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Safety Verification Trials of mFOLFIRI and Sequential Irinotecan + Bevacizumab as First- or Second-Line Therapies for Metastatic Colorectal Cancer in Japanese Patients

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Key Words
Advanced colorectal cancer · Irinotecan · Bevacizumab · S-1 · Randomized trial

Abstract
Objective: S-1 is effective in sequential combination with irinotecan (IRIS) in treating metastatic colorectal cancer. We conducted a randomized phase II trial of modified leucovorin, fluorouracil and irinotecan (mFOLFIRI) + bevacizumab and sequential IRIS + bevacizumab as first- or second-line therapies. ***Methods:*** Sixty metastatic colorectal cancer patients were randomly assigned to receive mFOLFIRI + bevacizumab or sequential IRIS + bevacizumab (7.5 mg/kg of bevacizumab and 150 mg/m^2 of irinitecan, and 80 mg/m^2/day of S-1 orally from day 3 until day 16 as a 3-week course). The primary endpoint was the safety of each method until week 12, with the secondary endpoint being the comparison of the safety and efficacy of the two methods. ***Results:*** The safety of the two treatments was comparable, except that G3 anorexia and diarrhoea were less frequent with sequential IRIS + bevacizumab. The overall response rate was 62% [95% confidence interval (CI) 40.1–79.8] versus 72% (95% CI 50.6–86.2), and progression-free survival was 324 days (95% CI 247–475) versus 345 days (95% CI 312–594) with mFOLFIRI + bevacizumab versus IRIS + bevacizumab, respectively. ***Conclusion:*** Sequential IRIS + bevacizumab is a safe and effective method of systemic chemotherapy against metastatic colorectal cancer and is compatible with mFOLFIRI + bevacizumab.

Introduction

Over the past 10 years, as a result of multidisciplinary therapies including systemic chemotherapy, there has been a dramatic improvement in the success of treat-

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ments against unresectable and/or recurrent colorectal cancer [1]. Particularly, based on the results of several clinical trials, bevacizumab was shown to extend progression-free survival (PFS) when used in combination with other chemotherapies including irinotecan, fluorouracil and leucovorin [2], leucovorin, fluorouracil and oxaliplatin (FOLFOX) [3], leucovorin, fluorouracil and irinotecan (FOLFIRI) [4], and 5-fluorouracil and leucovorin (5-FU/LV) [5]. These results are further supported by large-scale observational studies [6, 7]; however, in standard chemotherapy treatments, as often represented by either FOLFOX or FOLFIRI, placement of a peripherally inserted central venous port (CV port) is required for continuous 5-FU infusion. The usage of CV ports can cause complications, including infections and thrombosis, resulting in decreasing the patient's quality of life [8, 9].

In consideration of these factors, chemotherapy regimens using oral fluoropyrimidines rather than continuous 5-FU infusion must be developed. The CapeOX regimen, which uses capecitabine, an oral fluoropyrimidine pro-drug of 5-FU rather than 5-FU/LV, plus oxaliplatin, has identical therapeutic effects to FOLFOX. Favourable results were also observed when used in combination with bevacizumab [10]. However, because of severe gastrointestinal toxicity associated with capecitabine in combination with irinotecan (CapeIRI or XELIRI), an effective alternative treatment to FOLFIRI has yet to be developed [4].

S-1 is a combination of tegafur, a pro-drug of 5-FU that consists of oral fluoropyrimidines, gimeracil (5-chloro-2,4-dihydoroxypyridine) and oteracil (potassium oxonate) at a molar ratio of 1:0.4:1 [11]. Gimeracil has a reversible competitive inhibitory effect on dihydropyrimidine dehydrogenase, a rate-limiting enzyme involved in the metabolic degradation of 5-FU. Oteracil reduces gastrointestinal toxicity and is effective against a wide range of carcinomas. Against metastatic colorectal cancer, S-1 showed a response rate of 39.5%, a PFS of 5.4 months and an overall survival time of 11.9 months when used as a monotherapy [12]. Because S-1 is expected to replace 5-FU/LV, there have been several prospective clinical trials in Japan using S-1 in combination with oxaliplatin (L-OHP or SOX) [13]. Clinical trials of S-1 combined with irinotecan (IRIS) were also conducted with various schedules or dosage regimens [14–16]. Among these, Yoshioka et al. [15] conducted phase I/II trials of sequential IRIS and the combined treatment of staggered irinotecan and S-1. These clinical trials were performed in order to avoid decreased therapeutic effects and increased toxicities caused by the inhibitory effect of 5-FU and its metabolites on the bioactivation of SN-38 from irinotecan [17, 18]. The authors reported on how this treatment regimen effectively avoided toxicity and rivaled the efficacy of previous FOLFIRI treatments; however, because the introduction of molecular targeted drugs in Japan was delayed, no studies were performed on the safety and efficacy of sequential IRIS in combination with bevacizumab. Thus, we report on the respective safety of sequential IRIS + bevacizumab and modified FOLFIRI (mFOLFIRI) + bevacizumab therapies against unresectable colorectal cancer. A secondary comparative study on the safety and efficacy of both therapies was also performed.

Patients and Methods

Patient Eligibility

The eligibility criteria were as follows: (1) patients histologically diagnosed with colorectal cancer; (2) patients with either an unresectable primary tumour or distal metastatic tumours; (3) an Eastern Cooperative Oncology Group performance status of 0 or 1; (4) the previous chemotherapy regimen had to be ≤1; (5) patients of post-operative adjuvant chemotherapy >6 months since last administration of drugs; (6) in the case of second-line therapy, first-line therapy had to be FOLFOX treatment; (7) internal organ function maintained, i.e. white blood cell count of 3,500–12,000/μl, platelet count ≥100,000/μl, aspartate aminotransferase (AST) ≤100 IU/l, alanine aminotransferase (ALT) ≤100 IU/l, total bilirubin ≤ 1.5 mg/dl, serum creatinine ≤1.2 mg/dl, serum creatinine clearance as estimated by Cockcroft-Gault equation ≥50 ml/min; (8) survival expected to be at least ≥3 months; and (9) written informed consent obtained from the patient for trial participation.

Exclusion criteria were as follows: (1) a history of abdominal irradiation; (2) any complications, such as intestinal paralysis, intestinal obstruction, poorly controlled diabetes, poorly controlled hypertension, unstable angina, hepatic cirrhosis, interstitial pneumonia, pulmonary fibrosis or severe pulmonary emphysema; (3) body cavity fluid retention requiring treatment; (4) poorly controlled peptic ulcerations; (5) concomitant gastrointestinal perforation or a history of perforation within 1 year prior to registration; (6) brain tumours or cerebral metastases confirmed on imaging; (7) concomitant symptoms of cerebrovascular nerve damage or any type of cardiac disease requiring treatment; (8) surgical treatment within 4 weeks prior to registration; (9) a bleeding tendency, coagulation disorder or excessive clotting factors; (10) awaiting or on treatment for chronic inflammatory disease such as rheumatoid arthritis, with any drugs that inhibit platelet function (aspirin or non-steroidal anti-inflammatory drugs); (11) women who are pregnant, may be pregnant, wish to become pregnant or are lactating; (12) men who wish their partner to become pregnant; (13) patients using irinotecan as post-operative adjuvant chemotherapy.

Treatment Methods

In the sequential IRIS + bevacizumab treatment regimen, on day 1, 7.5 mg/kg of bevacizumab was administered for >30 min, and 150 mg/m^2 of irinotecan was administered continuously for >90 min. Then, for the 2-week period from days 3 to 16, divided doses of S-1 were administered twice daily. The dosage of S-1 was as follows: body surface area (BSA) <1.25 m^2, 80 mg/day; BSA 1.25–1.5 m^2, 100 mg/day, and BSA >1.5 m^2, 120 mg/day as a 3-week course. Dosage for the mFOLFIRI + bevacizumab treatment regimen was as follows: 5 mg/kg of bevacizumab, 150 mg/m^2 of irinotecan, 200 mg/m^2 of L-leucovorin, 400 mg/m^2 of 5-FU by rapid intravenous infusion on day 1, and 2,400 mg/m^2 of 5-FU for 46 h by continuous intravenous infusion as a 2-week course. The treatment protocol period was set at 12 weeks in both groups, and treatment was continued until the criteria for discontinuation of the trial were met.

The criteria for commencement of treatment in each course were as follows: white blood cell count ≥3,000/μl, platelet count ≥75,000/μl (mFOLFIRI + bevacizumab) or ≥100,000/μl (IRIS + bevacizumab), AST ≤100 IU/l, ALT ≤100 IU/l, total bilirubin ≤1.5 mg/dl, and serum creatinine ≤1.2 mg/dl. In addition, diarrhoea of grade 0 and improvement in any other non-haematologic toxicity (excluding constipation, loss of appetite, loss of hair, chromatosis and dysgeusia) of grade ≤1 was required. In patients where the criteria for commencement of treatment were not met, treatment was delayed until all necessary requirements were completely satisfied. Treatment was discontinued in those patients where the criteria for commencement of treatment were not met even after a delay of ≥3 weeks.

The criteria common to both groups for discontinuation of bevacizumab treatment were as follows: (1) any grade of haemoptysis, gastrointestinal perforation, reversible leucoencephalopathy syndrome; (2) grade ≥3 thromboembolism, haemorrhage or hypersensitivity reaction, and (3) grade 4 proteinuria or hypertension. In patients with grade 2 haemorrhage, treatment was withdrawn until improvement to grade 0, and treatment was discontinued in patients where grade 2 haemorrhage recurred. Treatment was discontinued in patients with grade 3 hypertension that could not be controlled by medication. Treatment was withdrawn in the following situation: patients with grade 2 or 3 proteinuria until proteinuria was ≤2 g as determined by 24-hour urine collection analyses, with grade 3 or 4 liver dysfunction until improvement to either grade 1 or baseline, and in instances of recurrence.

In the IRIS group, S-1 administration was stopped if any of the following adverse effects occurred during the course: (1) grade ≥3 leucopenia or neutropenia in addition to other grade ≥3 non-haematological toxicity, until patient recovery; (2) grade ≥2 thrombocytopenia, diarrhoea, stomatitis, nausea or vomiting; (3) serum creatinine ≥1.5× the upper limit of normal, and (4) AST or ALT ≥100 IU/l. Any patients exhibiting grade ≥4 leucopenia or neutropenia, grade ≥3 thrombocytopenia, diarrhoea, stomatitis, nausea or vomiting, non-haematological toxicity, or AST or ALT ≥200 IU/l during the study were administered a lower dosage of IRIS in the next course of treatment. The low dosage of S-1 (level 1) was 50 mg/day for BSA <1.25 m^2, 80 mg/day for BSA 1.25–1.50 m^2, and 100 mg/day for BSA >1.5 m^2. For irinotecan, level 1 was 120 mg/m^2 and level 2 was 100 mg/m^2; no increase was made once dosage decreased. Also, in the mFOLFIRI + bevacizumab regimen, dosage was reduced in patients with grade ≥4 leucopenia or neutropenia, grade ≥3 thrombocytopenia, diarrhoea, stomatitis, nausea or vomiting or non-haematological toxicity as follows: 120 mg/m^2 of irinotecan and 200 mg/m^2 of 5-FU (bolus) for level 1, and 100 mg/m^2 of irinotecan, 200 mg/m^2 of 5-FU (bolus) and 2,000 mg/m^2 of 5-FU (infusion) for level 2.

With regard to safety data, the patients' health status was observed and blood samples were tested during weekly medical examinations by the attending physician until 4 weeks after commencing treatment and repeated after the fifth week at the start of each new course of treatment. Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events version 3.0, and effectiveness was observed according to the Response Evaluation Criteria in Solid Tumors 1.0. Computed tomographic scans were performed every 6 weeks. Effectiveness was judged comprehensively using blinded tests on the treatment methods by 3 or more physicians not including primary physicians.

Interim Analysis about Safety

After 3 cases have been registered in each group, registration was stopped to evaluate the safety of the two treatments (step 1). After the confirmation of the safety of the two treatments by the efficacy and safety evaluation committee, registration was reopened with 60 patients enrolled (30 per group; step 2).

Statistical Analysis

While attempting to detect a frequency of ≥10% with 95% probability for the occurrence of adverse events, we determined that the sample size would include 30 patients in each experimental group or 60 patients overall in the two experimental groups [19]. Patients' background, safety and efficacy data were summarized as frequencies and percentages. The χ^2 test was used to compare between groups, while the Kaplan-Meier method was used to analyse PFS.

Results

Patient Background

From November 2007 to February 2010, 60 patients were registered from the 12 institutes of the Tohoku Clinical Oncology Research and Education Society. These patients were randomly assigned to either the mFOLFIRI + bevacizumab or sequential IRIS + bevacizumab groups, with 30 patients in each group. Patient backgrounds are presented in table 1; the median age was 62.5 (range 46–77) and 62 years (range 31–73) in the mFOLFIRI + bevacizumab and sequential IRIS + bevacizumab group, respectively. Many patients were receiving first-line treatment (24 patients in the mFOLFIRI + bevacizumab group and 23 patients in the IRIS + bevacizumab group). No significant bias was seen between the two groups.

Safety Verification Test (Step 1)

Step 1 of this trial was to register 3 patients at a time into the two experimental chemotherapy regimen groups and evaluate the initial safety for 12 weeks. The last patient was registered in April 2008 when patient registration was temporarily suspended and initial safety was assessed. Except for 1 patient in the mFOLFIRI + bevacizumab group with gastrointestinal perforation (G3), no other severe adverse events occurred. Because international phase III and verification trials in combination with FOLFOX treatment in a Japanese population cite gastrointestinal perforation as an expected adverse event, the efficacy and safety evaluation committee recommended proceeding to step 2 while maintaining utmost vigilance with regard to patient safety.

Safety Verification Trial (Step 2)

By February 2010, 60 patients had been registered in the study, including the 6 patients from step 1 and were randomly allocated to the two experimental groups (table 1). Although one adverse event of gastrointestinal perforation (G5) was observed in the mFOLFIRI + bevacizumab group, this was determined to be due to progression of an underlying disease (table 2) and not due to the experimental treatment. With regard to G3/4 haematological toxicities in the mFOLFIRI + bevacizumab and sequential IRIS + bevacizumab treatment groups, neutropenia was seen at a rate of 48 and 38%, respectively. Although statistical differences were not observed, G3/4 gastrointestinal toxicities were more frequent in the mFOLFIRI + bevacizumab group than in the sequential IRIS + bevacizumab group (anorexia 17.9 and 3.4%, nausea 7.1 and 0%, diarrhoea 14.3 and 6.9%, respectively). G3/4 severity in hypertension, which is the representative adverse event of bevacizumab, was confirmed as 3.6% in the mFOLFIRI + bevacizumab group, whereas it was not observed in the sequential IRIS + bevacizumab group. No patient experienced severe proteinurea, thrombosis or haemorrhage in either group.

Comparison of Efficacy

The treatment methods were blind, and efficacy was compared by judging the response rate with a 3-person decision committee. The overall response rate (ORR) in the mFOLFIRI + bevacizumab group versus the sequential IRIS + bevacizumab group was 61.5% [95% confidence interval (CI) 40–80] and 72.0% (95% CI 51–86), respectively (table 3). Two patients showed complete response in the sequential IRIS + bevacizumab group. The median PFS was 324 days (95% CI 247–475) in the mFOLFIRI + bevacizumab group and 345 days (95% CI 312–594) in the sequential IRIS + bevacizumab group (fig. 1). Statistical significance was not observed between the two groups (p = 0.71).

Table 1. Characteristics of patients

	mFOLFIRI + bevacizumab (n = 30)	IRIS + bevacizumab (n = 30)
Age, years		
Median	62.5	62
Range	46–77	31–73
Males/females	18/12	17/13
ECOG performance status		
0	24	27
1	6	3
Primary legion		
Colon	17	17
Rectum	12	13
Both	1	0
Cancer		
Advanced	22	20
Recurrent	8	10
Histology		
Well	7	7
Moderately	20	22
Poor	2	0
Other	1	1
Primary site		
Yes	5	6
No	25	24
Number of metastases		
1	17	16
2	9	10
3	4	4
Adjuvant chemotherapy		
Yes	5	7
No	25	23
Prior chemotherapy		
Yes	24	25
No	6	5

ECOG = Eastern Cooperative Oncology Group.

Discussion

Systemic chemotherapy against unresectable or recurrent colorectal cancer was developed on the basis of the successful combination therapy of 5-FU and L-leucovorin. Continuous 5-FU infusion and cytotoxic drugs (e.g. irinotecan and L-OHP, as well as other molecular target-

Table 2. Adverse events of the two treatments

Adverse event	mFOLFIRI + bevacizumab							IRIS + bevacizumab							p value (χ^2 test; G3,4)
	G0	G1	G2	G3	G4	G5	grade >3, %	G0	G1	G2	G3	G4	G5	grade >3, %	
Non-haematological															
Anorexia	10	5	8	5			17.9	13	10	5	1			3.4	0.076
Nausea	10	7	9	2			7.1	16	11	2				0.0	0.143
Vomiting	20	6	1	1			3.6	28			1			3.4	0.980
Diarrhoea	12	12		4			14.3	15	11	1	2			6.9	0.364
Mucositis	17	10	1				0.0	23	6					0.0	(–)
Fatigue	14	8	4	2			7.1	17	9	3				0.0	0.143
GI perforation	26			1		1	7.1	29						0.0	0.143
Bleeding	20	7	1				0.0	21	8					0.0	(–)
Hypertension	20	3	2	1			3.6	24	2	1				0.0	0.304
Proteinuria	20	3	2				0.0	22	2	3				0.0	(–)
Haematological															
Leucopenia	5	6	12	4			14.3	12	3	9	5			17.2	0.409
Neutropenia	3[1]		11	8	5		48.1	12[1]		6	7	4		37.9	0.598
Thrombopenia	23	4					0.0	22	6		1			3.4	0.286

GI = Gastrointestinal. [1] Frequency of G0 and G1.

Table 3. Overall response of the two treatments

	mFOLFIRI + bevacizumab	IRIS + bevacizumab
CR	0	2
PR	16	16
SD	8	5
PD	2	2
NE	4	5
Total	30	30
RR, %	61.5 (40.1–79.8)	72.0 (CI 50.6–86.2)

Figures in parentheses are 95% CIs.
CR = Complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = not evaluated.

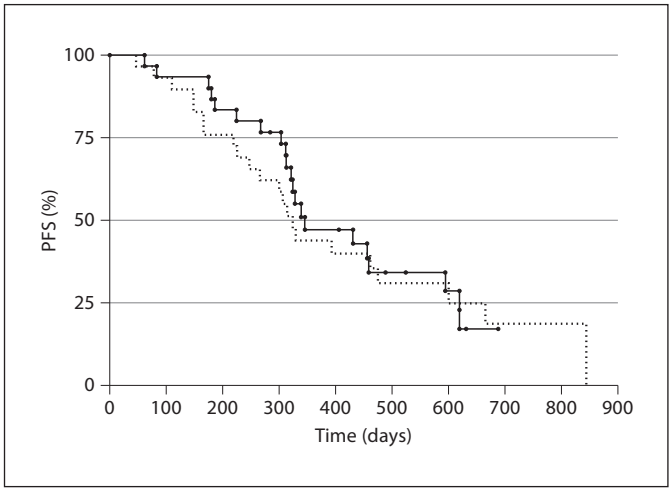

Fig. 1. Kaplan-Meier PFS curves of patients with metastatic colorectal cancer treated with mFOLFIRI + bevacizumab (dotted line) and IRIS + bevacizumab (solid line).

ed drugs, such as bevacizumab, cetuximab and panitumumab) are used concomitantly or sequentially to yield a median survival time that exceeds 2 years; however, continuous 5-FU infusion necessitates the insertion of a peripherally inserted central catheter or CV port, which can increase infection and thromboembolism risks. In order to circumvent these drawbacks, novel treatment options with oral fluoropyrimidines are being developed to replace the need for 5-FU infusions. The oral fluoropyrimidine S-1 exhibits a lower frequency of diarrhoea and hand-foot syndrome when compared with capecitabine, and S-1 has a higher tolerance level among Japanese people. Therefore, treatments such as SOX and IRIS are being developed in Japan to replace FOLFOX and FOLFIRI therapies, and it has been suggested that S-1 may be

able to replace 5-FU/LV [12–14]. Furthermore, because molecular targeted drugs, such as bevacizumab, cetuximab and panitumumab, have been introduced into routine clinical use in Japan, it has become important to evaluate the safety and efficacy of combined therapies on the basis of these drugs and on the new oral fluoropyrimidines.

Prior to this study, we tested the safety and efficacy of sequential IRIS therapy, which we found to have a low toxicity and high efficacy [13]. In this study, among patients with G3 or higher haematological toxicities, no significant differences between the two groups were observed with regard to neutropenia and/or leucopenia, although a lower trend was observed in the sequential IRIS + bevacizumab group. Muro et al. [16] performed a phase II/III trial comparing mFOLFIRI with irinotecan + S-1 therapy as a second line of treatment for patients with unresectable recurrent colorectal cancer. Although their administration method differed from our sequential IRIS therapy, as Muro et al. [16] did not use bevacizumab in their study, the frequency of G3/4 neutropenia in the mFOLFIRI (150 mg/m^2/2 weeks of irinotecan) and IRIS groups showed a similar trend to our data (52.1 and 36.2%, respectively), indicating that IRIS exhibits less neutropenic toxicity.

The incidence of gastrointestinal toxicity observed in this study in the mFOLFIRI + bevacizumab group was nearly identical to that in the FOLFIRI group (43.2–53.6%) as reported by a BICC-C study [4]. As with haematological toxicities, the frequency of non-haematological toxicity was lower in the sequential IRIS + bevacizumab group than in the mFOLFIRI + bevacizumab group. Furthermore, the frequency of reported gastrointestinal toxicities, such as loss of appetite (11%) and diarrhoea (20.5%), in the sequential IRIS + bevacizumab group of our study tended to be lower than that in the IRIS group in the study of Muro et al. [16]. This difference may be due to the following reasons: (1) all patients in the study of Muro et al. [16] were undergoing second-line treatment, and (2) the different administration method used placed a greater emphasis on irinotecan dose intensity than our sequential IRIS method. Muro et al. [16] also mentioned that raising the dose intensity of irinotecan was among the effective strategies for patients resistant to oxaliplatin-based chemotherapy; however, with regard to these adverse events, we believe that raising the dose intensity of S-1 rather than that of irinotecan is the better strategy for first-line treatment with regard to safety. Finally, as regards efficacy, the median PFS in both groups was about nearly a year. Although the number of patients in the current study was small, the level of efficacy seems to be higher than that in previous studies. The data on overall survival time are currently being analysed in a follow-up study.

Recently, Yamada et al. [20] reported the results of a phase II study on IRIS combined with bevacizumab (SIRB study). In the SIRB regimen, S-1 is administered on days 1–14 of a 21-day cycle, but the dose intensity of S-1, irinotecan and bevacizumab was equivalent to that of the sequential IRIS + bevacizumab regimen. Toxicity in the SIRB regimen was low and manageable (G3/4 neutropenia 26%, G3/4 anorexia 12%, G3/4 diarrhoea 8%). The ORR was 67% (95% CI 52.1–79.1) and the median PFS was 373 days (95% CI 299–440), which is comparable with our sequential IRIS + bevacizumab therapy.

From these results, we concluded that the combination of S-1, irinotecan and bevacizumab could be an effective primary therapy in Japanese patients, compared with mFOLFIRI + bevacizumab. Moreover, this regimen could reduce the risk of infection because it does not require a CV port. Therefore, sequential IRIS + bevacizumab therapy, a very promising treatment method, should be developed further in a larger randomized clinical trial. We are currently in the process of planning a phase III clinical trial in Japan comparing IRIS + bevacizumab with CapOX/FOLFOX + bevacizumab.

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