A Phase II Trial of Combined Chemotherapy with Oral S-1 and 24-Hour Infusions of Irinotecan plus Bevacizumab in Patients with Metastatic Colorectal Cancer

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Key Words

S-1 · Irinotecan · Bevacizumab · 24-Hour infusions ·
Colorectal cancer · Phase II study

Abstract

Objectives: Protracted low-dose infusion of irinotecan has been suggested to enhance antitumor activity. A phase II study was conducted to evaluate the safety and efficacy of oral S-1 combined with 24-hour infusion of irinotecan and intravenous bevacizumab for metastatic colorectal cancer (MCRC). **Methods:** The subjects were 79 patients with MCRC; 57 were chemotherapy naïve. Irinotecan (125 mg/m²) was administered as a 24-hour infusion on days 1 and 15, S-1 (80 mg/m²) was administered orally on days 1–14, and bevacizumab (5.0 mg/kg) was given on days 1 and 15. The treatment was repeated every 4 weeks. **Results:** Median follow-up was 20.0 months, and the mean number of cycles was 7. The overall response rate was 79.7% (95% CI, 69.2–88.0), 86.0% (95% CI, 74.2–93.7) for first-line and 63.6% (95% CI, 40.7–82.8) for second-line treatment. The median progression-free survival was 16.4 months (95% CI, 13.9–21.0) for first-line and 9.4 months (95% CI, 4.9–16.5) for second-line treatment. The median overall survival was not reached. Grade 3–4 toxicities were neutropenia (43%), leukopenia

(20.3%), anorexia (19.0%), and diarrhea (10.1%). Toxicity was tolerable. **Conclusions:** Combination chemotherapy with oral S-1 and biweekly 24-hour infusions of irinotecan plus bevacizumab appears to be highly active and well tolerated both as first-line and second-line chemotherapy for MCRC.

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Introduction

Regimens combining 5-fluorouracil (5-FU) plus leucovorin with oxaliplatin (FOLFOX) or irinotecan (FOLFIRI) have been established as standard chemotherapy for metastatic colorectal cancer (MCRC) [1–4]. Molecular-targeted agents, such as bevacizumab, cetuximab, and panitumumab, have been shown to enhance the effectiveness of FOLFOX or FOLFIRI and are currently included as standard treatment [5–11]. Since orally active fluoropyrimidine derivatives are very convenient to use, 5-FU plus leucovorin is now often replaced by oral UFT (uracil/tegafur) plus leucovorin, capecitabine, or S-1 in the combined chemotherapy regimens described, and such regimens are now widely used [5, 12–16].

Irinotecan is usually given as a 90-min intravenous infusion every 2 weeks (biweekly) or every 3 weeks (tri-

weekly). However, the cytotoxic effects of irinotecan are specific to the S-phase of the cell cycle, and low doses of irinotecan given by protracted infusion or frequent bolus injection can prevent the saturation of carboxylesterases, enzymes that convert irinotecan to its active metabolite SN-38, and thereby enhance antitumor activity [17, 18]. We have previously performed phase I/II clinical studies of a 24-hour continuous intravenous infusion of irinotecan, given every 2 weeks, combined with oral UFT and with oral UFT plus leucovorin in patients with MCRC and reported that these regimens are therapeutically useful and have low incidences of diarrhea and other adverse events [19, 20]. However, there has been no randomized clinical trial comparing a 24-hour continuous infusion to the standard 90-min infusion of irinotecan up to now.

Toxic effects of irinotecan are intimately related to the activity of metabolizing enzymes, and the expression of enzyme activity is largely controlled at the gene level. More than 60 polymorphisms have been identified in UGT1A1, the key metabolizing enzyme of irinotecan [21]. The most important polymorphic variant is thought to be UGT1A1*28. We have previously studied the pharmacokinetics of irinotecan combined with S-1 and reported that the recommended biweekly dose of irinotecan is 125 mg/m² in patients who are not homozygous for UGT1A1*28 [22].

S-1 is an oral anticancer drug that combines tegafur, a prodrug of 5-FU, with 5-chloro-2,4-dihydropyrimidine (CDHP) and potassium oxonate (Oxo) in a molar ratio of 1:0.4:1 [23, 24]. CDHP, a reversible inhibitor of dihydropyrimidine dehydrogenase, suppresses the degradation of 5-FU [25, 26], thereby maintaining high concentrations of 5-FU in plasma and tumor cells for prolonged periods. Oxo inhibits the phosphorylation of 5-FU, a reaction catalyzed by orotate phosphoribosyltransferase in the gastrointestinal tract, thereby reducing the incidence of gastrointestinal toxicity, the main dose-limiting toxicity of 5-FU [27]. S-1 has shown favorable antitumor activity and good compliance in patients with gastrointestinal cancer and other solid tumors [23]. In patients with advanced colorectal cancer, S-1 monotherapy had response rates of 35 and 39.5% with easily manageable toxicities in two phase II studies [28, 29].

The FIRIS study, a phase II/III clinical study comparing S-1 plus irinotecan (IRIS) with FOLFIRI as second-line treatment in patients with unresectable colorectal cancer demonstrated the noninferiority of IRIS [15]. Combination chemotherapy with irinotecan, S-1, and bevacizumab has been reported to have a high response rate and good progression-free survival (PFS) in previ-

ously untreated patients with advanced colorectal cancer [30–32]. We now report the results of a phase II study of combined chemotherapy with oral S-1, irinotecan, given biweekly as a 24-hour continuous infusion, and bevacizumab in patients with previously treated or previously untreated MCRC.

Patients and Methods

Patients

The eligibility criteria were as follows: a histologically confirmed diagnosis of colorectal cancer with measurable metastatic disease; an Eastern Cooperative Oncology Group performance status of ≤ 1 ; a life expectancy of at least 3 months; an age between 20 and 80 years; adequate organ function, as defined by a leukocyte count of $\geq 4,000/\mu\text{l}$ and $\leq 12,000/\mu\text{l}$, a neutrophil count of $\geq 2,000/\mu\text{l}$, a platelet count of $\geq 100,000/\mu\text{l}$, a hemoglobin level of $\geq 9\text{ g/dl}$, a serum bilirubin level of $\leq 1.5\text{ mg/dl}$, serum aspartate aminotransferase and alanine aminotransferase levels of $\leq 100\text{ U/l}$, a serum creatinine level of $\leq 1.2\text{ mg/dl}$, a normal electrocardiogram, and an international normalized ratio of ≥ 1.5 . Patients also had to have adequate oral intake and not to have received prior radiotherapy for metastatic lesions. Patients who had not received prior chemotherapy for metastatic lesions or those who received only 1 regimen of chemotherapy were eligible. If recurrence occurred during or within 180 days of the completion of postoperative adjuvant chemotherapy, patients who had received up to 1 regimen for metastatic lesions were eligible.

Patients were excluded if they had a history of treatment with S-1 or irinotecan or if they had active infection, bowel obstruction, interstitial pneumonia, pulmonary fibrosis, uncontrolled diabetes, pleural effusion or ascites, or known drug allergies. Pregnant and nursing women were also excluded. Patients with metastasis or recurrence only in the liver were excluded because they were enrolled in clinical trials of other regimens, including hepatic artery infusion.

This study was approved by the Institutional Review Board of Tokai University School of Medicine (10R-121), and all patients provided written informed consent.

Treatment Plan

Treatment comprised irinotecan (125 mg/m²), administered as a 24-hour intravenous infusion on days 1 and 15, and S-1 (80 mg/m²), administered orally in two divided daily doses on days 1–14. Bevacizumab (5.0 mg/kg) was given as an intravenous infusion on days 1 and 15. In patients who were homozygous for UGT1A1*28, the initial dose of irinotecan was reduced to 100 mg/m². Treatment cycles were repeated every 4 weeks. All patients were hospitalized for the infusion of irinotecan for 2 days. Immediately before the infusion of irinotecan, the patients were confirmed to have a leukocyte count of $\geq 3,000/\mu\text{l}$, a neutrophil count of $\geq 1,500/\mu\text{l}$, and a platelet count of $\geq 100,000/\mu\text{l}$ and to be free of diarrhea, infection, or fever suggestive of infection ($\geq 38^\circ\text{C}$). Treatment was delayed for up to 1 week if any of these requirements was not satisfied.

If hematologic toxicity (leukocyte count, $<2,000/\mu\text{l}$; neutrophil count, $<1,000/\mu\text{l}$; platelet count, $<75,000/\mu\text{l}$; or serum total bilirubin level, $\geq 2.5\text{ mg/dl}$) or grade ≥ 3 severe nonhematologic toxicity

occurred, or if treatment was delayed for more than 7 days, the doses of both irinotecan and S-1 were reduced by 20% in the next course. The dose of bevacizumab was not reduced. In patients who had grade ≥ 3 hypertension, bleeding, thrombosis, or gastrointestinal perforation, treatment with bevacizumab was discontinued. If the second or subsequent courses of treatment could not be started after more than 28 days or had elapsed since the completion date of the previous course, the protocol treatment was discontinued.

Assessments

Pretreatment evaluation included a clinical history and physical examination, complete blood cell count, blood chemistry, urinalysis, electrocardiography, chest radiography, and computed tomography (CT) of the chest and abdomen. During therapy, toxicity was assessed weekly according to the National Cancer Institute – Common Toxicity Criteria (NCI-CTC), version 4.0. Physical examination was conducted, and the results were recorded before each cycle, or more frequently if clinically indicated. Tumor response was assessed by CT scans. Efficacy was evaluated every cycle according to the Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1).

Statistical Analysis

The primary endpoint was the overall response rate. Secondary endpoints were PFS, overall survival, and safety. The primary analysis was performed in the intention-to-treat population. Safety analyses were performed in patients who had received the protocol treatment at least once.

Assuming that the lower threshold of the response rate was 40% in patients who had not previously received chemotherapy (first line) and that the expected response rate was 60%, with an alpha value of 0.05 and a beta value of 0.1, we calculated the target number of previously untreated patients to be 51. The target number of patients was therefore set at 55, including dropouts and excluded patients [22, 30, 31]. Assuming that the lower threshold of the response rate was 10% in patients who had previously received chemotherapy (second line) and that the expected response rate was 30%, with an alpha value of 0.05 and a beta value of 0.2, we estimated the target number of previously untreated patients to be 19. The target number of patients was therefore set at 20, including dropouts and excluded patients [15, 33].

Results

Patient Characteristics

A total of 79 patients were enrolled in the study, which was conducted from January 2011 through June 2013. All patients were eligible. The median age was 68 years, 33 patients (41.8%) were women, and 54 (68.4%) had colon cancer. The metastatic site was the liver in 44 patients (55.7%) and the lung in 30 (38.0%) (table 1). Only 3 patients (3.8%) were homozygous for UGT1A1*28. Fifty-seven patients had not previously received chemotherapy for metastatic lesions, and 11 of them received postoperative adjuvant chemotherapy or preoperative chemora-

Table 1. Baseline patient characteristics

Age, years	
Median (range)	68 (38–85)
Sex	
Male	46 (58.2)
Female	33 (41.8)
ECOG performance status	
0	40 (50.6)
1	39 (49.4)
UGT1A1*28	
TA6•TA6	56 (70.9)
TA6•TA7	20 (25.3)
TA7•TA7	3 (3.8)
UGT1A1*6	
A•A	2 (2.5)
G•A	19 (24.1)
G•G	58 (73.4)
Primary tumor	
Colon	54 (68.4)
Rectum	25 (31.6)
Metastatic site	
Liver	44 (55.7)
Lung	30 (38.0)
Lymph node	13 (16.5)
Locoregional	19 (24.1)
Histology	
Well differentiated	49 (62.0)
Moderately differentiated	24 (30.4)
Poorly differentiated	1 (1.3)
Mucinous	2 (2.5)
Neuroendocrine	1 (1.3)
Undetermined	2 (2.5)
Treatment line	
First line	57 (72.2)
Second line	22 (27.8)

Values are presented as numbers with percentages in parentheses, unless otherwise indicated. ECOG = Eastern Cooperative Oncology Group.

diotherapy. Twenty-two patients had a history of chemotherapy, including 2 patients who had received adjuvant chemotherapy with oral UFT plus leucovorin. Among the other 20 patients, 17 had received FOLFOX or capecitabine plus oxaliplatin (XELOX) as first-line chemotherapy for MCRC, and the other 3 patients had received oral UFT plus leucovorin.

Safety

A total of 702 treatment cycles were administered. The median number of cycles per patient was 7 (range, 1–30). Among all treatment cycles, a temporary cessation of treatment or dose reduction was required in 48 patients

Fig. 1. PFS for all patients (n = 79).

Fig. 2. PFS for first-line (n = 57) and second-line treatment (n = 22).

Table 2. Adverse events (n = 79 patients)

	Any grade	Grade 3/4
Hematological events		
Leukopenia	56 (70.9)	16 (20.3)
Neutropenia	59 (74.7)	34 (43.0)
Hemoglobin decreased	59 (74.7)	2 (2.5)
Thrombocytopenia	16 (20.3)	1 (1.3)
Nonhematological events		
Abnormal hepatic function	16 (20.3)	2 (2.5)
Anorexia	72 (91.1)	15 (19.0)
Vomiting	8 (10.1)	2 (2.5)
Diarrhea	56 (70.9)	8 (10.1)
Fatigue	76 (96.2)	1 (1.3)
Stomatitis	30 (38.0)	0
Skin rash	1 (1.3)	1 (1.3)
Alopecia	20 (25.3)	–

Values are presented as numbers with percentages in parentheses. The worst values are shown. Grades were assessed according to the Common Terminology Criteria for Adverse Events, version 4.0.

(60.8%). Adverse events (grade ≥ 3) with an incidence of $\geq 5\%$ were neutropenia (43.0%) and leukopenia (20.3%) as hematologic toxicities and anorexia (19.0%) and diarrhea (10.1%) as nonhematologic toxicities. All adverse events were tolerable, and there were no serious complications or treatment-related deaths (table 2).

Table 3. Response rates

	First line (n = 57)	Second line (n = 22)	All patients (n = 79)
Complete response	6 (10.5)	2 (9.1)	8 (10.1)
Partial response	43 (75.4)	12 (54.5)	55 (69.6)
Stable disease	1 (1.8)	3 (13.6)	4 (5.1)
Progressive disease	7 (12.3)	5 (22.7)	12 (15.2)
Not evaluable	0	0	0
Overall response rate	86.0 (74.2–93.7)	63.6 (40.7–82.8)	79.7 (69.2–88.0)
Disease control rate	87.7 (76.3–94.9)	77.3 (54.6–92.2)	84.8 (75.0–91.9)

Values are presented as numbers with percentages in parentheses or percentages with 95% CI in parentheses.

Efficacy

The response rate was 79.7% [95% confidence interval (CI), 69.2–88.0] overall, 86.0% (95% CI, 74.2–93.7) for first-line treatment, and 63.6% (95% CI, 40.7–82.8) for second-line treatment. The disease control rate was 84.8% (95% CI, 75.0–91.9) overall, 87.7% (95% CI, 76.3–94.9) for first-line treatment, and 77.3% (95% CI, 54.6–92.2) for second-line treatment (table 3).

As of April 2014, the median follow-up was 20.0 months (range, 2.7–39.5). The median PFS was 15.3 months (95% CI, 12.9–19.2) overall (fig. 1), 16.4 months (95% CI, 13.9–21.0) for first-line treatment, and 9.4 months (95% CI, 4.9–16.5) for second-line treatment (fig. 2). The median overall survival was not reached.

Discussion

FOLFIRI is widely used as first-line chemotherapy for MCRC. Administration of FOLFIRI requires port insertion and the use of an infusion pump to deliver the continuous intravenous infusions of 5-FU. The use of oral 5-FU derivatives instead of a continuous intravenous infusion of 5-FU does not require port insertion and eliminates the need for an infusion pump, which is troublesome for some patients. Daily treatment with oral S-1 has been reported to be pharmacokinetically equivalent to the continuous intravenous infusion of 5-FU [34]. However, in this study, all patients needed a 2-day hospitalization for the irinotecan infusion. Two phase II clinical trials have reported that S-1 is as effective as 5-FU plus leucovorin as first-line chemotherapy for metastatic and recurrent colorectal cancer [28, 29]. The IRIS regimen, in which irinotecan is combined with oral S-1, is more convenient to use than 5-FU plus leucovorin and has been shown to be noninferior to FOLFIRI as second-line treatment in a phase III study [15].

We have previously conducted a series of studies of irinotecan given as a 24-hour continuous intravenous infusion biweekly. First, we performed a phase I/II study of oral UFT combined with a 24-hour continuous intravenous infusion of irinotecan in patients with MCRC. The response rate was 62.9%, including 3 patients with a complete response, and the PFS was 5.6 months. No patient had grade ≥ 3 nonhematologic toxicity [19]. In a subsequent phase I/II study evaluating a 24-hour continuous intravenous infusion of irinotecan combined with oral UFT plus leucovorin in patients with MCRC, the response rate was 63.9%, including 4 patients who had a complete response, and the PFS was 8.3 months. Grade ≥ 3 nonhematologic toxicities were diarrhea in 16.7% of patients, anorexia in 13.6%, vomiting in 5.6%, and anemia in 5.6% [20]. These studies demonstrated that UFT or UFT plus leucovorin combined with a biweekly 24-hour continuous intravenous infusion of irinotecan (100 mg/m²) has a high response rate with a low incidence of adverse events. In a phase I study combining a 24-hour continuous intravenous infusion of irinotecan with S-1 (IRIS) instead of UFT or UFT plus leucovorin, the response rate was 34.4%, and grade ≥ 3 adverse events comprised diarrhea in 17.2% of patients, nausea in 10.3%, and vomiting in 6.8% [22]. At the same time, we studied the effects of UGT1A1 polymorphisms, for which testing is approved under Japanese National Health Insurance, on pharmacokinetics and adverse events. On the basis of the results, the recommended dose was determined to be 125

mg/m² for irinotecan and 80 mg/m² for S-1 [22], which we evaluated in the present phase II trial.

The usual dose of irinotecan is 180 mg/m² biweekly in FOLFIRI and 250 mg/m² triweekly in CapeIRI (capecitabine plus irinotecan). In our study, the administered dose of irinotecan was lower. However, recent studies have reported good outcomes with oral S-1 and irinotecan plus bevacizumab, used instead of FOLFIRI plus bevacizumab, in patients with MCRC who had not previously received chemotherapy [30–32]. The effectiveness of combination chemotherapy with S-1, irinotecan, and bevacizumab in our study was consistent with the findings of previous studies.

In previous studies, irinotecan was administered in the following doses: 100 mg/m² biweekly by Komatsu et al. [30], 80 mg/m² biweekly by Mizushima et al. [32], and 150 mg/m² triweekly by Yamada et al. [31]. In all of these studies, irinotecan was given as a 90-min infusion. The administered doses of bevacizumab were as follows: 5 mg/m² biweekly by Komatsu et al. [30], 7 mg/m² biweekly by Mizushima et al. [32], and 7.5 mg/m² triweekly by Yamada et al. [31]. The duration of the treatment cycles was 2 weeks in the study by Komatsu et al. [30], 5 weeks in the study by Mizushima et al. [32], and 3 weeks in the study by Yamada et al. [31], and the response rates were 58, 47.4, and 67%, respectively. The median PFS was 16.7, 11.9, and 12.0 months, respectively. Good outcomes were thus obtained in all three studies.

In our study, the response rate was 86.0% in patients who had not previously received chemotherapy and 63.6% in those who received the study treatment as second-line chemotherapy. These rates compare favorably with the response rates in previous studies. As for adverse events (grade ≥ 3) associated with combination chemotherapy with irinotecan, S-1, and bevacizumab, in the studies by Komatsu et al. [30] and Yamada et al. [31], the incidences of adverse events were 27 and 26% for neutropenia, 8 and 17% for diarrhea, and 8 and 21% for hypertension, respectively. In our study, the incidence of neutropenia was high (43.0%), but the incidences of other adverse events were similar to those in the studies performed by Komatsu et al. [30] and Yamada et al. [31]. Moreover, these adverse events could be controlled by dose reduction; the median number of treatment cycles administered in our study was 7, and the maximal number of cycles was 30. The treatment schedule used in our study was generally similar to that used in the study by Komatsu et al. [30], the major differences being the dose of irinotecan (100 vs. 125 mg/m²) and infusion time (90-min vs. 24-hour infusion). The response rate was slightly

higher in our study. Although our study was small, the response rate to combination chemotherapy with S-1, irinotecan, and bevacizumab as second-line treatment was 63.6%, indicating good results. It remains unclear whether the good response to treatment was primarily attributed to the dose of irinotecan or the infusion time. In our study, however, the dose of irinotecan given as a 24-hour infusion was 125 mg/m², which was higher than that used in the study by Komatsu et al. [30]. In addition, protracted infusions or frequent bolus injections of low-dose irinotecan have been suggested to increase antitumor activity [17, 18]. These factors may have contributed to the good results of our study.

Combination chemotherapy with oral S-1, 24-hour infusions of irinotecan, and bevacizumab appears to be highly active and well tolerated both as first- and second-line chemotherapy for MCRC. Currently, we are conducting a randomized clinical trial comparing this regimen with FOLFIRI plus bevacizumab, in which a port and an infusion pump are used in all patients. Treatment is performed on an outpatient basis.

Disclosure Statement

The authors indicate no potential conflicts of interest. None of the authors received any funding support for this work.

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