

Combination Phase I Trial of a Novel Oral Fluorouracil Derivative S-1 with Low-Dose Cisplatin for Unresectable and Recurrent Gastric Cancer (JFMC27-9902)

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ABSTRACT

Purpose: The Japanese Foundation for Multidisciplinary Treatment of Cancer conducted a Phase I study of a novel oral fluorouracil derivative, S-1, combined with a low dose of cisplatin in unresectable and recurrent gastric cancer.

Experimental Design: S-1 was administered orally at 80–120 mg/body/day, depending on body surface area. One course consisted of consecutive administration for 28 days followed by a rest of 14 days. Low-dose cisplatin was given i.v. on days 1–5, 8–12, 15–19, and 22–26 of each course. The dose escalation of cisplatin began with an initial dose of 1 mg/m²/day as level 1 and was stepped up to 2, 3, 4, and 6 mg/m²/day as level 2, 3, 4, and 5, respectively. The regimen was repeated for at least two courses.

Results: A total of 24 patients was entered in the study. There was no treatment-related death. At level 5, consisting of 5 evaluable patients, dose-limiting toxicity was experienced as grade 3 appetite loss in 2 patients and grade 4 neutropenia in 1 patient. The maximum-tolerated dose of cisplatin was estimated to be 6 mg/m²/day. We decided on a recommended dose of cisplatin of 4 mg/m²/day because the dosage was one level under the maximum-tolerated dose. All 3 patients at level 4 showed partial response, suggesting promising clinical efficacy with this dosage. The serum con-

centration of cisplatin at level 4 was 918 ± 92 ng/ml on day 26 of the first course.

Conclusions: S-1 with low-dose cisplatin may become an effective regimen with acceptable toxicity for gastric cancer.

INTRODUCTION

The prognoses of patients with unresectable or recurrent gastric cancer are very poor. Although no standard therapy for advanced gastric cancer has emerged, either cisplatin-based or 5-fluorouracil (5-FU)-based combination chemotherapy has been recommended (1–3). Since 1999, the oral chemotherapeutic agent S-1 has been clinically available for patients with gastric cancer in Japan. S-1 consists of tegafur (a prodrug of 5-FU) and two modulators, 5-chloro-2,4-dihydropyridine and potassium oxonate, at a molar ratio of 1:0.4:1 (4). 5-Chloro-2,4-dihydropyridine is a reversible competitive inhibitor of dihydropyrimidine dehydrogenase, which is an enzyme for 5-FU degradation. Therefore, 5-chloro-2,4-dihydropyridine with tegafur is expected to yield prolonged and high serum and tumor tissue 5-FU concentration. Oxonate is a reversible competitive inhibitor of orotate phosphoribosyltransferase, which is an enzyme for 5-FU phosphoribosylation in the gastrointestinal mucosa. It is reported that oxonate concentrates selectively in gastrointestinal tissues after oral administration and suppresses gastrointestinal toxicity caused by phosphoribosylation of 5-FU in the gastrointestinal tract without decreasing the antitumor activity (5). In an early Phase II clinical study of S-1, the partial response rate for gastric cancer was 53.6% (15 of 28), the mean survival time (MST) was 298 days, and the incidence of adverse effect was low (6). In a late Phase II clinical study, the partial response rate was 44.2% (19 of 43), and the MST was 207 days, whereas the frequencies of adverse effect were 2–4% at grade 3 and none at grade 4 (7). In another Phase II clinical trial, the response rate was 49% (25 of 51), including 1 (2%) complete responder, the MST was 250 days, and the grade 3 and 4 adverse reactions were 18 and 2%, respectively (8). Oral formulation of S-1 and the low incidence of adverse reactions to it permit chemotherapy on an outpatient basis. One would expect additional therapeutic benefits by combination therapy of S-1 with cisplatin because cisplatin has been well known to exert a synergistic antitumor effect with 5-FU (9, 10).

In response to these earlier findings, the Japanese Foundation for Multidisciplinary Treatment of Cancer (JFMC) conducted a Phase I trial entitled “JFMC27-9902” to examine the tolerability, clinical efficacy, and serum concentration of 5-FU and cisplatin by administering a combination therapy of S-1 with low-dose cisplatin for patients with unresectable or recurrent gastric cancer.

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PATIENTS AND METHODS

Eligibility Criteria. Patients between 20 and 75 years of age with a histological diagnosis of unresectable or recurrent gastric cancer were eligible. Eastern Cooperative Oncology Group performance status (PS) ≤ 2 , and life expectancy ≥ 12 weeks were required. Patients were required to have measurable or assessable disease and to have had no prior therapy ≤ 28 days before registration. Other eligibility requirements included adequate bone marrow function (Hb ≥ 9.0 g/dl, WBCs between 4,000 and 12,000/ μ l, neutrophils $\geq 2,000$ / μ l, platelets $\geq 100,000$ / μ l), total bilirubin ≤ 1.5 mg/dl, aspartate aminotransferase and alanine aminotransferase ≤ 100 IU/liter, alkaline phosphatase \leq two times the upper normal level, and BUN and serum creatinine \leq the upper normal level.

Assessment of Toxicity. Blood counts and biochemical profiles were performed at least once weekly. We monitored patients for the occurrence of nonhematological toxicities such as general fatigue, nausea/vomiting, stomatitis, diarrhea, skin pigmentation, eczema, and hand-foot syndrome. Toxicity during each course was evaluated according to the National Cancer Institute-Common Toxicity Criteria version 2.0.

Treatment Regimen. S-1 (Taiho Pharmaceutical Co., Tokyo, Japan) was administered orally at a standard dose of 40 mg/m² twice daily after a meal. Three initial doses of S-1 were established according to body surface area (BSA) as follows: body surface area < 1.25 m², 80 mg/day; 1.25 m² \leq BSA < 1.5 m², 100 mg day/day; and 1.5 m² \leq BSA, 120 mg/day. One course consisted of consecutive administration for 28 days followed by 14 days' rest. Low-dose cisplatin in 100 ml of normal saline was administered i.v. over 30 min on days 1–5, 8–12, 15–19, and 22–26 of each course. Hydration to protect against nephrotoxicity was not given to any patient. The scheduled dose of cisplatin was initially 1 mg/m²/day for level 1, with a dose escalation to 2, 3, 4, and 6 mg/m² for level 2, 3, 4, and 5, respectively. This therapy was administered for three courses (at least two courses) in repeated administration.

Dose-Limiting Toxicity (DLT). DLT was defined as the occurrence of any one of the following: (a) grade 4 leukopenia lasting for ≥ 3 days, grade 4 neutropenia for ≥ 3 days, or grade 4 thrombocytopenia; (b) nonhematological toxicity \geq grade 3 excluding alopecia, nausea/vomiting, and general fatigue; or (c) total treatment interruption lasting > 3 weeks during any course.

Interruption, Resumption, Cessation of the Regimen. The occurrence of grade 3 hematological toxicity, grade 2 nonhematological toxicity, or a PS of 3 prompted interruption of the regimen. The regimen was resumed as soon as patients recovered from these adverse effects. The regimen was stopped when nonhematological DLT, total treatment interruption lasting > 3 weeks during any course, or a PS of 4 occurred.

Dose Modification. Doses of S1 were modified in accordance with the following guidelines: when hematological DLT appeared, the dose of S-1 was reduced from 120 to 100 mg/day, from 100 to 80 mg/day, and from 80 to 50 mg/day, respectively. The cisplatin dose was not reduced.

Study Design. The courses were repeated every 6 weeks. A minimum of 3 patients in each cohorts were evaluated at each dose level, and sequential dose levels were studied in the absence of DLT. If no DLT was observed in the initial 3 patients,

the dosage of cisplatin was escalated to successive cohorts. If 1 or 2 of the initial 3 patients at any level developed treatment-related DLT, 3 additional patients were studied at that level before escalation. If only 1 or 2 of 6 patients experienced DLT, dose escalation would continue. There was no dose escalation in individual patients. The maximum-tolerated dose (MTD) of the combination was defined as the dose level that produced DLT in ≥ 3 of 6 patients or in all of the initial 3 patients. The recommended dose (RD) is defined as the dose level that is one level under MTD.

Sample Collection. The blood samples were drawn on day 1 of the first and second course, before administration of S-1 in the morning and on days 1, 5, 12, and 26 of the first course at 4 h after administration of S-1 in the morning. The sample collection timing of 4 h after administration of S-1 was selected because the maximum serum concentration of 5-FU is reported to occur at that time (11).

Each peripheral blood sample was collected into a tube at a volume of 6 ml, stored for 30 min at room temperature, and centrifuged at 3000 rpm for 10 min. The serum was stored at -20°C until the measurement of 5-FU and cisplatin concentration.

Drug Assay. 5-FU was extracted with ethyl acetate from each serum sample and analyzed using a high-performance liquid chromatograph system HP-1100 (Hewlett Packard, Palo Alto, CA) equipped with a QUATTRO II mass spectrometer (Micromass, Cheshire, United Kingdom) in the electrospray ionizing mode. Cisplatin was analyzed by the flameless atomic absorption spectrometry method described elsewhere (12). The Student's *t* test was used to compare serum concentrations of 5-FU or cisplatin. $P < 0.05$ was considered statistically significant.

Assessment of Response. Lesions noted at baseline and within 1 week after each course were measured or evaluated by computed tomography, ultrasonography, magnetic resonance imaging, gastroscopy, and upper gastrointestinal radiography. Objective responses were classified according to WHO criteria (13) for metastatic lesion and according to the criteria for response assessment of chemotherapy for gastric carcinoma established by the Japanese Research Society of Gastric Cancer (14) for primary lesions. Patient eligibility and response to treatment were reviewed extramurally. The extramural review was done by three clinical oncologists and one radiologist from independent institutes.

RESULTS

Patients Characteristics. Patients with unresectable or recurrent gastric cancer were enrolled in this trial between February 2000 and January 2002. A total of 24 patients was enrolled from five institutions in this study. One patient at level 5 was excluded from this study because the patient's doctor missed the administration dosage of cisplatin. Therefore, 23 patients were analyzed. The demographic characteristics of the patients are listed in Table 1. Mean \pm SD of age was 60.3 ± 9.9 years, ranging 39–75 years. The prior therapies had been given for 4 patients (oral 5-FU for 2 patients, oral tegafur for 1 patient, and hepatic arterial infusion of 5-FU for 1 patient); however, these therapies were stopped at least 28 days before registration.

Table 1 Patient population

Parameter	No. of patients ^a					Total (%)
	Level 1	Level 2	Level 3	Level 4	Level 5	
Total no.	3	6	6	3	5	23 (100)
Sex						
Male	2	3	6	3	4	18 (78.2)
Female	1	3	0	0	1	5 (21.8)
Age						
30–39	0	0	1	0	0	1 (4.4)
40–49	0	1	0	0	1	2 (8.7)
50–59	3	1	0	1	0	5 (21.7)
60–69	0	3	4	2	2	11 (47.8)
70–75	0	1	1	0	2	4 (17.4)
Performance status						
0	2	3	5	3	2	15 (65.2)
1	1	3	1	0	1	6 (26.1)
2	0	0	0	0	2	2 (8.7)
Diagnosis						
Unresectable	2	3	5	2	5	17 (73.9)
Recurrent	1	3	1	1	0	6 (26.1)
Histologic differentiation						
Well or moderately	2	2	3	2	2	11 (47.8)
Poorly or signet-ring cell	1	4	3	1	3	12 (52.2)
Hepatic metastasis						
Negative	2	5	3	1	4	14 (60.9)
Positive	1	1	3	2	1	9 (39.1)
Peritoneal metastasis						
Negative	2	2	5	2	4	15 (65.2)
Positive	1	4	1	1	1	8 (34.8)

^a 1, 2, 3, 4, 6 mg/m² of cisplatin with 80 mg/m² of S-1 were given at Level 1, 2, 3, 4, 5, respectively.

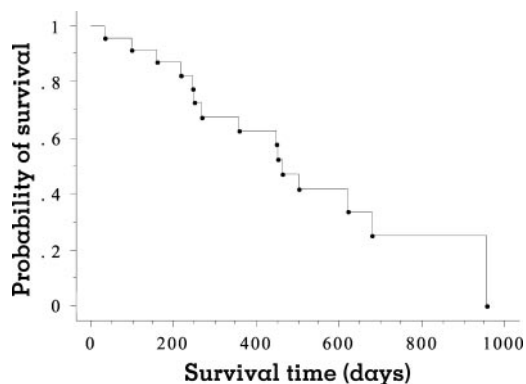


Fig. 1 Probability of survival after the initiation of an S-1 plus low-dose cisplatin regimen in patients with unresectable and recurrent gastric cancer.

The MST of total patients studied here was 461 days (95% confidence interval, 268–679 days), ranging from 34 to 958 days (Fig. 1). The 1-year and 2-year survival rates were 62.8 and 25.1%, respectively.

Toxicity. All 23 patients were assessable for toxicity. Among the hematological toxicity at grade 3, neutropenia was most frequently observed, and it occurred independent of cisplatin dose (Table 2). Hematological toxicity at grade 4 was experienced by 1 patient each at level 2 and level 5. Nonhematological toxicities of grade 3 and 4 occurred in 4 patients as treatment-related toxicities (Table 3). There was no treatment-related death during this study.

Dose modifications of S-1 were made for 2 of the level 2 patients and 1 of the level 3 patients. DLT was observed in one of the initial 3 patients at level 2 during the first course, who developed grade 4 diarrhea (Table 4 and Fig. 2). An additional 3 patients were entered in level 2. One of them developed grade 4 leukopenia, grade 4 neutropenia, grade 4 thrombocytopenia, and grade 3 hepatotoxicity. One patient experienced grade 4

Table 2 Hematologic toxicity

Adverse effect	No. of patients ^a				
	Level 1 (n = 3)	Level 2 (n = 6)	Level 3 (n = 6)	Level 4 (n = 3)	Level 5 (n = 5)
Leukopenia					
Grade 1, 2	2	4	5	2	3
Grade 3	0	1	0	1	1
Grade 4	0	1	0	0	0
Neutropenia					
Grade 1, 2	0	1	2	2	1
Grade 3	1	3	3	1	1
Grade 4	0	1	0	0	1
Anemia					
Grade 1, 2	2	4	5	1	3
Grade 3	0	2	0	1	1
Grade 4	0	0	0	0	0
Thrombocytopenia					
Grade 1, 2	1	1	4	0	0
Grade 3	0	1	0	0	2
Grade 4	0	1	0	0	0

^a 1, 2, 3, 4, 6 mg/m² of cisplatin with 80 mg/m² of S-1 were given at Level 1, 2, 3, 4, 5, respectively.

Table 3 Nonhematologic toxicity

Adverse effect	No. of patients ^a				
	Level 1 (n = 3)	Level 2 (n = 6)	Level 3 (n = 6)	Level 4 (n = 3)	Level 5 (n = 5)
Appetite loss					
Grade 1, 2	2	2	3	2	2
Grade 3	0	0 + 1 ^b	0	0	2
Grade 4	0	0	0	0	0
Nausea/Vomiting					
Grade 1, 2	2	4	4	0	3
Grade 3	0	0	0	0	0
Grade 4	0	0	0	0	0
Stomatitis					
Grade 1, 2	1	2	0	0	0
Grade 3	0	0	0	0	0
Grade 4	0	0	0	0	0
Diarrhea					
Grade 1, 2	0	3	3	0	0
Grade 3	0	0	0	0	0
Grade 4	0	1 + 1 ^b	0	0	0
Skin					
Grade 1, 2	0	1	1	0	1
Grade 3	0	0	0	0 + 1 ^c	0
Grade 4	0	0	0	0	0
General fatigue					
Grade 1, 2	1	3	1	1	2
Grade 3	0	0	0	0	0
Grade 4	0	0	0	0	0
Hepatotoxicity					
Grade 1, 2	2	3	4	3	2
Grade 3	0	1	0	0	0
Grade 4	0	0	0	0	0
Nephrotoxicity					
Grade 1, 2	0	5	2	0	1
Grade 3	0	0	0	0	0
Grade 4	0	0	0	0	0

^a 1, 2, 3, 4, 6 mg/m² of cisplatin with 80 mg/m² of S-1 were given at Level 1, 2, 3, 4, 5, respectively.

^b Due to influenza.

^c Due to dermatomyositis.

diarrhea and grade 3 appetite loss; however, the symptoms were considered to be the result of severe influenza, and the patient was successfully treated for two courses interrupted by a drug-free period.

Two of 6 patients at level 2 developed DLTs. In accordance with the study design, dose escalation to level 3 did occur. We thought level 3 should be carefully examined, and 6 patients were enrolled at level 3. All 6 patients tolerated the level 3 dosage with no DLT. At level 4, 1 patient stopped the regimen because of dermatomyositis, although the patient's grade 3 skin toxicity was considered to be a treatment-unrelated toxicity by a dermatologist and a specialist in internal medicine. The other 2 patients completed the regimen. At level 5, 2 patients experienced DLT of grade 3 appetite loss and could not continue the chemotherapy beyond the first course. The body weights of these patients decreased 5–10% during the regimen, but their appetites recovered after cessation of the regimen. One patient at level 5 developed grade 4 leukopenia, so chemotherapy was stopped. The other 2 patients did not experience DLT; however, 1 of the patients developed grade 3 thrombocytopenia (minimum platelet, 28,000/mm³), for which a transfusion of blood

platelets was given in the third course. Finally, MTD was reached at level 5, at which the dose of cisplatin was 6 mg/m²/day. The RD of cisplatin combined with S-1 is the level 4 dose of 4 mg/m².

Serum Concentrations of 5-FU. The serum concentrations of 5-FU at each dose level did not significantly differ from each other during any single day of the regimen (Fig. 3). Moreover, in the patients treated with the same dosage level, no differences of the serum concentrations of 5-FU were observed during the regimen (on day 1, 5, 12, and 26). The serum concentrations of 5-FU in individual patient were widely distributed; however, each individual patient showed a stable 5-FU concentration on any given day during the regimen. The results were predictable, probably because the S-1 dosages for all levels were the same. One important finding is that high serum concentrations of 5-FU were obtained after 4 h of the standard dose of S-1: mean \pm SD, 141.7 \pm 56.1 ng/ml, ranging from 36 to 278 ng/ml. The other noteworthy finding was that serum concentra-

Table 4 Dose limiting toxicity

Adverse effect	No. of patients ^a				
	Level 1 (n = 3)	Level 2 (n = 6)	Level 3 (n = 6)	Level 4 (n = 3)	Level 5 (n = 5)
Total patients no. of DLT ^b	0	2	0	0	3
Leukopenia	0	1	0	0	0
Neutropenia	0	1	0	0	1
Anemia	0	0	0	0	0
Thrombocytopenia	0	1	0	0	0
Appetite loss	0	0	0	0	2
Diarrhea	0	1	0	0	0
Stomatitis	0	0	0	0	0
Skin toxicity	0	0	0	0	0
Hepatotoxicity	0	1	0	0	0
Nephrotoxicity	0	0	0	0	0

^a 1, 2, 3, 4, 6 mg/m² of cisplatin with 80 mg/m² of S-1 were given at Level 1, 2, 3, 4, 5, respectively.

^b DLT, dose limiting toxicity.

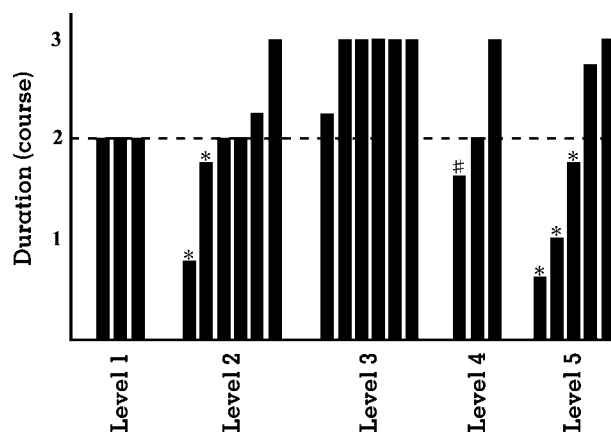


Fig. 2 The duration of the regimen. The completion of the regimen is defined as achievement of at least second course. The reasons for noncompletion are as follows: *, dose-limiting toxicity; #, treatment-unrelated toxicity (dermatomyositis).

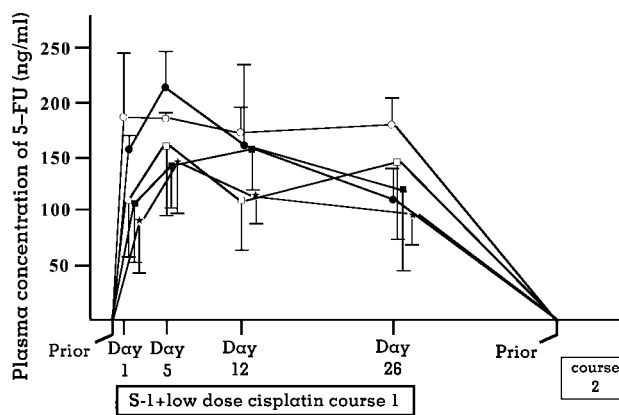


Fig. 3 Serum concentration of 5-fluorouracil (5-FU) during the regimen of S-1 plus low-dose cisplatin. ○, level 1; ●, level 2; □, level 3; ■, level 4; ★, level 5. No significant differences of 5-FU concentrations are observed at each level of cisplatin administration.

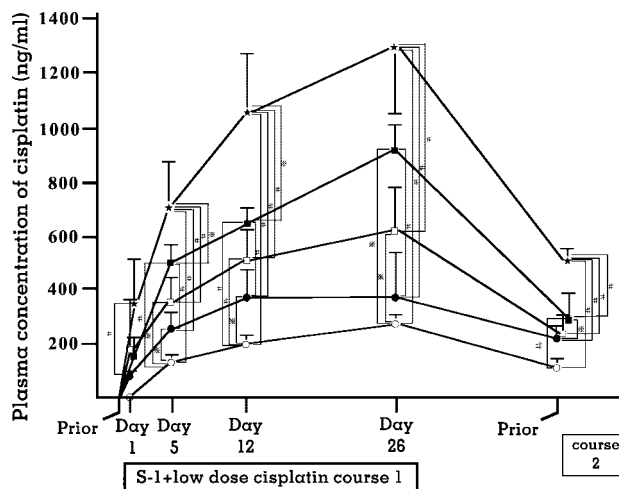


Fig. 4 Serum concentration of cisplatin during the regimen of S-1 plus low-dose cisplatin. ○, level 1; ●, level 2; □, level 3; ■, level 4; ★, level 5. Statistically significant differences of the cisplatin concentrations are observed between the levels: *, $P < 0.05$; #, $P < 0.01$.

tion of 5-FU did not increase concurrently with increased dosage of cisplatin at the dosages studied in this study.

Serum Concentration of Cisplatin. The serum concentrations of cisplatin increased depending on the levels of cisplatin with significant differences (Fig. 4). The concentrations at each level also increased in a time-dependent manner, meaning cisplatin gradually accumulated in serum after the consecutive i.v. infusions. Cisplatin clearance was so slow that approximately half of the serum concentrations on day 26 remained after 2 weeks of drug-free rest. The day 26 serum concentrations of cisplatin at level 4 reached 918 ± 92 ng/ml, ranging from 816 to 995 ng/ml. Concentrations at level 5 were 1306 ± 261 ng/ml, ranging from 1032 to 1651 ng/ml.

Efficacy. Antitumor effects were evaluable in 20 patients. The clinical efficacies of each level are shown in Table 5.

DISCUSSION

In Japan, for the last decade, numerous patients with highly advanced gastric cancers have been treated with low-dose FP therapy, consisting of 5-FU ($200\text{--}350$ mg/m²/day, 24-h continuous infusion, every day) and cisplatin ($2\text{--}10$ mg/m²/day, 1-h infusion on day 1–5 every week) for 4 weeks (15–17). The response rates and MSTs by low-dose FP therapy for advanced gastric cancer have been reported to be 35–50% and 7–11 months, respectively, with mild adverse effects.

It has been reported that cisplatin enhances the antitumor effect of 5-FU by following mechanism: cisplatin can inhibit methionine uptake into tumor cells and perturbate the methionine pools in the cells. As a response to the lack of methionine pools, the cells may increase methionine biosynthesis and the pools of folate cofactors. The increased 5,10-methylenetetrahydrofolate enhances the 5-FU cytotoxicity by increasing the reduction of thymidylate synthase to make the ternary complex, which is the tight binding of a 5-FU metabolite fluorodeoxyuridylylate, thymidylate synthase, and 5,10-methylenetetrahydrofolate (5, 9).

One of the advantages of low-dose cisplatin is the avoidance of renal failure and the lack of requirement for hydration of several hours' duration, which is necessary with a high dose ($70\text{--}100$ mg/m²) of cisplatin. The other advantage of low-dose cisplatin is that clinicians can omit the administration of antiemetics such as 5-hydroxytryptamine antagonists because of the lower incidence of nausea and vomiting than occurs at the high dose. These merits of low-dose cisplatin enable outcome-based treatment because of the shorter infusion time and fewer adverse effects.

S-1 is a novel 5-FU derivative providing high clinical response rates without severe adverse effects (6–8). It has been reported that the serum concentration of 5-FU with S-1 administration is substantially high, equal to that by continuous 5-FU infusion (11, 18). Therefore, it would be ideal for patient convenience if S-1 could be used instead of 5-FU continuous infusion because patients would not be restricted. We planned this Phase I study to test the efficacy of S-1 plus low-dose cisplatin as an alternative low-dose FP therapy.

On the basis of early Phase II clinical trials, the RD of S-1 was determined to be 40 mg/m² twice daily, and one course consisted of 28 days of consecutive administration followed by 14 days of rest (6). In this Phase I study, the S-1 dosage chosen

Table 5 Clinical efficacy

Efficacy	No. of patients ^a				
	Level 1 (n = 3)	Level 2 (n = 6)	Level 3 (n = 6)	Level 4 (n = 3)	Level 5 (n = 5)
Complete response (CR)	0	1	0	0	0
Partial response (PR)	2	0	4	3	1
Stable disease	0	3	1	0	1
Progressive disease	1	0	1	0	0
Not evaluable	0	2	0	0	3
Percentage of CR + PR to evaluable patients	66.7	25	66.7	100	50

^a 1, 2, 3, 4, 6 mg/m² of cisplatin with 80 mg/m² of S-1 were given at Level 1, 2, 3, 4, 5, respectively.

was a standard dose, but it was unknown how much cisplatin would be needed for modulation of the S-1 effect. Therefore, we escalated the dose of cisplatin stepwise from a very low dose of 1 mg/m². Patients enrolled in this study tolerated the dose of 4 mg/m² of cisplatin well. However, DLTs were observed in 3 of 5 patients at level 5, and MTD was defined to be level 5. The RD of cisplatin combined with S-1 is the level 4 dose of 4 mg/m² according to the present protocol. Moreover, 4 (66.7%) of 6 patients at level 3, and all 3 patients at level 4 obtained partial response, suggesting the promise of good clinical efficacy at these dosage of cisplatin.

On the basis of the data obtained from this study, we found that serum concentrations of 5-FU were not affected by cisplatin at these low doses. It is an intriguing result that at level 5, the serum concentration of cisplatin exceeded 1000 ng/ml, and highly frequent DLTs were observed, suggesting an association between serum concentration of cisplatin and toxicity.

Recently, there was a case report in which the patient demonstrated a histologically complete response after two courses of the same regimen as was used in this study, *i.e.*, with a cisplatin dose of 3–4 mg/day and the standard dose of S-1 (19). This report by Iwahashi *et al.* (19) supports our conclusion that such low-dose cisplatin may be suitable for combination with S-1. However, the *i.v.* infusion of cisplatin five times a week may be impractical. JFMC has planned a new Phase I/II trial in which low-dose cisplatin is given twice a week with daily administration of S-1. In this coming regimen, the optimal dosage of cisplatin will be found referring the results of JFMC27-9902.

We conclude that an S-1 plus low-dose cisplatin regimen may be one of the treatments showing a high efficacy with acceptable toxicity in cases of unresectable and recurrent gastric cancer. The RD of cisplatin in this combination is 4 mg/m².

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