

Phase I Study of the Sequential Administration of S-1 and Cisplatin for Metastatic Gastric Cancer

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Abstract. The combination of 5-fluorouracil (5-FU) and cisplatin (CDDP) has been reported to be active against metastatic gastric cancer (MGC) and great synergy has been shown in vivo and in vitro when 5-FU precedes CDDP. The sequential combination of S-1 (tegafur, oxonic acid, 5-chloro-2,4-dihydropyridine) followed by CDDP for MGC was investigated. A phase I trial applying increasing doses of oral administration of S-1 (65-80 mg/m²) for 21 days and increasing doses of CDDP (60-80 mg/m²) on day 22 every 35 days was conducted in order to determine the maximum tolerated dose (MTD) and recommended phase II dose. Patients with metastatic or recurrent gastric cancer, no prior chemotherapy, measurable disease, ECOG performance status less than 3 and adequate organ functions were eligible for the study. Three patients were treated at each dose level with escalation based on toxicity. Fifteen patients were included and evaluated for dose-limiting toxicity (DLT) and MTD. DLT included NCICTC grade 3 anorexia and fatigue in patients treated at S-1 80 mg/m² and CDDP 80 mg/m² (dose level 5). The other toxicities, grade 3 or higher, included neutropenia (grade 3) and nausea/vomiting (grade 3). Non-hematological toxicities were grade 1/2 and included diarrhea, nausea and stomatitis. There was no treatment-related mortality. Therefore, the recommended dose was a combination of S-1 at 80 mg/m² and CDDP at 70 mg/m².

This sequential administration of S-1 and CDDP every 35 days is tolerable and warrants a phase II trial. A multicenter phase II study is currently under way.

Although the survival benefit of 5-fluorouracil (5-FU)-based chemotherapy has been shown, in comparison to the best supportive care (BSC) for unresectable advanced or metastatic gastric cancer (MGC) patients (1-3), the prognosis of such patients is still poor, with a median survival of less than 9 months. In order to improve the clinical efficacy of chemotherapy for patients with MGC, many clinical trials employing anticancer agents such as 5-FU, cisplatin and new classes of drugs, such as taxanes and irinotecan, have been conducted. However, no specific regimen has shown survival benefit superior to that of continuous infusion of single agent 5-FU in randomized phase III clinical trials (4). Therefore, it is still necessary to develop effective chemotherapy for MGC.

S-1 is an oral fluoropyrimidine consisting of tegafur, a prodrug of 5-FU, 5-chloro-2,4-dihydropyridine (CDHP), which inhibits dihydropyrimidine dehydrogenase, and potassium oxonate (Oxo), which is protective against tegafur-inducing toxicity (5). The feasibility of single agent S-1 for MGC was assessed in phase I and early phase II studies and a recommended regimen of 80 mg/m²/day, oral administration for 28 consecutive days, followed by a 14-day interval was established. The clinical activity of S-1 for MGC is reported to be 26% to 45% (6-8). Combination therapy of S-1 was also attempted with other agents such as CDDP, irinotecan and taxanes (9-12). The S-1 plus CDDP regimen was one of the most promising combination therapies and a phase I/II trial revealed a prominent response rate of 76% and mean survival time (MST) of 12.6 months (9). This study was scheduled as S-1 at 40 mg/m² twice daily for 21

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Table I. Summary of the toxicities experienced in all cycles.

Dose level (n)	1 (3 patients)				2 (3 patients)				3 (3 patients)				4 (3 patients)				5 (3 patients)			
	65 mg/m ²				65 mg/m ²				80 mg/m ²				80 mg/m ²				80 mg/m ²			
Dose of S-1	60 mg/m ²				70 mg/m ²				60 mg/m ²				70 mg/m ²				80 mg/m ²			
Dose of CDDP	60 mg/m ²				70 mg/m ²				60 mg/m ²				70 mg/m ²				80 mg/m ²			
NCI-CTC Grade	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Leukocyte	1	0	0	0	1	1	0	0	0	2	0	0	2	0	0	0	0	1	0	0
Neutrocyte	0	1	0	0	1	1	0	0	0	2	0	0	2	0	0	0	0	0	1	0
Platelet	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Hemoglobin	0	1	0	0	0	2	0	0	0	2	0	0	0	1	0	0	0	1	0	0
ALT	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0
Nausea/Vomiting	2	0	0	0	2	0	1	0	1	2	0	0	0	1	1	0	1	0	2	0
Fatigue	0	2	0	0	0	1	0	0	1	0	0	0	0	0	0	0	1	0	1	0
Anorexia	2	0	0	0	0	2	0	0	1	1	0	0	2	0	0	0	0	1	2	0
Alopecia	2	0	φ	φ	1	0	φ	φ	0	0	φ	φ	0	0	φ	φ	0	0	φ	φ
Fever	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Diarrhea	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0	0	0
Stomatitis	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0

n: Number of patients

consecutive days and a 2-h infusion of CDDP at 60-70 mg/m² on day 8, followed by a 14-day interval.

The combination of 5-FU and CDDP has been shown to exhibit great synergy in *in vitro* and *in vivo* studies when 5-FU precedes CDDP (13, 14). Since this sequence-dependent interaction would be exhibited in a combination of S-1 and CDDP, a phase I trial was conducted applying increasing doses of S-1 (65-80 mg/m²) for 21 days and increasing doses of CDDP (60-80 mg/m²) on day 22 every 35 days. This report presents the safety data of this regimen and recommends doses of the agents for phase II trial.

Patients and Methods

Patients. The main eligibility criteria included a histologically proven, unresectable, locally advanced or metastatic gastric adenocarcinoma; age, 20 to less than 75 years; Eastern Cooperative Oncology Group (ECOG) performance status, 2 or less; measurable disease; leukocyte count 3,500/mm³, or more; neutrophil count 1,500/mm³, or more; platelet count 100,000/mm³, or more; serum creatinine 1.5 mg/dl, or less; serum bilirubin 2.0 mg/dl, or less; aspartate aminotransferase (AST) 100 IU/l or less; alanine aminotransferase (ALT) 100 IU/l, or less; a life expectancy of 3 months or more; and no prior chemotherapy or radiotherapy except adjuvant chemotherapy more than 30 days prior to entry. This study was approved by the local Ethics Committee at each institution and patients were informed of the investigational nature of the study and provided their written informed consent before registration in the study.

Patients with the following criteria were not eligible: central nervous system metastasis with neurological symptoms, unresolved bowel obstruction or diarrhea, and known contraindication to fluorouracil (angina pectoris, myocardial infarction in the past 6 months).

Study design and treatment. The study was designed as a phase I dose-finding study to determine the maximum tolerated dose (MTD) and recommended dose of S-1 and CDDP. Treatment consisted of CDDP in 500 ml of saline, given intravenously (*i.v.*) over a 120-min period with appropriate hydration. The MTD was defined as the dose level associated with the same dose-limiting toxicity (DLT) in at least two out of three, or two out of six patients. DLT was defined as the occurrence of one or more of the following National Cancer Institute (NCI) common toxicity criteria (CTC): grade 3 or greater nonhematological toxicity, except for nausea and vomiting; grade 4 neutropenia lasting for more than 4 days; grade 3 neutropenic fever; or grade 4 thrombocytopenia.

Drug administration and dose escalation. S-1 was administered orally for 21 consecutive days and CDDP was administered on day 22, and cycles were repeated every 35 days. The starting dose of S-1 was 65 mg/m² plus CDDP 60 mg/m². Dose escalation then proceeded as listed in Table I. No inpatient dose escalation was permitted during the study. The number of patients per dose level was based on any DLT experienced during cycles 1 and 2. If a DLT was observed in one of the first three patients treated at a particular dose level, three further patients were recruited. If the same DLT occurred in two out of the six patients, this dose was defined as the MTD.

Treatment was continued until evidence of progression, unacceptable toxicity, or patient refusal. S-1 administration was delayed if, on the planned day of treatment, there was leukopenia (leukocytes less than 3,000/mm³); platelets less than 75,000/mm³; total bilirubin, ALT and AST more than three times the upper limit of the normal range; serum creatinine more than 1.2x the upper limit of the normal range; or nonhematological toxicities greater than grade 3, except for nausea and vomiting. When the S-1 treatment was delayed over 21 consecutive days, the administration was restarted after the disappearance of the above causes and was continued over 21 days. If a delay exceeded more than 8 days, the present course was discontinued and starting of the next course was postponed until recovery. When a next course was not started 15

days after the planned day, treatment was discontinued. CDDP administration was delayed on day 22, if leukocytes were less than 2,000/mm³; platelets less than 50,000/mm³; serum creatinine more than 1.2X the upper limit of the normal range; creatinine clearance less than 50 ml/min; or diarrhea greater than grade 2. When these causes still remained on day 31, CDDP treatment was skipped and the next cycle was started after a 14-day interval. When a patient experienced DLT, S-1 was reduced by approximately 20% and CDDP was reduced by 10 mg/m². In the event of life-threatening toxicities, treatment was definitively interrupted. To prevent nausea and vomiting, 5-hydroxytryptamine-3 antagonists and/or dexamethasone were administered *i.v.* before chemotherapy. Granulocyte colony-stimulating factor (G-CSF) was used when neutrophils were reduced to 500/mm³ or there was febrile neutropenia (neutrophils less than 1,000/mm³).

Assessability, toxicity and response criteria. The pretreatment evaluation included a history and a physical examination, performance status assessment, complete blood count with differential and platelet counts, complete blood profile, carcinoembryonic antigen, carbohydrate antigen (CA) 19-9, urinalysis, ECG, chest radiograph or computed tomography (CT) scan, abdominal CT scan and/or ultrasonography, and any other appropriate diagnostic procedure to evaluate the metastatic sites. During treatment, a physical examination was performed every week, a complete blood cell count twice a week and a blood profile and urinalysis every week. Sites of metastatic disease were re-evaluated every 8 weeks. Chest radiography and/or an abdominal CT scan or ultrasonography were repeated at least every 3 months, if there was no evidence of lung or abdominal disease. Toxicities were monitored weekly and were scored according to standard NCI-CTC. Responses were evaluated every 8 weeks according to the World Health Organization criteria.

Results

Patient characteristics. Fifteen patients were enrolled in this study. There were 9 men and 6 women. The median age was 61 years, with range of 44 to 72 years. ECOG performance status was 0 to 1 in the 15 patients. Ten patients were unresectable and 5 patients had a recurrent tumor. No patient had prior chemotherapy, including adjuvant setting chemotherapy. Four patients out of 15 had only the original gastric lesion, 7 patients had the original gastric and metastatic lesion, and 4 patients had a metastatic lesion alone. The average number of chemotherapy cycles was 3.6, with range of 1 to 17 cycles.

Dose escalation. The first three patients received S-1 at 65 mg/m² and CDDP at 60 mg/m² (dose level 1) and, because after two cycles no DLT had occurred, the subsequent group of three patients received S-1 at 65 mg/m² and CDDP at 70 mg/m² (dose level 2; Table I). After confirming that no DLT had occurred in the patients at each dose level, dose escalation proceeded to level 3 (S-1 at 80 mg/m² and CDDP at 60 mg/m²) and subsequently level 4 (S-1 at 80 mg/m² and CDDP at 70 mg/m²). Since DLT did

not occur in these 6 patients at dose levels 3 and 4, an additional three patients were recruited at dose level 5 (S-1 at 80 mg/m² and CDDP at 80 mg/m²). Two out of three patients at this dose level had grade 3 anorexia and grade 3 fatigue. As a result, two out of three patients had DLT at level 5 and this level was considered as the MTD. Therefore, the recommended phase II dose is S-1 80 mg/m² and CDDP 70 mg/m².

Toxicity. All patients were assessable for toxicities. There was no treatment-related death in the entire number of cycles in the study. A summary of the hematological toxicity is listed in Table I. At dose level 5, only one of the three patients experienced grade 3 neutropenia. All other hematological toxicities in all cycles were less than grade 2. Overall, no patient required dose reduction of S-1 and CDDP. Three out of 51 cycles were delayed for more than 7 days because of toxicity. G-CSF was not used for neutropenia in this study. As a result, the relative dose intensities for S-1 and/or CDDP, calculated as the actual dose delivered divided by the intended dose, were 93.1% and 87.2% respectively at all courses and 100% and 100% at dose level 4. A decrease of platelets below 75,000/mm³ (grade 2 or greater) was not observed in any of the cycles. The effects on red blood cells were also mild. Anemia below 8.0 g/dl (grade 3 or greater) did not occur. Nonhematological toxicities were major problems in this study. The incidences of major nonhematological toxicities are listed in Table I. Two patients with grade 3 anorexia and one patient with grade 3 fatigue were observed in the first cycle of dose level 5. These symptoms completely disappeared several days after stopping the administration. Grade 3 nausea was observed in two patients at dose level 5, one at dose level 4 and one at dose level 2.

Response. Response to therapy was a secondary outcome and was measured in all patients. All patients were assessable for response. Of the 15 patients, 3 experienced a partial response (PR) and 5 had stable disease (SD) (Table II). An overall response rate of 20.0% was observed. Two patients out of 10 patients with the original gastric lesion showed a PR (20.0%). However, one out of 6 patients with liver metastasis and none of 3 patients with peritoneal lymph nodes metastasis had PR.

Discussion

S-1 is currently the one of the most promising agents against MGC in Japan. According to several clinical trials of combination chemotherapy using S-1 and CDDP, the combination therapy shows a superior response rate and feasibility. Koizumi *et al.* reported a response rate of 76% for Japanese MGC patients in a phase II study (9) and a 49% response rate was observed in Western MGC patients (15), although the administration schedule and doses of these agents were different.

Table II. Patient characteristics.

Level	Gender	DLT	Response	No. chemotherapy cycles	Reasons for discontinuation	Survival (days)	
1							
1-1	F	-	NC	3	Patient's withdrawal	866.0	
1-2	M	-	NC	4		PD	638.0
1-3	M	-	NC	4		PD	544.0
2							
2-1	M	-	PR	4	Gastrectomy	1537.0	
2-2	F	-	NC	4	PD	638.0	
2-3	F	-	PR	17	Unknown	1448.0	
3							
3-1	M	-	PD	3	PD	361.0	
3-2	M	-	PD	1	PD	156.0	
3-3	M	-	PR	2	Doctor's decision	584.0	
4							
4-1	M	-	NC	2	PD	175.0	
4-2	F	-	PD	2	PD	404.0	
4-3	M	-	NE	2	Unknown	414.0	
5							
5-1	F	-	NE	1	Doctor's decision	198.0	
5-2	M	G3 Fatigue G3 Anorexia	NE	1	Adverse events	606.0	
5-3	F	G3 Anorexia	NE	1	Adverse events	146.0	

NC, No change; RR, partial response; PD, progressive disease; NE, not evaluable; DLT, dose-limiting toxicity.

The present study employed sequential administration of S-1 and CDDP based on the rationale obtained by preclinical studies showing that 5-FU preceding CDDP augmented the cytotoxicity of CDDP or could even circumvent CDDP resistance by inhibiting the repair machinery of CDDP-induced platinum-DNA interstrand crosslinks (13). The excision repair enzyme, ERCC1, has been shown to be involved in the repair of CDDP-induced DNA damage (16); 5-FU-mediated down-regulation of the expression of its gene may account for this synergy (17). In addition, reduction of glutathione contents due to 5-FU-induced inhibition of gamma-glutamylcysteine synthetase (gamma-GSC) was also been shown as a mechanism for the synergistic effect (18).

In the phase I trial of single administration of S-1, leukocytopenia and gastrointestinal toxicities more than grade 3 were reported to appear in the patients with rates of 7-10% (6, 7). A dose-escalation study was designed, starting with a reduced amount of S-1 in levels 1 and 2 and a standard dose of S-1 was administered in levels 3-5 for combination with CDDP. The safety profile of the present protocol demonstrated that hematological toxicities more than grade 3 were not shown in all courses at levels 1-4 but grade 3 neutropenia appeared at level 5 (1 out of 15 cases). In addition, nonhematological toxicities more than grade 3, namely anorexia (2 out of 15 cases) and fatigue (1 out of 15 cases), were observed. Therefore level 4 was considered to be the recommended phase II dose.

As previously reported, the recommended doses of 80 mg/m²/day of S-1 may result in considerable toxicities in the patients in Western countries (6, 19, 20). Ajani *et al.* reported a phase II trial of 50 mg/m²/day (day 1-21) of S-1 and 75 mg/m² (day1) of CDDP for MGC to show 26% of patients with fatigue and 13% with anorexia, which were both more than grade 3 (15). A phase II study with administration of S-1 for 21 days and 60 mg/m² (day 8) of CDDP for Japanese MGC patients showed incidences of severe neutropenia (16%), anemia (16%), anorexia (26%), nausea (16%) and diarrhea (5%; (9)). The other phase I/II study in Japan with S-1 for 14 days and 70 mg/m² CDDP (day 8) resulted in 9.1% of patients with severe neutropenia (21). Therefore, the present study with higher S-1 and CDDP dose intensities showed equivalent or less toxicity than the previous reports. It may be possible that S-1 administered prior to CDDP could achieve a higher dose intensity more safely. Several randomized phase III studies for MGC employing cytotoxic and molecular targeting drugs are ongoing and their results may strongly reflect establishing a standard therapy for MGC (22-27).

Conclusion

Sequential S-1 plus CDDP administration in this study was feasible and might be a promising therapy for MGC. A phase II study using the recommended doses is currently underway.

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