A Phase I Study of Combination Therapy of the Oral Fluorinated Pyrimidine Compound S-1 with Low-dose Cisplatin Twice-a-week Administration (JFMC27-9902 Step2) in Patients with Advanced Gastric Cancer Using a Continual Reassessment Method

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Objective: We conducted a Phase I study to evaluate the safety and efficacy of a combination of S-1 with semi-weekly low-dose cisplatin in patients with unresectable/recurrent gastric cancer to determine the recommended dose (RD) for a subsequent Phase II study.

Methods: S-1 was administered orally at 80–120 mg/body/day based on body surface area. One cycle consisted of the consecutive administration of S-1 for 28 days followed by 14 days rest. Three dose levels, 7.5, 10, and 15 mg/m²/day, were set for cisplatin, which was administered twice-a-week for 4 weeks followed by 2 weeks of rest in each cycle. Dose-limiting toxicity (DLT) data were continually monitored to enable decisions regarding cisplatin dose escalation and deescalation based on a new dose-finding algorithm using a continual reassessment method (CRM). The CRM target toxicity level to estimate the RD was set at 20%.

Results: Eight and five patients were treated at cisplatin dose levels of 10 and 15 mg/m²/day, respectively. Two DLTs occurred at both dose levels. On the basis of this data, the CRM estimated the RD to be 10 mg/m²/day of cisplatin. Three patients of eight patients treated with 10 mg/m²/day of cisplatin exhibited a confirmed partial response during the treatment period.

Conclusion: For future trials examining the safety and efficacy of daily S-1 with semi-weekly cisplatin in patients with unresectable/recurrent gastric cancer, we found a cisplatin RD of 10 mg/m²/day.

Key words: S-1 – low-dose cisplatin – continual reassessment method – gastric cancer – Phase I clinical study

INTRODUCTION

The oral dihydropyrimidine dehydrogenase inhibiting fluoropyrimidine S-1 is both safer and more effective than other therapies for the treatment of recurrent and/or unresectable gastric cancer (1–3), and S-1 has been incorporated into standard gastric cancer treatment regimens in Japan. A variety of S-1 based combination chemotherapies have been studied to establish a more effective treatment regimen that minimizes the occurrence of adverse events. In particular, combinations of cisplatin (CDDP) (4–8), docetaxel (9,10), paclitaxel (11), or irinotecan (12) with S-1 have shown promise for the treatment of gastric cancer through Phase...
I or II study. Two regimens combining different doses of CDDP with S-1 were examined: a high-dose regimen with 60 mg/m² CDDP once in 5 weeks (7) or 75 mg/m² once in 4 weeks (8) or a low-dose regimen involving weekly 25 mg/m² or less administration of CDDP (4–6). Additionally, Hyodo et al. (4) conducted a dose-finding Phase I study and determined that weekly administration of 20 mg/m² CDDP was optimal when combined with 70 mg/m² of S-1 administered daily for 2 weeks followed by a 1-week washout period. With this regimen, 58% of patients responded to therapy, but 54% of patients experienced Grade 2 gastrointestinal toxicity during the first two cycles. This is particularly concerning because oral anticancer agents such as S-1 must achieve high concentrations to be maximally effective, and gastrointestinal toxicity including nausea and anorexia severely limits this. A lower dose of CDDP administered more frequently may be as effective with less gastrointestinal toxicity.

The Japanese Foundation for Multidisciplinary Treatment of Cancer carried out a Phase I clinical trial (JFMC27-9902) examining the safety of escalating low doses of CDDP given in combination with a fixed dose of S-1 five times per week (5). Among the doses of CDDP examined, 1, 2, 3, 4, or 6 mg/m², 4 mg/m² given 5 days per week was optimal. However, the dosing schedule would require a large degree of hospitalization that is not compatible with the current medical and economic environment in Japan. The reality of this situation suggests that a new Phase I/II study is needed to determine an optimal twice-a-week CDDP administration schedule that maintained or increased regimen efficacy while minimizing adverse events (13). Data from the previous Phase I trial was used as a baseline for the development of a twice-a-week CDDP dosing schedule in the current Phase I study (JFMC27-9902 Step2), and we adopted a new dose-finding algorithm using a continual reassessment method (CRM) (14,15) to estimate a recommended dose (RD) for the new dosing schedule. Data from the present study will be used to develop a Phase II study to examine the efficacy of a novel CDDP, S-1 combination regimen for the treatment of unresectable and/or recurrent gastric cancer.

PATIENTS AND METHODS

TRIAL ELIGIBILITY

Patients with a histologic diagnosis of unresectable or recurrent gastric cancer and a performance status (PS) of Eastern Cooperative Oncology Group of 0 to 1 were eligible for study participation. Additional eligibility criteria included: (i) age ranging from 20 to 75 years, (ii) no anti-tumor therapy within 28 days prior to enrollment except for hormone-therapy and immunotherapy completed 2 weeks before enrollment into this trial and postoperative adjuvant chemotherapy not using CDDP completed 1 month before enrollment into this trial, (iii) life expectancy longer than 12 weeks, (iv) adequate bone marrow function (Hb ≥ 9.0 g/dl, white blood cells between 4000 and 12 000/µl, platelets ≥ 100 000/µl), and (v) sufficient organ function (total bilirubin ≤ 1.5 mg/dl, GOT and GPT ≤ 2.5 times the upper normal level, alkaline phosphatase ≤ two times the upper normal level, and blood urea nitrogen (BUN) and serum creatinine ≤ the upper normal level). Informed consent was obtained from each patient before enrollment. Each institutional review board for human experimentation approved the protocol of this study.

TREATMENT REGIMEN

S-1 was administered orally twice daily after a meal at one of three initial doses based on body surface area (BSA): (i) BSA <1.25 m², 80 mg per day, (ii) 1.25 m² ≤ BSA < 1.5 m², 100 mg day per day, and (iii) 1.5 m² ≤ BSA, 120 mg per day. One cycle consisted of twice daily S-1 administration for 28 consecutive days followed by 14 days of withdrawal. CDDP in 100 ml of normal saline was given as a 1-h intravenous injection twice a week for 4 weeks on days 1, 4, 8, 11, 15, 18, 22, and 25, followed by 2 weeks of withdrawal in each cycle. Three CDDP dose levels, 7.5 mg/m² per day (Level 1), 10 mg/m² per day (Level 2; starting dose (see below)), and 15 mg/m² per day (Level 3), were chosen. These doses were determined using data from the previously conducted Phase I trial JFMC27-9902 (5). No patient was given hydration to protect against nephrotoxicity.

Patients underwent at least two consecutive cycles of combination therapy. Patients remained in the study unless (i) dose-limiting toxicities (DLTs) (within the first cycle) or Grade 4 hematological or Grade 3 or 4 non-hematological toxicities (after the first cycle) occurred, (ii) objective evidence of tumor progression appeared, or (iii) the patient refused to continue the treatment. Additionally, therapy was discontinued if hematologic toxicities including Grade 2 or greater leukopenia, neutropenia and thrombocytopenia, Grade 2 or greater non-hematologic toxicities (except alopecia), and a deterioration in PS of two or more during each treatment cycle were observed. If the toxicity causing treatment discontinuation was Grade 3 or greater leukopenia, neutropenia or Grade 2 or greater thrombocytopenia, the S-1 dose was reduced from 80, 100, and 120 mg per day to 50, 80, and 80–100 mg per day, respectively. The dose of CDDP was not modified during the first and second cycles.

ASSESSMENTS OF TOXICITY AND EFFICACY

Adverse events were evaluated according to the National Cancer Institute—Common Toxicity Criteria version 2.0. DLT was defined for this study as the occurrence of any of the following observed within the first cycle of treatment: (i) Grade 3 or 4 leukopenia for 3 days or more, (ii) Grade 3 or 4 neutropenia along with fever (febrile neutropenia), (iii) Grade 3 or 4 thrombocytopenia, (iv) Grade 3 or greater non-hematologic toxicity, excluding alopecia, nausea/vomiting, and general fatigue, (v) total treatment interruption lasting > 3 weeks, or (vi) patient’s refusal to continue treatment due to adverse events or related matters. The assessment of
tumor response was based on the RECIST criteria. In addition, the tumor response data were reviewed extramurally. The protocol was approved by the Protocol Review Committee of the Japanese Foundation for Multidisciplinary Treatment of Cancer (JFMC).

**STUDY DESIGN AND STATISTICAL ANALYSES**

The RD was estimated using a CRM proposed by O’Quigley and Shen (15). We adapted this approach, because a CRM defines the RD more precisely than a conventional ‘3 + 3’ cohort design, thus the CRM was considered to suit the objective of this study. Dose escalations and deescalations for consecutive patient cohorts and the size of each cohort were based on the dose-finding CRM algorithm and clinical judgment. Skipping from Levels 1 to 3 was not allowed in the CRM calculations. The target toxicity level of the CRM to estimate the RD was set at 20%, which is the minimum value typically used in Phase I trials (15). Prior to starting the trial, participating clinicians predicted possible DLT occurrence probabilities of dose levels 1, 2, and 3 as 10% (5–30%), 20% (10–40%), and 40% (20–70%), respectively, based on the previous Phase I trial (JFMC27-9902) data (5). The ranges in the parentheses represent the pretrial clinician uncertainty of the DLT occurrence probability at each of the three dose levels. We determined the starting dose level in this trial to be Level 2, with the first two enrolled patients (first patient cohort) treated at this level. According to the pre-specified dose-escalation rule, if no DLT was observed in the first two patients, one patient enrolled in the second cohort was treated at Level 3. The projected sample size for the Phase I study was expected to require 10–16 patients, taking the simulation studies performed by O’Quigley et al. (14) into account.

In the CRM calculations, sensitivity analysis for parameters in the dose-toxicity model was performed. Four clinical scenarios for DLT occurrence probabilities at the three dose levels were established based on the pretrial prediction of the probabilities by the clinicians. We used scenarios (i) 10, 20, and 40%, (ii) 5, 10, and 20%, (iii) 30, 40, and 70%, and (iv) 5, 30, and 60% for DLT occurrence probabilities at Levels 1, 2, and 3, respectively. We considered bringing the Phase I to an early close when clear separation of the confidence intervals for the three dose levels appeared. This decision was also made according to clinical judgment. In addition, the trial was designed to be halted at the end of the Phase I if the selected regimen at the RD was insufficiently active when the hypothesis that the response rate (RR) at the RD is over 60% was statistically rejected (16). The Independent Data and Safety Monitoring Committee (IDSMC) independently reviewed the interim analysis and monitored protocol compliance, safety, and on-schedule study progress. The IDSMC considered stopping the trial from clinical as well as statistical points of view.

**RESULTS**

**PATIENT CHARACTERISTICS**

A total of 13 patients were enrolled from the three sites (Osaka City University Hospital, Kochi Health Sciences Center, and Tohoku Employees’ Pension Welfare Hospital) from December 2003 to March 2006. Eight and five patients were treated at Levels 2 and 3, respectively, and their baseline clinical characteristics are summarized in Table 1. The total number of cycles administered ranged from one to five and one to four for patients treated at Levels 2 and 3, respectively. Treatment was discontinued in two patients at Level 2 and two patients at Level 3 during the first cycle of therapy due to the occurrence of DLT. Treatment was discontinued in two patients at Level 2 and one patient at Level 3 during the second cycle, caused by the progression disease. Treatment was discontinued in three and two patients at Levels 2 and 3, respectively, due to the initiation of subsequent therapy. One patient at Level 2 underwent surgery after obtaining a partial response within the second cycle.

**TOXICITY**

Hematologic and non-hematologic toxicities for the 13 patients observed during the first cycle are detailed in Table 2. Grade 3/4 toxicities were observed more frequently in patients treated at Level 3. Two patients treated at Level 3

<table>
<thead>
<tr>
<th><strong>Table 1. Patient characteristics</strong></th>
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<tr>
<td><strong>Level 2 (n = 8)</strong></td>
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<tr>
<td><strong>Gender</strong></td>
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<tr>
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<tr>
<td>Female</td>
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<td>1</td>
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suffered Grade 3 anorexia during the first cycle, causing the two DLTs observed on Level 3 therapy. Grade 2 gastrointestinal toxicity (vomiting) was observed in only one patient (12.5%) at Level 2. Additionally, one patient suffered Grade 2 anorexia in the second cycle (data not shown). Therefore, two (25%) out of the eight patients at Level 2 experienced Grade 2 gastrointestinal toxicities through the completion of the first and the second cycle.

DOSE ESCALATION/DEESCALATION

The first two patients treated at Level 2 did not experience any DLT. According to the pre-specified dose-escalation rules of this study, the dose level for the second patient cohort was escalated to Level 3. Although the one patient in the second cohort did not experience any DLT, one of two patients in the third cohort experienced DLT (anorexia, Grade 3). At this point, the CRM was invoked and estimated the DLT occurrence probabilities as 3.1, 8.7, and 24.9% at Levels 1, 2, and 3, respectively. Thus, in the forth cohort, one patient was still assigned to Level 3, and this patient did not experience any DLT. The next single patient enrolled in the fifth cohort suffered DLT (anorexia, Grade 3), and the recalculated DLT occurrence probabilities estimated using the CRM were 5.9, 13.8, and 32.4% at Levels 1, 2, and 3, respectively. Consequently, the estimated Level 3 DLT probability considerably exceeded the target level, and the next patient cohort was treated at Level 2. In the subsequent six patients treated at Level 2, two DLTs (total treatment interruption lasting >3 weeks, patient’s refusal to continue treatment due to Grade 2 toxicity) were observed. Figure 1 shows the probabilities of DLT occurrence at Levels 2 and 3, estimated using all DLT data observed in the 13 patients under the 4 clinical scenarios used for sensitivity analysis. When the results of the sensitivity analysis and the observed toxicities at each dose level were considered, the IDSMC suggested that combination therapy at Level 2 was acceptable in terms of safety.

RESPONSE TO TREATMENT

The clinical responses of nine patients who did not experience any DLT on the combination therapy were assessed (Table 3). Three patients treated at Level 2 responded to treatment during the Phase I study, and they all exhibited a confirmed PR during treatment. The upper bound of the 95% confidence interval of the RR at Level 2 was 75.5%. Thus, the hypothesis that the RR at the RD is over 60% was not rejected, and these data indicate that the combination therapy regimen is effective and supports proceeding to the Phase II trial.

DISCUSSION

We conducted a dose-finding Phase I trial in 13 patients with unresectable or recurrent gastric cancer to determine the RD of a regimen combining S-1 and low-dose CDDP with twice-a-week administration (JFMC27-9902 Step2). We found that the intensity of CDDP per week at the RD level

<table>
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<tr>
<th>Dose level</th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
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CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; NE, non-evaluable.
of this regimen (10 mg/m^2, twice-a-week) was identical to that identified by the previous JFMC27-9902 study. (4 mg/m^2, five times per week) (5). In the JFMC27-9902 trial, three and five patients were treated with 4 mg/m^2 CDDP, five times-a-week (the dosage is identical to Level 2 in the current study) or 6 mg/m^2 CDDP, five times-a-week (corresponding to Level 3 in the current study), respectively. Although none of the three patients treated with 4 mg/m^2 CDDP experienced a DLT, two of the five treated with 6 mg/m^2 CDDP suffered Grade 3 anorexia. Thus, the JFMC27-9902 research team selected a dose of 4 mg/m^2 CDDP for future research. Additionally, Grade 1 anorexia was observed in two out of the three patients treated with 4 mg/m^2 CDDP, but no Grade 2/3/4 anorexia occurred in JFMC27-9902 at this treatment level. In the current JFMC27-9902 Step2 study, Grade 1 anorexia was observed in two out of the eight patients on Level 2 treatment, but Grade 2/3/4 anorexia was not observed in the first cycle. During the twice-a-week administration of 10 mg/m^2 CDDP, two patients (25%) experienced Grade 2 gastrointestinal toxicities during the two cycles. An additional study reported that with the weekly administration of 20 mg/m^2 CDDP, 54% patients suffered Grade 2 gastrointestinal toxicity during the two cycles (4). These results suggest that the mild gastrointestinal adverse events caused by twice-a-week CDDP administration with S-1 may provide adequate safety. Additionally, no other Grade 3/4 non-hematological toxicities were observed at the RD level in the current study.

The present study showed three (37.5%) of the eight patients were assessed at the RD acquired PR. The overall RR in the 13 patients was 23.1%. Therefore, twice-a-week CDDP administration with S-1 may seem to provide lower efficacy, compared with the weekly CDDP administration with S-1 proposed by Hyodo et al. (RR: 61%) (4), the high-dose CDDP administration with S-1 (RR: 74%) (7), and the S-1 mono-therapy (RR: 44–54%) (1–3). However, because the present study was a Phase I trial examining the efficacy of the regimen in such a small number of patients, the estimation of RR was not necessarily reliable. The examination of the RR at the RD is underway in a larger population of patients in the subsequent Phase II trial. With respect to the CDDP concentrations achieved, one report showed that twice-a-week administration of 7 mg/m^2 CDDP maintained a serum CDDP concentration comparable to that attained by 5 weekly doses of 3.5 mg/m^2 CDDP. Additionally, the CDDP concentration attained by the administration of 10 mg/m^2 twice-a-week might be equal to that attained by 4 mg/m^2 five times per week (17). In the ongoing JFMC27-9902 Step2 Phase II study, the pharmacokinetics of CDDP at the RD level determined here (10 mg/m^2, twice-a-week) will be compared with those determined with the 4 mg/m^2, five times per week regimen used in JFMC27-9902.

We applied the CRM to determine a final recommended treatment dose for future Phase II trial(s). In the present study, it took 28 months to enroll all the 13 patients. Although CRM designs have not been used so often because of their longer study duration compared with conventional study designs (18), the long time period for patient enrollment of this study was also due to low patient enrollment rate. The assessment of DLT was carried out during the first treatment course consisting of 6 weeks. Thus, if patients had been treated in cohorts of one and all patients had been consecutively enrolled with no gap, it would have taken at most 20 months to complete a study. In addition, Goodman et al. (18) reported that if one assigns more than one subject at a time to each dose level, the study duration can be reduced by >50% compared with the one-patient/cohort CRM design. Due to the relatively small number of patients enrolled in this study, the confidence intervals for the probability of DLT events at the three treatment levels are not clearly separable. Such uncertainty, however, is typical for Phase I dose-finding trials (19). However, we further performed a sensitivity analysis to estimate the DLT occurrence probabilities under a variety of assumptions to more clearly define the dose-toxicity relationship, and this analysis suggested that treatment Level 2 most closely approximated the study treatment goals. The robust results obtained through the sensitivity analysis supports the validity of the dose recommendation we reached. However, we must continue monitoring both the toxicity and efficacy of the combination regimen in the Phase II trial. A study design simultaneously monitoring both efficacy and toxicity, as proposed by Thall and Cook (20,21), may be useful in this context. Given the small number of patients we studied, despite the CRM algorithm, it is essential that the safety of the combination therapy be evaluated further with a larger patient population. As described in the study protocol, the RR of the RD will be further examined during the subsequent Phase II trial, and we will also monitor toxicity using CRM to reconfirm the safety of the RD (13). The sample size for the Phase II was set at 42.

In conclusion, we demonstrated that the combination regimen consisting of S-1 40 mg/m^2 twice daily for days 1–28 and CDDP 10 mg/m^2 on days 1 and 4 per week for 4 weeks followed by a 2-week washout period should be evaluated further in a Phase II trial in patients with unresectable or recurrent gastric cancer.

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Conflict of interest statement
None declared.

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