A Phase II Study of Third-Line Combination Chemotherapy with Bevacizumab Plus S-1 for Metastatic Colorectal Cancer with Mutated KRAS (SAVIOR Study)

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Key Words

Bevacizumab · Mutated KRAS · Metastatic colorectal cancer · S-1 Treatment · Chemotherapy

Abstract

Objective: No salvage treatment had been established for metastatic colorectal cancer (mCRC) with mutated KRAS before the emergence of the new drugs regorafenib and TAS-102. We performed a phase II study of third-line chemotherapy with combined bevacizumab and S-1 for mCRC. **Methods:** Subjects were mCRC patients with mutated KRAS who showed disease aggravation even after two regimens with oxaliplatin and irinotecan. Bevacizumab was given intravenously every 2 weeks, and S-1 was administered orally on

days 1–28 of a 42-day cycle. The primary endpoint was disease control rate (DCR). **Results:** In total, 31 subjects were enrolled between August 2009 and June 2011. Three subjects in whom antitumor effects could not be evaluated were excluded. The median follow-up period was 8.6 months. The DCR was 67.9%, the response rate 0%, median progression-free survival 3.7 months, and overall survival 8.6 months. In 30 subjects evaluated for safety, there was no treatment-related death. The most common adverse events were anorexia (grade ≥3, 20%), diarrhea (grade 3, 10%), and decreased hemoglobin (grade ≥3, 17%). **Conclusions:** The results suggest that third-line chemotherapy with combined bevacizumab and S-1 is safe and may delay the progression of mCRC resistant to oxaliplatin and irinotecan with mutated KRAS.

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Introduction

Metastatic colorectal cancer (mCRC) is associated with unfavorable prognoses. Used alone, chemotherapy has been associated primarily with prolonging life rather than with achieving a cure. Previous clinical trials of chemotherapy for the treatment of unresectable CRC indicated that the use of all three key drugs – 5-fluorouracil (5-FU)/leucovorin, irinotecan, and oxaliplatin – in the course of their treatment had a beneficial effect on prognosis [1]. Furthermore, recent developments in molecularly targeted agents such as anti-vascular endothelial growth factor (bevacizumab) and anti-epidermal growth factor receptor (anti-EGFR; cetuximab and panitumumab) antibodies have demonstrated beneficial effects in terms of prolonging survival, and these drugs have been extensively integrated into standard treatment [2]. Anti-EGFR antibody therapy is particularly effective against KRAS/NRAS wild-type mCRC and recommended as standard treatment in third-line or subsequent therapies [3, 4]. By contrast, effective third-line or subsequent therapy for treating RAS mutant-type mCRC had not been established before the emergence of the new drugs regorafenib and TAS-102, which have recently demonstrated superior overall survival (OS) compared to placebo [5, 6].

S-1, an oral fluoropyrimidine anticancer agent, has been widely used for the treatment of various carcinomas including gastric, colorectal, and pancreatic cancers and approved in 38 countries in Asia and Europe. S-1 was developed in order to increase the blood concentration of 5-FU, thereby enhancing anticancer activity, and to reduce gastrointestinal toxicity by combining tegafur, a prodrug of 5-FU, with two modulators, gimeracil and oteracil potassium [7]. The efficacy and safety of S-1 were demonstrated for the treatment of mCRC as first-line therapy in a phase III trial conducted in combination with oxaliplatin and bevacizumab (SOFT trial), and as second-line therapy in a phase III trial conducted in combination with irinotecan (FIRIS trial) [8, 9]. Results obtained from a phase II trial, demonstrating a disease control rate (DCR) of 42.9%, suggested that S-1 monotherapy was also likely to be effective as a third-line therapy [10]. The efficacy of bevacizumab used in combination as second-line therapy following its use in first-line therapy was verified [11]. For third-line or subsequent therapies, agents with disease control capability and low toxicity are favored. In this study, we assessed the efficacy and safety of the S-1 plus bevacizumab combination therapy in patients receiving third-line treatment for KRAS mutant-type mCRC (SAVIOR study).

Materials and Methods

The present study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the Japanese Ethical Guidelines for Clinical Research to maximally ensure the human rights, welfare, and safety of the subjects. Written informed consent was obtained from all patients. The protocol was approved by the relevant institutional review boards or ethics committees at each center after a careful review of the ethical and scientific aspects of the study.

Patients

The main inclusion criteria were as follows: (1) histologically confirmed colorectal cancer (adenocarcinoma); (2) mutated KRAS genes detected (laboratory procedures were conducted in accordance with the institutional policy); (3) at least one measurable metastatic lesion according to the Response Evaluation Criteria in Solid Tumors (RECIST); (4) age 20–79 years; (5) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2; (6) failure of two prior chemotherapies, one including oxaliplatin and the other irinotecan, for mCRC, and (7) adequate renal, liver, hematologic, and coagulation function.

The main exclusion criteria were as follows: (1) moderate or severe ascites or pleural effusion requiring treatment; (2) prior S-1 therapy or radiotherapy, and (3) history or evidence of inherited bleeding diathesis or coagulopathy with risk of bleeding [patients treated with low-dose aspirin therapy (<325 mg/day) could be enrolled].

Protocol Treatment

A 42-day regimen, in which 5 mg/kg of bevacizumab was administered by intravenous infusion over 30–90 min on days 1, 15, and 29, was repeated until the discontinuation criteria of the protocol treatment were met. S-1 was orally administered twice daily (after breakfast and dinner) from day 1 to day 28, followed by a 14-day rest period. The dose of S-1 was calculated according to body surface area (BSA) as follows: BSA <1.25 m², 80 mg/day; 1.25 m² ≤ BSA <1.5 m², 100 mg/day; BSA ≥1.5 m², 120 mg/day.

The criteria for dose reduction were as follows: neutrophil count <500/mm³; platelet count <50,000/mm³; aspartate or alanine aminotransferase ≥200 IU/l; serum creatinine <1.5 mg/dl, or presence of grade ≥3 diarrhea or stomatitis. If any of these conditions were met, the next dose of S-1 was reduced by one step.

The main discontinuation criteria for the protocol treatment were as follows: inability to initiate the regimen within 28 days of the final administration of S-1; exacerbation of the original illness; a requirement for further dose reduction owing to adverse events and other causes following the reduction of the S-1 dose by two steps, or a proposal by the patient to discontinue the protocol treatment.

Safety and Response Evaluation

Adverse events manifesting during the protocol treatment or in the 30 days following completion of treatment were evaluated according to Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. Antitumor effects were evaluated every 6 weeks in compliance with RECIST version 1.1 and assessed by the independent review committee.

Endpoints

The primary endpoint of this study was DCR, defined as the rate of a complete or partial response plus stable disease. Secondary endpoints, response rate, progression-free survival (PFS: time between randomization and disease progression or death from any cause), OS (time between randomization and death from any cause or the date of last follow-up), and frequency and grade of adverse events were also evaluated.

Statistical Methods

The sample size was decided by using the following conditions. The acceptable minimum DCR for S-1 plus bevacizumab was assumed to be 30% and the expected value of DCR to be achieved was 50%, which means that if the DCR is <30%, the treatment is not accepted, while if the DCR is >50%, the treatment is accepted. When the type I error rate and the power were set at 0.05 and 0.80, respectively, the required number of subjects was calculated to be 35. However, an actual sample size of 40 was chosen, considering the potential dropout rate of 12.5%.

The survival time was analyzed using Kaplan-Meier curves to estimate the median survival time. Descriptive statistics and 95% confidence intervals (CIs) were also used. The exact 95% CI was calculated by the Clopper-Pearson method.

Results

Patient Characteristics

Thirty-one patients with KRAS mutant-type mCRC from 12 institutions were registered during the period from August 2009 to June 2011. Of the 31 patients, 30 were subject to safety analysis, following the exclusion of 1 patient whose protocol treatment was not initiated. After enrollment, 2 additional patients were excluded – 1 with a history of previous S-1 treatment and another previously treated with only one chemotherapy drug. A total of 28 patients were therefore assessable by RECIST and subject to efficacy analysis. The median observation period was 8.65 months (range 0.8–27.8). The clinical characteristics of the patients are shown in table 1. The ages of the 28 patients subject to efficacy analysis ranged from 38 to 78 years; they included 19 men (68%) and 9 women (32%). Analysis of the ECOG PS shows that 20 patients (71.4%) scored a PS of 0, 6 patients (21.4%) a PS of 1, and 2 patients (7.1%) a PS of 2. The number of patients who had previously received oxaliplatin- and irinotecan-based first-line therapy was 24 (86%) and 4 (14%), respectively. The number of patients who had previously received oxaliplatin- and irinotecan-based second-line therapy was 4 (14%) and 24 (86%), respectively. Twenty-five patients (89%) had previously been treated with bevacizumab, of whom 8 had been treated with bevacizumab as both first- and second-line therapy consecutively.

Table 1. Patient characteristics

Patient characteristics	Patients, n (%)
Age, years	
Median	68
Range	38–78
Sex	
Male	19 (68)
Female	9 (32)
ECOG PS	
0	20 (71)
1	6 (21)
2	2 (7)
Cancer site	
Cecum	3 (11)
Colon	15 (54)
Rectum	10 (36)
Metastatic site	
Liver	21 (75)
Lung	9 (32)
Abdominal lymph node	3 (11)
Other	8 (29)
Surgical history	
Primary cancer	23 (82)
Metastatic liver cancer	4 (14)
Metastatic lung cancer	0 (0)
None	3 (11)
Prior chemotherapy	
Oxaliplatin-based 1st/2nd	24 (86)/4 (14)
Irinotecan-based 1st/2nd	4 (14)/24 (86)
Bevacizumab	25 (89)

Table 2. Response to treatment

CR	PR	SD	PD	NE
0	0	19 (67.9)	8 (28.6)	1 (3.6)

The response was assessed by each investigator and confirmed by the central evaluation committee. Data are the number of patients (%) (total, n = 28) in each category. CR = Complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluated. DCR (CR+PR+SD) was 67.9%.

Efficacy

The response to treatment is shown in table 2. Although none of the 28 patients achieved either complete response or partial response, 19 patients achieved stable disease, and DCR was 67.9% (95% CI 47.6–84.1). The relative dose intensity of S-1 and bevacizumab was 83.3% (range 37.1–100) and 70.9% (range 33.3–100), respectively. The median values of time to treatment failure, PFS,

Fig. 1. Survival analysis of patients (n = 28). The median values of PFS and OS were 3.7 months (95% CI 2.1–5.6) and 8.6 months (95% CI 7.0–11.2), respectively.

and OS were 3.0 months (95% CI 1.8–4.3), 3.7 months (95% CI 2.1–5.6), and 8.6 months (95% CI 7.0–11.2), respectively (fig. 1). The median OS in the efficacy analysis from the initiation of first-line treatment was 23.3 months (95% CI 18.3–30.3), and from the initiation of second-line treatment, 16.4 months (95% CI 11.3–18.8).

Safety

The most common adverse events manifesting in 30 patients evaluated in the safety analysis are listed in table 3. Grade ≥ 3 decreased hemoglobin, anorexia, and diarrhea were induced in 5 (17%), 6 (20%), and 3 patients (10%), respectively; however, there were no cases of treatment-related death.

Discussion

The efficacy of a molecularly targeted agent, regorafenib, and an antimetabolite, TAS-102, as third-line therapy following the standard treatment for mCRC has been recently demonstrated in phase III trials [5, 6]. Although patients with wild-type KRAS are known to respond well to anti-EGFR antibody therapy, there was no effective third-line treatment available for patients with mutant-type KRAS prior to the emergence of regorafenib and TAS-102. Here, we conducted a pioneering prospective study of a third-line treatment intended for advanced CRC patients with mutated KRAS who fail to respond to prior irinotecan and oxaliplatin. The primary endpoint,

Table 3. Adverse events

	Grade				Any grade, %	Grade ≥ 3 , %
	1	2	3	4		
Laboratory findings						
Neutropenia	2	4	1	0	23	3
Thrombocytopenia	13	3	0	0	53	0
Hemoglobin	13	6	4	1	80	17
Total bilirubin	8	11	2	0	70	7
AST (GOT)	13	3	1	0	57	3
ALT (GPT)	9	2	1	0	40	3
Creatinine	3	0	0	0	10	0
Proteinuria	5	6	0	0	37	0
INR	12	1	0	0	43	0
Clinical findings						
Mucositis/stomatitis	6	5	1	0	40	3
Anorexia	6	9	5	1	70	20
Nausea	8	4	2	0	47	7
Vomiting	4	1	0	0	17	0
Diarrhea	5	5	3	0	43	10
Hyperpigmentation	15	0	–	–	50	0
Rash/desquamation	3	2	1	0	20	3
Fatigue	9	11	2	0	73	7

Safety analysis of 30 eligible patients. For each adverse event, data are the number of patients with a grade 1–4 adverse event, total percentage of patients with any grade of adverse event, and percentage with a grade ≥ 3 adverse event. AST (GOT) = Aspartate transaminase/glutamate oxalacetate transaminase; ALT (GPT) = alanine transaminase/glutamate pyruvate transaminase; INR = international normalized ratio.

DCR, was 67.9%, and the median PFS and OS were 3.7 and 8.6 months, respectively.

In the phase III studies cited above, the DCR, median PFS, and median OS were 41%, 1.9 months, and 6.4 months, respectively, for regorafenib, and 44%, 2.0 months, and 7.1 months for TAS-102. For patients with best supportive care, the median OS was 5.0 and 5.3 months, respectively, in the same studies. Although the results reported here are from a phase II study and only include patients who received third-line therapy, without reflecting those receiving fourth-line or subsequent therapies, the efficacy of S-1 plus bevacizumab treatment was historically comparable to the efficacy obtained in the above clinical trials assessing third-line or subsequent treatment.

The validity of this study, however, is limited in that, unlike the 2 phase III clinical trials mentioned above, it is not a randomized placebo-controlled study. However, despite this limitation, the median OS from the initiation of the first- and second-line treatment obtained in this study was 23.3 and 16.4 months, respectively, which is similar to the OS values reported in other clinical trials assessing first- and second-line therapies [12]. Although this study was geared towards particular patients for whom a shift to third-line treatment was possible, it seems unlikely that only those patients with a favorable prognosis were enrolled in this study. For these reasons, we believe that the S-1 plus bevacizumab combination therapy will prove effective as third-line treatment.

In this study, the bevacizumab plus S-1 regimen was demonstrated to be effective in patients who had received prior therapy with 5-FU. S-1 is an oral FU drug that contains a dihydropyrimidine dehydrogenase inhibitor, so it may be effective even in patients resistant to other FU-based agents. In the FIRIS trial, a phase III trial of second-line therapy regimens, the IRIS regimen (S-1 plus irinotecan) led to an improvement in PFS and OS in patients who had received prior therapy with FOLFOX [9]. It was suggested that changing from 5-FU to S-1 may potentially be effective.

Twenty-five (89%) of the 28 patients evaluated had been treated with bevacizumab as either first- or second-line therapy: 15 patients (54%) as first-line and 18 patients (64%) as second-line. Although an observational study had reported an association between bevacizumab beyond progression and prolonged OS [13], verified clinical trials [11] were not available at the start of this study, which may explain why only 8 of the patients in our study were treated with both first-line and second-line bevacizumab.

However, the use of bevacizumab as combination third-line treatment was effective when bevacizumab had been used in both first- and second-line therapy.

As the incidences of adverse events of grade ≥ 3 were generally 10% or lower, we consider that sufficient tolerability of the protocol treatment was demonstrated when compared to the data obtained in the studies assessing S-1 monotherapy, capecitabine plus bevacizumab combination therapy, and regorafenib as therapies given as third-line or subsequent treatment [5, 10, 14]. Grade ≥ 3 diarrhea was an adverse event characteristic of S-1, with a reported incidence of 10%, which called for special attention. Although grade ≥ 3 hypertension, an adverse event characteristic of bevacizumab, was reported in 24% of capecitabine plus bevacizumab-treated patients and in 7% of regorafenib-treated patients, no incidence of grade ≥ 3 hypertension was induced by our protocol treatment. The sufficient tolerability of S-1 plus bevacizumab therapy has also been demonstrated in a phase II clinical trial conducted in elderly patients [15].

For predictors of a lack of response to anti-EGFR antibody therapy, although the mutations in KRAS exon 2 have been predominantly reported, a small number of mutations in KRAS exon 3 or 4 or in NRAS have also been reported to be important [16–18]. In this study, however, only KRAS mutations in exon 2 satisfied the eligibility criteria as, prior to the start of this study, these were the only mutations that had been reported on. At the time this study was conducted, only KRAS exon 2 mutations were measurable in clinical settings in Japan; furthermore, testing for KRAS gene mutations was conducted at each participating institution, and data accumulation was not centralized, making it difficult to carry out additional analysis after completion of the study. The fact that there have been no studies demonstrating clear differences in treatment efficacy of either S-1 or bevacizumab associated with the presence or absence of RAS mutations may suggest that this would also be true for S-1 plus bevacizumab therapy.

In conclusion, this study was a phase II study and exploratory in nature; however, the tolerability and high therapeutic effect of S-1 plus bevacizumab as third-line therapy for the treatment of mCRC with mutated KRAS was demonstrated. We consider this S-1 plus bevacizumab regimen to be useful in patients receiving outpatient chemotherapy.

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Disclosure Statement

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