was performed every 3 weeks. Compliance with S-1 was monitored by questioning patients and counting their remaining pills at each outpatient visit.

Response and toxicity criteria

Tumor response was evaluated according to the RECIST criteria every two cycles. NCI-CTCAE version 3.0 (http://www.cancer.gov) were used to assess toxicity. Patients who received a minimum of two treatment cycles were considered evaluable for response unless rapid progression occurred in which case they were also considered evaluable.

Statistical considerations

The primary end point of the phase II portion was to assess the overall response rate (RR). Simon's optimal two-stage design was used to test the null hypothesis $P_0 \leq 0.3$ versus the alternative hypothesis $P_1 \geq 0.55$. The first stage required at least 6 or more patients out of 15 to have a confirmed response with $\alpha = 0.05$ and $\beta = 0.1$ before proceeding to the second stage. In the second stage, 25 assessable patients could be added and if a total of 17 or more patients achieved a confirmed response, then the primary end point would have been met. Kaplan–Meier estimates were used in the analysis of progression-free survival (PFS) and overall survival (OS). The actual administered dose of both drugs and the intervals between treatments were used to calculate the DI over the first six cycles of therapy. As the RD of S-1 was modified in the phase II portion, repeated measure of ANOVA was used to evaluate changes of DI and relative dose intensity (RDI) for both drugs and to compare the change between the series [17]. SPSS for Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analyses.

Results

Patient characteristics

From February 2004 to January 2006, 62 eligible patients were entered in this study. The patient characteristics are listed in Table 1. Among 62 patients, 8 patients had undergone curative gastrectomy and 5 had received adjuvant 5-FU based chemotherapy. The majority of patients had an ECOG performance status of 1 or better and had two or more sites of metastases.

Table 1 Patient characteristics enrolled onto phase I/II study

	Phase I	Phase II[a]
	No. of patients ($N = 21$, %)	No. of patients ($N = 43$, %)
Age, years		
Median (range)	52 (38–72)	52 (28–70)
BSA, m^2		
Median (range)	1.63 (1.29–1.83)	1.67 (1.35–1.98)
Sex		
Male	12 (57%)	31 (72%)
Female	9 (43%)	12 (28%)
Performance status (ECOG)		
0	0	20 (47%)
1	20 (95%)	22 (51%)
2	1 (5%)	1 (2%)
Histologic differentiation		
WD/MD	4 (19%)	12 (29%)
PD	11 (52%)	18 (42%)
Mucinous/signet ring cell	4 (19%)	5 (12%)
NA	2 (10%)	8 (19%)
Disease status		
Metastatic	14 (67%)	40 (93%)
Recurrent	5 (24%)	3 (7%)
Locally advanced	2 (10%)	0
Metastatic sites		
Abdominal LN	11 (52%)	35 (81%)
Liver metastasis	7 (33%)	27 (63%)
Peritoneal seeding	10 (48%)	17 (40%)
Lung	0	1 (2%)
Bone	2 (10%)	1 (2%)
No. of metastatic organs		
1	8 (38%)	10 (23%)
2	8 (38%)	23 (54%)
≥ 3	3 (14%)	10 (23%)
Prior adjuvant chemotherapy		
Doxifluridine	1 (5%)	1 (2%)
5-FU + Adriamycin + MMC	1 (5%)	1 (2%)
Doxifluridine + MMC	1 (5%)	0

[a] Included two patients with measurable lesions assigned to level 4 in the phase I study

Determination of MTD and RD

At level 1 dose (S-1 60 mg/m^2/day), one patient developed prolonged grade 2 neutropenia with concomitant upper

respiratory tract infection during the first course and required 23 days to start the second cycle, but the other five patients including additional three patients in the same cohort showed no DLT. DLT was not observed in the three patients treated at dose level 2 and 3. At level 4 (S-1 90 mg/m^2/day), one out of three patients experienced grade 3 asthenia and anorexia during the second cycle which was not improved within 2 days. The level 4 dose cohort was expanded to six patients, but no additional patient developed DLT. At level 5 (S-1 100 mg/m^2/day), two of three patients exhibited DLTs in the second course, one of them had grade 3 diarrhea for 5 days despite anti-diarrheal medication, and the other had grade 3 febrile neutropenia and grade 3 nausea and vomiting. Based on these results, dose level 5 was declared as the MTD, and level 4 was defined as the RD in the phase II portion.

A total of 131 courses were given in the phase I portion. Toxicity for the first two treatment cycles in the phase I portion is depicted in Table 2. A total of nine patients out of 13 with measurable lesions had a confirmed partial response (PR) in the phase I portion (Table 3).

In the phase II portion, initially 20 patients were enrolled (series I), including two patients with measurable lesions assigned to level 4 in the phase I portion. As the study progressed, we encountered delayed hematologic recovery which required dose reduction and/or delay and resultant decreased DI of both agents. In addition, it inconvenienced patients and compliance deteriorated. To improve the feasibility, the final RD was set at the level 3 dose of 80 mg/m^2/day of S-1 in the following phase II portion (series II, $N = 23$).

Extent of exposure to study medication in phase II portion

In series I, 20 patients received 110 cycles of treatment, with a median of 5 cycles per patient (range 2–12). In

Table 2 Toxicity in the phase I study (first two courses)

Category	Level I ($N = 6$)		Level II ($N = 3$)		Level III ($N = 3$)		Level IV ($N = 6$)		Level V ($N = 3$)	
	S-1 60 mg/m^2/day		S-1 70 mg/m^2/day		S-1 80 mg/m^2/day		S-1 90 mg/m^2/day		S-1 100 mg/m^2/day	
	All events	Grade 3–4	All events	Grade 3–4	All events	Grade 3–4	All events	Grade 3–4	All events	Grade 3–4
Anemia	5	1	3	0	3	0	6	1	3	0
Leukopenia	3	0	2	0	2	0	4	0	3	1
Granulocytopenia	6	2	2	0	2	2	4	0	1	1
Thrombocytopenia	0	0	0	0	1	0	0	0	2	0
Febrile neutropenia	0	0	0	0	0	0	0	0	1	1
Asthenia	5	0	2	0	3	0	5	1	3	1
Anorexia	6	0	3	0	3	0	4	1	3	1
Nausea	6	0	3	0	2	0	4	0	2	1
Vomiting	3	0	2	0	1	0	2	0	3	1
Stomatitis	1	0	1	0	1	0	2	0	1	0
Diarrhea	0	0	1	0	1	0	1	0	2	1
Abdominal pain	3	0	2	0	2	0	4	1	1	0

Table 3 Objective response rates

	Phase I					Phase II		
	Level I ($N = 6$)	Level II ($N = 3$)	Level III ($N = 3$)	Level IV ($N = 6$)	Level V ($N = 3$)	Series I ($N = 20$)	Series II ($N = 23$)	Combined ($N = 43$, %)
CR	0	0	0	0	0	0	0	0
PR	1	2	2	2	2	8	12	20 (47.6%)
SD	1	1	1	0	1	9	6	15 (35.7%)
PD	0	0	0	0	0	3	4	7 (16.6%)
NE	4[a]	0	0	4[a]	0	0	1[b]	1[b]

CR completer response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluable

[a] Patients had no measurable lesions

[b] Patient withdrew consent and did not return to clinic after the first cycle just to receive alternative medicine

series II, 23 patients received 162 cycles of treatment with a median of 7 (range 1–12). Dose reductions of S-1 were necessary in 24 (59%) patients out of 41 patients who received two or more cycles and treatment delay was also required in 24 patients. The median DI was 331.1 mg/m^2/week for S-1, representing 88% of the planned DI in series II ($N = 21$), conversely the median DI of S-1 was 321.9 mg/m^2/week with a RDI of 77% in series I ($N = 18$) ($P = 0.685$ for DI and $P = 0.053$ for RDI). The median DI for cisplatin was increased from 17.1 mg/m^2/week in series I to 18.9 mg/m^2/week in series II ($P = 0.039$). No patient required dose reduction of cisplatin, and treatment delay was only required in three patients, who received nine or more cycles of chemotherapy. Figure 1 shows serial DI and RDI for S-1 and cisplatin over the first four treatment cycles. It confirmed steady decrease in RDI and DI for S-1 over cycles of the treatment in both series ($P = 0.037$, $P = 0.033$). As expected, treatment with S-1 80 mg/m^2/day resulted in higher RDI of S-1 compared with S-1 90 mg/m^2/day ($P = 0.032$) at each treatment cycle with similar DI for S-1 in both series ($P = 0.836$). The DI and RDI of cisplatin in series II was higher, but not with the statistical significance, than those in series I ($P = 0.071$). The ANC decreased and was not fully recovered on the scheduled day 1 of the subsequent treatment cycle (data not shown), which explains the frequent requirement for dose reduction and/or delay.

Most patients discontinued their treatment due to disease progression (32 patients, 74%). Five patients completed 12 cycles and 6 patients discontinued for various other reasons.

Efficacy

Twenty among 42 assessable patients achieved confirmed PR (47.6%, 95% CI, 32.5–62.7, Table 3) with a median response duration of 4.5 months. Another 15 patients (35.7%) had stable disease. At a median follow-up duration of 12.1 months (range 9.8–23.3), the median PFS was 5.3 months (95% CI, 4.6–6.0 months) and median OS was 10.0 months (95% CI, 5.1–14.8 months, Fig. 2).

Safety

The main adverse events are reported in Tables 4 and 5. The frequently observed grade 3/4 hematological toxicity was neutropenia (14 cases, 33.4%; 26 cycles, 9.8%) and anemia (13 cases, 31.0%; 15 cycles, 5.6%). Although severe thrombocytopenia was observed in two patients, none of them developed clinically significant bleeding. Frequently observed grade 3 non-hematological toxicities were anorexia (23.8% of patients; 3.8% of cycles) and asthenia (14.3% of patients; 3.0% of cycles). All other toxicities were observed in less than 10% of patients, and neither febrile neutropenia nor treatment-related death was observed.

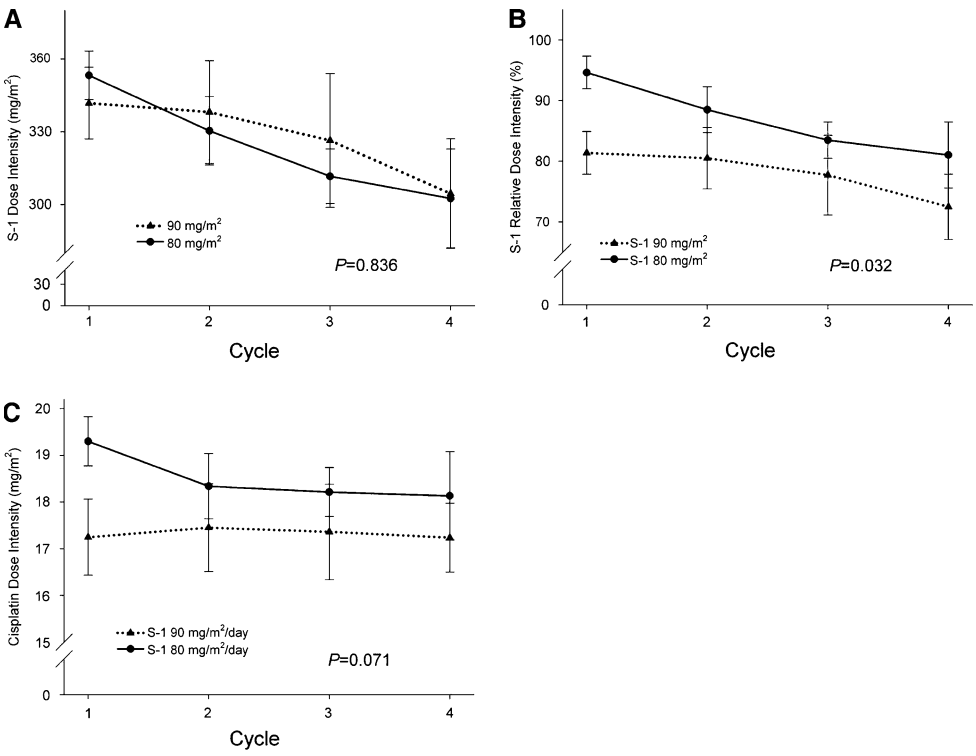

Fig. 1 Serial dose intensity (**a**) and relative dose intensity (**b**) for S1 and dose intensity (**c**) for DDP over the first four treatment cycles ($N = 12$ for series I, $N = 18$ for series II)

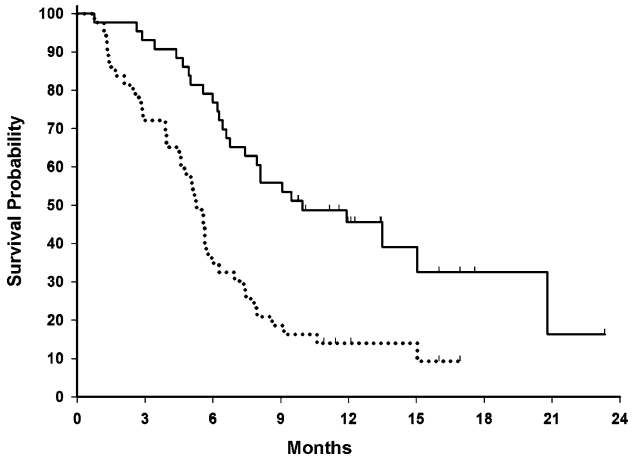

Fig. 2 Progression-free survival (*dotted line*) and overall survival (*solid line*)

Discussion

This study is the first clinical trial of S-1, given for 2 weeks followed by 1-week rest, combined with cisplatin on day 1 in patients with AGC. The RD was determined to be 90 mg/m^2/day of S-1 with 60 mg/m^2 of cisplatin. However, this resulted in frequent dose reduction and/or delay, mainly due to delayed hematologic recovery, which reduced patient compliance. S-1 80 mg/m^2/day was more feasible while maintaining or improving the DI of S-1 and cisplatin. The phase II study using this combination and schedule obtained a RR of 48% with a mild toxicity profile, although dose reduction and/or delay were not as reduced as we had expected.

S-1 plus cisplatin has demonstrated promising activity against AGC in studies performed in Japan [10, 16, 19, 23, 25]. In those studies, S-1 was administered at 80 mg/m^2/day, but the dosing regimen is not fine-tuned using three dosage categories, assigned according to patient's BSA, and the treatment schedules varied. In addition, the majority of the trials focused on defining MTD/RD and enrolled only a limited number of patients, which hinders interpretation of the actual activity of this combination. When it comes to cisplatin dosage, the DI of cisplatin (12–13.3 mg/m^2/week) in those schedules [4, 10, 16, 19, 23, 25] was much lower than the dosages which have been widely accepted as reference regimens in AGC (20–25 mg/m^2/week) [11, 12, 21, 27, 29, 30]. In North America, Ajani et al. [1, 2] reported phase I and II studies of S-1 given for 3 weeks plus cisplatin every 4 weeks. The RD was set at 50 mg/m^2/day of S-1 with 75 mg/m^2 of cisplatin on day 1. As the established dose of S-1 is significantly lower than that reported in Japanese trials, we find it hard to accept this for Asian patients.

Japanese post-marketing surveillance of S-1 revealed that more than half of the patients discontinued the treatment within the first two treatment cycles, when S-1 was

Table 4 Toxicity per patient in phase II

Category	Phase II Series I (N = 20)				Phase II Series II (N = 22)[a]				Phase II (N = 42)	
	S1 90 mg/m^2/day				S1 80 mg/m^2/day					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4	All events(%)	Grade 3–4(%)
Anemia	4	11	5	0	3	11	6	2	42 (100.0)	13 (31.0)
Leukopenia	8	4	1	0	11	6	0	1	31 (73.8)	2 (4.8)
Granulocytopenia	4	5	6	0	5	6	7	1	34 (81.0)	14 (33.4)
Thrombocytopenia	1	0	0	0	4	5	2	0	12 (28.6)	2 (4.8)
Bleeding	0	0	1	0	1	0	0	0	2 (4.8)	1 (2.4)
Febrile neutropenia	NA	NA	0	0	NA	NA	0	0	0	0
Asthenia	8	8	2	0	7	11	4	0	40 (95.2)	6 (14.3)
Anorexia	7	7	4	0	6	8	6	0	38 (90.5)	10 (23.8)
Nausea	10	5	1	0	9	7	0	0	32 (76.2)	1 (2.4)
Vomiting	6	3	1	0	4	8	1	0	23 (54.8)	2 (4.8)
Stomatitis	9	0	0	0	11	3	0	0	23 (54.8)	0
Diarrhea	8	1	3	0	7	3	1	0	23 (54.8)	4 (9.5)
Abdominal pain	7	6	0	0	11	8	0	0	32 (76.2)	0
Neuropathy	12	0	0	0	15	3	0	0	30(71.4)	0
Hand-foot syndrome	17	0	0	0	8	5	0	0	30 (71.4)	0
Allergic reaction	4	0	0	0	5	1	0	0	10 (23.8)	0

[a] One patient who withdrew consent and did not return to clinic after the first cycle was not evaluable for toxicity

Table 5 Toxicity per cycles in phase II (total of 266 cycles)

Category	Phase II Series I (N = 109 cycles)				Phase II Series II (N = 157 cycles)				Phase II (N = 266 cycles)	
	S1 90 mg/m^2/day				S1 80 mg/m^2/day					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4	All events(%)	Grade 3–4(%)
Anemia	57	46	5	0	88	54	8	2	260 (97.7)	15 (5.6)
Leukopenia	25	14	1	0	48	12	0	1	10 (38.0)	2 (0.8)
Granulocytopenia	16	20	14	0	33	34	11	1	129 (48.5)	26 (9.8)
Thrombocytopenia	2	0	0	0	23	11	2	0	38 (14.3)	2 (0.8)
Bleeding	0	0	1	0	1	0	0	0	2 (0.8)	1 (0.4)
Febrile neutropenia	NA	NA	0	0	NA	NA	0	0	0	0
Asthenia	35	9	4	0	69	34	4	0	155 (58.3)	8 (3.0)
Anorexia	37	11	4	0	46	22	6	0	126 (47.4)	10 (3.8)
Nausea	43	7	1	0	48	11	0	0	110 (41.4)	1 (0.4)
Vomiting	23	6	1	0	15	14	1	0	63 (23.7)	2 (0.8)
Stomatitis	13	0	0	0	47	3	0	0	63 (23.7)	0
Diarrhea	19	1	3	0	14	6	1	0	44 (16.5)	4 (1.5)
Abdominal pain	26	7	0	0	39	9	0	0	81 (30.5)	0
Neuropathy	15	0	0	0	74	5	0	0	94 (35.3)	0
Hand–foot syndrome	65	0	0	0	56	11	0	0	132 (49.6)	0
Allergic reaction	4	0	0	0	7	1	0	0	12 (4.5)	0

given for four consecutive weeks followed by 2-week rest, because of symptom exacerbation or adverse events [18]. In Western studies, S-1 was given for 3–4 weeks followed by 1-week rest [6, 7, 9, 28]. The development of late-onset diarrhea was a major concern in these studies. Considering the fact that most toxicities occurred during the third week of administration, the provision of a drug-free interval in the third week of the drug cycle might reduce the incidence of adverse reactions, which could improve the efficacy [18]. The new dosing schedule in which S-1 was given for two consecutive weeks, every 3 weeks has been evaluated [14, 26, 31]. These studies report lower incidence of toxicities and improved patient compliance, implying the superiority of this schedule [14, 26]. In addition, the use of a relatively high and toxic dose of cisplatin (100 mg/m^2) has been questioned, given better toxicity data from phase III trials using moderate doses of cisplatin (60–80 mg/m^2), indicating potentially better tolerance to therapy without compromising activity [11, 12]. We therefore conducted a phase I/II study of a new treatment schedule of 3-week combination of S-1 plus moderate dose of cisplatin.

The MTD was determined to be 100 mg/m^2/day of S-1. Although the treatment schedule was different, the MTD in the current study was much higher than that of a phase I study conducted in North America [1]. Our results confirm that the dose of S-1 tolerated by Asian patients is much higher than that tolerated by Western patients [1, 2, 8, 9]. It has been suggested that the different efficiency in the conversion rate of tegafur to 5-FU by the CYP450 enzyme is related to genetic polymorphisms in CYP2A6 [31], the activity of which was found to be higher in Caucasian than in Asian populations [24]. A prospective genetic association study of S-1 with pharmacokinetics, toxicity, and CYP2A6 polymorphism is being conducted in our institution.

In the current trial, treatment with 3-week S-1 plus cisplatin regimen resulted in an overall RR of 48% and disease stabilization in 36% with a median PFS of 5.3 months and OS of 10.0 months. These efficacy results are comparable to previous studies on cisplatin plus S-1 or capecitabine [2, 11, 13, 16]. In consideration of the high proportion of liver metastases (63%) and peritoneal seeding (40%) in this study, which are known as poor prognostic factors [5], these results are promising and warrant further investigation. The non-hematologic toxicity was moderate, with anorexia representing the leading grade 3 toxicity without any grade 4 toxicities. Although grade 3/4 granulocytopenia was reported in 33% of patients, no patient developed febrile neutropenia. Furthermore, grade 3/4 hematologic or non-hematologic toxicities developed in less than 10 and 5% of all treatment cycles, which underscores the adequacy of 3-week schedule and dose.

In this phase I study, to find out safer, more applicable, and more adequate RD, we assessed the DLT for the first two treatment cycles rather than the usual practice in clinical trial design of evaluating the first cycle only. Actually, the majority of DLTs were encountered not in the first cycle but in the second cycle in phase I portion. However, we had

to modify the RD in the phase II study because of delayed hematologic recovery, which occurred more frequently with cycle progression. The provision of drug-free interval in the third week did neither adequately prevent bone marrow suppression nor provide enough time for its recovery when S-1 was combined with cisplatin. The dose reduction from 90 mg/m^2/day to 80 mg/m^2/day made the regimen more tolerable, clinically more feasible and improved RDI, while maintaining DI and improving the efficacy, although it did not significantly reduce the incidence of adverse events and still required frequent dose delay. In an era when cytotoxic chemotherapy has reached a plateau for many advanced solid tumors, in addition to the development of newer targeted agents, further efforts to optimize the administration of the most active chemotherapeutic agents currently identified is needed to optimize patient compliance and improve therapeutic effects.

In conclusion, 3-week combination of S-1 plus cisplatin is highly active against AGC with a favorable toxicitiy profile in Korean patients. Considering the frequent dose delay, further research on the optimal schedule of S-1 and cisplatin combination is needed. Meanwhile, this 3-week regimen of S-1 and cisplatin provides an important option for patients with advanced gastric cancer.

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