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ORIGINAL ARTICLE

Phase I/II and pharmacokinetic study of S-1 and oxaliplatin in previously untreated advanced gastric cancer

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Abstract
Background We aimed to determine the maximum-tolerated dose (MTD) of S-1 when given with oxaliplatin, to evaluate S-1 pharmacokinetics, and to determine the efficacy and safety of this regimen as a first-line treatment for advanced gastric cancer (AGC).
Methods Oxaliplatin was fixed at a dose of 130 mg/m^2 on day 1 (D1). S-1 was administered from D1 to D14 of a 3-week cycle, and escalated by 10 mg/m^2 per day from 70 mg/m^2 per day up to 100 mg/m^2 per day. Pharmacokinetic analyses were performed following a single dose of S-1 on D-5 and D1 of the first cycle.
Results In phase I ($n = 18$), MTD was not defined. In phase II ($n = 47$) with the planned maximum dose, partial response was achieved in 26 patients (55.3%) and stable disease in 14 patients (29.8%). The median time to progression was 6.6 months (95% CI 4.0–9.2 months) and the median overall survival was 12.5 months (95% CI 9.2–15.9 months). Frequent grade 3/4 toxicities included thrombocytopenia (39%), neutropenia (28%), anemia (17%), and leukopenia (13%). There was one grade 5 febrile neutropenia during the first cycle.
Conclusions The pharmacokinetics of S-1 was not influenced by oxaliplatin. S-1/Oxaliplatin combination therapy is highly active against AGC and has a favorable toxicity profile.

Keywords S-1 · Oxaliplatin · Advanced gastric cancer · Phase I · Phase II

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Introduction

Stomach cancer is one of the leading causes of cancer death worldwide. Although the worldwide incidence of stomach cancer is decreasing, the incidence in eastern Asia is still high [1]. Surgical resection is the only curable treatment for advanced gastric cancer (AGC), but many patients are diagnosed with advanced, unresectable state [2]. In such patients, palliative chemotherapy can prolong survival and improve quality of life [3–5]. To date, there is no consensus standard chemotherapy regimen for AGC. Until recently, cisplatin plus 5-FU (CF) or epirubicin plus cisplatin plus 5-FU (ECF) have been widely used for the treatment of patients with AGC [2].

Oral fluoropyrimidines have been developed as substitutes for 5-FU which is administered by continuous infusion via central venous catheter. Recent studies have demonstrated that oral fluoropyrimidines have efficacy and toxicities comparable with intravenous 5-FU [6, 7]. S-1 is a novel oral fluoropyrimidine mixture that consists of tegafur, 5-chloro-2,4-dihydropyrimidine (CDHP), and potassium oxonate (Oxo). S-1 is active against AGC and beneficial in terms of convenience and quality of life [8–11]. In a preclinical model, S-1 and cisplatin exhibited synergism similar to that of 5-FU and cisplatin [12]. Several phase I/II trials with various dosing schedules of S-1 plus cisplatin

showed that this combination was safe and active against AGC [13–16]. A recent Japanese phase III study (SPIRITS trial) showed S-1 plus cisplatin was superior to S-1 alone, with median overall survival (OS) of 13.0 months, median progression-free survival (PFS) of 6.0 months, and response rate of 54% [17].

Oxaliplatin, a platinum analog, is reported to be less toxic than cisplatin in terms of nausea, vomiting, nephrotoxicity, and ototoxicity [18, 19]. Recent phase III studies have shown that 5-FU plus oxaliplatin had comparable efficacy and less toxicity compared with 5-FU plus cisplatin [6, 20].

In the present study, we developed a new treatment protocol for AGC consisting of S-1 and oxaliplatin. The purpose of the phase I portion of this study was to determine the maximum-tolerated dose (MTD) and recommended dose (RD) of S-1 in a 3-week cycle when administered with a fixed dose of oxaliplatin in patients with AGC. The phase II portion of this study evaluated the activity, safety, and pharmacokinetic profiles of this combination regimen at the RD when used as a first-line treatment for AGC.

Materials and methods

Patients

Patients aged from 18 to 70 years with histologically confirmed unresectable or metastatic adenocarcinoma of the stomach, with the following inclusion criteria, were eligible: Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; no prior palliative chemotherapy or radiotherapy; adequate bone marrow, renal, and liver functions; and written informed consent. Prior to adjuvant chemotherapy that did not contain 5-FU derivatives or platinum was allowed if it was completed at least 6 months before enrollment. In phase II study, measurable lesions according to the Response Evaluation Criteria in Solid Tumors (RECIST) were required. Patients were excluded if they had brain metastasis, obvious gastrointestinal obstruction, significant gastrointestinal bleeding, serious comorbid medical illness, or peripheral neuropathy ≥grade 2. This study was approved by the institutional review board of the Asan Medical Center, Seoul, Korea.

Phase I dose escalation scheme

Oxaliplatin was administered intravenously over 2 h on day 1 (D1) at a fixed dose of 130 mg/m^2. S-1 was administered orally twice per day, within an hour after a meal on D1 through D14. S-1 dose was calculated in mg/m^2 body surface area (BSA) and was rounded down to the nearest 5 or 10 mg. The starting dose of S-1 was 70 mg/m^2 per day (level 1), and the dose was escalated by 10 mg/m^2 per day up to 100 mg/m^2 per day (level 4). The treatment was repeated every 3 weeks. The next course was started when the absolute neutrophil count (ANC) ≥1,500 per μL, platelet count ≥100,000 per μL and non-hematological toxicities ≤grade 1.

Dose-limiting toxicities (DLTs) were defined as: (1) ANC <500 per μL for ≥5 days; (2) febrile neutropenia; (3) grade 4 thrombocytopenia; (4) any other grades 3–4 non-hematological toxicities except alopecia that did not improve to at least grade 1 within 2 days following the institution of appropriate therapy; (5) toxicity-related discontinuation of S-1 treatment for more than eight doses; or (6) any toxicities that delayed S-1 and oxaliplatin treatment for more than 2 weeks. The standard 3 + 3 phase I scheme was used, with the toxicity observation during the first treatment cycle. Dose escalation was continued until DLTs occurred in two or more of six patients and this was defined as the MTD. Intrapatient dose escalation was not permitted.

Phase II treatment dose modification scheme

The RD for the phase II study was defined as one dose level below the MTD. On the day of treatment, the ANC had to be ≥1,500 per μL and platelet count ≥100,000 per μL. If the treatment was delayed because of toxicity, both drugs were withheld til recovery. If the ANC and platelet count did not recover to ≥1,500 per μL and ≥100,000 per μL after 2-week delay, respectively, the patient was withdrawn from the study. The S-1 dosage was adjusted at any time during the phase II study. S-1 was interrupted until recovery to grade 1 or better in cases of non-hematological toxicity (except alopecia) ≥grade 2, thrombocytopenia ≥grade 3, or grade 4 neutropenia. S-1 and oxaliplatin were reduced by 25% if patients experienced the following conditions: first occurrence of grade 4 thrombocytopenia, grade 4 neutropenia lasting for ≥5 days, febrile neutropenia, or grade 3 non-hematological toxicity; second occurrence of grade 3 thrombocytopenia, grade 4 neutropenia lasting for <5 days, or grade 2 non-hematological toxicity, and by 50% on subsequent recurrence of the same toxicities mentioned above or the first occurrence of grade 4 non-hematological toxicity. If the same toxicities with the same severity recurred after a 50% dose reduction then, the treatment was discontinued and the patient was withdrawn from the study.

Oxaliplatin dose adjustment was performed according to the oxaliplatin-specific neurosensory toxicity [21]. Treatment was interrupted until neurotoxicity resolved to grade 1 or better. Oxaliplatin was reduced by 25% on the first occurrence of grade 2 neurotoxicity and by 50% on the second occurrence. Treatment was discontinued upon

occurrence of subsequent grade 2 neurotoxicity, grade 3/4 neurotoxicity, or treatment delay for >2 weeks. Treatment continued for a maximum of nine treatment cycles or until disease progression, appearance of unacceptable toxicities, or withdrawal of consent.

Pre-treatment and on-treatment evaluation for response and toxicities

Two weeks before the entry into the study, patients underwent the following evaluations; such as medical history; physical examination; CBC, serum chemistry, and electrolytes; urinalysis; electrocardiography; chest X-ray; and computed tomography (CT) scans of the abdomen and pelvis. Tumor response was evaluated according to the RECIST criteria every two treatment cycles [22]. Safety evaluation was performed every cycle using NCI CTCAE version 3.0. CBC was performed weekly. Compliance with S-1 was monitored by patient query and counting of pills at each outpatient visit.

Pharmacokinetic analysis of S-1

Six patients in the phase II portion who did not have liver metastasis or previous gastrectomy were enrolled for pharmacokinetic analysis of S-1. These patients were given a single oral dose of S-1 5 days before the first cycle and then treated with the ordinary study protocol except that S-1 was given only once on D1. Quantification and calculation of C_{max}, T_{max}, and AUC were performed as described previously [23]. Blood was sampled at 0, 1, 2, 4, 6, 8, and 12 h after S-1 administration on D-5 and D1. C_{max} and T_{max} were determined from the raw concentration–time data on D-5 and D1. AUC_{0-last} was computed from the raw concentration–time data on D-5 and D1 by the linear trapezoidal method.

Statistics and sample size calculation

The primary end point of the phase II portion was to assess the overall response rate (ORR). Simon's optimal two-stage design was used to test the null hypothesis $P_0 = 0.4$ versus $P_1 = 0.6$, with $\alpha = 0.05$ and $\beta = 0.1$. The first stage required at least 12 confirmed responses out of 28 patients. In the second stage, accrual was planned for a total of 41 patients and the primary end point would be met if there were 21 confirmed responses. Assuming a 10% drop-out rate, 46 patients were required. Kaplan–Meier estimates were used in the analysis of time to progression (TTP) and OS. The actual administered dose of both drugs and intervals between treatments were used to calculate the dose intensity. SPSS for Windows version 14.0 (SPSS Inc., Chicago, IL) was used for statistical analyses.

Results

Patient characteristics

From May 2005 to September 2006, a total of 63 patients were enrolled, including 18 patients in the phase I study. The cutoff date for data analysis was 1 January 2008. Table 1 shows the pretreatment characteristics of patients. Among the 63 patients, 4 had gastrectomy and 2 received adjuvant chemotherapy with FAM regimen [24] or doxifluridine alone. The majority of patients had ECOG performance status ≤1.

Determination of MTD and RD

At dose level 1, no patients experienced DLTs. At dose level 2, one of three patients experienced mental change

Table 1 Pretreatment characteristics of patients

	Phase I (n = 18) No. of pts (%)	Phase II[a] (n = 47) No. of pts (%)
Age (years)		
Median (range)	47 (30−66)	55 (31−70)
BSA (m^2)		
Median (range)	1.60 (1.30−1.84)	1.66 (1.38−1.95)
Sex		
Male	6 (33%)	36 (77%)
Female	12 (67%)	11 (23%)
ECOG PS		
0–1	18 (100%)	42 (89%)
2	0	5 (11%)
Disease status		
Metastatic	16 (89%)	42 (89%)
Recurrent	0	4 (9%)
Locally advanced	2 (11%)	1 (2%)
Sites of metastasis		
M1 LNs	4 (22%)	34 (72%)
Liver	3 (17%)	28 (60%)
Peritoneum	13 (72%)	18 (38%)
Lung/bone	0	2 (4%)
No. of metastatic organs		
1	9 (56%)	10 (22%)
2	5 (31%)	19 (41%)
≥3	2 (13%)	17 (37%)
Location of tumor		
Cardia/fundus	1 (6%)	4 (9%)
Body	6 (33%)	19 (40%)
Antrum/pylorus	6 (33%)	16 (34%)
Diffuse	5 (28%)	8 (17%)

BSA body surface area, *PS* performance status, *LN* lymph node

[a] Including two patients with measurable disease allocated to dose level 4 in the phase I portion

Table 2 Toxicities according to the dose level in the phase I portion of the study during the first cycle

Toxicity	Level 1 ($n = 3$)		Level 2 ($n = 6$)		Level 3 ($n = 3$)		Level 4 ($n = 6$)	
	All events	Grades 3–4	All events	Grades 3–4	All events	Grades 3–4	All events	Grades 3–4
Anemia	3	0	6	1	3	0	6	0
Leukopenia	1	0	2	0	1	0	3	0
Neutropenia	1	0	2	0	1	0	5	0
Thrombocytopenia	0	0	0	0	0	0	0	0
Febrile neutropenia	0	0	0	0	0	0	0	0
Anorexia	3	0	5	0	3	0	5	0
Asthenia	3	0	4	0	2	0	5	0
Nausea	3	0	5	0	3	0	5	0
Vomiting	3	0	3	0	1	0	3	0
Stomatitis	1	0	2	0	0	0	2	0
Diarrhea	0	0	0	0	1	0	0	0
Neuropathy	0	0	0	0	0	0	3	0
Hand–foot syndrome	0	0	2	0	1	0	1	0
Allergic reaction	0	0	1	0	0	0	0	0

Table 3 Objective response rates according to the dose level

Response	Phase I[a] ($n = 18$)				Phase II[b]	
	Level 1	Level 2	Level 3	Level 4	ITT ($n = 47$)	PP ($n = 43$)
CR	0	0	0	0	0	0
PR	1	4	0	1	26 (55.3%)	26 (60.5%)
SD	0	1	0	0	14 (29.8%)	13 (30.2%)
PD	0	0	0	1	3 (6.4%)	3 (7.0%)
NE	2	1	3	4	4 (8.5%)	1 (2.3%)

ITT intention to treat, *PP* per protocol, *CR* complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluable

[a] In phase I portion, ten patients without measurable lesion were classified as NE

[b] Including two patients with measurable disease allocated to dose level 4 in the phase I portion

that resulted from hyponatremia induced by syndrome of inappropriate antidiuretic hormone. We expanded level 2 cohort to six patients, but no additional DLTs occurred. There were also no DLTs at dose levels 3 and 4. To confirm the safety, the level 4 cohort was expanded to six patients and none of whom experienced DLTs. We were unable to establish the MTD up to dose level 4, so we used dose level 4 as the RD for the phase II portion (Table 2). We administered 119 cycles in the phase I study, with a median of eight cycles per patient (range 2–9 cycles). Six of eight patients with measurable lesions had a confirmed partial response (PR) in the phase I portion (Table 3).

Efficacy and safety of phase II portion

In the phase II portion, we administered study medication to 47 patients, including two patients with measurable lesions enrolled at dose level 4 in the phase I portion. We administered 250 chemotherapy cycles, with a median of six cycles per patient (range 1–9 cycles). The median relative dose intensity (RDI) of S-1 and oxaliplatin was 81.3% (range 47.5–106.7%) and 80.8% (range 45.3–102.6%), respectively.

Of the 47 patients, we did not include four patients in per protocol analysis because of treatment refusal after one cycle. Twenty-six patients achieved a confirmed PR (55.3%, 95% CI 53–57%; Table 3), 13 had stable disease (SD) (29.8%, 95% CI 28–32%), and the remaining four patients had progressive disease (PD). The median response duration for patients with PR was 5.9 months (range 1.0–19.5 months). With a median follow-up duration of 19.1 months (range 15.6–24.3 months), the median TTP was 6.6 months (95% CI 4.0–9.2 months), and the median OS was 12.5 months (95% CI 9.2–15.9 months) (Fig. 1).

Table 4 summarizes adverse events. Among the grade 3/4 hematological toxicities, anemia ($n = 8$, 17.4%), leukopenia

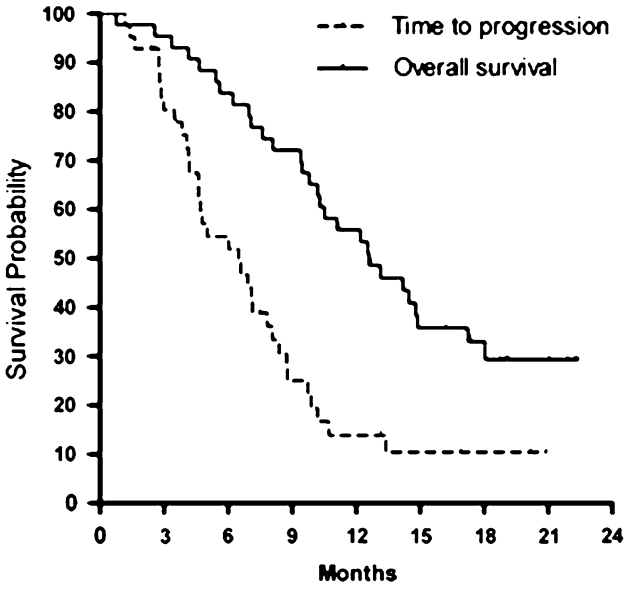

Fig. 1 Kaplan–Meier survival curves. Median time to progression was 6.6 months (95% CI 4.0–9.2 months) and median overall survival was 12.5 months (95% CI 9.2–15.9 months)

($n = 6$, 13.0%), neutropenia ($n = 13$, 27.6%), and thrombocytopenia ($n = 18$, 38.7%) were frequent. Four patients (8.5%) experienced grade 3 bleeding and febrile neutropenia, and one patient had grade 5 febrile neutropenia during the first cycle. Asthenia, anorexia, nausea, and neuropathy were frequently observed, but there were few other grade 3/4 non-hematological toxicities.

Twenty-eight patients (66.7%) underwent dose reduction of S-1 and oxaliplatin at least once during their treatment. The reasons for dose reduction were thrombocytopenia ($n = 12$, 28.6%), leukopenia ($n = 7$, 16.7%), both leukopenia and thrombocytopenia ($n = 3$, 7.1%), diarrhea ($n = 2$, 2.4%), asthenia ($n = 1$, 2.4%), hyperbilirubinemia ($n = 1$, 2.4%), neuropathy ($n = 1$, 2.4%), and vomiting ($n = 1$, 2.4%). The reasons for stopping treatment were disease progression ($n = 20$, 42.5%), unacceptable toxicity ($n = 13$, 27.7%), completion of planned cycles ($n = 9$, 19.1%), and patient's own will ($n = 5$, 10.6%). Median RDI after the completion of all chemotherapy cycles for S-1 and oxaliplatin was 81.3% (range 47.5–106.7) and 80.8% (range 45.3–102.6), respectively. However, the RDI had a tendency to get lower as patients progressed through more chemotherapy cycles (Fig. 2).

Pharmacokinetic analysis

The pharmacokinetic parameters of S-1 on D-5 are comparable to those of D1, indicating that oxaliplatin does not appreciably affect the PK of S-1 (Table 5).

Discussion

This is the first study of S-1/oxaliplatin combination chemotherapy for the treatment of AGC. The MTD was not reached in the phase I portion, so we established RD for phase II study as 100 mg/m^2 per day of S-1 and 130 mg/m^2 of oxaliplatin for a 3-week cycle, indicating that full single agent doses of both drugs can be used in combination.

Using this dose schedule, very promising efficacy was obtained in the phase II study: an ORR of 55.3%, a median TTP of 6.6 months, and a median OS of 12.5 months.

Table 4 Toxicities by patients in the phase II portion of the study ($n = 47$)

Toxicity	Grade 1	Grade 2	Grade 3	Grade 4	All events (%)	Grades 3–4 (%)
Anemia	8	26	8	0	42 (91.3)	8 (17.4)
Leukopenia	11	11	2	4	28 (60.9)	6 (13.0)
Neutropenia	5	10	9	4	28 (60.9)	13 (27.6)
Thrombocytopenia	7	16	12	6	31 (89.1)	18 (38.7)
Bleeding	2	2	4	0	8 (17.4)	4 (8.5)
Febrile neutropenia	–	–	3	1		4 (8.5)
Asthenia	20	14	4	0	38 (82.6)	4 (8.5)
Anorexia	28	13	4	0	45 (97.8)	4 (8.5)
Nausea	30	3	2	0	35 (76.1)	2 (4.3)
Vomiting	18	4	1	0	23 (50.0)	1 (2.2)
Stomatitis	20	6	0	0	26 (56.5)	0
Diarrhea	16	8	2	0	26 (56.5)	2 (4.3)
Abdominal pain	8	7	3	0	18 (39.1)	3 (6.5)
Neuropathy	36	7	1	0	44 (95.7)	1 (2.1)
ALT elevation	7	1	2	0	10 (21.7)	2 (4.3)
Hyperbilirubinemia	16	8	1	0	25 (54.3)	1 (2.2)

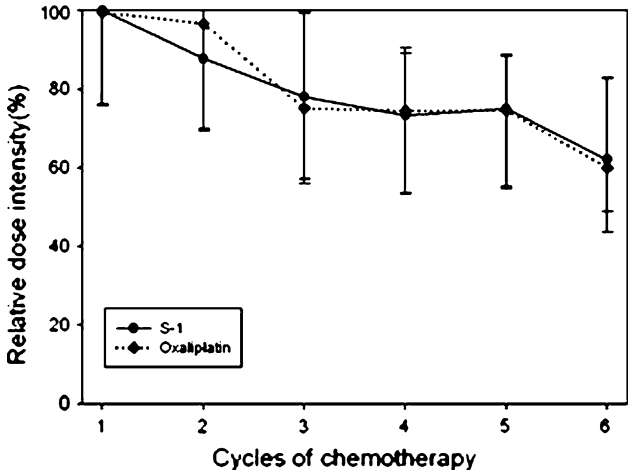

Fig. 2 Relative dose intensities of S-1 and oxaliplatin of patients during the first six cycles

Our efficacy results are comparable to those of other recently developed fluoropyrimidine plus platinum regimens for AGC. A phase II study of capecitabine and oxaliplatin combination (XELOX) showed an ORR of 63%, a median PFS of 5.8 months, and a median OS of 11.9 months [25]. And a phase II study of 3 weekly S-1 and cisplatin combination demonstrated an ORR of 48%, a median PFS of 5.3 months, and a median OS of 10.0 months [26]. Phases II and III studies of a 3-week cycle of capecitabine/cisplatin combination therapy showed an ORR of 41–55%, a median TTP/PFS of 5.6–6.3 months, and a median OS of 10.1–10.5 months [7, 27]. Although no studies have compared two oral fluoropyrimidines in combination with oxaliplatin, both S-1 and capecitabine seem to be comparable in efficacy and safety. In a randomized multicenter phase II trial of S-1 and capecitabine for elderly patients with AGC, each drug was active and tolerable when given as monotherapy and there were no significant differences in efficacy and toxicity [28].

Previous researchers have tested many different dose schedules of S-1 for the treatment of AGC. Initially, S-1 was developed in Japan and was mostly given on 6-week cycle (4 weeks on/2 weeks off). However, a subsequent Japanese post-marketing survey of S-1 showed that this schedule resulted in a median time to worst toxic events on D22 for hematological toxicities and on D15 for diarrhea and stomatitis, with a median recovery time of about 2 weeks from these toxicities. This suggests that a 3-week cycle may have some advantages [29]. Two clinical studies examined S-1 employing 3-week cycles (2 weeks on/1 week off) and reported fewer adverse events and prolonged medication periods [30, 31]. A recent randomized trial showed a tendency towards better toxicity profiles and similar efficacy of S-1 when it was given on a 3-week cycle rather than on a 6-week cycle for patients with head and neck cancer [32]. These results motivated us to use a 3-week cycle for S-1/oxaliplatin combination therapy.

In our series, toxicities were in general also well tolerated. Grade 3/4 hematological toxicities were 17.4% anemia, 27.6% neutropenia, and 38.7% thrombocytopenia.

Table 5 Pharmacokinetics of S-1 at a dose of 50 mg/m^2 ($n = 6$)

	FT		CDHP	
	S-1 alone on D-5 ($n = 6$)	S1 with OX on D1 ($n = 6$)	S-1 alone on D-5 ($n = 6$)	S1 with OXon D1 ($n = 6$)
C_{max} (ng/ml)	2,422.3 ± 701.1	2,282.7 ± 716.2	302.8 ± 196.0	239.6 ± 145.4
T_{max} (h)	2.8 ± 1.9	3.0 ± 1.6	2.5 ± 1.8	2.2 ± 1.5
AUC_{0-t} (ng h/ml)	17,456.1 ± 4,510.0	16,999.1 ± 2,852.3	1,426.2 ± 896.8	1,147.6 ± 429.5
AUC_{inf} (ng h/ml)	29,883.3 ± 9,047.9	27,544.2 ± 5,649.1	1,573.3 ± 978.1	1,306.1 ± 479.16
$T_{1/2}$	8.6 ± 1.7	7.7 ± 1.3	3.2 ± 0.4	3.7 ± 0.9
	5-FU		Oxo	
	S-1 alone on D-5 ($n = 6$)	S1 with OX on D1 ($n = 6$)	S-1 alone on D-5 ($n = 6$)	S1 with OXon D1 ($n = 6$)
C_{max} (ng/ml)	177.8 ± 59.7	143.9 ± 48.3	81.0 ± 62.2	52.8 ± 33.1
T_{max} (h)	3.7 ± 1.5	3.3 ± 1.0	2.5 ± 1.8	3.0 ± 1.1
AUC_{0-t} (ng h/ml)	1,031.6 ± 461.6	803.9 ± 247.0	367.8 ± 270.2	284.1 ± 121.3
AUC_{inf} (ng h/ml)	1,077.6 ± 477.8	848.2 ± 259.7	402.9 ± 299.8	351.1 ± 179.0
$T_{1/2}$	2.0 ± 0.3	2.2 ± 0.4	2.9 ± 0.7	4.8 ± 2.9

C_{max} maximum concentration, T_{max} time required to reach C_{max}, AUC_{0-t} area under curve until last sampling time after S-1 administration, AUC_{inf} area under curve from time zero extraplated to infinite time, $T_{1/2}$ half life, *OX* oxaliplatin, *FT* tegafur, *CHDP* 5-chloro-2,4-dihydroxypyridine, *Oxo* potassium oxonate

However, there was only one treatment-related death from septic shock. Gastrointestinal toxicities and constitutional symptoms were even milder. Sensorineural toxicity presumably caused by oxaliplatin and hand–foot syndrome frequently noticed with capecitabine was also generally tolerable with the current regimen. Similarly, a Japanese group reported a phase I/II study of a 3-week cycle of S-1/oxaliplatin combination therapy for the treatment of colorectal cancer [33]. They fixed the dose of S-1 at 80–120 mg/day on D1–D14 and determined the recommended dose of oxaliplatin as 130 mg/m^2 on D1. The toxicity profile of this study was also quite favorable with only 27% grade 3/4 thrombocytopenia, 14% grade 3 neutropenia, and 3% grade 3 diarrhea.

On the other hand, oxaliplatin seems to have advantages over cisplatin in both efficacy and tolerability. In SPIRITS trial [17], grade 3/4 hematological toxicities with S-1/cisplatin combination included leukopenia (11%), neutropenia (40%), thrombocytopenia (5%), and febrile neutropenia (3%). Frequent grade 3/4 non-hematological toxicities included anorexia (30%) and nausea (11%). In phase II portion of S-1/cisplatin by Lee et al. [26], grade 3/4 hematological toxicities included leukopenia (4.8%), neutropenia (33.4%), thrombocytopenia (4.8%), and febrile neutropenia (0%). Frequent grade 3/4 toxicities included anorexia (23.8%), asthenia (14.3%). When compared with these two studies of S-1/cisplatin, non-life-threatening thrombocytopenia was frequent, but other hematological toxicities were comparable and non-hematological toxicities, such as anorexia, nausea, and asthenia were less frequent in our study. Hence, S-1/oxaliplatin combination has at least comparable efficacy and safety with S-1/cisplatin. A recent phase III study of epirubicin/fluoropyrimidine/platinum triplet (REAL-2) also suggested certain therapeutic advantages of oxaliplatin over cisplatin [6].

The dose of S-1 that we used (100 mg/m^2 per day) is greater than both the typical single agent dose of S-1 (80 mg/m^2 per day) and the 80–120 mg/day dose used in the aforementioned Japanese study [33]. We set our RD at 100 mg/m^2 per day because we observed no DLTs with this dose during the first cycle. We did not expand the dose level of phase I study referring to previous phase I/II study of S-1 and cisplatin in AGC conducted in our center [26]. In our previous study of S-1/cisplatin combination, we used a lower dose of S-1 (80 mg/m^2 per day) after the first 20 patients were treated with 90 mg/m^2 per day, which had been decided as RD in the phase I portion of the study, because of poor bone marrow recovery after chemotherapy. During our entire treatment period, dose modification was frequently needed due to the delayed recovery of hematological toxicities. This suggests that our regimen may have caused cumulative myelosuppression. The RDI of the S-1/cisplatin regimen became lower as patients went through more chemotherapy cycles, and that modification of RD resulted in improved RDI and better tolerability. In this study of S-1/oxaliplatin combination, most of the grade 3/4 hematological toxicities occurred after three cycles of chemotherapy, and the RDI of S-1/oxaliplatin regimen also became lower over chemotherapy cycles. Thus, we suggest a lower dose of S-1 (80 mg/m^2 per day) with oxaliplatin (130 mg/m^2) may improve tolerability and maintain the RDI over chemotherapy cycles.

The pharmacokinetic data of our study showed that the absorption and metabolism of S-1 were unaffected by co-administration of oxaliplatin. In a previous pharmacokinetic study of S-1 and cisplatin, 5-FU concentration was also unaffected by cisplatin [13]. Other studies showed that the concentration of 5-FU and Oxo after administration of S-1 did not differ between patients with gastrectomy and patients without gastrectomy [13, 34]. Another study comparing pre- and post-gastrectomy pharmacokinetics of S-1 showed that the concentration of 5-FU, CDHP, and Oxo were higher in post-gastrectomy status rather than pre-gastrectomy status [35]. Taken together, these previous studies and our series indicate that S-1 can be used with platinum compounds to treat recurrent stomach cancer regardless of gastrectomy.

In conclusion, the RD of our S-1/oxaliplatin combination regimen was determined at the dose of 100 mg/m^2 per day of S-1 from day 1 to 14 in combination with 130 mg/m^2 of oxaliplatin on D1 in a 3-week cycle. Pharmacokinetic profile of S-1 was not influenced by co-administration of oxaliplatin. Our regimen incorporating 2 weeks of administration and 1 week of rest was highly active against AGC with a favorable toxicity profile.

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