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ORIGINAL ARTICLE

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A phase I/II study of S-1 plus cisplatin in patients with advanced gastric cancer: 2-week S-1 administration regimen

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Abstract
Background. The combination of a new oral dihydropyrimidine dehydrogenase-inhibitory fluoropyrimidine (S-1) and cisplatin (CDDP) is one of the most active chemotherapy regimens for gastric cancer. However, the optimum schedule for this combination has not yet been determined. This study was conducted to establish the maximum tolerated dose (MTD) and the recommended dose of CDDP when combined with 2-week S-1 administration, and to observe the safety and efficacy of the regimen as treatment for patients with advanced gastric cancer.
Methods. S-1 was administered orally at a dose of 80 mg/m^2 per day for 2 weeks, followed by a 2-week rest. CDDP was administered intravenously on day 8 of each course; the initial dose of CDDP was 60 mg/m^2 and it was increased in 10-mg/m^2 increments. Treatment was repeated every 4 weeks unless disease progression was observed.
Results. Eleven patients were enrolled. The main toxicities were leucopenia, neutropenia, nausea, and anorexia. These toxicities were not severe, and were reversible and manageable. The MTD for CDDP was established as 80 mg/m^2, as 2 of 5 (40%) patients developed dose-limiting toxicity (DLT) at this level. Therefore, the recommended dose of CDDP was determined to be 70 mg/m^2. All 11 patients were evaluable for a response: 8 achieved a partial response and 1 had stable disease. The overall response rate was 73%.
Conclusion. This regimen is considered to be generally well-tolerated and has substantial antitumor activity.

Key words Chemotherapy · Cisplatin · Gastric cancer · S-1

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Introduction

Early detection and curative surgery have led to remarkable improvements in the survival rates of patients with gastric cancer. However, patients with unresectable, advanced, and recurrent gastric cancer still have a poor prognosis, with 5-year survival rates of less than 5%.[1] Several randomized trials have reported that fluorouracil (FU)-based combination regimens provide superior survival rates in patients with advanced gastric cancer compared with the best supportive care.[2–4] The response rates of various single agents such as 5-FU, cisplatin (CDDP), doxorubicin, and mitomycin-C are all less than 20%.[5–7] Therefore, with no standard regimen as yet established, there is a real and immediate need to develop new agents with improved antitumor effect, which could be added to the chemotherapy armamentarium for gastric cancers.

S-1 is a novel oral fluoropyrimidine derivative consisting of tegafur (FT), a prodrug of 5-FU,[8] and two modulators, 5-chloro-2,4-dyhydroxypyridine (CDHP), and potassium oxonate (Oxo).[9] CDHP is a reversible competitive inhibitor of dihydropyrimidine dehydrogenase (DPDase; EC 1.3.1.2), an enzyme involved in 5-FU degradation.[10] Oxo is a reversible competitive inhibitor of orotate phosphoribosyltransferase (EC 2.4.2.10), an enzyme for 5-FU phosphoribosylation in the gastrointestinal mucosa. Because the combination of CDHP with FT, in the drug S-1, yields high and sustained intracellular concentrations of 5-FU in plasma and tumor tissue, there is increased exposure to 5-FU and therefore increased antitumor activity. The addition of the other modulator, Oxo, helps limit the systemic toxic gastrointestinal effects commonly seen with 5-FU-based regimens.

Phase I and early phase II studies of S-1 as a single agent established a dosing regimen of 80 mg/m^2 per day, given orally over 28 consecutive days, followed by a 2-week rest, as the tentative recommended dose.[11,12] Two late phase II studies of S-1 for advanced gastric cancer, which used similar dosing regimens, showed high response rates, of 49% (25/51 patients) and 44% (19/43 patients), respectively.[13,14]

These results suggest that S-1 is one of the most effective single agents for advanced gastric cancer.

Although CDDP on its own has a moderate response rate of only 17%, when it is given in combination with 5-FU and 5-FU derivatives, superior antitumor effects have been reported.[15,16] Koizumi et al.[17] conducted a phase I/II study with S-1 and CDDP combination chemotherapy. S-1 was administered for 3 weeks, followed by a 2-week rest, and the recommended dose of CDDP (60 mg/m^2) was given on day 8. The overall response rate of all eligible patients was 76%. The incidence of severe (grades 3 and 4) neutropenia and anemia was 16%, and nonhematological toxicities (grades 1–4) were frequently observed; for example, anorexia, nausea, and vomiting, which were reported in 95%, 68% and 37% of patients, respectively.

However, post-marketing surveillance of S-1 in Japan revealed that 55% of the patients who had received S-1 were unable to complete one or two courses of the drug when given in this single administration schedule, and that most toxicities occurred during the third week of administration. The present study was, therefore, designed to determine the maximum tolerated dose (MTD) and recommended dose of CDDP when combined with S-1 and administered over 2 weeks.

Patients and methods

Patient eligibility

All patients had histologically proven unresectable or recurrent gastric cancer, and had not received prior chemotherapy, although adjuvant chemotherapy was allowed if it had been completed more than 30 days prior to entry. Other eligibility criteria included the following: 20–75 years of age, Eastern Cooperative Oncology Group performance status (PS) of at least 2; measurable disease; white blood cell count, 4000/ml or more; absolute neutrophil count, more than 2000/ml; hemoglobin level, more than 9.0 g/dl; platelet count, more than 100 000/ml; serum bilirubin level, less than 1.5 mg/dl, aspartate transaminase and alanine transaminase levels, within three times the upper limit; serum blood urea nitrogen, less than 25 mg/dl; creatinine, less than 1.5 mg/dl; creatinine clearance, less than 50 ml/min. All patients gave their written informed consent; the institutional review board of Tonan hospital approved this study.

Treatment protocol

The initial dose of S-1, based on the patient's body surface area (BSA), was 40 mg (BSA $< 1.25\,m^2$); 50 mg (BSA 1.25–$1.5\,m^2$); or 60 mg (BSA $\geq 1.5\,m^2$). Patients received their assigned dose of S-1, orally, twice a day. One course of therapy consisted of S-1 administered for 14 days, followed by a 14-day period with no treatment.

CDDP was administered on day 8 of the course, for 2 h, with 500 ml of 0.9% sodium chloride solution. Patients were given intravenous hydration with 2500 ml of normal saline. A 3-mg dose of a 5-HT$_3$ receptor antagonist and 8 mg of dexamethasone in 100 ml of 0.9% sodium chloride solution were given before the administration of CDDP (as prophylactic antiemetics). Three incremental dose levels were planned for CDDP, with a starting dose of 60 mg/m^2. At least three patients were treated at each dose level. If one of three patients at a given dose developed any dose-limiting toxicity (DLT), another three patients were to be entered at that same dose. Before proceeding to the next dose level, all previously treated patients had to have completed at least one course.

Evaluation

The National Cancer Institute common toxicity criteria (NCI-CTC Version 2, January 30, 1998) were used to evaluate the grade of toxicity. A DLT was defined as: non-hematological toxicities of grade 3–4; or hematological toxicities of grade 4 platelet count, grade 3 platelet count with bleeding tendency, grade 4 leucopenia, grade 4 neutropenia lasting at least 3 days, and grade 3 or 4 febrile neutropenia. A delay of the second course by at least 14 days was also included in the definition of DLT. The MTD was defined as the dose at which 33% or more patients experienced DLTs during the first course.

Response to treatment was assessed according to the Japanese response criteria proposed by the Japanese Research Society for Gastric Cancer. A complete response (CR) was defined as the disappearance of all evidence of cancer for at least 4 weeks, and a partial response (PR) was defined as less than complete, but more than 50% reduction of tumor volume for at least 4 weeks without any evidence of new lesions or progression. No change (NC) was defined as less than a 50% reduction or less than a 25% increase without any new lesion. Progressive disease (PD) was defined as more than a 25% increase in a solitary lesion or the appearance of new lesions.

Results

Patient characteristics

Eleven patients (seven men, four women) were enrolled between August 2001 and July 2003 (Table 1); they had a median age of 57 years (range, 29–74 years). Five patients had undergone a prior gastrectomy and 2 patients had received adjuvant chemotherapy with S-1 alone before entering the study. Histological evaluation revealed that 8 patients had diffuse-type adenocarcinoma and 3 had intestinal type.

Toxicities

Toxicities that occurred during the first course are summarized in Table 2. The incidence of hematological toxicities was low, and grade 3 or 4 neutropenia, leucopenia,

thrombocytopenia, and anemia were not observed at CDDP dose levels 1 or 2. The main nonhematological toxicities were nausea anorexia, and malaise. Grade 1–2 nausea and/or anorexia were frequently observed during the period from the administration of CDDP to the end of S-1 administration.

The DLT of grade 4 neutropenia, which lasted for 3 days, was observed in one patient at CDDP dose level 3 (80 mg/m^2); the patient also had grade 4 anorexia. In another patient at level 3, the start of the second course was delayed for more than 14 days because of grade 3 anorexia and nausea.

Because DLT was observed in two of the five patients entered at dose level 3, according to the protocol, the recommended dose of CDDP in this combination chemotherapy was determined as 70 mg/m^2.

Table 1. Patient characteristics

No. of patients	11
Sex	
Male	7
Female	4
Median age; years (range)	57 (29–74)
Performance status	
0	2
1	7
2	2
Histology	
Intestinal	3
Diffuse	8
Prior gastrectomy	5
Adjuvant chemotherapy	2
Metastatic site	
Abdominal lymph nodes	7
Liver	3
Ascites	7

Response

The median numbers (and ranges) of courses administered are shown in Table 3. All patients were evaluable for response. The overall response rate was 73%. The response rates at CDDP dose levels 1, 2, and 3 were: 100% (3/3 patients), 100% (3/3 patients), and 40% (2/5 patients) (Table 4).

The response rate was 67% (4/6 patients) for the primary lesion, 100% (3/3 patients) for liver metastasis, 57% (4/7 patients) for lymph node metastasis, and 43% (3/7 patients) for ascites. The response rate according to tissue type of gastric adenocarcinoma was 100% (3/3 patients) for the intestinal type and 63% (5/8 patients) for the diffuse type.

Discussion

In this study, we chose a 2-week administration regimen for S-1 for the following two reasons. Firstly, it was shown in post-marketing surveillance that most toxicities increased during the third week of standard S-1 administration, and that 55% of patients were not able to complete a standard 4-week administration regimen of S-1 as a single agent when it was given in two courses. Secondly, in order to maximize the potential efficacy of CDDP, it is preferable to administer CDDP at least once every 4 weeks.[16,18,19] Because of this, and despite the fact that the duration of S-1 administration was limited, an augmented effect of CDDP could be anticipated. The results of this present study are promising and confirm the good response in advanced gastric cancer reported in previous studies with a combination of S-1 plus CDDP.

Table 2. Toxicities in the first course

CDDP	Level 1; 60 mg/m^2 (n = 3)		Level 2; 70 mg/m^2 (n = 3)		Level 3; 80 mg/m^2 (n = 5)	
	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4	Grade 1–2	Grade 3–4
Hematological						
Leukopenia	1	0	0	0	0	1
Neutropenia	1	0	0	0	0	1
Thrombocytopenia	0	0	0	0	2	0
Anemia	1	0	0	0	2	0
Nonhematological						
Nausea	2	0	3	0	4	1
Anorexia	2	0	2	0	1	2
Malaise	2	0	1	0	3	0
Diarrhea	0	0	2	0	0	0
Stomatitis	0	0	1	0	0	0

n, number of patients

Table 3. Duration of administration

CDDP	Level 1; 60 mg/m^2 (n = 3)	Level 2; 70 mg/m^2 (n = 3)	Level 3; 80 mg/m^2 (n = 5)
Number of courses administered			
Total	11	14	14
Median (range)	4 (2–5)	5 (4–5)	2 (1–6)

Table 4. Objective tumor response

CDDP	Level 1; 60 mg/m^2 (n = 3)	Level 2; 70 mg/m^2 (n = 3)	Level 3; 80 mg/m^2 (n = 5)	Total no. of patients 11
PR	3	3	2	8
NC	0	0	1	1
PD	0	0	2	2
Response rate (%)	100	100	40	73

In Japan, two late phase II studies of S-1 in patients with advanced gastric cancer have been conducted;[13,14] there were high response rates to S-1 in these studies, of 49% (25/51 patients) and 44% (19/43 patients), respectively, and no serious, unexpected toxicity. This suggested that the antitumor efficacy of S-1 was comparable to that of multiple-drug chemotherapy and higher than that of monotherapy with conventional agents. The authors of these two studies[13,14] therefore concluded that S-1 may become a state-of-the-art drug as first-line therapy for unresectable, advanced gastric cancer. Indeed, S-1 has already been included as one of the treatment arms in an ongoing phase III study being conducted by the Japan Clinical Oncology Group. Furthermore, clinical trials of combination chemotherapy containing S-1 have already started in several institutions. As combinations of CDDP and 5-FU derivatives have been widely used and have been associated with a good response, without severe toxicities, we selected CDDP as the agent to be combined with S-1 for the study reported here.

Koizumi et al.[17] conducted a phase I/II study with combination chemotherapy of S-1 and CDDP. S-1 was administered for 3 weeks, followed by a 2-week rest. They reported response an overall rate of 76% (19/25 patients). The response rate achieved in our study was 73%, which was very similar.

The main toxicities in our study were leucopenia, neutropenia, nausea, and anorexia. However, the frequencies of hematological toxicities were much lower than those in the previous phase I/II study,[17] where incidences of hematological toxicities (grades 1–4) in the first course were: leucopenia (67%), neutropenia (83%), thrombocytopenia (33%), and anemia (50%). The corresponding incidences (grades 1–4) in the first course in the present study were: 18% (2/11 patients), 18% (2/11 patients), 18% (2/11 patients), and 27% (3/11 patients), respectively. Grade 3–4 severe hematological toxicities in our study were neutropenia and leucopenia, and these were observed in only 1 patient (9.1%), at the highest CDDP dose level. Grade 3–4 anemia and thrombocytopenia were not observed at any CDDP dose level. These results suggest that the incidence and severity of hematological toxicities are related to the duration of S-1 administration.

Gastrointestinal toxicities, nausea and anorexia, increased in severity in the period after the start of CDDP administration, on day 8 of the course, until the end of S-1 administration. Despite the fact that antiemetic drugs (5-HT$_3$ receptor antagonists and steroids, etc.) were used, these toxicities were frequently observed, and their frequency was almost the same as that previously reported for the same S-1 combination regimen when it was given as a 3-week regimen. However, the frequency of diarrhea or stomatitis was not so high.

In the previous study, of Koizumi et al.,[17] the median number of courses administered was four, compared with the present study, where the median number of courses was five at the recommended dose. In this present study, only 2 out of 11 (18%) patients had PS 0, whereas in the previous study, 9 out of 12 (75%) patients had PS 0. If this is taken into consideration, this regimen may be able to be continued still longer in patients with a good PS.

In addition to the phase I/II studies of a 3-week S-1 administration regimen discussed above, another phase I study of the combination of S-1 and CDDP for gastric cancer has been reported.[20] In that study, CDDP was infused weekly on days 1 and 8, while S-1 was administered at 70 mg/m^2 per day for 2 weeks, followed by a 1-week rest. The recommended dose of CDDP was reported to be 20 mg/m^2. The overall response rate was 61% (11/18 patients) and the response rate of patients with no prior chemotherapy was 78%. This low-dose CDDP regimen was not considered to require a hospital stay because the requirement for hydration was minimal. However, the incidence of hematological toxicity during the first course was slightly higher than that in our study.

In conclusion, the present study showed that combination therapy of 2-week S-1 administration and CDDP could be administered safely as repeat courses. To evaluate its clinical usefulness and adverse effects, this regimen is currently the subject of a phase II study.

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