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A phase I study of S-1 combined with weekly cisplatin for metastatic gastric cancer in an outpatient setting

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Abstract

A dose-escalation study was conducted for patients with metastatic gastric cancer to determine the recommended dose of weekly intravenous (i.v.) cisplatin combined with a fixed dose of a new oral dihydropyrimidine dehydrogenase-inhibitory fluoropyrimidine, S-1, on an outpatient basis. Secondary endpoints were to define the toxicity profile and to determine tumour responses. S-1 was fixed at a dose of 70 mg/m^2/day and was administered for 2 weeks followed by a 1-week rest. Three dose levels of cisplatin (10, 15 and 20 mg/m^2) were studied. Cisplatin was infused over 30 min on days 1 and 8. 20 patients were enrolled. No dose-limiting toxicities (DLTs) were recorded during the administration of cisplatin up to 20 mg/m^2, except for grade 3 diarrhoea and stomatitis in one patient at dose level 3. No grade 4 adverse events occurred. However, grade 2 gastrointestinal adverse reactions, such as nausea and anorexia, were seen in 7 of 13 patients at dose level 3 within the first two treatment cycles. This was determined to be the maximum acceptable level that would not negate the advantages observed with use of an oral drug such as S-1. An objective tumour response was seen at all dose levels, and the overall response rate in the 18 patients evaluated was 61%. A higher response rate of 78% was observed in 9 patients who had received no prior chemotherapy. Oral S-1 with weekly cisplatin is a feasible and promising combination regimen that is appropriate for an outpatient setting. A randomised phase II study comparing this combination with S-1 alone in chemo-naïve patients is warranted.

Keywords: Chemotherapy; Cisplatin; Gastric cancer; Phase I study; S-1

1. Introduction

Although gastric carcinoma is an uncommon disease in North America and Western Europe, its incidence is high in Asia and it remains one of the leading causes of death in Japan [1,2]. The prognosis for patients with unresectable or metastatic gastric carcinoma is poor. The median survival time for such patients is 6–9 months [3]. In the past 20 years, several anticancer drugs such as 5-fluorouracil (5-FU), cisplatin, methotrexate, doxorubicin, epirubicin, mitomycin and etoposide, have been studied either alone or in combination as treatments for this disease. Several phase III studies have been conducted, but no new combination has emerged that is superior in terms of survival to 5-FU alone or to 5-FU plus cisplatin [4–8].

Recently, several new classes of drugs have demonstrated activity against advanced gastric cancer. These include the taxanes (paclitaxel and docetaxel), camptothecins (irinotecan), and fluorouracil prodrugs (uracil and tegafur (UFT), S-1 and capecitabine) [9–15]. Early results with either single-agent therapy or combinations of these new agents are encouraging [16–18]. Quality of life, convenience and cost benefits have been emphasised for their use in the treatment of cancer. This has increased interest in the oral agents, and, at present, a few promising oral agents are being studied in clinical trials [19]. S-1 is a rationally developed combination of tegafur, a prodrug of 5-FU; 5-chloro-2,4-dihydroxypyridine (CDHP), an inhibitor of 5-FU catabolism; and potassium oxonate (Oxo), an inhibitor of 5-FU-induced diarrhoea [20]. Phase I and early phase II trials of S-1

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were undertaken in Japan. On the basis of these trial results, a 28-day consecutive, oral regimen was recommended, in which 80 mg/m^2/day S-1 was given daily in two divided doses, followed by a 2-week rest [21,22]. In two independent phase II studies for advanced gastric cancer conducted in Japan, S-1 showed high response rates of 49% (25/51) and 44% (19/43), respectively [12,13]. The incidence of adverse reactions of grades 3 and 4 was very low. Thus, S-1 was reported to be highly active and well tolerated, and was approved for use in the treatment of advanced gastric cancer in Japan.

Based on the synergism between S-1 and cisplatin seen in preclinical studies, a phase I/II combination study of these two drugs was performed recently [23]. S-1 was administered orally (80 mg/m^2/day) twice a day for 21 consecutive days, and cisplatin was infused over 2 h (levels 1, 2, 3: 60, 70, 80 mg/m^2) on day 8. The treatment was repeated every 5 weeks. The recommended dose was set to level 1 (cisplatin 60 mg/m^2) and objective responses were observed in 19 of the 25 patients, with a response rate of 76%. Toxicities were reported to be generally mild. However, this treatment regimen required a short-term hospital stay for hydration to prevent the renal toxicity induced by cisplatin, and this therefore negates the convenience of using an orally administered drug such as S-1.

On the basis of these findings, we conducted a phase I study of S-1 combined with weekly cisplatin in an outpatient setting.

2. Patients and methods

2.1. Patients

All patients had to fulfill the following eligibility criteria: (1) histological confirmation of gastric adenocarcinoma; (2) inoperable metastatic disease or recurrent metastatic disease after surgery; (3) measurable lesions; (4) age 20–75 years old; (5) performance status (PS) <2 on the Eastern Cooperative Oncology Group (ECOG) scale; (6) no or only one prior chemotherapy received for advanced disease (prior adjuvant chemotherapy for gastric cancer must have been completed at least 6 months prior to enrollment, and prior chemotherapy for advanced disease must have been completed at least 4 weeks prior to enrollment); (7) adequate bone marrow function (absolute granulocyte count $\geqslant 1.5\times10^9$ cells/l and platelet count $\geqslant 100\times10^9$ cells/1); (8) adequate liver function (serum bilirubin level <1.5 mg/dl and serum transaminase levels <100 U/l); (9) adequate renal function (serum creatinine level $\leqslant 1.2$ mg/dl); (10) no other severe medical conditions; (11) no other active malignancies; (12) no pregnant or lactating patients; and (13) provision of written informed consent.

This study protocol was approved by the institutional review board of the National Shikoku Cancer Center.

2.2. Treatment schedule

S-1 (Taiho Pharmaceutical Co., Tokyo, Japan) is generally administered at 80 mg/m^2/day (the dose divided equally after breakfast and dinner), and the individual daily dose is set as follows: body surface area (BSA) <1.25 m^2; 80 mg/day, 1.25 m^2 $\leqslant$BSA <1.5 m^2; 100 mg/day, and 1.5 m^2 $\leqslant$; 120 mg/day [12,13]. In this study, S-1 was administered at a fixed dose of 70 mg/m^2/day for 2 weeks, followed by a 1-week rest. Twenty and 25 mg capsules of S-1 were combined appropriately and administered at the defined doses (80, 90, 100, 110 and 120 mg/day), and adherence to recommended doses according to the BSA was stricter than that required for the standard administration method. The starting dose of cisplatin was 10 mg/m^2. Cisplatin doses were escalated to 15 or 20 mg/m^2 in subsequent cohorts. At least 3 patients were treated at each dose. 3 additional patients were entered at the same dose if DLT was observed in 1 of the first 3 patients. Cisplatin was infused over 30 min with a minimum prehydration of 500 ml normal saline, including granisetron, on days 1 and 8. This treatment was repeated every 3 weeks (one cycle each) until disease progression or unacceptable toxicity was seen. The first cycle of the treatment was performed in our centre in an inpatient setting. If the patient experienced DLT followed by no disease progression, the subsequent cycle was started at the next lower level after complete recovery from the toxic effect of the previous cycle.

2.3. Evaluation of toxicity and tumour response

Baseline evaluation included a complete medical history, physical examination, complete blood cell count, serum chemistry, creatinine clearance, urinary analysis, electrocardiogram (ECG), gastroscopy, gastrography, abdominal computerised tomography (CT) scan and chest X-ray. Blood, chemistry, urinary analyses and subjective/objective symptoms for toxicity were monitored on a weekly basis during treatment. Toxicities were evaluated according to the National Cancer Institute (NCI) Common Toxicity Criteria (CTC) (version 2.0). Blood cell counts were examined at least every 2 days, if haematological toxicities of grade 3 or more were seen in the first treatment cycle. Tumour responses were assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) [24]. To assess an objective response, patients were evaluated every 6 weeks. Patients who completed two cycles (6 weeks) were considered assessable for response. All responses were confirmed by a second measurement of target lesions and a second evaluation of non-target lesions.

2.4. Definition of DLTs and MTD

Dose-limiting toxicities (DLT) were determined during the first treatment cycle. The definition of DLTs was as follows: (1) grade 4 neutropenia lasting at least 3 days or grade 3 or 4 neutropenia with fever, (2) grade 4 thrombocytopenia, (3) grade 3 other non-haematological toxicity (including nausea and vomiting), (4) treatment delay of more than 2 weeks following the last administration of S-1. The maximum-tolerated dose (MTD) was defined as the dose at which 2 of the 3–6 treated patients experienced DLT. The recommended dose was determined by considering the efficacy, toxicity and tolerability in an outpatient setting, and this determination was the primary endpoint of this study.

3. Results

Between April 2000 and August 2002, 20 patients were enrolled in this study. All of the patients were eligible. The patient characteristics are shown in Table 1. Only one patient had a performance status of 2 and the remaining patients had a good performance status. 6 patients had undergone gastrectomy for the primary tumour resection, and 1 of them had completed adjuvant chemotherapy with UFT 6 months before entry into this study. 11 patients had received prior chemotherapy for metastatic disease. The prior chemotherapy regimens were as follows: capecitabine (3), 5-FU plus cisplatin (3), 5-FU continuous infusion (2), 5-FU plus methotrexate (2), irinotecan plus cisplatin (1). The number of involved organs were: one in 5 patients, two in 9 patients and three or more in 6 patients. Major metastatic sites were the lymph nodes, peritoneum and liver.

Table 1
Patient's characteristics

	No. of patients
Total	20
Male/female	15/5
Age (years)	
Median (range)	62 (44–75)
ECOG PS	
0	10
1	9
2	1
Prior treatment	
Gastrectomy	6
Adjuvant chemotherapy	1
Chemotherapy	11
Histological type	
Differentiated	8
Undifferentiated	12
Metastatic site	
Lymph nodes	13
Peritoneum	9
Liver	6
Lung	1

ECOG PS, Eastern Cooperative Oncology Group Performance Status.

The oral administration of dose level 1 to 1 patient was discontinued early (day 10) due to gastro-oesophageal stenosis by the primary lesion, and his response could not be evaluated. A total of 4 patients were enrolled at this dose level. 3 patients were enrolled at level 2. At dose level 3, DLT was observed in 1 of the first 3 patients, and 3 additional patients were entered at this level. To explore the responses to and continuity of the treatment, 7 additional patients were enrolled at this level. One of them refused tumour response evaluation because of a personal issue that did not relate to the toxicity, and his treatment was stopped after four cycles of the treatment. As a result, 13 patients entered dose level 3.

3.1. Toxicities and treatment cycles

Major adverse events seen at each dose level are shown in Table 2. Nausea, anorexia, leucopenia, and neutropenia were commonly observed toxicities. However, severe toxicities of grade 3 or 4 were rarely seen. The prevalence of grade 3 or 4 toxicity in the first cycle and in all treatment cycles was 15 and 38% of all patients, respectively. The median time (range) to the nadir of absolute neutrophil count in the first cycle was 11.5 (6–21) days for level 1, 17 (12–21) days for level 2, and 14 (7–20) days for level 3. Only 1 patient at dose level 3 experienced DLTs (grade 3 diarrhoea and stomatitis). The MTD was not reached. Grade 2 nausea and/or anorexia was observed in 5 of 6 patients within the initial two cycles given to the first 2 cohorts at dose level 3. Subsequently, these toxicities were also observed in 2 of the 7 additional patients. In total, 7 of the 13 patients (54%) experienced grade 2 nausea and/or anorexia. Grade 2 nausea and anorexia were frequently seen during the period from the second administration of cisplatin to the end of S-1 administration (days 8–15). Further dose escalations of cisplatin were considered unnecessary because of the possibility that these toxicities would impair the oral administration of S-1. Dose level 3 (cisplatin 20 mg/m^2) was therefore set as the recommended dose.

The median and range of the treatment cycles, the relative dose intensity, the number of patients that received a dose reduction, and the proportion of cycles carried out in the outpatient clinic at each dose level are shown in Table 3. The median number of cycles delivered at dose level 3 was six, and the relative dose intensity of S-1 ranged from 0.8 to 1. Only 3 of 13 patients at

Table 2
Number of patients experiencing adverse events in the first cycle (in all cycles)

Toxicity	Dose level 1 ($n=4$)		Dose level 2 ($n=3$)		Dose level 3 ($n=13$)	
	Grades 1–2	Grades 3–4	Grades 1–2	Grades 3–4	Grades 1–2	Grades 3–4
Nausea	2 (3)	0 (0)	0 (0)	0 (0)	6 (7)	0 (0)
Vomiting	1 (1)	0 (0)	0 (0)	0 (0)	2 (2)	0 (0)
Anorexia	2 (3)	0 (1)	1 (1)	0 (0)	6 (6)	0 (0)
Diarrhoea	1 (1)	0 (0)	0 (0)	0 (0)	2 (2)	1[a] (1)
Stomatitis	1 (1)	0 (0)	0 (0)	0 (0)	1 (1)	1[a] (1)
Fatigue	1 (2)	0 (0)	0 (0)	0 (0)	3 (3)	0 (0)
Hand–foot syndrome	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Leucocytopenia	2 (3)	1 (2)	1 (1)	0 (0)	4 (6)	0 (1)
Neutropenia	2 (3)	1 (2)	1 (1)	0 (0)	5 (8)	1 (3)
Anaemia	0 (1)	0 (0)	1 (1)	0 (0)	3 (6)	0 (0)
Thrombocytopenia	1 (1)	0 (0)	1 (1)	0 (0)	3 (6)	0 (0)
Total (%)	100 (100)	25 (50)	67 (67)	0 (0)	69 (77)	15 (38)

DLT, dose-limiting toxicity. Numbers in parentheses indicate the number of patients experiencing the adverse events over 82 cycles.
[a] DLT case.

Table 3
Duration of administration and dose intensity

	Dose level 1 $n=4$	Dose level 2 $n=3$	Dose level 3 $n=13$
Administration cycles			
Total	10	7	65
Median (range)	2.5 (1–5)	3 (1–3)	6 (2–9)
Relative dose intensity of S-1			
Median (range)	1 (0.7–1)	1 (1–1)	1 (0.8–1)
No. of patients with dose reduction cisplatin	0	0	3[a] (23%)
Proportions of administered cycles in outpatient clinic	70	29	89[b]

[a] Grade 2 anorexia resulted in a dose reduction in 2 patients, and DLT was observed in 1 patient.
[b] Treatments of 3 patients were started in an outpatient setting.

dose level 3 needed to reduce their dose of cisplatin. Approximately 90% of the treatment cycles at this dose level were delivered in the outpatient clinic.

3.2. Responses

The objective responses at each dose level are summarised in Table 4. Tumour responses were seen at all dose levels, and the overall response rate was 61% for the 18 patients evaluated. The response rate at dose level 3 was 58%. The response rate for nine chemo-naïve patients was 78% (complete response (CR) =2, partial response (PR) =5, stable disease (SD) =1 and progressive disease (PD) =1; 95% Confidence Interval (CI) 40–97%), and for the remaining nine patients who had received prior chemotherapy, it was 44% (PR 4, SD

Table 4
Objective tumour response in patients evaluated

Dose level (enrolled patients)	No. of patients	Response				Response rate (%)	95% CI (%)
		CR	PR	SD	PD		
Level 1 ($n=4$)	3	1	1	0	1	67	–
Level 2 ($n=3$)	3	0	2	0	1	67	–
Level 3 ($n=13$)	12	1	6	5	0	58	28–85
Total	18	2	9	5	2	61	36–83

CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; CI, confidence interval.

4 and PD 1; 95% CI 14–79%). The median duration of response was 92 (42–702) days.

4. Discussion

S-1 has been demonstrated to be a highly active drug for metastatic gastric cancer in two phase II studies conducted in Japan [12,13]. One study showed a CR in 1 patient and PR in 24 patients, producing a response rate of 49% (25/51). The other study reported a 44% (19/43) response rate. On the basis of these promising data, S-1 has been adopted as one of the treatment arms (5-FU alone versus irinotecan plus cisplatin versus S-1) in the present phase III study being carried out by the Japan Clinical Oncology Group. S-1 is currently undergoing only limited evaluation in both Europe and the United States, and its safety and activity have so far been inconclusive [25,26]. To enhance the efficacy of S-1, we conducted this study in an attempt to maintain the same dose intensity as that used in the standard S-1 administration, but in combination with cisplatin, on an outpatient basis. Both of the clinical trials for the new drug approval, as well as the postmarket survey of S-1 in Japan, revealed that low grades of gastrointestinal toxicities, including nausea, vomiting, and anorexia, and of myelotoxicities such as neutropenia, occurred frequently during the third week of S-1 administration [12,13]. Therefore, we adopted a three-week schedule (2 weeks on and 1 week off) of S-1 to avoid severe toxicity, and a weekly administration schedule of cisplatin combined with S-1 was chosen for the outpatient setting of this study.

The myelosuppression, especially neutropenia, as frequently seen in the 5-FU plus cisplatin combination therapy, was predicted as the main toxicity of the current combination therapy before the initiation of this study. However, nausea and anorexia were observed frequently within the initial two treatment cycles in the first 6 patients of level 3. 7 additional patients were then added at this treatment level. As a result, 54% of this entire group of patients experienced grade 2 nausea and/or anorexia. Antiemetic drugs (5-HT3 receptor antagonists, corticosteroids, etc.) were used, but their effect was limited in some patients. Furthermore, these toxicities lasted for approximately a week. Grade 2 nausea and/or anorexia are defined as a marked decrease of oral intake. Regular monitoring revealed these substantial and long-lasting toxicities caused distress in some of the patients at level 3. From these results, we strongly suspected that a further dose escalation of cisplatin would increase these toxicities. We considered this dose level to be the maximum feasible level for the recommended dose, because this level was unlikely to affect the patient's preference based on convenience and tolerability.

On the one hand, for the 101 patients who were enrolled in previous single agent studies of S-1, it was reported that the incidence of grade 3 and 4 toxicities was very low: leucopenia 2.0%, a decrease of haemoglobin 4.9%, diarrhoea 2.0% and fatigue 1.0% [12,13]. On the other hand, substantial toxicities were observed in the previous phase I/II study of S-1 plus cisplatin [23]. Among the 19 patients given the recommended dose level of 60 mg/m^2 cisplatin, grade 3 or 4 toxicity rates were 26% for anorexia, 16% for nausea, 11% for vomiting, 5% for diarrhoea, 5% for leucopenia, 16% for neutropenia and 16% for a decrease of haemoglobin. In the present study, only 1 of 13 patients at dose level 3 experienced grade 3 diarrhoea and stomatitis. With regard to the haematological toxicities, the prevalence of grade 3 toxicities seen over all treatment cycles was similar to the previous study and no grade 4 haematological toxicity was observed. From these results, our combination therapy appears less toxic than the combination therapy using a modest dose of cisplatin, but more toxic than the monotherapy with S-1.

A median number of three or four cycles were administered in the previous phase II studies with S-1 alone [12,13]. At dose level 3 in our study, treatments were delivered for a median number of six cycles, and the dose intensity of S-1 was relatively high. The doses of S-1 administered in this combination study were almost equivalent to those given in the three cycles administered in the standard S-1 treatment. Furthermore, only three of 13 patients at dose level 3 needed a dose reduction of cisplatin, and approximately 90% of the treatment cycles at this dose level were performed at the outpatient clinic. These results indicate this combination is quite feasible in the outpatient treatment setting.

In conclusion, this phase I study revealed the feasibility of combining S-1 treatment with weekly cisplatin in an outpatient setting. DLT of diarrhoea and stomatitis was observed in 1 patient, but the primary reasons for stopping the dose escalation of cisplatin were grade 2 nausea and anorexia. Our regimen indicated a high response rate (61%) and seems promising. A randomised phase II study including chemo-naïve gastric cancer patients comparing this combination with S-1 alone (or with conventional cisplatin-combined regimens) is warranted.

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