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Phase II Study of a Combination of Irinotecan and S-1 in Patients with Advanced Gastric Cancer (OGSG0002)

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Key Words
CPT-11 · Gastric cancer · Irinotecan · S-1

Abstract
Background/Aims: To investigate the efficacy and safety of the combination therapy of irinotecan (CPT-11) plus S-1 in patients with advanced gastric cancer at the dose recommended by a previous phase I study. ***Methods:*** A total of 23 patients received 80 mg/m^2 of CPT-11 on days 1 and 15, and S-1 at a dose level set on the basis of the body surface area (BSA): 40 (BSA <1.25 m^2), 50 (BSA ≥1.25 to <1.5 m^2) or 60 mg (BSA ≥1.5 m^2) b.i.d. was given from days 1–21. ***Results:*** The overall response rate was 47.8% (11 of 23, 95% confidence interval, CI: 27.4–68.2%). The median time to progression (TTP) was 210 days (95% CI: 145–322 days) and the median survival time was 394 days (95% CI: 241–484 days). The incidence of grade 3 or 4 hematological and non-hematological toxicity was 17.4 and 8.7%. The most common hematological toxicity was anemia and the most common non-hematological toxicity was diarrhea. ***Conclusion:*** The combination therapy of CPT-11 and S-1 provided prolonged TTP with low toxicity, and the results warrant a further phase III study to define the efficacy in improvement of survival in patients with advanced gastric cancer.

Introduction

The prognosis of unresectable advanced or recurrent gastric cancer is still dismal, although 5-fluorouracil (5-FU)-based chemotherapy provides significant survival benefit compared with best supportive care [1–3]. In Japan, 5-FU monotherapy, with a median survival time (MST) of 7.1 months, remains the reference arm for clinical trials of advanced gastric cancer. However, various combination therapies have been attempted to achieve better anti-tumor effects resulting in relief of symptoms or prolongation of survival, or both, in patients with advanced gastric cancer [4, 5]. New chemotherapeutic agents, including thymidylate synthase (S-1), irinote-

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can (CPT-11), taxanes and oxaliplatin, have been introduced to chemotherapy regimens, but at present no regimen has been regarded as definitely superior to any other.

S-1, an oral 5-FU derivative which was developed in Japan in 1999, consists of tegafur and two modulators, 5-chloro-2,4-dihydroxypyridine (a potent dihydropyrimidine dehydrogenase inhibitor) and potassium oxonate (an orotate phosphoribosyl transferase inhibitor), at a molar ratio of 1:0.4:1 [6, 7]. In three phase II trials of S-1 monotherapy for advanced gastric cancer performed in Japan, a high overall response rate (RR) of 44–54% and an MST of 8–10 months were reported, being comparable with the results of other combination chemotherapies [8–10]. Furthermore, since S-1 is administered orally, patients can be treated on an outpatient basis facilitating compliance. Therefore, since S-1 is one of the most active antitumor agents currently available for clinical use, it is anticipated to be a key drug for advanced gastric cancer.

CPT-11, which inhibits DNA topoisomerase-I [11], yielded an RR of 18.4% in patients with advanced gastric cancer when administered as monotherapy [12]. It is also regarded as a key drug in combination chemotherapy for both non-small cell lung carcinoma [13, 14] and small cell lung carcinoma [15]. In colorectal cancer, there is clear evidence of the superiority of the combination of CPT-11 with 5-FU compared with 5-FU chemotherapy alone [16–18].

Previously, we performed a phase I study on a combination of CPT-11 plus S-1 in patients with advanced gastric cancer [19]. In that study, CPT-11 was administered at fixed dosages of S-1, 40–60 mg b.i.d. according to body surface area (BSA), on days 1 and 15 during a 3-week cycle. The dosage of CPT-11 was escalated from 40 mg/m^2 in 20-mg/mg^2 increments, and dose-limiting toxicities including diarrhea and rash occurred in 50% of the patients (3/6) at 100 mg/m^2. Therefore, the recommended dosage (RD) was set at 80 mg/m^2, and the overall RR in phase I was 58.3% (14/24) with tolerable toxicity suggesting promising clinical efficacy. Then, we performed a multicenter phase II study to investigate the efficacy and safety of the CPT-11 plus S-1 combination in patients with advanced gastric cancer.

Patients and Methods

Eligibility Criteria

Patients with inoperable, advanced gastric cancer or recurrent gastric cancer who met the following conditions were enrolled in this study: (1) histologically proven gastric adenocarcinoma; (2) presence of measurable lesions; (3) no prior chemotherapy except for adjuvant chemotherapy completed ≥4 weeks before study entry, (4) age 20–75 years; (5) an Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤1; (6) life expectancy of at least 3 months; (7) preservation of major organ function reflected by a leukocyte count of ≥4,000 to <12,000/mm^3; platelet count ≥100,000/mm^3; hemoglobin ≥8.0 g/dl; serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≤100 U/I; alkaline phosphatase ≤2× the upper limit of the normal range (ULN); serum bilirubin level ≤1.5 mg/dl; serum creatinine ≤ULN, and normal ECG; (8) ability of oral administration; (9) no diarrhea, and (10) written informed consent to participate in this study. Patients who had completed adjuvant chemotherapy at least 4 weeks before study entry could be included. The study protocol was approved by the institutional review boards of each participating facility.

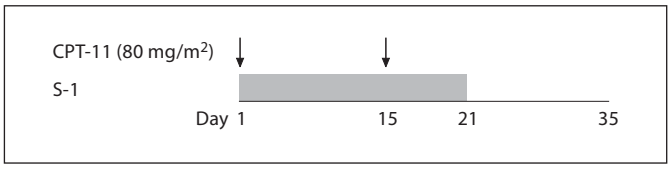

Fig. 1. The 5-week treatment schedule of the combination therapy of CPT-11 plus S-1. The S-1 dosage was based on BSA: 40 (BSA <1.25 m^2), 50 (BSA ≥1.25 to <1.5 m^2) or 60 mg b.i.d. (BSA ≥1.5 m^2) were administered.

Treatment Schedule

On days 1 and 15, 80 mg/m^2 of CPT-11 (Yakult Honsha, Tokyo, Japan) was mixed in 500 ml of 0.9% saline or 5% glucose solution and infused intravenously over a period of 90 min. The oral S-1 (Taiho Pharmaceutical, Tokyo, Japan) dosage was based on BSA: 40 (BSA <1.25 m^2), 50 (BSA ≥1.25 to <1.5 m^2) or 60 mg (BSA ≥1.5 m^2) b.i.d. were given orally for 21 days followed by 2 weeks without treatment. Five weeks made up a single course and each patient received at least two courses (fig. 1). Treatments were repeated unless disease progression or severe toxicity was observed, or the patients refused to continue.

Subsequent courses were withheld until recovery if the following criteria were not met before the start of a new cycle: leukocyte count ≥3,000/mm^3; platelet count ≥100,000/mm^3; hemoglobin ≥8.0 g/dl; serum AST and ALT level ≤100 U/I; serum bilirubin level ≤1.5 mg/dl; serum creatinine ≤ULN, neither diarrhea nor fever >38°C. If the abnormality did not disappear by day 35 of the cycle, the protocol was discontinued. If diarrhea or stomatitis ≥grade 2 developed, S-1 administration was interrupted until recovery.

If grade 4 neutropenia or ≥grade 3 diarrhea developed, the dosage of both drugs was reduced to 60 mg/m^2 for CPT-11 and by 10 mg b.i.d. for S-1. If the previous course was delayed or interrupted because of toxicity, only the dosage of CPT-11 was reduced to 60 mg/m^2. If stomatitis ≥grade 3 occurred, only the dosage of S-1 was reduced by 10 mg b.i.d. Once the dose of CPT-11 or S-1 was lowered, it remained at that level.

The initial doses of S-1 and CPT-11 were administered during admission, but patients received subsequent courses in the outpa-

Table 1. Characteristics of the patients

Patients	23
Sex	
Male	17
Female	6
Median age (range), years	59 (35–74)
Performance status	
0	13
1	10
Prior treatment	
None	14
Surgery	6
Surgery + chemotherapy	3
Initial treatment	
Primary cancer	16
Recurrence	7
Histological type	
Intestinal	10
Diffuse	13
Metastatic sites	
Lymph node	11
Liver	10
Lymph node + liver	1
Lymph node + peritoneum	1

tient clinics in each facility. Use of granulocyte-colony stimulating factor was allowed if leukocyte count decreased <1,000/mm^3 with fever >38°C or granulocyte count <500/mm^3. All patients received a 5-hydroxytryptamine-3-receptor antagonist and dexamethasone 30 min before CPT-11 administration, to prevent nausea and vomiting. Atropine was not used as premedication of CPT-11.

Evaluation

Electrocardiography, chest X-ray and computed tomography of the chest and the abdomen were performed before study entry. Patients who received at least two treatment courses were included in the analysis. Anti-tumor effects were determined according to RECIST (Response Evaluation Criteria in Solid Tumors) [20], and toxicity, time to progression (TTP) and overall survival were evaluated. Complete and partial responses required subsequent confirmation of response after an interval of at least 4 weeks. Toxicities were assessed according to National Cancer Institute Common Toxicity Criteria (version 2.0) [21]. Complete blood cell count and blood chemistry were evaluated, and non-hematological toxicities were verified by patient interview and physical examination at least every week during the first course and on days 1 and 15 of the second or later courses. In case of a symptom suggesting an adverse event, patients were asked to visit the outpatient clinic to receive consultation and blood testing. Eligibility and objective response to treatment were reviewed extramurally.

Statistical Methods

The RR of S-1 alone in the late phase II study was 44.6% with a 95% confidence interval (CI) of 35.2–54.3% [8]. Thus, the expected RR of the combination of S-1 and CPT-11 was set at 65%, which exceeded the 95% upper confidence limit of the RR for S-1 alone by 10%, and the threshold RR was set at 35% (~95% lower confidence limit). The calculated minimum sample size was estimated to be 20, with an α value of 0.05 and a β value of 0.20. Considering possible patient exclusion or dropouts, the required sample size was raised to 25. For the analysis in this study, 4 patients treated at the RD level were included in the phase I study. Overall and progression-free survivals were calculated using the Kaplan-Meier method from the date of treatment initiation.

Results

Patient Characteristics

Between February 2001 and May 2002, 25 patients were enrolled, but 1 patient with a platelet count of 7.2 × 10^4/mm^3 and 1 patient with a target lesion <1 cm were excluded, leaving 23 patients who met all the required criteria. The characteristics are shown in table 1. Nine patients had undergone surgery and 3 of them received prior adjuvant chemotherapy using tegafur plus uracil, doxifluridine and 5-FU plus cisplatin (CDDP), respectively. Histological evaluation revealed 10 patients of the intestinal type and 13 of the diffuse type. Metastatic sites were lymph nodes in 11 patients, liver in 10, lymph node and liver in 1, and lymph node and peritoneum in 1. All eligible patients received at least one course of treatment. The 23 patients received a total of 95 courses and a median of four (range: 1–9) courses per patient. Seventeen patients received second-line chemotherapy: S-1 plus paclitaxel in 6 patients, S-1 alone in 3, paclitaxel in 4, S-1 plus CDDP in 2, CDDP plus 5-FU in 1 and paclitaxel plus CDDP in 1, and 1 patient underwent gastrectomy. Supportive care was the only treatment in 5 patients after finishing the treatment.

Tumor Response and Overall Survival

All patients had at least one measurable lesion. The RR was 47.8% (11 of 23, 95% CI: 27.4–68.2%); 8 patients had stable disease as their best response, and 2 patients had progressive disease. Response was not evaluable in 2 patients because 1 patient developed ileus and became seriously ill, and 1 developed adverse events including neutropenia, nausea/vomiting, anorexia and diarrhea during the first course and the protocol was discontinued before examination. With respect to the histological type, RR was 60.0% for the intestinal type and 38.5% for the diffuse type (table 2). The median TTP was 210 days (95% CI: 145–322 days, fig. 2), and MST was 394 days (95% CI: 241–484 days, fig. 3). One- and two-year survival rates were 52.9 and 30.9%, respectively.

Table 2. Response rate

	Patients, n						
	total	CR	PR	SD	PD	NE	RR, %
Overall	23	1	10	8	2	2	47.8
95% CI							27.4–68.2
Histological type							
Intestinal	10	1	5	4			60.0
Diffuse	13		5	5	1	2	38.5

CR = Complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluated.

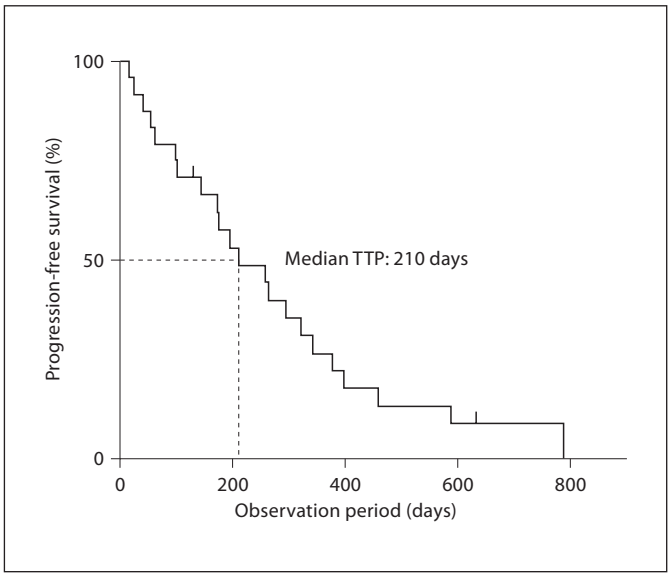

Fig. 2. Progression-free survival in patients treated with CPT-11 plus S-1.

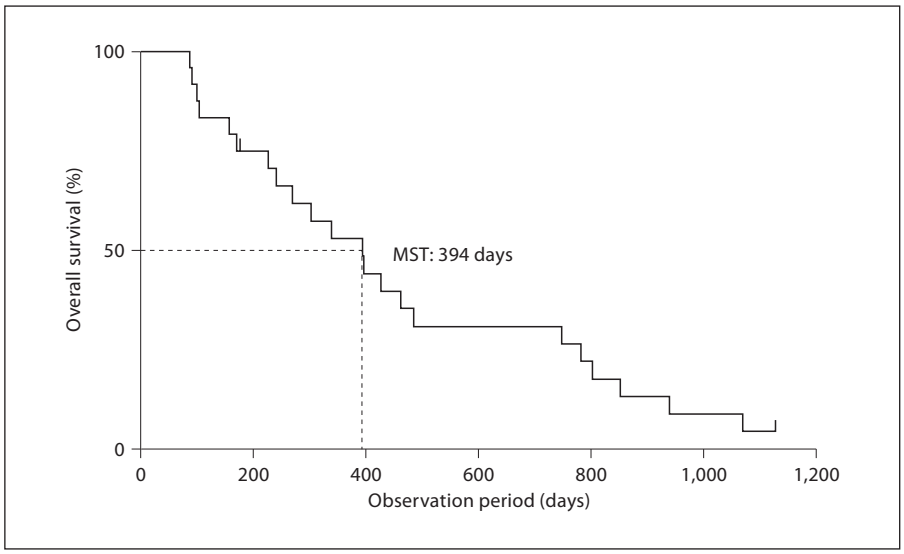

Fig. 3. Overall survival in patients treated with CPT-11 plus S-1.

Toxicity

Toxicity was summarized according to the worst grade per patient in table 3. There was no treatment-related death. The most common hematological toxicity was anemia, but the incidence of grade 3 or 4 was very low (2 patients, 8.7%). The most common non-hematological toxicity was diarrhea, which was usually mild. Overall, myelosuppression and gastrointestinal toxicity were common reactions, but were generally mild and tolerable. CPT-11 was decreased in 2 patients due to prolonged neutropenia, and both CPT-11 and S-1 were reduced in 1 due to the development of grade 4 anemia. The protocol was discontinued owing to toxicity in the patient who experienced grade 2 neutropenia, nausea/vomiting, anorexia and diarrhea during the first course, and efficacy was also not evaluated in this patient. He was adjudged to be too debilitated to continue the subsequent courses.

Discussion

In this study, we evaluated the efficacy and safety of the combination chemotherapy using 80 mg/m^2 CPT-11 plus S-1 in patients with advanced gastric cancer, and

good efficacy (RR 47.8%, TTP 210 days) with low toxicity (17.4% hematological and 8.7% non-hematological) was found.

To date, several 5-FU-based combination chemotherapy regimens have been reported in patients with advanced gastric cancer. In a study by Kim et al. [22] in advanced gastric cancer, the combination of CDDP with continuous infusion of 5-FU achieved a significantly better RR (51%) than 5-FU alone (26%), in agreement with the present study. The CDDP plus S-1 combination resulted in a striking RR of 74% [23]. However, despite the good RR, the TTPs of CDDP combinations (162 days) were relatively short. Furthermore, limitations of regimens including CDDP are higher incidences of non-hematological toxicities (nausea and vomiting, 58.3 and 26.3%) and the need for diligent hydration to prevent renal damage. With a triple combination of epirubicin, cisplatin and 5-FU, Webb et al. [24] achieved a good RR of 45% and TTP of 225 days, being comparable to our results . However, their study used portable pump infusion of 5-FU from a central venous catheter for up to 6 months. S-1 is administered orally and does not require pump infusion, yet it showed pharmacokinetic [25] and anti-tumor features [26] equivalent to those of continuous intravenous infusion of 5-FU. The combination of docetaxel (TXT) and CDDP with 5 days of continuous infusion of 5-FU yielded an RR of 42.5% and median TTP of 171 days, but grade 3 or 4 hematological toxicity was seen in 86% of cases [27]. Employing S-1 instead of 5-FU with TXT obtained a better RR of 56.2% and TTP of 222 days, but grade 3 or more neutropenia developed in 58.3% of cases [28]. We considered that a high incidence of hematological toxicity is a shortcoming of the TXT combination regimens when performed on an outpatient basis. In conclusion, combination therapy of CPT-11 with S-1 is a promising regimen offering benefits in terms of safety and survival compared with other regimens.

Other schedules of the CPT-11 plus S-1 combination for patients with advanced gastric cancer have been reported (table 4). Yamada et al. [29] conducted a phase I study in which CPT-11 was administered on day 1 with subsequent administration of S-1 for 14 days followed by 1 week of rest. The RD of CPT-11 for the phase II studies was set at 150 mg/m^2, and the overall RR was 71% (5 of

Table 3. Toxicity according to National Cancer Institute Common Toxicity Criteria (version 2.0) in the study patients

	G1	G2	G3	G4	G3/G4 %	Overall %
Anemia	8	9	1	1	2 (8.7)	19 (82.6)
Leukopenia	7	8	1	0	1 (4.3)	16 (69.6)
Neutropenia	6	9	2	0	2 (8.7)	17 (73.9)
Thrombocytopenia	2	0	0	0	0	2 (8.7)
Diarrhea	11	3	1	0	1 (4.3)	15 (65.2)
Anorexia	11	2	1	0	1 (4.3)	14 (60.9)
Nausea/vomiting	11	1	0	0	0	12 (52.2)
Fatigue	8	2	0	0	0	10 (43.5)
Abdominal pain	9	1	0	0	0	10 (43.5)
Constipation	3	1	0	0	0	4 (17.4)
Stomatitis	2	1	0	0	0	3 (13.0)
Dysgeusia	1	1	–	–	0	2 (8.7)
Alopecia	10	1	–	–	0	11 (47.8)
Pigmentation	4	0	–	–	0	4 (17.4)
Skin reaction	4	0	0	–	0	4 (17.4)
Fever	1	1	0	0	0	2 (8.7)

G1, G2, G3, G4 = Grades 1, 2, 3 and 4, respectively.

Table 4. Results of regimens reported for S-1 and CPT-11

Doses		Cycle days	Patients n	RR %	Median TTP days	MST days	Grade 3/4 toxicity, %		Reference No. (year)
S-1, mg	CPT-11, mg/m^2						hematological	non-hematological	
40–60 b.i.d. (days 1–14)	150 (day 1)	21	12	71	ND	ND	25	26.3	29 (2003)
40–60 b.i.d. (days 1–14)	80 (days 1, 8)	21	10	20	ND	311	10	30	30 (2003)
40–60 b.i.d. (days 1–14)	80 (days 1, 8)	21	42	62	195	444	19	10	31 (2006)
40–60 b.i.d. (days 1–14)	125 (days 1, 15)	21	24	54.2	ND	581	16.7	17	33 (2006)
40–60 b.i.d. (days 1–21)	80 (days 1, 15)	35	23	47.8	210	395	17.4	8.7	present study

ND = Not described. The S-1 dose level was set on the basis of BSA: 40 (BSA <1.25 m^2), 50 (BSA ≥1.25 to <1.5 m^2) or 60 mg b.i.d. (BSA ≥1.5 m^2).

7). Katsube et al. [30] and Inokuchi et al. [31] administered 80 mg/m^2 of CPT-11 on days 1 and 8 with 14 days of S-1 using the same dosage as in our regimen, followed by a 2-week rest. Katsube et al. [30] obtained a rather low RR in their small study population, whereas Inokuchi et al. [31] showed a good RR of 62%. Although the RR of the current study was relatively low, our regimen showed equivalent median TTP with a lower incidence of adverse events. They administered the second CPT-11 on day 8 because diarrhea induced by S-1 mostly occurred on day 15 [32], to avoid overlapping of common adverse events for each drug. In our experience, the second administration of CPT-11 on day 15 was more conductive for subsequently continuing treatment because CPT-11-induced anorexia did not disappear by day 8 in some patients. Komatsu et al. [33] conducted a phase I study in which CPT-11 was administered on days 1 and 15 combined with 14 days of S-1 and 2 weeks of rest. They determined the RD of CPT-11 to be 125 mg/m^2, and obtained an RR of 54.2% and a surprising MST of 518 days. Taken together with these data, this combination showed reproducible efficacy with tolerable toxicity in patients with advanced gastric cancer.

In this study, our actual RR of 47.8% did not meet the expected RR of 65%, which was calculated based on the previously reported RR for S-1 as monotherapy (44.6%). One explanation for the lower RR might be an overestimation of the RR in S-1 monotherapy. In early reports of three recent phase III trials including S-1 alone, RRs of only 26.9–31% were reported [34–36]. Especially, Chin et al. [36], who used our regimen as a treatment arm, indicated the superiority of the combination of CPT-11 with S-1 to S-1 monotherapy regarding RR in their phase III study. To elucidate its efficacy in improving survival, data from further investigations are awaited.

We have investigated the efficacy of the combination of CPT-11 and S-1 for the following reasons. Basic studies have indicated that CPT-11 has a synergistic effect on the anti-tumor activity of 5-FU. The combination of SN-38, an active metabolite of CPT-11, followed by 5-FU inhibited TS for a longer time period and increased the integration of 5-FU metabolites in DNA [37, 38]. Fukushima et al. [39] reported that CPT-11 reduced TS activity in a human gastric cancer cell line with high TS expression, and that combined use of CPT-11 plus S-1 has a more potent anti-tumor effect on 5-FU-resistant cell lines than either CPT-11 alone or S-1 alone. Moreover, our previous phase I study showed that the combination with CPT-11 did not affect the pharmacokinetics of S-1 [19].

In conclusion, our results of the phase II study in advanced gastric cancer patients substantiated the efficacy and safety of the combination therapy of CPT-11 plus S-1. The regimen warrants a further phase III study to define its efficacy regarding survival of patients with advanced gastric cancer.

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