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ORIGINAL ARTICLE

Efficacy and safety of ramucirumab plus modified FOLFIRI for metastatic colorectal cancer

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Abstract

Background Dose modification of chemotherapy for metastatic colorectal cancer (MCRC) is often needed, especially in second-line and later-line treatments due to adverse events of previous treatment and poor patient condition. No study has focused on ramucirumab plus modified dose of FOLFIRI for MCRC, and whether low relative dose intensity (RDI) affects treatment efficacy has not been clarified.

Methods MCRC patients who received ramucirumab plus FOLFIRI, which consisted of 150 mg/m^2 of irinotecan, at six institutions were retrospectively analyzed.

Results A total of 43 patients were assessed. Median age was 63 years, and 22 patients (51%) were women. Twenty-six patients (60%) were given ramucirumab plus FOLFIRI as second-line therapy, and 17 (40%) as third or later-line. The median relative dose intensity (RDI) of irinotecan was 60.6%, which is lower than that in the pivotal phase 3 study (RAISE), and other agents showed the same trend. Median progression-free survival was 4.8 [95% confidence interval (CI) 3.2–5.7] months for all patients, 5.4 (95% CI 3.5–7.2) months for second-line patients, and 2.8 (95% CI 1.6–5.8) months for third or later-line patients. Median overall survival was 17.3 (95% CI 11.5–22.4) months for all patients. Patients with irinotecan RDI less than 60% showed similar treatment efficacy. Hematological toxicities of grade 3 or worse were observed in 21 patients, but all were manageable.

Conclusion Low RDI did not compromise the treatment efficacy of ramucirumab plus modified FOLFIRI for MCRC patients.

Keywords Colorectal cancer · Ramucirumab · Irinotecan · Relative dose intensity

Introduction

Colorectal cancer (CRC) is the fourth most common cause of cancer deaths in the world, and approximately 700,000 people die annually from CRC [1]. Standard therapy for metastatic CRC (MCRC) is chemotherapy, and many new agents have been developed to improve their poor prognosis. The efficacy of antiangiogenic treatments, which block vascular endothelial growth factor (VEGF) signaling, has been verified since 2000. Addition of the anti-VEGF monoclonal antibody bevacizumab to irinotecan-based chemotherapy significantly improved progression-free survival

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(PFS) in first-line treatment in patients with MCRC [2]. A similar effect of bevacizumab was confirmed when combined with oxaliplatin-based chemotherapy [3], and bevacizumab-combined chemotherapy is now frequently used as standard care for MCRC. Although a recent first-line study of MCRC showed median overall survival (OS) of around 30 months [4], the 5-year survival rate for MCRC remained at 12.5%, so further improvement of therapy is urgently needed.

VEGF receptor-2 (VEGFR-2)-expressing endothelial cells bind selectively to VEGF-A, C, and D, and play major roles in tumor angiogenesis and proliferation. Ramucirumab is a human IgG1 monoclonal antibody that binds directly to VEGFR-2 and disrupts the VEGF-mediated signaling pathway, resulting in an antitumor effect. In a preclinical model, colon cancer cell line HT-29, which is resistant to murine anti-VEGF-A antibody S12, was sensitive to a VEGFR-2 inhibitor [5]. Ramucirumab was then expected to be effective in patients who had disease progression after bevacizumab-combined therapy.

A pivotal phase 3 clinical study (the RAISE study) examining the effectiveness of the addition of ramucirumab to FOLFIRI treatment in second-line for MCRC patients who were previously treated with bevacizumab, oxaliplatin, and fluoropyrimidine was conducted [6]. In this study, ramucirumab plus FOLFIRI significantly improved OS over placebo plus FOLFIRI [median OS 13.3 months versus 11.7 months; hazard ratio 0.84; 95% confidence interval (CI) 0.73–0.98; $p = 0.022$]. Since 14% of the global RAISE study patients were Japanese, ramucirumab was approved in Japan as a therapeutic agent for MCRC in 2016. As a result, in addition to bevacizumab and aflibercept, which is a decoy receptor for the VEGF family, ramucirumab has come to be used in second-line treatment of MCRC. A clinical study that directly compares continuing bevacizumab and switching to another antiangiogenic agent after failure of bevacizumab-containing treatment has not yet been reported.

In terms of application of the findings from the RAISE study, several points do not correspond with Japanese clinical practice. First, an irinotecan dose of 150 mg/m^2 is the standard used in Japan, but 180 mg/m^2 was used in the RAISE study. Second, though the initial dose of fluorouracil was fixed in the RAISE study, a reduced fluorouracil dose, which was administered in the prior treatment of oxaliplatin-based regimen according to patient status, was usually continued in the following treatment with FOLFIRI. Third, patients who are naive to antiangiogenic agents can be treated with ramucirumab in second-line. Finally, ramucirumab can be administered in third-line or later-line treatments. Because of these differences from the RAISE study, the efficacy and safety of ramucirumab plus FOLFIRI treatment in clinical practice are not clear. To clarify these issues, the treatment courses of MCRC patients who received ramucirumab plus FOLFIRI in second-line and third or later-line treatments were retrospectively analyzed.

Patients and methods

Patients

Patients who started ramucirumab plus FOLFIRI at any treatment line between May 2016 and July 2018 at any of six institutions were assessed. This study was approved by the Ethics Committee of Kyushu University Hospital (approval no. 29-190) and was performed according to the guidelines for biomedical research specified in the Declaration of Helsinki. Because of the retrospective nature of this study, informed consent was not obtained from each patient.

Treatments

Patients were treated with the standard regimens for metastatic colorectal cancer in Japan as follows: patients received 8 mg/kg ramucirumab as a 60-min intravenous infusion, followed by the FOLFIRI regimen (150 mg/m^2 intravenous irinotecan given over 90 min followed by or concurrent with 200 mg/m^2 intravenous l-leucovorin given over 120 min, followed by 400 mg/m^2 fluorouracil given as an intravenous bolus over 2–4 min, and then 2400 mg/m^2 of fluorouracil given as a continuous infusion over 48 h) on day 1 every 2 weeks. Initial dose reduction was allowed according to prior treatment course or patient status at the discretion of the investigators. Outpatients generally visited the investigators every 2 weeks. At each visit, physical examinations, laboratory tests, and assessments for adverse events (AEs) were performed. The treatment was continued until disease progression, unacceptable toxicity, or the decision to discontinue by the patient or the investigator. Dose reduction and treatment delay were performed basically following the dose modification and interruption protocol of the RAISE study and the guidance for proper usage of ramucirumab published by Eli Lilly and Company.

Assessment

Assessment of tumor lesions was basically performed by computed tomography (CT) scan, which was planned every 2–3 months. In cases of worsening subjective symptoms or laboratory findings, CT was performed. Lower gastrointestinal endoscopy, magnetic resonance imaging, and positron-emission tomography were also used for examination of lesions if necessary. Tumor responses were assessed according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [7]. PFS and OS were defined as the period from the initiation of ramucirumab plus FOLFIRI to

the day of tumor progression or the day of death from any cause, respectively. All AEs were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 [8].

Statistical analysis

PFS and OS were estimated using the Kaplan–Meier method. Based on the previous reports showing several factors related to survival [9, 10], patient subgroups were defined as follows, baseline serum concentration of carcinoembryonic antigen (CEA) ≤ 10 versus > 10 μg/l and baseline absolute neutrophil counts (ANCs) ≤ 5600/μl versus > 5600/μl. Comparisons of two specific patient groups were performed using Fisher's exact test and the log-rank test. Hazard ratios were calculated using a Cox proportional hazard model. Values of $p < 0.05$ were considered significant. All statistical analyses were carried out using JMP software (SAS Institute Japan, Tokyo, Japan).

Results

Patients' characteristics

A total of 43 MCRC patients were analyzed. The patients' characteristics are shown in Table 1. The median age was 63 years (range 37–76 years), and 22 patients (51%) were women. PS 0 or 1 was observed in 38 patients (89%). Twenty-six patients (60%) were given ramucirumab plus FOLFIRI treatment as second-line therapy, and 17 (40%) were given it as a third- or later-line therapy, all of whom had a good PS of 0 or 1. Fifteen of 26 patients given the treatment as second-line were eligible for the RAISE study; specifically, they had failed first-line therapy containing bevacizumab, oxaliplatin, and fluoropyrimidine. Remaining eleven second-line patients had background different from RAISE study. Four patients relapsed within 6 months of completion of oxaliplatin-based adjuvant therapy, the other four patients received oxaliplatin and fluoropyrimidine-combined therapy without bevacizumab as a first-line therapy, the other three patients were previously treated with irinotecan and fluoropyrimidine-combined therapy with bevacizumab. Ten of 17 patients treated as third or later-line were refractory to bevacizumab, oxaliplatin, irinotecan, and fluoropyrimidine.

Table 1 Baseline characteristics of all patients ($n = 43$)

Characteristic	No	%
Median age (range), years	63 (37–76)	–
Gender		
Male	21	49
Female	22	51
PS		
0	21	49
1	17	40
2	5	11
Site of primary tumor		
Colon	25	58
Rectum	18	42
Site of metastatic disease		
Liver	25	58
Lung	22	51
Distant lymph node	15	35
Peritoneum	9	21
Other	18	42
RAS mutation status		
Mutant	27	63
Wild-type	15	35
Not tested	1	2
Number of prior chemotherapies		
1	26	60
2 or more	17	40

PS performance status

Treatment and efficacy

The median number of cycles of ramucirumab plus FOLFIRI was 5 (range 1–26), and that of FOLFIRI was 6 (range 1–26). The initial dose of irinotecan or fluorouracil was reduced in seven patients (27%) in the second-line and seven patients (44%) in the third or later-line according to the prior treatment course or the patient's status. Fluorouracil was reduced in 7 patients, and irinotecan was reduced in 13 patients (Table 2).

Dose reduction and treatment delay were performed in 18 patients treated in second-line and 10 patients treated in third or later-line. The relative dose intensity (RDI) of each agent is shown in Table 2. Taking account of the fact that the treatment dose of irinotecan in Japan is 150 mg/m^2, which is 83% of the 180 mg/m^2 in Western countries, 60.6% of the median RDI in the present study corresponds to 50.3% of the RDI on the Western basis. An RDI of 50.3% is much lower than that of the RAISE study, in which it was 77%. The RDIs of other agents showed the same trend.

The median PFS (mPFS) was 4.8 (95% CI 3.2–5.7) months for all patients, 5.4 (95% CI 3.5–7.2) months for second-line patients, and 2.8 (95% CI 1.6–5.8) months for third or later-line patients (Fig. 1a, b). Median OS (mOS) was 17.3 (95% CI 11.5–22.4) months for all patients, 17.4 (95% CI 11.2-not reached) months for second-line patients, and 13.0 (95% CI 7.5–22.0) months for third or later-line patients (Fig. 1c, d). The best response to ramucirumab plus FOLFIRI is shown in Table 3. The overall response rate

Table 2 Details of ramucirumab plus FOLFIRI treatment

	All patients ($n=43$)		Second-line patients ($n=26$)		Third or later-line patients ($n=17$)	
	No	%	No	%	No	%
Initial dose reduction of any agents						
Yes	14	33	7	27	7	41
Initial dose reduction of fluorouracil						
Yes	7	54	3	12	4	24
Initial dose of irinotecan						
150 mg/m^2	30	70	19	73	11	65
< 150 mg/m^2	13	30	7	27	6	35
	Median	Range	Median	Range	Median	Range
RDI of infusion fluorouracil (%)	57.9	13.5–100	58.7	13.5–100	57.9	21.4–100
RDI of bolus fluorouracil (%)	55.2	0–100	54.7	0–100	55.6	0–100
RDI of l-leucovorin (%)	70.0	20.3–100	67.0	20.3–100	70.7	23.9–100
RDI of irinotecan (%)	60.6	31.1–100	51.9	31.1–100	64.6	44.1–100
RDI of ramucirumab (%)	74.4	24.0–100	75.0	31.1–100	73.4	24.0–100

RDI relative dose intensity

(ORR) was 12%, and the disease control rate (DCR) was 58%. Second-line patients showed ORR of 19% and DCR of 73%, while third or later-line patients showed worse results, 0% and 35%, respectively.

Reasons for discontinuation of ramucirumab plus FOLFIRI included progressive disease in 37 patients and AEs in two. Subsequent chemotherapy was administered to 15 patients (58%) in second-line and 13 (76%) patients in third or later-line, including trifluridine/tipiracil (TFTD) plus bevacizumab (nine patients), TFTD (eight patients), regorafenib (seven patients), irinotecan plus panitumumab (five patients) and so on.

Safety

Various hematological and non-hematological toxicities were observed (Table 4). Severe hematological toxicities of grade 3 or worse were observed in 21 patients, and non-hematological toxicities of grade 3 or worse were observed in 12 patients. Severe adverse events (SAEs) defined as AEs requiring extra hospitalization or prolongation of admission were seen in six patients. Grade 1 or 2 hypertension and grade 3 or worse proteinuria, related to the antiangiogenic agent, were observed more frequently than in the RAISE study. The incidence of SAEs was not significantly different between second-line and third or later-line patients (11.5% and 17.7%, respectively, $p=0.67$). Severe hematological toxicities of grade 3 or worse were not frequently seen in those who were treated as third or later-line either (57.7% and 35.3%, respectively, $p=0.22$). Hence, later-line patients were safely treated with ramucirumab plus FOLFIRI. As previously described, dose modification and treatment delay were performed due to adverse events in 28 patients, the major reason for which was neutropenia (20 patients).

Efficacy and safety analyses according to RDI

Since median RDI of irinotecan was 60.6%, the efficacy and safety were compared between two groups, patients with RDI of 60% or higher (RDI-high group; 23 patients) and patients with RDI of less than 60% (RDI-low group; 20 patients). The mPFS of the RDI-high group and RDI-low group was 3.2 (95% CI 1.9–4.5 months) months and 5.7 (95% CI 3.5–8.0) months, respectively (HR 2.7, 95% CI 1.4–5.4, $p=0.004$) (Fig. 2a). The mOS of each group was 18.5 (95% CI 11.5–not reached) months and 14.4 months (95% CI 0.3–22.4), respectively (Fig. 2b). The RDI-low group suffered from severe hematological toxicity more frequently (RDI-low group; 75%, RDI-high group; 26%, $p=0.002$). Initial dose reduction which may lead to reduced RDI did not affect PFS (initial dose reduction group; 5.2 months, none initial dose reduction group; 5.8 months, $p=0.39$) or OS (initial dose reduction group; 14.4 months, none initial dose reduction group; 18.5 months, $p=0.28$) either.

Specific interest

Patient subgroups based on the baseline serum concentration of CEA showed no differences in PFS ($p=0.17$), but mOS was longer in lower CEA group (22.4 months versus 11.47 months, hazard ratio = 0.26, $p=0.005$). In the

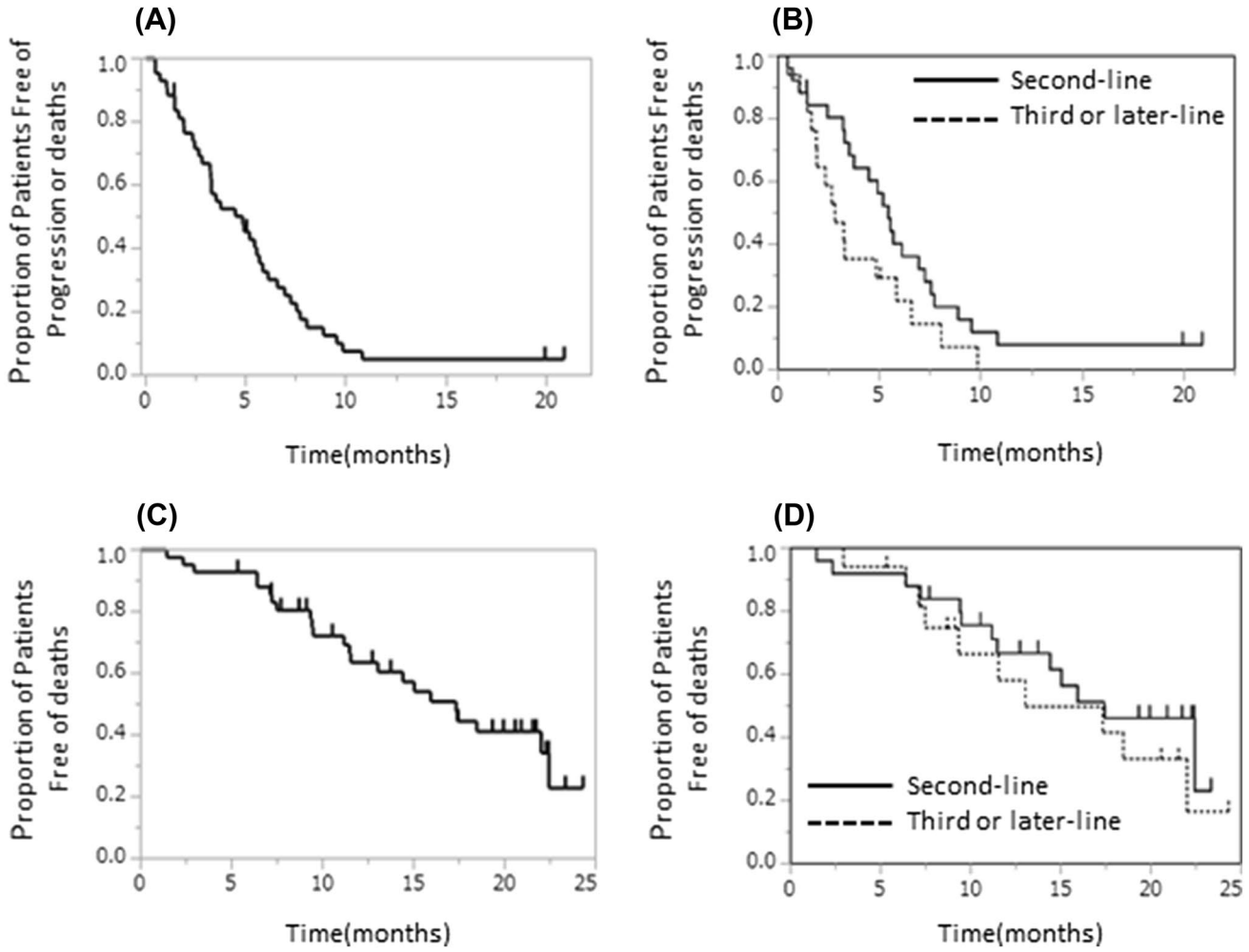

Fig. 1 Kaplan–Meier curves of progression free survival in all patients (**a**) and patients treated as second-line and third or later-line (**b**). Kaplan–Meier curves of overall survival in all patients (**c**) and patients treated as second-line and third or later-line (**d**). Solid lines indicate second-line group and the dotted lines indicate third or later-line group

Table 3 Best objective response of patients treated with ramucirumab plus FOLFIRI

	All patients	Second-line patients	Third or later-line patients
Number of patients	43	26	17
Efficacy			
CR	1	1	0
PR	4	4	0
SD	20	14	6
PD	17	6	11
NE	1	1	0
ORR	12%	19%	0%
DCR	58%	73%	35%

CR complete response, *PR* partial response, *SD* stable disease, *PD* progressive disease, *NE* not evaluable, *ORR* overall response rate, *DCR* disease control rate

subgroups defined by baseline ANC, patients with lower ANC had longer mOS (17.4 months versus 6.4 months, hazard ratio = 0.26, $p = 0.003$), but PFS was not significantly different between both groups.

Discussion

This study demonstrated that ramucirumab plus FOLFIRI for MCRC patients was associated with mPFS of 4.8 months, mOS of 17.3 months, and DCR of 58% in clinical practice in Japan. In the patients treated in second-line, mPFS was 5.43 months, which was equivalent to the RAISE study. Because differences between patient backgrounds in the RAISE study and in the present retrospective study exist, careful consideration should be paid. The median RDIs of irinotecan in the RAISE study were reported to be 77.0% in the ramucirumab plus FOLFIRI arm and 85.9% in the placebo plus FOLFIRI

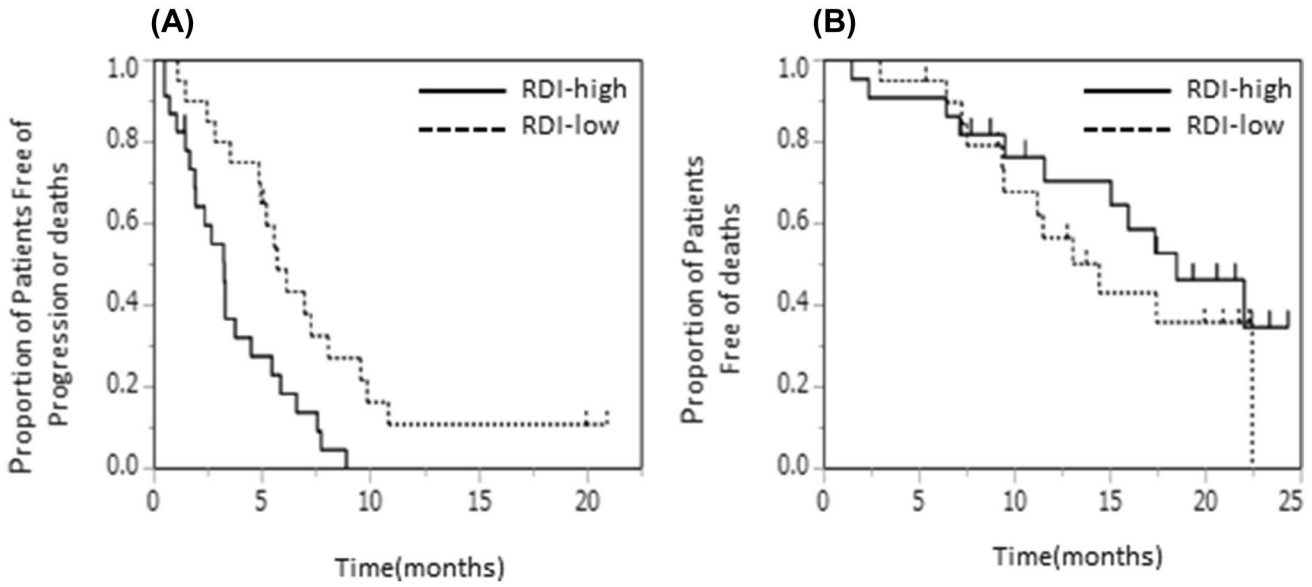

Fig. 2 Kaplan–Meier curves of progression-free survival (**a**) and overall survival (**b**) according to relative dose intensity (RDI) of irinotecan. Solid line indicates the RDI-high group (RDI of 60% or higher), and the dotted line indicates the RDI-low group (RDI less than 60%)

Table 4 Adverse events of patients with all patients and subgroup analyses

Adverse event	All patients *n* (%) *n* = 43		Second-line patients *n* (%) *n* = 26		Third or later-line patients *n* (%) *n* = 17	
	All grade	Grade 3/4	All grade	Grade 3/4	All grade	Grade 3/4
Hematological						
Neutropenia	28 (65)	20 (47)	18 (70)	14 (54)	10 (59)	6 (35)
Anemia	13 (30)	2 (5)	7 (27)	2 (8)	6 (35)	0 (0)
Thrombocytopenia	15 (35)	1 (2)	9 (35)	1 (4)	6 (35)	0 (0)
Non-hematological						
Stomatitis	7 (16)	0 (0)	4 (15)	0 (0)	3 (18)	0 (0)
Diarrhea	11 (26)	0 (0)	9 (35)	0 (0)	2 (12)	0 (0)
Nausea	7 (16)	1 (2)	4 (15)	1 (4)	3 (18)	0 (0)
Anorexia	12 (28)	2 (5)	6 (23)	2 (8)	6 (35)	0 (0)
Fatigue	12 (28)	0 (0)	6 (23)	0 (0)	6 (35)	0 (0)
Febrile neutropenia	3 (7)	3 (7)	1 (4)	1 (4)	2 (12)	2 (12)
Adverse events-related ramucirumab						
Hypertension	12 (28)	2 (5)	6 (23)	1 (4)	6 (35)	1 (6)
Proteinuria	13 (30)	6 (14)	8 (31)	2 (8)	5 (29)	4 (24)
Bleeding	9 (21)	0 (0)	4 (15)	0 (0)	5 (29)	0 (0)
Thrombosis	1 (2)	0 (0)	1 (4)	0 (0)	0 (0)	0 (0)

arm, and other agents showed the same trends. The low RDI in the ramucirumab arm was due to the high frequency of dose modification and treatment delay caused by AEs. In the present study, the median RDI of irinotecan was 60.6% for all patients. To assess the influences of reduced RDI on efficacy and safety, we compared patients' subgroups divided by RDI of irinotecan. In first-line setting, a higher RDI of irinotecan had a significant positive impact on PFS and OS [11]. In this study, the RDI-low group had better PFS and OS was comparable. To clarify the reasons for the different trend of efficacy is difficult, but different treatment line may be a potential reason. From these observations, reduction of RDI might not cause a decrease of treatment efficacy of ramucirumab plus FOLFIRI.

Continuous use of bevacizumab in combination with standard second-line chemotherapy in MCRC patients progressing after standard first-line bevacizumab-based treatment is reported to be beneficial [12]. Aflibercept conferred a survival benefit to second-line patients regardless of prior exposure to bevacizumab in the phase 3 VELOUR study [13]. All patients in the RAISE study were previously treated with bevacizumab, and about 30% of patients were in the VELOUR study. These results suggest that sustained use of an antiangiogenic agent after progression of first-line bevacizumab-based treatment is effective. However, the approach to proper selection of these agents remains uncertain. Recently, a high serum concentration of VEGF-D was reported to potentially predict the efficacy of ramucirumab in second-line treatment [14], and aflibercept was reported to be more effective in patients who have *BRAF* V600E mutation [15]. Further study is needed to establish proper usage of antiangiogenic agents.

The anti-epithelial growth factor receptor antibody panitumumab combined with irinotecan showed mPFS of 5.5 months and mOS of 9.7 months for third or later-line treatment patients who were RAS-wild [16]. On the other hand, RAS-mutant patients have few therapeutic choices in later-line treatment. Aflibercept was reported to be beneficial not only in second-line, but also in third or later-line therapy, with mPFS of 4.3 months and mOS of 11.1 months for third-line and 3.4 months and 8.1 months for fourth-line therapy [17]. This is the first report to show the efficacy of ramucirumab for third or later-line patients, the mPFS and mOS of which was comparable to that of aflibercept used in third or later-line treatment. Though we need to select patients in good condition, the regimen can be an important treatment option for heavily treated MCRC patients.

In the basic research field, it is hypothesized that antiangiogenic agents not only disrupt tumor vessels, but also transiently normalize the abnormal structure and function of tumor vasculature to make it more efficient for oxygen and drug delivery [18]. Higher blood vessel permeability of abnormal tumor vasculature leads to increased pressure of the tumor stroma and, finally, insufficient drug permeability [19]. Taking these findings into account, continuous use of antiangiogenic agents may contribute to normalization of tumor vasculature, which keeps the tumor susceptible to cytotoxic agents. In addition, tumor endothelial cells, which express VEGFR-2 highly, contribute to the acquisition of drug resistance by upregulation of MDR1 [20]. Disrupting VEGFR-2-mediated signaling by ramucirumab may contribute to overcoming drug resistance and provide favorable treatment results.

Hematological toxicities such as neutropenia were more frequently observed in the present study than in the RAISE study. Disrupting VEGFR-2, which is expressed by hematopoietic stem cells, by ramucirumab may enhance hematological toxicities [21]. The lower RDI in the ramucirumab arm induced by hematological toxicities was a matter of concern and is expected to affect treatment efficacy, but the post hoc analysis showed that neutropenia during treatment and subsequent dose modifications did not compromise treatment efficacy [10].

Prior to the RAISE study, a phase 1b study was conducted in Japan [22]. In the study, severe neutropenia of grade 3 or worse was seen in five of six patients (83.3%) partly due to irinotecan dose of 180 mg/m^2. In this study, severe hematological toxicities that required dose modifications were observed in 15 (57.7%) second-line patients and 6 (35.3%) third or later-line patients. Despite this frequency, severe infection was not seen in the present study, since two febrile neutropenia patients recovered quickly. Taken together, ramucirumab plus FOLFIRI was safely administered by appropriate dose modification and treatment delay.

Notably, the frequency of antiangiogenic agent-related AEs such as proteinuria and hypertension were higher than in the RAISE study. The frequency was almost equal to that of the Japanese subset of the RAISE study, and Japanese patients were reported to be affected by hypertension or proteinuria caused by bevacizumab more often in some studies [23]. Genetic background factors may be related to this phenomenon. Hypertension was easily manageable by antihypertensive agents, but ramucirumab had to be completely withdrawn in one case due to nephrotic syndrome. Grade 3 or worse proteinuria was promptly reversed by cessation of ramucirumab, including the nephrotic syndrome patient. Proteinuria may occur frequently between ramucirumab plus FOLFIRI treatment, and urinalyses must be performed regularly so that ramucirumab can be stopped in cases of grade 1 or 2 proteinuria.

A post hoc analysis of the RAISE study reported that baseline CEA and ANC are correlated with survival [9, 10]. High baseline CEA was associated with poor prognosis of MCRC patients who received bevacizumab-contained therapy [24]. High number of ANC was also associated with poor survival of MCRC patients who underwent surgery [25] and patients given bevacizumab plus FOLFIRI as second-line treatment showed same trend as the RAISE study [10]. Following these reports, we analyzed PFS and OS in terms of subgroups defined by CEA and ANC in this study. Interestingly, lower CEA patients and lower ANC patients showed longer OS than each counter patient group, which were similar to the results of the RAISE study. Hence, CEA and ANC are suggested to be useful to predict prognosis of MCRC patients treated with ramucirumab plus FOLFIRI in clinical practice. Although the present study has retrospective nature and employed only limited number of MCRC patients, we thought that similar results obtained in these subgroup analyses to the previous phase 3 study might be helpful to understand clinical course of MCRC.

The results of the present study show that ramucirumab plus FOLFIRI is an effective and safe treatment option for both second-line and third or later-line patients. Especially in second-line patients, a low RDI due to dose modification due to AEs did not compromise treatment efficacy.

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Compliance with ethical standards

Conflict of interest Akitaka Makiyama have received a speaker honorarium from Eli Lilly. Taito Esaki has received a speaker honorarium from Daiichi Sankyo and Eli Lilly and has received research grants from Daiichi Sankyo. Koichi Akashi has received speaker honorarium from Kyowa Hakko Kirin. Koichi Akashi has received research grants from Kyowa Hakko Kirin, Yakult, Eli Lilly and Daiichi Sankyo. Eishi Baba has received a speaker honorarium and research grants from Eli Lilly. The other authors have no conflict of interest.

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