Original Article

Phase II study of combined chemotherapy with irinotecan and S-1 (IRIS) plus bevacizumab in patients with inoperable recurrent or advanced colorectal cancer

Running title: IRIS plus bevacizumab for advanced colorectal cancer

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ABSTRACT

Background. In Japan, a study comparing the effectiveness and safety of irinotecan plus S-1 (IRIS) with those of a combination of 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI) as second-line treatment in patients with advanced or recurrent colorectal cancer demonstrated that IRIS was non-inferior to FOLFIRI. We previously reported that IRIS is also effective as first-line treatment.

Patients and Methods. Eligibility criteria included inoperable recurrent colorectal cancer with a confirmed diagnosis of adenocarcinoma, age ≥20 years, and no history of prior chemotherapy. S-1 (40–60 mg twice daily) was given orally on days 1 to 14, and irinotecan (100 mg/m^2) and bevacizumab (5 mg/kg) were given intravenously on days 1 and 15 of a 28-day cycle. The primary endpoint was safety. The secondary endpoints included overall response (OR), progression-free survival (PFS), and overall survival (OS).

Results. A total of 52 eligible patients were enrolled from October 2007 through March 2009. In safety analysis, the incidences of grade 3 or 4 adverse reactions were as follows: neutropenia, 27%; hypertension, 21%; and diarrhea, 17%. The overall response rate was 57.7%. Median progression-free survival was 16.7 months.

Conclusion. IRIS plus bevacizumab is a well-tolerated, highly effective

chemotherapeutic regimen that is easy to administer.

Introduction

In Japan, the incidence of colorectal cancer is increasing. Treatment outcomes have improved in patients with relatively early disease, but remain disappointing in those with advanced or recurrent colorectal cancer. About 20% of patients who undergo curative resection have recurrence. Overall, about one third of all cases of colorectal cancer eventually progress to advanced or recurrent disease. Surgery is indicated for about 30% of all colorectal cancers associated with hematogenous metastasis or local metastasis [1-5]. The remaining cases are candidates for chemotherapy. The recent advent of oxaliplatin, irinotecan, and molecular-targeted agents has steadily improved treatment outcomes [6-8].

First-line treatment with a combination of irinotecan, 5-fluorouracil (5-FU), and leucovorin (FOLFIRI) plus bevacizumab has produced a progression-free survival (PFS) of 12.8 months [9]. Although combined therapy with oral fluoropyrimidine capecitabine and irinotecan has produced good outcomes in a phase II study [10], these results were not supported by the findings of the BICC-C study [9].

Combination chemotherapy with oral fluoropyrimidine S-1 plus irinotecan (IRIS) therapy has been shown to be very effective and safe for the first-line treatment of unresectable colorectal cancer, with a response rate of 52.5% and a median PFS of 8.6 months [11]. Subsequently, a

phase III clinical trial comparing FOLFIRI with IRIS as second-line treatment in patients with unresectable colorectal cancer (FIRIS study) confirmed that IRIS was equivalent to FOLFIRI in terms of both efficacy and safety [12].

Bevacizumab was approved for clinical use in Japan in 2007, allowing this molecular-targeted agent to be combined with IRIS. If IRIS plus bevacizumab is confirmed to be safe and as effective as conventional regimens such as FOLFIRI, this new, more convenient regimen offers additional benefits in terms of convenience and less stress for patients and healthcare workers because it does not require use of an infusion pump, in contrast to FOLFIRI or 5-FU, leucovorin, and oxaliplatin (FOLFOX). However, caution is necessary, because treatment with bevacizumab has been associated with increased incidences of gastrointestinal perforation, cerebrovascular events, transient cerebral ischemic attacks, and arterial thromboembolism, including myocardial infarction. The present study was designed to evaluate the safety and efficacy of IRIS combined with bevacizumab in patients with inoperable or recurrent colorectal cancer. To our knowledge, similar studies have not been reported previously. This was the first clinical trial to evaluate S-1 combined with irinotecan + bevacizumab. The main objective was to obtain information on safety, and the target number of patients was decided accordingly.

Patients and methods

Eligibility

Patients with inoperable or recurrent colorectal cancer were eligible for the study if they met the following criteria: a histopathologically confirmed diagnosis of colorectal adenocarcinoma; assessable lesions according to the Response Evaluation Criteria in Solid Tumors (RECIST) [13]; an age of 20 years or older; an Eastern Cooperative Oncology Group performance status of 0 or 1; no history of anticancer chemotherapy or abdominal radiotherapy (patients who had received adjuvant chemotherapy completed at least 6 months before study entry were eligible); and the ability to receive S-1 orally. Eligible patients also had to have a leukocyte count of ≥3.5 x 10^3/μL to ≤12.0 x 10^3/μL, a platelet count of ≥100 x 10^3/μL, a hemoglobin level of ≥9.0 g/dL, aspartate aminotransferase and alanine aminotransferase levels not exceeding 2.5 times the respective upper limits of normal (excluding patients with liver metastases), a total bilirubin level of ≤1.5 mg/dL, a serum creatinine level of <1.2 mg/dL (creatinine clearance [CCr] estimated by the Cockcroft-Gault formula >50 mL/min; the initial dose was reduced by one level if the CCr was between ≥50 and <80 mL/min), a normal electrocardiogram (excluding clinically unproblematic arrhythmias and ischemic changes), and an expected survival of at least 3 months. All

patients gave written informed consent before enrollment.

The study protocol was approved by the institutional review boards of all participating hospitals.

Treatment

S-1 was given orally in 2 divided doses for 14 consecutive days, followed by a 14-day rest. S-1 is provided in 20 or 25 mg tablets, the actual dosage of S-1 was decided according to the patient's body surface area as follows: patients with a body surface area of less than 1.25 m^2 received 40 mg; those with a body surface area of 1.25–1.5 m^2 received 50 mg; and those with a body surface area of more than 1.5 m^2 received 60 mg. The starting dose was decreased by one step for patients with CCr of ≥50 mL/min and <80 mL/min. Bevacizumab was given as a continuous intravenous infusion on days 1 and 15 in a dose of 5 mg/kg per administration. This 28-day cycle was defined as one course of treatment. Treatment was repeated until any of the criteria for discontinuing the study treatment were met. Irinotecan was administered as a continuous intravenous infusion over 90 minutes on days 1 and 15 of a 28-day cycle at a dose of 100 mg/m^2. In a phase I study of the IRIS regimen in gastric cancer, irinotecan was administered at 125 mg/m^2 [14]. However, as adverse drug reactions are intense at 125 mg/m^2, the Data and Safety Monitoring Committee

recommended that the dose of irinotecan to be used in this study be lowered by 1 level.

Initiation of a treatment cycle and administration of irinotecan on day 15 required that neutropenia was grade 2 or lower and nonhematologic toxicity was grade 1 or lower. Administration of bevacizumab additionally required confirmation of grade 2 or lower hypertension, grade 2 or lower proteinuria or a 24-hour urinary protein excretion of less than 2 g, and grade 1 or lower bleeding, as well as no evidence of thrombosis. If grade 4 hematologic toxicity or grade 3 or higher nonhematologic toxicity occurred, the dosage level was decreased by one step for the next course of therapy. Specifically, S-1 was decreased by 20 mg/day and irinotecan by 20 mg/m^2. When the following criteria were met, the study treatment was discontinued: 1) The subsequent course could not be started when 28 days had elapsed since the final S-1 administration; 2) An adverse event that met the criteria for dose reduction developed even when S-1 was decreased to the lowest level; 3) An adverse event developed that made it difficult to continue the administration; 4) Disease progression was noted; 5) There was a patient's request for discontinuation; 6) It became evident after registration that the patient was ineligible for the study.

Assessments

All toxicity was graded according to the Common Terminology Criteria for Adverse Events, version 3.0 [15]. Patients underwent laboratory tests and computed tomography (CT) of the chest and abdomen at enrollment. Subsequently, laboratory tests (complete blood count and differential count, liver and renal function tests) were conducted at 2-week intervals before treatment with irinotecan. CT scanning was performed at 8-week intervals after the start of treatment to assess tumor response. Tumor response was evaluated in accordance with the RECIST [13]. Complete responses and partial responses were confirmed after an interval of at least 4 weeks. When calculating on-treatment PFS, data on the date of confirming no progressive disease during the protocol treatment were censored for patients who had “progressive disease” 30 or more days after the completion of the protocol treatment [6].

Statistical analysis

Focus was made on blood pressure elevation, a frequent adverse effect of bevacizumab. Assuming that the incidence of grade 3 or higher blood pressure elevation was 10%, with a threshold level of 24%, an alpha level of 0.05, and a beta level of 0.20, we set the target number of patients at 50. Secondary endpoints were response rate, PFS, and overall survival. The Kaplan-Meier method was used to estimate overall survival and PFS.

Results

Patient characteristics

A total of 52 patients were enrolled from October 2007 through March 2009 (excluding 1 patient who withdrew informed consent). Their demographic characteristics are shown in Table I. Median age was 63.5 years. The general condition of all patients was good.

Efficacy

The 52 patients received a total of 511 cycles of treatment. Median follow-up was 627 days. The median number of treatment cycles per patient was 8.5 (range 1–26). Tumor responses are summarized in Table II. On an intention-to-treat basis, the response rate (complete response + partial response) was 57.7% (95% confidence interval [CI] 43.2%–71.3%), and the disease control rate (complete response + partial response + stable disease) was 90.4%. The median PFS was 16.7 months (95% CI 13.1–18.7) (Figure 1), and the on-treatment PFS was 18.7 months (95% CI 16.7 to unknown). The reasons for discontinuing treatment were progressive disease in 19 patients and adverse events in 19. Major adverse events that led to discontinuation of the study included 4 cases of lung disorder, such as bronchiolitis obliterans with organizing pneumonia

(BOOP) and interstitial pneumonia, 3 cases of neutropenia, 3 cases of total bilirubin increased, 1 case of diarrhea, and 1 case of hypertension. Toxicity required treatment delays in 36 patients and dose reduction in 11 patients. As for second-line treatment, 22 patients were switched to oxaliplatin-based chemotherapy, 14 continued to receive irinotecan-based treatment, and five underwent debulking surgery.

Safety

Adverse events are listed in Table III. The most common grade 3 or 4 adverse events were neutropenia (27%) and diarrhea (17%). Grade 3 or 4 hypertension (21%) was attributed to bevacizumab, but there were no life-threatening adverse events, such as gastrointestinal perforation. Most adverse events were grade 1 or 2 and could be controlled.

The median relative dose intensity was 0.923 for S-1 (range 0.607–1), 0.917 for irinotecan (range 0.883–1), and 0.902 for bevacizumab (range 0.407–1). The median dose intensity was 216 mg/m^2/week for S-1, 46 mg/m^2/week for irinotecan, and 2.25 mg/m^2/week for bevacizumab.

Discussion

S-1 is an oral fluoropyrimidine agent that was rationally-developed for use in combination with tegafur (a prodrug of 5-FU),

5-chloro-2,4-dihydroxypyrimidine (CDHP; an inhibitor of 5-FU catabolism), and potassium oxonate (Oxo; an inhibitor of 5-FU–induced diarrhea) [16]. Two independent phase II studies of S-1 for advanced colorectal cancer obtained response rates of 35% (22/62) and 39.9% (15/38), respectively, while the observed toxicities were generally mild [17,18]. S-1 is also used in a wide range of other cancers, such as gastric cancer, lung cancer, and urologic cancer [19-21].

IRIS is the only oral fluoropyrimidine-based regimen confirmed to be non-inferior to FOLFIRI as second-line treatment in a phase III study [13]. The present study was the first clinical trial to confirm the efficacy and safety of IRIS, combination of S-1 and irinotecan, added with bevacizumab of 28-day cycle as first line treatment in patients with inoperable recurrent or advanced colorectal cancer.

Combined therapy with S-1 and irinotecan is characterized by the occurrence of neutropenia and gastrointestinal toxicity [11,22,23]. Grade 3 or higher diarrhea is particularly common, as seen in the FIRIS study. Whether combining bevacizumab with IRIS would exacerbate toxicity was an important concern; however, only one patient had to discontinue the study treatment because of diarrhea, and there was no grade 4 diarrhea. In other patients, the study treatment could be safely continued by allowing rest periods or decreasing the dosage. There was no increase in the

incidence or severity of other adverse events usually associated with the IRIS regimen.

Many studies have reported on the safety of bevacizumab [24,25]. In the present study, adverse events potentially associated with bevacizumab, such as blood pressure elevation, proteinuria, and nasal bleeding, occurred at their usual frequencies, but there were no serious adverse events such as gastrointestinal perforation or thrombosis. Twenty-one percent of the patients had grade 3 or higher hypertension, but treatment with two antihypertensive agents was begun soon after the start of chemotherapy to control blood pressure. The study treatment was terminated because of hypertension in only one patient, who requested that treatment be discontinued. Overall, the study treatment could be administered without any problem. It was noteworthy that grade 2 or higher hypertension occurred in 19 patients, in whom the median PFS was 529 days, which was longer than 457 days observed as the median PFS in those with grade 1 or lower hypertension. This indicated a possible role of the onset of hypertension as a predictive marker for the treatment efficacy [26].

Several studies have reported promising response rates and median PFS in patients who received S-1 plus irinotecan [11,22,23]. In one phase II study, IRIS regimen produced a response rate of 52.5%, with a

median PFS of 8.6 months [11]. In the present study, the addition of bevacizumab to IRIS did not appreciably increase the response rate, but did show substantially longer median PFS, although we did not directly compare the bevacizumab-combined regimen.

Although an add-on effect of bevacizumab in the oxaliplatin-based regimen was demonstrated [7,8] the effect was not as high as expected. In contrast, a marked add-on effect of bevacizumab was seen in the irinotecan-based regimen [6,9]. While the combination therapy with capecitabine and irinotecan has a high effect, clinical development has been difficult because it causes severe toxicities. However, a recent report showed that the incidence of grade 3 or higher diarrhea was decreased to as low as 7% by changing the capecitabine regimen [10]. Although the gastrointestinal toxicity of the IRIS therapy is far from low, most of the reported toxicities occurred during an initial phase of treatment. High feasibility of the study could be maintained by reducing the doses of study drugs or performing a symptomatic therapy, which may be one reason leading to the increased median PFS in the present study.

Currently, a phase III study is being planned. IRIS has been confirmed to be effective as second-line chemotherapy for unresectable colorectal cancer. The results of this study were very promising, and IRIS would be an appropriate candidate arm for a phase III comparative study in

the future.

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Declaration of interest:

Y. Komatsu has received honoraria form Taiho Pharmaceutical Co., LTD, Yakult Honsha Co., LTD, Daiichi Sankyo Co., LTD, and Chugai Pharmaceutical Co., LTD. Y. Sakata has received honoraria form Taiho Pharmaceutical Co., LTD, Yakult Honsha Co., LTD, and Daiichi Sankyo Co., LTD. All remaining authors have declared no conflicts of interest.

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Figure Legends

Figure 1. Progression-free survival.

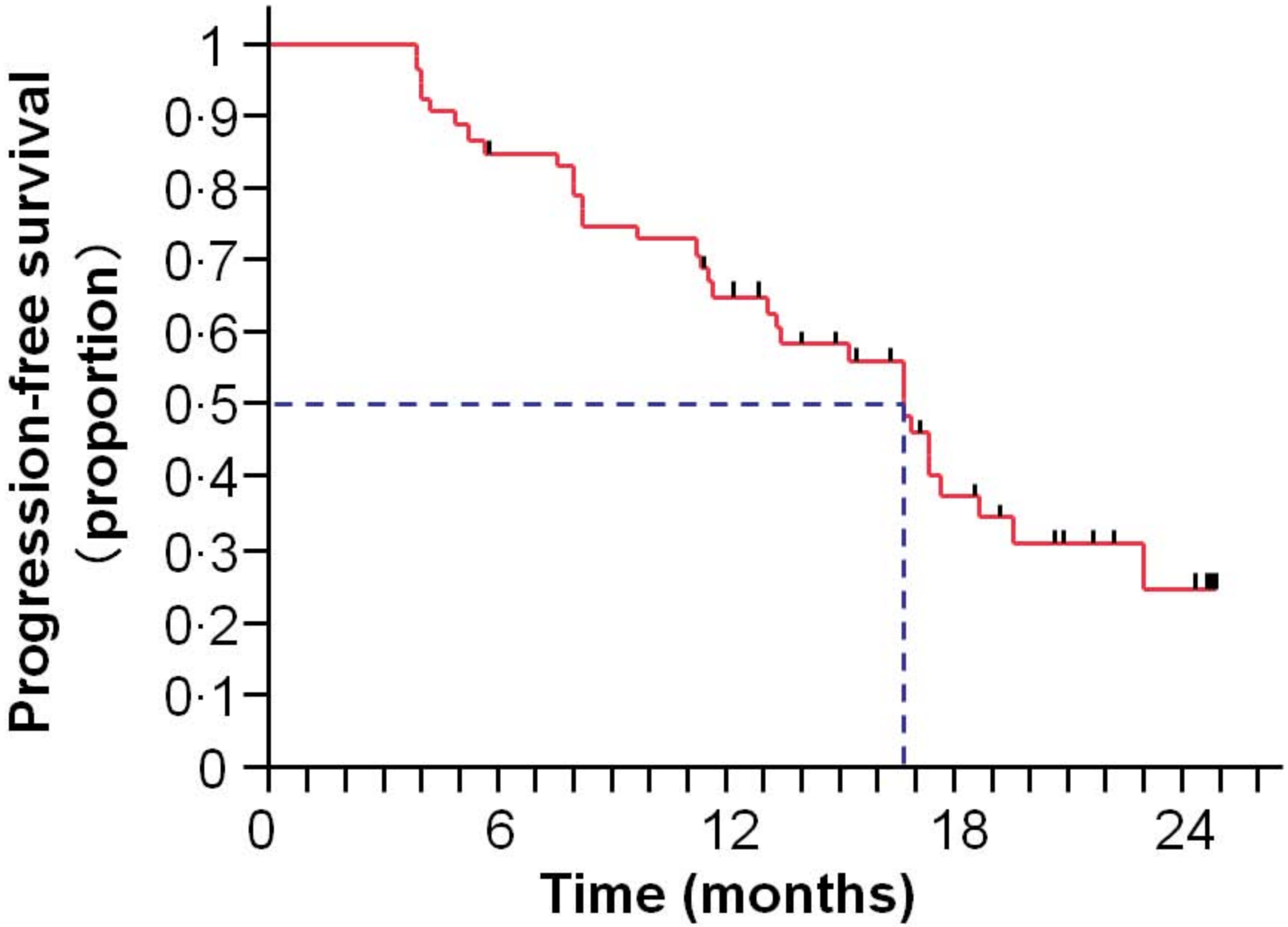
Progression-free survival
(proportion)
1
0·9
0·8
0·7
0·6
0·5
0·4
0·3
0·2
0·1
0
0
6
12
18
24
Time (months)

Table I. Patient baseline characteristics.

Variable	No. of Patients (*N* = 52)	%
Age, years		
Median	63·5	
Range	48-82	
Gender		
Male	33	63·5
Female	19	36·5
ECOG PS		
0	52	100
1	0	0
Tumor sites		
Colon	35	67·3
Rectum	17	32·7
Metastatic sites		
Liver	35	67·3
Lung	23	44·2
Lymph nodes	23	44·2
Peritoneal	7	13·5
Number of metastatic sites		
Median	2	
1	24	
≥2	28	
Previous adjuvant therapy	4	7.7

ECOG PS, Eastern Cooperative Oncology Group performance status.

Table II. Response rates.

Response	No. of Patients (N = 52)	%
Complete response	2	3·8
Partial response	28	53·8
Stable disease	17	32·7
Progressive disease	0	0
Not evaluable	5	9·6

Table III. Adverse events (worst value)

Event	No. of patients (*N* = 52)				All grades (%)	Grade ≥3 (%)
	Grade					
	1	2	3	4		
Neutropenia	4	15	12	2	63	27
Anemia	13	17	6	0	69	12
Leukocytopenia	10	21	3	0	65	6
Diarrhea	18	11	9	0	73	17
Fatigue	26	3	3	0	62	6
Anorexia	23	12	2	0	71	4
Hyperbilirubinemia	12	9	3	0	46	6
Stomatitis	23	3	1	0	52	2
Hyperpigmentation	29	6	0	0	67	0
Alopecia	25	1	0	0	50	0
Hypertension	10	8	11	0	56	21
Proteinuria	6	20	0	0	50	0
Epitaxis	20	0	0	0	38	0
Hand-foot syndrome	8	0	0	0	15	0

Note: Grades were assessed according to Common Terminology Criteria for Adverse Events version 3.0.