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PHASE II STUDIES

A phase II study of S-1 and oxaliplatin (SOx) combination chemotherapy as a first-line therapy for patients with advanced gastric cancer

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Summary *Background* Palliative chemotherapy has been shown to have a survival benefit for patients with recurrent or metastatic gastric cancer. 5-fluorouracil (5-FU) and cisplatin have been widely used in a variety of combinations. We conducted a phase II study of combination chemotherapy with new agents, S-1 and oxaliplatin (SOx), in advanced gastric cancer patients in an effort to evaluate the efficacy and toxicity of this regimen. *Method* Histologically confirmed recurrent or metastatic gastric cancer were treated by the oral administration of S-1 80 mg/m^2/day on days 1–28, and oxaliplatin 85 mg/m^2 administered as a 90-min intravenous infusion on days 1, 15, and 29. Treatment courses were repeated every 6 weeks. Patients received a maximum of four cycles. *Results* From Feb 2006 to May 2008, 41 patients were enrolled in this study. The ratio of males to females was 28 to 13. The median patient age was 61 years (range, 36–74 years), and 85.4% (35/41) of the patients had a performance status (ECOG) of 1. The median number of chemotherapy cycles administered was 3 (range, 1–4). According to the results of our Intent-to-Treat analysis, 22 patients (53.7%) achieved a partial response (95% CI, 38–70%). 15 patients (36.6%) evidenced a stable disease, and 1 patient (2.4%) progressed during the course of the treatment. 3 patients were lost to follow-up prior to evaluation. The median time to progression and overall survival time were 4.6 months (95% CI, 3.4–5.8 months) and 7.8 months (95% CI, 6.9–8.7 months) from the start of the chemotherapy, respectively. A total of 114 cycles were assessed for toxicity. The major hematologic toxicities included grade 2 anemia (41.2%), grade 1-2 neutropenia (28.1%), and grade 1 thrombocytopenia (23.7%). Only 1 cycle of neutropenic fever occurred. The non-hematological toxicities observed were grade 3 vomiting (12.2%) and grade 3 diarrhea (4.9%). No treatment-related deaths occurred in our patient population during the study period. *Conclusion* The SOx regimen evidenced a relatively high response rate and was well tolerated as a first-line therapy for advanced gastric cancer.

Keywords S-1 · Oxaliplatin · Advanced gastric cancer

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Introduction

Gastric cancer is a common malignancy worldwide, with a high mortality rate. Combination chemotherapy regimens involving two or three agents have more than doubled

survivorship as compared with best supportive care [1–3]. Recent clinical trials have included the evaluation of docetaxel, cisplatin, and 5-fluorouracil (5-FU), which were shown to confer a survival advantage compared with cisplatin and 5-FU; however, these compounds were associated with high rates of toxicity, and particularly neutropenia and neutropenic fever [4].

S-1 is a novel orally administered drug, and consists of a combination of tegafur (FT), 5-chloro-2,4-dihydroxypyridine (CDHP), and oteracil potassium (Oxo) in a 1 : 0.4 : 1 molar concentration ratio [5]. 5-chloro-2,4-dihydroxypyridine is a competitive inhibitor of dihydropyrimidine dehydrogenase, which is involved in the degradation of 5-FU, and helps to maintain efficacious concentrations of 5-FU in plasma and tumor tissues [6]. Oteracil potassium, a competitive inhibitor of orotate phosphoribosyltransferase, inhibits 5-FU phosphorylation in the gastrointestinal tract, thereby ameliorating the serious gastrointestinal toxicity associated with 5-FU [7]. The antitumor effect of S-1 has been previously demonstrated in a variety of solid tumors, including gastric cancer [8, 9], colorectal cancer [10], non-small-cell lung cancer [11], and head and neck cancer [12]. The efficacy of S-1 in the treatment of gastrointestinal cancer has also been reported, and the response rates for advanced gastric cancer (AGC) and colorectal cancer were 32 and 24%, respectively [13, 14].

Oxaliplatin, a platinum analog, is reported to be less toxic than cisplatin in terms of nausea, vomiting, nephrotoxicity, and ototoxicity [15, 16]. Recent phase III studies have shown that 5-FU plus oxaliplatin had comparable efficacy and less toxicity than the combination of 5-FU and cisplatin [17, 18].

We conducted a phase II study involving the application of a combination chemotherapy consisting of S-1 and oxaliplatin to previously untreated AGC patients, in order to evaluate prospectively the efficacy and toxicity of this regimen.

Patients and methods

Eligibility

Patients must have had histologically confirmed adenocarcinoma of the stomach and at least one measurable lesion. Patients that had undergone previous adjuvant chemotherapy were eligible if they had completed treatment more than 6 months prior to enrollment in this study. Additionally, patients had to have no central nervous system metastases; no active infection; no serious or uncontrolled concurrent medical illness; no history of other malignancies; sufficient hepatic, renal and bone marrow functions; an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; and an age exceeding 20 years. Patients were required to provide written informed consent to participate in the study. This prospective clinical trial was approved by the local ethical committee of Gyeong-Sang National University Hospital.

Treatment protocol and dose modification

AGC patients were treated with S-1 40 mg/m^2 administered orally twice daily on days 1–28, and 85 mg/m^2 of oxaliplatin administered as a 90-min intravenous infusion on days 1, 15, and 29. Treatment courses were repeated every 6 weeks. Dose modifications were made to the S-1 or oxaliplatin for hematologic, gastrointestinal, or neurologic toxicity, based on the most severe grade of toxicity occurring during the previous cycle. The patients were assessed prior to the beginning of each cycle, in accordance with the National Cancer Institute-Common Toxicity Criteria (NCI-CTC), except in the case of neurotoxicity, in which case, an oxaliplatin-specific scale was employed: grade 1, paresthesias or dysesthesias of short duration, but resolving prior to the next cycle; grade 2, paresthesias persisting between cycles (2 weeks); and grade 3, paresthesias interfering with function. Treatment was delayed for up to 2 weeks in cases in which symptomatic toxicity persisted, ANC were <1,500/μL, and platelet count <100,000/μL. The dose of S-1 was reduced by 25% for subsequent courses in cases involving NCI-CTC grade 3 diarrhea, stomatitis, or dermatitis, and the oxaliplatin dose was reduced by 25% in subsequent cycles in cases in which persistent paresthesias between cycles or paresthesias with functional impairment persisted for more than 7 days. Treatment was continued until signs of disease progression or unacceptable toxic effects developed, or until a patient refused further treatment. Relative dose-intensity (RDI) was calculated by dividing the dose-intensity by the planned dose-intensity, and is expressed as a percentage. Planned dose-intensities, expressed as mg/m^2/week, were 373.3 for S-1 and 42.5 for oxaliplatin.

Follow-up evaluation and response assessment

Prior to each course of treatment, a physical examination, routine hematologic studies, blood chemistry, and chest X-ray were conducted. CT scans were also conducted in order to define the extent of disease and response after every cycle of chemotherapy, or sooner in cases in which there was evidence of any clinical deterioration.

Responses were evaluated according to RECIST criteria [19].

Statistical methods

This trial was designed to detect a response rate of 50%, as compared to the minimal clinically meaningful response

rate of 30%. A two-stage minimax design was adopted, as previously proposed by Simon, with a statistical power of 80% for hypothesis acceptance and 5% significance for hypothesis rejection. The first-stage sample size was calculated as 19. The study was to be terminated if six or fewer responses were received. The total sample size required was 38 patients with measurable disease. Allowing for a follow-up loss rate of up to 10%, the total sample size required was 41 patients.

Categorical variables in the two groups were compared via the χ^2 test or Fisher's exact test. *P* values of less than .05 were considered statistically significant and all *P* values corresponded to two-sided significance tests. Time to progression (TTP) and overall survival (OS) were calculated via the Kaplan-Meier method. Survival curves were compared via the log-rank test. All tests were two-sided, and a *P* value of <0.05 was considered statistically significant. TTP was calculated from the date of initiation of therapy to the date of disease progression, death, or final follow-up. OS was calculated from the date on which therapy was initiated to the date of death or final follow-up. All data were analyzed using SPSS software (version 18.0, Chicago-IL).

Results

Patient characteristics

Between Feb 2006 and May 2007, 41 patients were assigned for treatment at the Department of Internal Medicine, Gyeongsang National University School of Medicine, Jinju, Korea. The male-to-female ratio was 28:13, and the median patient age was 61 years (range, 36–74 years). 35 patients were newly diagnosed as a metastatic disease and 6 patients evidenced gastric cancer relapse following curative surgery. The most frequent metastatic sites were the lymph node (63.4%) and liver (43.9%). 85.4% of the patients had an ECOG performance status of 0 or 1. The basal characteristics of the patients are provided in Table 1.

Table 1 Patient characteristics

	No. of patients	%
Total number of patients	41	
Gender		
Male	28	68.3
Female	13	31.7
Age		
Median (Range)		61 (36–74)
Performance status (ECOG)		
0–1	35	85.4
2	6	14.6
Hemoglobin		
≥12 g/dL	14	34.1
<12 g/dL	27	65.9
Carcinoembryonic antigen		
<5 ng/mL	20	48.8
≥5 ng/mL	21	51.2
Previous operation		
Curative	6	14.6
Adjuvant chemotherapy	5	
Adjuvant chemoradiotherapy	1	
Palliative	4	9.8
None	31	75.6
Previous exposure to 5-fluorouracil		
Yes	3	7.3
No	38	92.7
No. of organ involved		
1	13	31.7
2	17	41.5
≥3	11	26.8
Organ involved (multiple involved)		
Metastatic lymph node	26	63.4
Peritoneum	18	43.9
Liver	11	26.8
Lung	7	17.1
Pancreas	5	12.2
Colon	3	7.3
Uterus	2	4.9
Other organ	4	9.8

Response

According to the results of Intent-to-Treat analysis, 22 patients (53.7%) achieved a partial response (95% CI, 38–70%), 15 patients (36.6%) evidenced stable disease, and 1 patients (2.4%) progressed over the course of treatment. 3 patients were lost to follow-up prior to evaluation. After progression, a total of 25 patients received second- and/or third-line chemotherapy; 21 patients were treated with an irinotecan-based FOLFIRI regimen and 9 patients received taxane-based salvage chemotherapy.

Survival and prognostic factor

The median follow-up duration was 37.8 months. The median time to progression and overall survival time were 4.6 months (95% CI, 3.4–5.8 months) and 7.8 months (95% CI, 6.9–8.7 months) from the start of the chemotherapy, respectively. TTP and OS were evaluated via Kaplan-Meier analysis, as shown in Fig. 1. The 6-month and one-year survival rates were 68% and 34%, respectively.

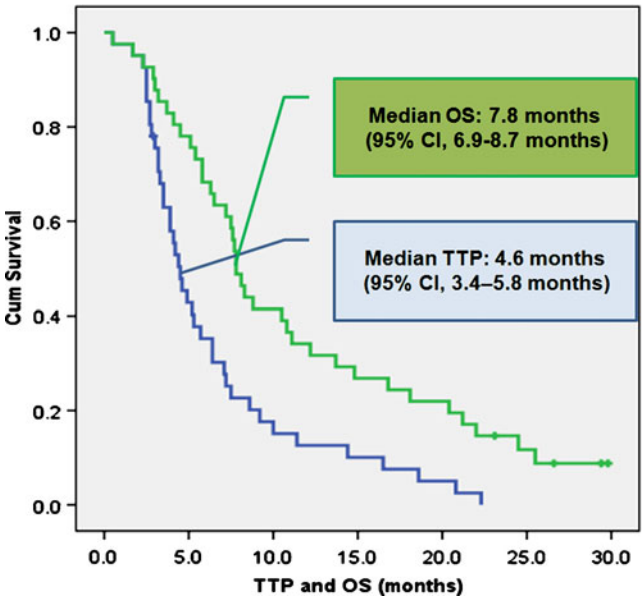

Fig. 1 The median time to progression and overall survival time were 4.6 months (95% CI, 3.4–5.8 months) and 7.8 months (95% CI, 6.9–8.7 months)

The analyzed factors and results are provided in Table 2. Gender, age, performance status, hemoglobin, CEA, initial metastasis, and numbers of metastasis were evaluated for analysis. However, according to multivariate analysis, no factor was determined to predict better response rates or longer TTP and OS duration.

Dose administration and Toxicity

Forty-one patients received a total of 114 treatment cycles. The median number of SOx cycles administered was 3 (range 1–4 cycles). The dose intensities of oxaliplatin and S-1 were 40.8 mg/m^2/week and 352.9 mg/m^2/week, and the RDIs of oxaliplatin and S-1 were 95.9% and 94.5%.

Table 2 Prognostic factors

	Response* (CR + PR)	TTP†	OS†
Sex (male)	0.524	0.064	0.187
Age≥60	1.000	0.304	0.594
Performance 2	1.000	0.590	0.490
CEA≥5 ng/mL	1.000	0.369	0.248
Hemoglobin <12 g/dL	0.346	0.071	0.061
Initially metastasis	1.000	0.185	0.352
Organ involvement ≥3	1.000	0.641	0.712

* Fischer's exact test (2-sided)

† Kaplan-Meier and Cox Regression Analysis

CR Complete Response, *PR* Partial Response, *CEA* carcinoembryonic antigen, *TTP* time to progression, *OS* overall survival

Toxicities observed during the treatment are listed in Table 3. The major hematologic toxicities detected included grade I anemia (50.9%), grade I-II neutropenia (27.2%), and grade I thrombocytopenia (24.6%). Only 1 cycle of neutropenic fever was recorded in this study. Grade I neuropathy was observed in 17 patients (41.3%). Grade I mucositis was noted in 8 patients (19.5%). Six patients (14.6%) experienced grade I vomiting. The more severe non-hematological toxicities observed included grade III vomiting (12.2%) and grade III diarrhea (4.9%). No treatment-related deaths were noted in this study.

Discussion

For patients with unresectable, recurrent, or advanced gastric cancer, systemic chemotherapy can provide significant palliation of symptoms [2, 3]. However, despite the introduction of new agents, such as paclitaxel, docetaxel, irinotecan, capecitabine, S-1, and oxaliplatin, the median survival rates of gastric cancer have remained substantially unchanged [20–25].

Phase 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 [24, 26]. Although no studies have compared two oral fluoropyrimidines in combination with oxaliplatin, both S-1 and capecitabine appear to be comparable in terms of efficacy and safety. In a randomized multicenter phase II trial of S-1 and capecitabine for elderly patients with AGC, each drug proved active and tolerable

Table 3 Toxicity of treatment

	NCI-CTC‡ grade (%)			
	1	2	3	4
Hematologic (n=114) *				
Anemia	58 (50.9)	46 (40.4)	5 (4.4)	
Neutropenia	26 (22.8)	5 (4.4)	1 (0.9)	1 (0.9)
Thrombocytopenia	28 (24.6)	13 (11.4)	11 (9.6)	1 (0.9)
Febrile neutropenia				1 (0.9)
Non-hematologic (n=41) [a]				
Nausea	7 (17.1)	2 (4.9)	5 (12.2)	
Vomiting	6 (14.6)	3 (7.3)		
Diarrhea	5 (12.2)	1 (2.4)	2 (4.9)	
Mucositis	8 (19.5)	4 (9.8)		
Neuropathy	17 (41.5)	3 (7.3)	1 (2.4)	
Fatigue			1 (2.4)	

* per cycle

[a] per person, maximum toxicity of each patient

‡ National Cancer Institute-Common Toxicity Criteria v3.0

Table 4 Comparison of efficacy and toxicity of 1st line SOx in AGC

Study	Park et al. [29]	Koizumi et al. [30]	Oh et al [this study]
No. of patients	47	55	41
Schedule			
S-1	100 mg/m^2 d1–14	80 mg/m^2 d1–14	80 mg/m^2 d1–28
Oxaliplatin	130 mg/m^2 d1	100 mg/m^2 d1	85 mg/m^2 d1,15,29
	q 3 weeks	q 3 weeks	q 6 weeks
No. of treatment			
Median (range)	6 (1–9)	6 (1–16+)	3 (1–4)
Efficacy			
Response rate (%)	55.3	59	53.7
Median TTP (95% CI, months)	6.6 (4.0–9.2)	6.5 (4.8–11.2)	4.6 (3.4–5.8)
Median OS (95% CI, months)	12.5 (9.2–15.9)	16.5 (13.2–22.3)	7.8 (6.9–8.7)
Toxicity: NCI-CTC G III-IV (%)			
Neutropenia	27.6	22	1.8
Anemia	17.4	9	4.4
Vomiting	2.2	0	12.2
Diarrhea	4.3	2	4.9
Mucositis	0	0	0
Neuropathy[§]	2.1	4	2.4

AGC Advanced gastric cancer, *TTP* Time to progression, *OS* Overall survival, *NCI-CTC G*: National Cancer Institute-Common Toxicity Criteria (v3.0) Grade

when administered as monotherapy, and no significant differences in efficacy and toxicity were noted [27].

According to the FLAGS trial results, cisplatin/S-1 could be considered a substitute for cisplatin/infusional fluorouracil, as it eliminates the need for portable infusional devices and frequent visits to the treating center, owing to its lower toxicity levels. Like an S-1 substitutable for 5-fluorouracil, a recent phase III study of epirubicin/Xuoropyrimidine/platinum triplet (REAL-2) has also suggested certain therapeutic advantages of oxaliplatin over cisplatin [28].

In some recent phase I/II studies of a 3-week interval-based SOx regimen for AGC patients, very promising efficacy was noted: an ORR of over 50%, and a median TTP and OS of 6.5–6.6 months and 12.5–16.5 months, respectively [29, 30].

Our results demonstrated that the overall response rate, TTP, and OS were 53.4%, 4.6 months, and 7.8 months, respectively. Despite the different schedule, the response rate was comparable to that of prior SOx studies. However, TTP and OS were substantially less than had been previously reported.

Three SOx trials, including this one, involved similar patient characteristics: gender proportion, prior curative treatment ratio, sites, and numbers of metastatic organs. Minimal differences in median age (55 versus (vs) 61), PS status 2 (11% vs 14.6%), and percentage of salvage therapy (not reported vs 61%) could be reasons for the shorter survival duration. The dosage and duration of treatment might be other reasons for this. When we compared our data to prior SOx studies, even though the median treatment duration was similar, the maximum numbers of cycles were shorter than those used in the Japanese trial and the dosage of treatment was less than that used in the Korean trial (Table 4) [29, 30] .

As in the phase II trials, even though the S-1/cisplatin combination chemotherapy used in the phase III SPIRITS trial resulted in a median OS of 13 months, other phase III FLAGS trials had a median OS of 8.6 months [31, 32]. This may be explained in relation to patient selection, burden of cancer, cultural practices in different regions, continued patient access to health care, and experience with treating investigators.

In our series, toxicities were also generally well tolerated. Grade 3/4 hematological toxicities were 4.4% anemia, 1.8% neutropenia, and 10.5% thrombocytopenia. With regard to the SOx trials, six weekly schedules (4 weeks of administration and 2 weeks of rest) comprises the standard guidelines for S-1. However, recently 3 weekly schedules (2 weeks of administration and 1 week rest) with less toxic profiles have also been introduced [33, 34]. Infusions of oxaliplatin at two-week intervals might prove more favorable to hematologic toxicity than infusions at 3-week intervals. Non-hematologic toxicities—such as vomiting/nausea and diarrhea—were noted in similar proportions of patients as in previous reports

In conclusion, the SOx regimen evidenced a relatively high response rate and was well tolerated as a first-line therapy for the treatment of advanced gastric cancer.

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