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ORIGINAL ARTICLE

A phase I study of combination therapy with S-1 and irinotecan in patients with previously untreated metastatic or recurrent colorectal cancer

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Abstract
Background To investigate the combination of S-1 and irinotecan (CPT-11) as an alternative to infusional 5-fluorouracil/leucovorin plus CPT-11, we performed a phase I trial to determine the maximum tolerated dose, recommended dose (RD), and dose-limiting toxicities (DLTs) in patients with metastatic or recurrent colorectal cancer.
Patients and methods S-1 and CPT-11 doses were escalated using a standard 3 + 3 design. S-1 was administered orally at 70 mg/m^2 (levels 1–3) or 80 mg/m^2 (levels 4 and 5) for 14 consecutive days followed by 1-week rest. CPT-11 was administered intravenously on day 1, at 175 mg/m^2 (level 1), 200 mg/m^2 (level 2), 225 mg/m^2 (levels 3 and 4), or 250 mg/m^2 (level 5). Treatment was repeated every 3 weeks, unless disease progression or severe toxicities were observed.
Results Twenty-three patients were treated. One patient at each of levels 2 and 4 developed a DLT, grade 3 ileus, and grade 3 diarrhea, respectively. At both levels, an additional three patients did not experience DLTs. At level 5, two of five patients experienced DLTs, including grade 3 enteritis and grade 4 neutropenia for more than 5 days. The RD was determined at level 4 (80 mg/m^2 S-1 and 225 mg/m^2 CPT-11). An objective response was observed in 7 of 17 patients with measurable disease: 2 of 5 at level 2; 3 of 4 at level 4; and 2 of 4 at level 5.
Conclusions The RDs of CPT-11 and S-1 were determined as 225 and 80 mg/m^2, respectively, and further phase II trials are warranted.

Keywords Colorectal cancer · Palliative chemotherapy · S-1 · Irinotecan · Phase I study

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Introduction

The current management of metastatic colorectal cancer consists of various cytotoxic drugs, either alone or in combination, including 5-fluorouracil (5-FU)/leucovorin (LV), capecitabine, irinotecan, and oxaliplatin [1–5]. Irinotecan (CPT-11) is a potent inhibitor of the enzyme topoisomerase I, which plays a critical role in DNA replication and transcription [6]. CPT-11 has shown synergistic effects with 5-FU [6, 7], and the combination of CPT-11 and infusional 5-FU/LV (FOLFIRI) was found to be superior to CPT-11 plus bolus 5-FU/LV [6, 7]. Thus, CPT-11 plus infusional 5-FU/LV has become a first-line chemotherapy regimen for patients with metastatic colorectal cancer [6, 7]. Infusional 5-FU regimens, however, are complicated, necessitating vascular access devices and portable delivery systems. Oral regimens that mimic infusional 5-FU are needed, and several studies have assessed the combination of CPT-11 and oral fluoropyrimidines, thus avoiding the complexities of infusional therapy [8–10].

The combination of CPT-11 and capecitabine has shown substantial activity and manageable toxicity in patients with advanced colorectal cancer [11]. Unlike capcetabine, S-1 has different mechanisms of action and shows only a partial overlap of key toxicities when combined with CPT-11.

S-1 is a novel oral fluoropyrimidine composed of three compounds: tegafur, 5-chloro-2,4-dihydroxypyridine (CDHP),

and potassium oxonate (Oxo), in a molar ratio of 1:0.4:1. Tegafur is a prodrug of 5-FU and acts as the effector; CDHP increases antitumor activity by inhibiting the degradation of 5-FU; and Oxo, an inhibitor of orotate phosphoribosyltransferase, reduces the incidence of gastrointestinal (GI) toxicities such as diarrhea by inhibiting the phosphorylation of 5-FU in the GI tract [12]. The activity observed with S-1 in the phase II studies is at least equivalent to, if not better than, continuous infusional and bolus 5-FU and the other oral fluoropyrimidines in patients with various GI cancers, including colorectal cancer, either as monotherapy or in combination with other agents [13, 14].

These findings suggested that the combination of CPT-11 and S-1, as an alternative to the FOLFIRI regimen, would have antitumor activity in patients with metastatic colorectal cancer. In this phase I study to investigate the combination of CPT-11 and S-1 as first-line chemotherapy, we determined the maximal tolerated doses (MTDs) and recommended doses (RDs) of the two drugs and assessed the feasibility of this combination in patients with recurrent or metastatic colorectal cancer.

Patients and methods

Patient population

All eligible patients had histologically or cytologically documented metastatic or recurrent colorectal adenocarcinoma after curative resection, as well as measurable or evaluable disease. Other eligibility criteria included age 18–70 years, Eastern Cooperative Oncology Group performance status (ECOG PS) ≤ 2 and adequate bone marrow function (absolute neutrophil count [ANC] $> 2 \times 10^9$/L, hemoglobin > 9.0 g/dL, and platelets $> 100 \times 10^9$/L), renal function (creatinine < 1.0 upper normal limit [UNL] or creatinine clearance ≥ 60 ml/min), and hepatic function (bilirubin < 1.0 UNL, aspartate aminotransferase [AST]/alanine aminotransferase [ALT]/alkaline phosphatase [ALP] < 2.5 UNL [<5 UNL for patients with liver metastases]). Patients who had received prior chemotherapy or radiotherapy were excluded; however, those who had finished adjuvant chemotherapy at least 6 months before enrollment or had received prior adjuvant radiotherapy for rectal cancer could be included. The protocol was approved by the institutional review board of our institution, and all patients provided written informed consent before enrollment.

Treatment

S-1 was supplied as 20 and 25 mg capsules. Patients received single oral doses of S-1 twice daily, within 1 h after breakfast and dinner, with doses calculated as milligrams per square meter of body surface area and rounded down to the nearest 5 or 10 mg. Patients were treated with S-1 for 14 consecutive days followed by a 7-day rest period. CPT-11 was given by intravenous infusion over 90 min on day 1 every 3 weeks. Treatment was continued until progressive disease (PD) or the development of unacceptable toxicity or patient discontinuation.

Dose-limiting toxicity

Treatment-related adverse events were evaluated according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0. Dose-limiting toxicity (DLT) was defined as any of the following during the first cycle: (1) ANC $< 0.5 \times 10^9$/L for more than 5 days; (2) ANC $< 1.0 \times 10^9$/L with fever; (3) grade 4 thrombocytopenia; (4) any other non-hematologic grade 3/4 toxicity, including nausea, diarrhea, and vomiting but excluding alopecia that did not improve to at least grade 1 within 2 days after the appropriate therapy; or (5) >2 weeks' treatment delay of S-1 and CPT-11.

Dose-escalation scheme and dose modification for adverse events

S-1 was administered orally at a dose of 70 mg/m^2 (levels 1–3) or 80 mg/m^2 (levels 4 and 5) from day 1 to 14. CPT-11 was administered intravenously on day 1 of each treatment cycle, at a dose of 175 mg/m^2 (level 1), 200 mg/m^2 (level 2), 225 mg/m^2 (levels 3 and 4), or 250 mg/m^2 (level 5). Three patients were entered into each dose level; if one patient experienced a DLT, three additional patients were entered into the same dose level. If no DLT was observed in the first three patients or in only one of six patients, the dose was increased to the next level. Dose escalation continued to the maximum planned dose or until two of six patients experienced DLTs during the first treatment cycle; this dose was defined as the MTD, and the next lowest dose was defined as the RD for further phase II study. Doses of both agents were reduced or omitted for hematologic and non-hematologic toxicities. If a hematologic or non-hematologic DLT occurred, treatment was interrupted and followed by a 25% or 50% dose reduction during the following cycle. Doses of CPT-11 and S-1 were adjusted for grade 2 or higher non-hematologic toxicities. At the first occurrence of a grade ≥ 2 non-hematologic toxicity (except alopecia), treatment was interrupted. At the second and third occurrences of the same toxicity, treatment was interrupted, followed by dose reductions of 25 and 50%, respectively. If the same toxicity with the same severity recurred after 50% dose reduction, treatment was discontinued and the patient was withdrawn from the study. Patients could resume treatment if they

met all of the following criteria during the next cycle: platelet count $\geq 100 \times 10^9$/L; ANC $\geq 1.5 \times 10^9$/L; and resolution or improvement of clinically significant non-hematologic adverse events to grade 0 or 1. During treatments, colony-stimulating factors are not permitted to be used prophylactically.

Assessment of efficacy and toxicity

The primary endpoint of this study was the MTDs of CPT-11 and S-1, and the secondary endpoints were toxicity and treatment response. Pretreatment evaluation included a medical history, performance status and physical examination, complete blood cell count with differentials, serum chemistry profile, chest X-ray, abdomino-pelvic computed tomography (CT) scan, and any other diagnostic procedure that was clinically indicated. During each treatment cycle, all patients were reviewed weekly for symptoms of toxicity and underwent clinical examinations and blood cell count with differentials. Chest X-rays and blood chemistry including liver and renal function tests were performed on day 1 or 1 day before of each cycle of chemotherapy. Tumor size was measured every two cycles. Tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors Guidelines [15].

Results

Patient characteristics

A total of 23 patients were recruited into this study between May 2005 and June 2008. Median patient age was 53 years (range, 25–65 years); 16 (69.6%) were men and 7 (30.4%) were women. All 23 patients showed good ECOG PS scores of 0 or 1 at study entry. Twenty patients had metastatic diseases at initial diagnosis, and three had recurrent colorectal cancer. Fourteen patients (60.9%) had moderately differentiated, seven (30.4%) had well-differentiated (30.4%), and two (8.7%) had poorly differentiated adenocarcinoma. Fourteen patients had two or more involved sites. Detailed clinical data are summarized in Table 1.

Toxicity and recommended dose level

All patients were evaluable for toxicity and adverse events during the first chemotherapy cycle (Table 2). The most commonly observed toxicities were asthenia, diarrhea, anemia, and neutropenia. No patient experienced febrile neutropenia. During dose escalation, one patient at level 2 experienced a DLT, grade 3 ileus. Three more patients were entered into level 2, with none developing at DLT. At level 3, no patient had severe toxicity. One of the first three patients entered into level 4 experienced a DLT (grade 3 diarrhea), but three more patients entered into this level did not experience DLTs. Of five patients entered into level 5, two showed DLTs, one each with grade 3 and grade 4 neutropenia for more than 5 days. Based on these results, the MTD was defined as dose level 5, and the RDs for subsequent phase trials were determined to be 80 mg/m^2 S-1 and 225 mg/m^2 CPT-11.

Patients treated at up to level 4 had relatively good dose intensities of both S-1 (90–100%) and CPT-11 (96–100%). At level 5, however, the dose intensities of S-1 (median, 84%) and CPT-11 (median, 83%) were low (Table 3). Doses of S-1 and CPT-11 were reduced in 10 of 23 patients (43%). The reasons for dose reduction included prolonged neutropenia in four patients, diarrhea in three, anorexia in one, asthenia in one, and thrombocytopenia in one. At the RD, the toxicities for all treatment courses (45 cycles) included three patients with grade 3/4 neutropenia and two patients with grade 3 diarrhea, including one with DLT. All of these toxicities were manageable, with relative dose intensities of 96% for CPT-11 and 95% for S-1.

Treatment outcomes

Six patients could not be assessed for response: five had no measurable disease and one had too short a treatment course for assessment. The objective responses at each dose level are summarized in Table 4. Seven of 17 patients with measurable lesions showed responses, with an additional 4 having stable disease. The median time to progression (TTP) of all study patients was 7 months (95% confidence interval [95% CI], 4.77–9.23 months). Above RD, the response rate was 62.5%, and the median TTP of 8 patients was 8 months (95% CI, 4.65–11.34 months).

Discussion

This phase I dose-escalation study was performed to determine the RD of CPT-11 and S-1 for phase II trials of 3-week cycles of these two agents as first-line treatment for patients with metastatic colorectal cancer. We found that the RD for CPT-11 was 225 mg/m^2 when administered on day 1 of 3-week cycles and that for S-1 was 80 mg/m^2 administered on days 1–14 of 3-week cycles. This combination was well tolerated, and adverse events were predictable and manageable, with only one DLT at the RD level (level 4). The relative dose intensities at the RD level were 95% for S-1 and 96% for CPT-11.

Although several phase I studies have assessed the combination of S-1 and CPT-11 (Table 5), it is difficult to compare their results directly, either with ours or with each other, owing to differences in treatment schedules (CPT-11

Table 1 Patient characteristics

Level CPT-11/S-1 (mg/m^2)	1 175/70	2 200/75	3 225/70	4 225/80	5 250/80	Total
No. of patients	3	6	3	6	5	23
Age (years)						
Median (ranges)	53 (25–65)					
Gender						
Male	2	6	3	4	1	16
Female	1	0	0	2	4	7
ECOG PS[a]						
0	1	2	0	0	0	3
1	2	4	3	6	5	20
Disease status						
Metastasis	3	5	2	5	5	20
Recurrence after curative resection	0	1	1	1	0	3
Primary site						
Right colon	2	1	0	2	1	6
Left colon	1	2	2	3	2	10
Rectum	0	3	1	1	2	7
Previous operation						
Curative	0	1	1	1	0	3
Palliative	2	5	2	5	3	17
Adjuvant chemotherapy	0	1	1	1	0	3
Adjuvant radiation therapy	0	1	1	0	0	2
Histological differentiation						
Well	1	4	0	0	2	7
Moderate	2	2	2	5	3	14
Poor	0	0	1	1	0	2
Metastatic site						
Liver	2	3	1	4	1	11
Lung	1	1	0	3	1	6
Lymph nodes	1	3	2	1	3	10
Peritoneum	1	3	2	2	1	9
Bone	0	0	1	0	0	0
Others	0	0	0	1	2	3
Number of involved sites						
1	1	3	0	3	2	9
2	2	2	2	2	3	11
≥3	0	1	1	1	0	3

[a] Eastern Cooperative Oncology Group performance status

administered every 1, 2, or 3 weeks, and S-1 administered daily for 2 or 3 weeks) and patient selection criteria. The RDs we observed, 225 mg/m^2 CPT-11 and 80 mg/m^2 S-1, were somewhat higher than previously observed using 3-week cycles [16, 17]. Moreover, although 150 mg/m^2 CPT-11 on day 1 and 80 mg/m^2 S-1 on days 1–14 every 3 weeks has previously been shown to be effective in patients with metastatic gastric cancer [18], that study did not include further escalation of CPT-11 dose, although DLTs did not occur at this dose level.

Other treatment schedules of the combination of CPT-11 and S-1 have been investigated in patients with recurrent/metastatic colorectal cancer. For example, a phase I study assessed 80 mg/m^2/day oral S-1 on days 1–21 and intravenous CPT-11 at an initial dose of 60 mg/m^2/day, escalating to 80 or 100 mg/m^2/day, on days 1 and 15 of 35-day

Table 2 Frequency of toxicities at each dose level

Dose level	1 ($n = 3$)		2 ($n = 6$)		3 ($n = 3$)		4 ($n = 6$)[b]		5 ($n = 5$)	
Toxicity (NCI-CTCAE version 3.0)	All events	Grade 3/4	All events	Grade 3/4	All events	Grade 3/4	All events	Grade 3/4	All events	Grade 3/4
Hematologic										
Leukopenia	0	0	4	0	1	0	3	0	3	1
Neutropenia	2	0	4	1	1	0	5	0	3	1[a]
Anemia	3	0	6	0	3	0	5	0	5	0
Thrombocytopenia	2	0	0	0	0	0	0	0	0	0
Febrile neutropenia		0		0		0		0		0
Non-hematologic										
Nausea	2	0	2	0	1	0	4	0	3	0
Vomiting	1	0	0	0	2	0	2	0	3	0
Diarrhea	1	0	5	0	1	0	4	1[a]	2	0
Stomatitis	2	0	2	0	1	0	2	0	3	0
Bilirubin	0	0	0	0	0	0	0	0	0	0
AST/ALT	1	0	0	0	1	0	1	0	0	0
ALP	0	0	2	0	1	0	1	0	0	0
Asthenia	2	0	4	0	2	0	4	0	4	1
Enteritis	1	0	0	0	0	0	0	0	1	1[a]
Ileus	0	0	0	1[a]	0	0	1	0	0	0

Data are presented as numbers of patients experiencing adverse events during the first cycle of combination therapy with CPT-11 and S-1

AST Aspartate transaminase, *ALT* alanine transaminase

[a] Dose-limiting toxicity

[b] Recommended dose

Table 3 Duration of administration and dose intensity

Level	1 ($n = 3$)	2 ($n = 6$)	3 ($n = 3$)	4 ($n = 6$)[a]	5 ($n = 5$)
S-1 (mg/m^2)	70	70	70	80	80
CPT-11 (mg/m^2)	175	200	225	225	250
Median number of cycles (range)	7 (2–10)	6.5 (2–9)	2 (2)	9 (1–9)	9 (5–9)
S-1, % RDI	98	90	100	95	84
CPT-11, % RDI	98	97	100	96	83

RDI Relative dose intensity

[a] Recommended dose

Table 4 Objective tumor response in evaluable patients

Dose level	CR	PR	SD	PD	ORR (%)
1 ($n = 1/3$[a])	0	0	1	0	0
2 ($n = 5/6$[a])	0	2	1	2	33
3 ($n = 3/3$[a])	0	0	0	3	0
4 ($n = 4/6$[a])	0	3	0	1	75
5 ($n = 4/5$[a])	0	2	2	0	50

[a] n = evaluable/total patients, *ORR* overall response rate

cycles. The RDs were 80 mg/m^2/day each for CPT-11 and S-1, and reported DLTs were anorexia, asthenia, and diarrhea [19]. In another study, patients were treated with 80 mg/m^2/day CPT-11, escalating to 100, 120, and 150 mg/m^2/day, on days 1 and 15, and 80 mg/m^2/day S-1 on days 1–14 of 4-week cycles. The RD of CPT-11 was determined to be 120 mg/m^2/day, and the main toxicities were diarrhea, neutropenia, and anorexia [20, 21]. Several studies showed that a 3-week regimen of S-1(administration for 2-week periods and 1-week drug-free intervals) may mitigate adverse reactions and prolong the medication periods than 6-week schedule of S-1 [22, 23]. Other studies suggested that 3-weekly CPT-11 schedule seemed advantageous than weekly CPT-11 schedule in terms of grade 3/4 diarrhea and patient conveniences [8, 24]. Based on these data, we decided to

Table 5 Overview of phase I studies of the combination of CPT-11 and S-1 in patients with colorectal cancer

Study	Escalated dose (mg/m^2/day)		Schedule		RD (mg/m^2/day)		RDI at RD (%)	
	CPT-11	S-1	CPT-11	S-1	CPT-11	S-1	CPT-11	S-1
Tsunoda et al. [36]	To 60, 80 or 100	80	Days 1, 15	Days 1–21 q 5 weeks	80	80	0.96	0.97
Kakeji et al. [16]	To 80, 120 or 150	80	Day 1	Days 1–14 q 3 weeks	150	80	NA	NA
Yoshioka et al. [17]	To 75, 100, 125 or 150	80	Day 1	Days 3–16 q 3 weeks	150	80	NA	NA
Shiozawa et al. [20]	To 100, 120 or 150	80	Days 1, 15	Days 1–14 q 4 weeks	120	80	78.9	93.0

RD Recommended dose, *RDI* relative dose intensity, *NA* not available

develop the 3-week schedule of combination of CPT-11 (day 1) and S-1 (days 1–14).

In the present study, the most common toxicities were asthenia, diarrhea, and neutropenia. At the RD, five patients were treated for a median of nine cycles, and one experienced a DLT. In subsequent cycles, two patients experienced grade 4 neutropenia and one patient experienced grade 3 diarrhea. None, however, experienced febrile neutropenia, and all patients recovered rapidly from other toxicities. Moreover, the dose intensity of both drugs at this level was maintained at more than 90% throughout all treatment cycles.

Although efficacy was not the primary interest of this phase I study, responses were observed in three of four patients at the RD level. Other phase II studies using different schedules of CPT-11 plus S-1 showed response rates of 53–63% in patients with advanced colorectal cancer [10] and 48–62% in patients with advanced gastric cancer [25–27], suggesting that the combination of CPT-11 plus S-1 is promising for patients with gastrointestinal cancers without the need for central venous catheters.

It is unlikely that these results can be applied to all populations. The MTD of S-1 as a single agent was found to be higher among Asians than among Western populations [28, 29]. This ethnic variability may be due to the pharmacogenetics of CYP2A6 [30]. Recently, our group reported that CYP2A6 genotypes were associated with differences in the biotransformation of S-1 without affecting its clinical efficacy or toxicity [31].

CPT-11 has also been reported to show interindividual variability. Genetic polymorphisms of UGT1A1, which is involved in CPT-11 metabolism, may affect the likelihood of patients developing severe adverse effects, especially neutropenia and diarrhea [32–35]. Therefore, prior to treatment with this combination, interindividual variations should be considered, to assess the relationships between genetic polymorphisms and the efficacy and toxicity of CPT-11 and S-1. Although we did not perform pharmacokinetic or pharmacogenetic analyses on our patients, we are currently conducting a phase II study of CPT-11 and S-1 that will include pharmacogenetic analyses of UGT1A1 and CYPT2A6genotypes.

Our phase I trial showed that the combination of CPT-11 and S-1 was well tolerated with an acceptable toxicity profile. Although this study has some limitations, a phase II study to confirm the efficacy and safety of this combination in patients with recurrent/metastatic colorectal cancer is ongoing.

Conclusion

We found that the RDs of CPT-11 and S-1 were 225 and 80 mg/m^2, respectively. Phase II trials assessing the safety and efficacy of this combination and including pharmacogenetic analyses are warranted.

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Conflict of interest None.

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