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ORIGINAL ARTICLE

Impact of prior bevacizumab therapy on the incidence of ramucirumab-induced proteinuria in colorectal cancer: a multi-institutional cohort study

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Abstract

Background The association between prior bevacizumab (BEV) therapy and ramucirumab (RAM)-induced proteinuria is not known. We aimed to investigate this association in patients with metastatic colorectal cancer (mCRC).

Methods mCRC patients who received folinic acid, fluorouracil, and irinotecan (FOLFIRI) plus RAM were divided into with and without prior BEV treatment groups. The cumulative incidence of grade 2–3 proteinuria and rate of RAM discontinuation within 6 months (6M) after RAM initiation were compared between the two groups.

Results We evaluated 245 patients. In the Fine-Gray subdistribution hazard model including prior BEV, age, sex, comorbidities, eGFR, proteinuria ≥ 2 + at baseline, and later line of RAM, prior BEV treatment contributed to proteinuria onset ($P < 0.01$). A shorter interval between final BEV and initial RAM increased the proteinuria risk; the adjusted odds ratios (95% confidence intervals) for the intervals of < 28 days, 28–55 days, and > 55 days (referring to prior BEV absence) were 2.60 (1.23–5.51), 1.51 (1.01–2.27), and 1.04 (0.76–1.44), respectively. The rate of RAM discontinuation for ≤ 6M due to anti-VEGF toxicities was significantly higher in the prior BEV treatment group compared with that in the no prior BEV treatment group (18% vs. 6%, $P = 0.02$). Second-line RAM discontinuation for ≤ 6M without progression resulted in shorter overall survival of 132 patients with prior BEV treatment ($P < 0.01$).

Conclusion Sequential FOLFIRI plus RAM after BEV failure, especially within 55 days, may exacerbate proteinuria. Its escalated anti-VEGF toxicity may negatively impact the overall survival.

Keywords Ramucirumab · Bevacizumab · Proteinuria · Colorectal cancer · FOLFIRI

Introduction

Colorectal cancer (CRC) is the second leading cause of cancer-related deaths worldwide, and the 5-year relative survival rate of patients with metastatic disease is 15% [1, 2]. In the past two decades, remarkable progress has been made in the treatment of metastatic colorectal cancer (mCRC) using more effective agents, such as fluoropyrimidines, oxaliplatin, irinotecan, anti-vascular endothelial growth factor (VEGF) biologics, and anti-epidermal growth factor receptor monoclonal antibodies. In recent years, precision medicine has progressed further: encorafenib, binimetinib, and cetuximab for BRAF V600E-mutated CRC [3]; pertuzumab plus trastuzumab for HER2-amplified CRC [4]; and immunotherapy for deficient DNA mismatch repair CRC [5–7].

With regard to the anti-VEGF biologics used in treating mCRC, the anti-VEGF-A antibody bevacizumab (BEV), anti-VEGF receptor 2 (VEGFR2) antibody ramucirumab (RAM), and VEGF-trap aflibercept are available. In patients

Extended author information available on the last page of the article

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who receive oxaliplatin-based chemotherapy as first-line treatment, the three biologics are equally recommended in combination with fluorouracil and leucovorin plus irinotecan (FOLFIRI) as second-line treatment [8–10]. Nephrotoxicity is a well-known toxicity associated with the therapeutic inhibition of VEGF signaling, which is critical to the glomerular development and the maintenance of mature glomerular function during homeostasis and disease occurrence in the kidney [11]. The main clinical manifestation of nephrotoxicity is proteinuria, which sometimes results in nephrotic syndrome and renal-specific thrombotic microangiopathy (TMA) [11].

In terms of RAM-induced proteinuria, a previous meta-analysis of individual patient safety data from six randomized, placebo-controlled trials showed that patients with mCRC examined in the RAISE study were most likely to develop grade ≥ 3 proteinuria: the number need to harm (NNH) for grade ≥ 3 proteinuria was 1 in 35 patients [12]. Interestingly, previous case reports of nephrotic syndrome/glomerular microangiopathy associated with RAM showed that its onset was observed immediately after RAM initiation in patients who received prior BEV therapy [13–16]. In the abovementioned RAISE study, patients with mCRC who received BEV ≤ 28 days before randomization were considered ineligible [17]. Patients with mCRC will administered with anti-VEGF biologics during the period between first- and second-line chemotherapy owing to the overall survival (OS) benefit of sequential anti-VEGF biologics after receiving first-line BEV treatment [17–19]. Therefore, a safer treatment strategy for patients with mCRC receiving second-line RAM needs to be developed. Hence, this study aimed to investigate the impact of prior BEV on the incidence of RAM-induced proteinuria in patients with mCRC receiving FOLFIRI plus RAM.

Patients and methods

This retrospective, nineteen-institutional cohort study was conducted in patients with mCRC who received FOLFIRI plus RAM after first-line chemotherapy between June 1, 2015, and November 29, 2020, in Japan. Eligible patients were divided into two cohorts according to the status of prior BEV therapy. The exclusion criteria were as follows: (1) Patients who were previously treated with multi-kinase inhibitors, (2) post-transplant patients, (3) patients who died within 1 month after FOLFIRI plus RAM initiation, (4) patients with nephrotic syndrome as comorbidity, (5) patients who did not undergo dipstick proteinuria test at RAM initiation (baseline), and (6) patients who had a dipstick proteinuria score of 4 + at baseline. The primary endpoints were the cumulative incidence of grade 2–3 proteinuria (grade 2: dipstick proteinuria 2 + or 3 +; grade 3: dipstick proteinuria 4 +) and worst random spot urine protein/creatinine (UPC) ratio between the two groups. The observation period for changes in proteinuria was set at 6 months after RAM initiation or the days of final RAM treatment plus 56 days (approximately 4 half-lives of RAM [20]), whichever came first. In patients with proteinuria at baseline, the outcome was considered in those with worsened proteinuria. The secondary endpoints were the incidence of UPC ratio of ≥ 3 and percentage of RAM discontinuation within 6 months between the two groups. We also investigated the percentage of eligible patients with kidney biopsy and biopsy-proven TMA. To evaluate the disadvantage of RAM discontinuation without progressive disease in patients with or without prior BEV, stratified OS was compared between patients with second-line RAM discontinuation within 6 months and those without discontinuation. In the time-to-event analysis, patients without grade 2–3 proteinuria or death were censored at their last patient record or at the end of the follow-up period (May 31, 2021), whichever occurred first.

Statistical analysis

Binary outcomes were compared using Fisher's exact test, whereas continuous outcomes were compared using the unpaired Student's *t* test or Mann–Whitney *U* test, as appropriate. For the primary endpoint analysis, the cumulative incidence of grade 2–3 proteinuria, accounting for death as a competing event between the two groups, was compared using Gray's test. The Fine-Gray subdistribution hazard model was used to determine the cumulative incidence of grade 2–3 proteinuria in the multivariable analysis. The possible confounders were chosen to determine their potential association with grade 2–3 proteinuria onset based on the status of prior BEV, age (per 10 years), sex, eGFR at baseline (per 10 mL/min), comorbidities at baseline (diabetes and hypertension), dipstick proteinuria score of ≥ 2 + at baseline, and later (≥ 3) lines of FOLFIRI plus RAM. To evaluate the impact of the interval between the final BEV and initial RAM on grade 2–3 proteinuria onset, a logistic regression model was used to determine the adjusted odds ratio (OR), which referred to the absence of prior BEV. The intervals were divided into three categories: < 28 days, 28–55 days, and > 55 days. These intervals were based on the following concepts: an interval of ≤ 28 days was excluded from the RAISE study [17], the National Comprehensive Cancer Network guidelines recommended an interval of at least 6 weeks between the final BEV and any elective surgery [21], and a certain interval was selected as it can be easily integrated in clinical practice.

With regard to the OS between patients with second-line RAM discontinuation within 6 months and those without RAM discontinuation, we estimated the Kaplan–Meier

Table 1 Characteristics at ramucirumab initiation between patients with prior bevacizumab treatment and those without prior bevacizumab treatment

Variables	Prior bevacizumab		*P* value
	Absent *N* = 64	Present *N* = 181	
Median age [range]—yr	68 [58–72]	68 [59–73]	0.91
Male sex—no. (%)	38 (59.4)	93 (51.4)	0.31
ECOG PS—no. (%)			
0 or 1	46 (71.9)	119 (65.7)	0.75
2, 3, or 4	3 (4.7)	11 (6.1)	
Missing	15 (23.4)	51 (28.2)	
Median eGFR [range]—mL/min/1.73m^2	65.7 [54.1–76.7]	63.8 [50.2–81.2]	0.58
Median diastolic BP [range]—mmHg	76 [68–81]	77 [68–86]	0.40
Median systolic BP [range]—mmHg	127 [118–136]	128 [116–140]	0.98
Right-sided tumors—no. (%)	9 (14.1)	53 (29.6)	0.02
BRAF V600E—no. (%)			
Mutated	1 (1.6)	7 (3.9)	0.14
Not tested	29 (45.3)	103 (56.9)	
RAS mutated—no. (%)	5 (7.8)	135 (74.6)	< 0.001
Median CEA [range]—ng/mL*	12.5 [6.8–53.6]	28.1 [9.3–171.0]	0.06
Dipstick proteinuria score of ≥ 2 + —no. (%)	2 (3.1)	21 (11.6)	0.05
Hypertension—no. (%)	23 (35.9)	101 (55.8)	0.01
Diabetes—no. (%)	13 (20.3)	21 (11.6)	0.09
Hyperlipidemia—no. (%)	14 (21.9)	31 (17.1)	0.45
Calcium channel blocker—no. (%)			
Concomitant	16 (25.0)	69 (38.1)	0.21
Missing	4 (6.2)	9 (5.0)	
Renin-angiotensin system inhibitors—no. (%)			
Concomitant	13 (20.3)	49 (27.1)	0.28
Missing	5 (7.8)	7 (3.9)	
Details of previous treatment—no. (%)			
FOLFOXIRI based	6 (9.4)	14 (7.7)	< 0.01
Irinotecan based	12 (18.8)	30 (16.6)	
Oxaliplatin based	31 (48.4)	127 (70.2)	
Others†	15 (23.4)	10 (5.5)	
Prior anti-EGFR antibody—no. (%)	50 (78.1)	0 (0.0)	< 0.001
Later (> 2)-line of FOLFIRI + ramucirumab—no. (%)	26 (40.6)	49 (27.1)	0.06
Median line of FOLFIRI + ramucirumab [range]	2 [2– 3]	2 [2–3]	0.06
Median duration of bevacizumab administration [range]—day	0 [0–0]	204 [84–379]	< 0.001
Median ramucirumab dosage [range]—mg/kg	8.0 [7.9–8.0]	8.0 [7.9–8.0]	0.28

*Data on the CEA levels were missing in 2 of 64 patients without prior bevacizumab treatment and in 8 of 181 patients with prior bevacizumab treatment

†Other regimens included panitumumab monotherapy, capecitabine, trifluridine/tipiracil, and fluorouracil plus leucovorin

ECOG PS Eastern Cooperative Oncology Group Performance Status Scale, *BP* blood pressure, *CEA* carcinoembryonic antigen, *FOLFOXIRI* fluorouracil, leucovorin, oxaliplatin, and irinotecan, *FOLFIRI* fluorouracil, leucovorin, and irinotecan

curves and used the stratified log-rank test according to the status of prior BEV. All statistical analyses were performed using EZR version 1.55 (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface of R (The R Foundation for Statistical Computing, Vienna, Austria). EZR is a modified version of R commander designed to add statistical functions frequently used in biostatistics [22]. Statistical significance was set at a p value of < 0.05.

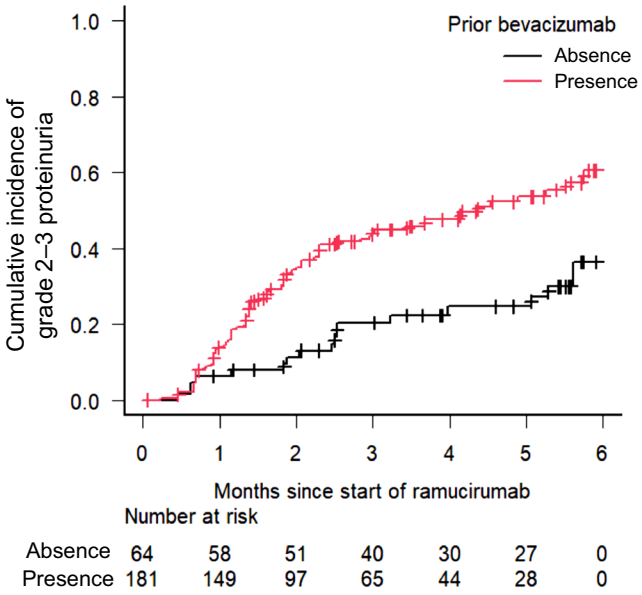

Fig. 1 Cumulative incidence of grade 2–3 proteinuria between the two groups. The cumulative incidence of grade 2–3 proteinuria was significantly higher in patients with prior BEV treatment ($P < 0.001$, Gray's test). Death as a competing risk event within 6 months was observed in 12 patients (nine with prior BEV treatment and three without prior BEV treatment). *BEV* bevacizumab

Ethical considerations and reporting guideline

This study was performed in accordance with the Declaration of Helsinki and its amendments, and the study protocol was approved by the Ethics Committee of each institution. Patients were allowed to opt out of this study at any time and were informed through the hospital website or onsite. This study was reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [23].

Results

Patient's characteristics

Two-hundred and fifty-three patients from 19 institutions met the inclusion criteria. Eight patients who did not undergo urinalysis after RAM initiation and whose BEV treatment period was unknown because of hospital transfer due to the coronavirus disease 2019 pandemic were excluded. Finally, 245 patients were assigned to two cohorts according to the absence ($n = 64$) or presence ($n = 181$) of prior BEV therapy. The patient's baseline characteristics are shown in Table 1. Right-sided and RAS-mutated tumors were more frequent in patients with prior BEV treatment. Hypertension and dipstick proteinuria score of ≥ 2 + were also frequent in patients with prior BEV. With regard to the chemotherapy status, the presence of prior anti-EGFR antibody and later treatment with FOLFIRI plus RAM were frequent in patients without prior BEV. The duration of prior BEV treatment was approximately 7 months.

Outcomes

During the follow-up period (median [interquartile range] follow-up days: absence of prior BEV treatment, 332 [204–448]; presence of prior BEV treatment, 250 [174–423]), the cumulative incidence of grade 2–3 proteinuria was significantly higher in patients with prior BEV treatment compared with that in patients without prior BEV treatment ($P < 0.001$) (Fig. 1). In the Fine-Gray subdistribution hazard model, the cumulative incidence of grade 2–3 proteinuria was only correlated with prior BEV treatment (sub-distribution hazard ratio [SHR]: 2.04, 95% confidence interval [CI]: 1.20–3.46, $P < 0.01$) (Table 2). Among the patients who had data on UPC ratio, the median (range) UPC ratio was significantly higher in patients with prior BEV treatment when compared with that in patients without prior BEV treatment:1.03 (0.08–10.2) vs. 0.27 (0.06–4.92),

Table 2 Multivariable analysis for cumulative incidence of grade 2–3 proteinuria using the Fine-Gray subdistribution hazard model

Variables	SHR	95% CI	*P* value
Age (per 10 year)	1.03	0.93–1.14	0.64
Female sex	1.47	0.99–2.18	0.06
eGFR at baseline (per 10 mL/min/1.73m^2)	0.90	0.80–1.03	0.12
Diabetes at baseline	1.05	0.54–2.02	0.90
Hypertension at baseline	1.21	0.79–1.86	0.38
Dipstick proteinuria score of ≥ 2 + at baseline	1.73	0.90–3.33	0.10
Later-line of FOLFIRI + ramucirumab (ref. second-line)	0.84	0.54–1.31	0.45
Prior bevacizumab (ref. absent)	2.04	1.20–3.46	< 0.01

FOLFIRI fluorouracil, leucovorin, and irinotecan, *ref* reference, *SHR* sub-distribution hazard ratio, *CI* confidence interval

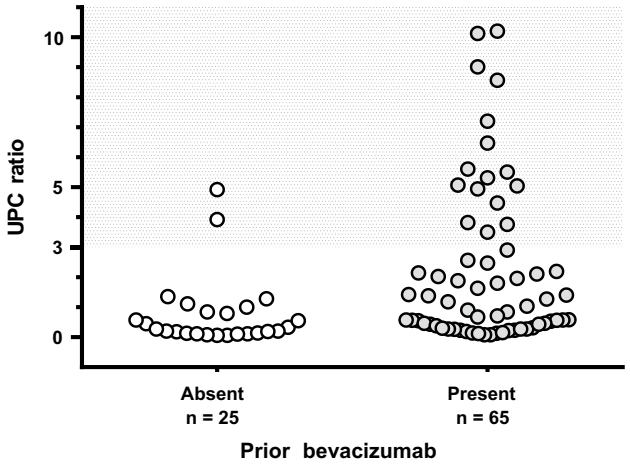

Fig. 2 Maximum UPC ratio between the two groups. Each plot represents the worst UPC ratio for each patient during the observation period. The shaded areas represent the level of permanent RAM discontinuation. *UPC* urine protein/creatinine, *RAM* ramucirumab

$P < 0.001$. Moreover, the percentage of patients with a UPC ratio of ≥ 3, which is the primary criterion for permanently discontinuing RAM, was higher in patients with prior BEV treatment than in those without BEV treatment (24.6% vs. 8.0%, $P = 0.14$) (Fig. 2). None of the patients underwent renal biopsy, although some patients, especially those with prior BEV treatment, had nephrotic-range proteinuria. Subsequently, the shorter interval between final BEV and initial RAM increased the incidence of grade 2–3 proteinuria (Table 3).

Then, we investigated the details of RAM therapy, including the treatment duration, the percentage of discontinuation within 6 months after initiation, and the reason for the difference between the two groups. Compared with patients without prior BEV treatment, a significantly shorter duration of RAM treatment and a higher RAM discontinuation rate were observed in patients with prior BEV treatment (Table 4). Interestingly, the RAM discontinuation rate due to anti-VEGF-related toxicities, such as proteinuria, bleeding, hypertension, and gastrointestinal perforation, was significantly higher in patients with prior BEV treatment than in those without prior BEV treatment (18% [32/181] vs. 6% [4/64], $P = 0.02$). Subsequently, stratified OS analysis was performed according to the status of prior BEV treatment among patients treated with second-line FOLFIRI plus RAM. RAM discontinuation not due to progressive disease

Table 3 Impact of the interval between final bevacizumab and initial ramucirumab on the onset of grade 2–3 proteinuria

Interval between final bevacizumab and initial ramucirumab	*N*	No. of event	Adjusted OR*	95% CI
Prior bevacizumab: absent	64	17 (26.6%)	Ref	
< 28 days	81	40 (49.4%)	2.60	1.23–5.51
28–55 days	64	32 (50.0%)	1.51	1.01–2.27
> 55 days	36	13 (36.1%)	1.04	0.76–1.44

*Covariates in the logistic regression model are as follows: age, sex, eGFR at baseline, diabetes at baseline, hypertension at baseline, and dipstick proteinuria score of ≥ 2 + at baseline

OR odds ratio, *CI* confidence interval, *ref* reference, *eGFR* estimated glomerular filtration rate

Table 4 Details of ramucirumab treatment between the two groups

	Prior bevacizumab		*P* value
	Absent *N* = 64	Present *N* = 181	
Median duration of ramucirumab administration [range]—day	149 [14–679]	80 [14–605]	< 0.001
Ramucirumab discontinuation within 6 months—no. (%)	41 (64.1%)	151 (83.4%)	< 0.01
Reasons—no. (%)			0.42
Best supportive care	3 (7.3)	19 (12.6)	
Progressive disease	26 (63.4)	77 (51.0)	
Bleeding	1 (2.4)	5 (3.3)	
Proteinuria	2 (4.9)	23 (15.2)	
Hypertension	1 (2.4)	2 (1.3)	
Gastrointestinal perforation	0 (0.0)	2 (1.3)	
Others	8 (19.5)	23 (15.2)	

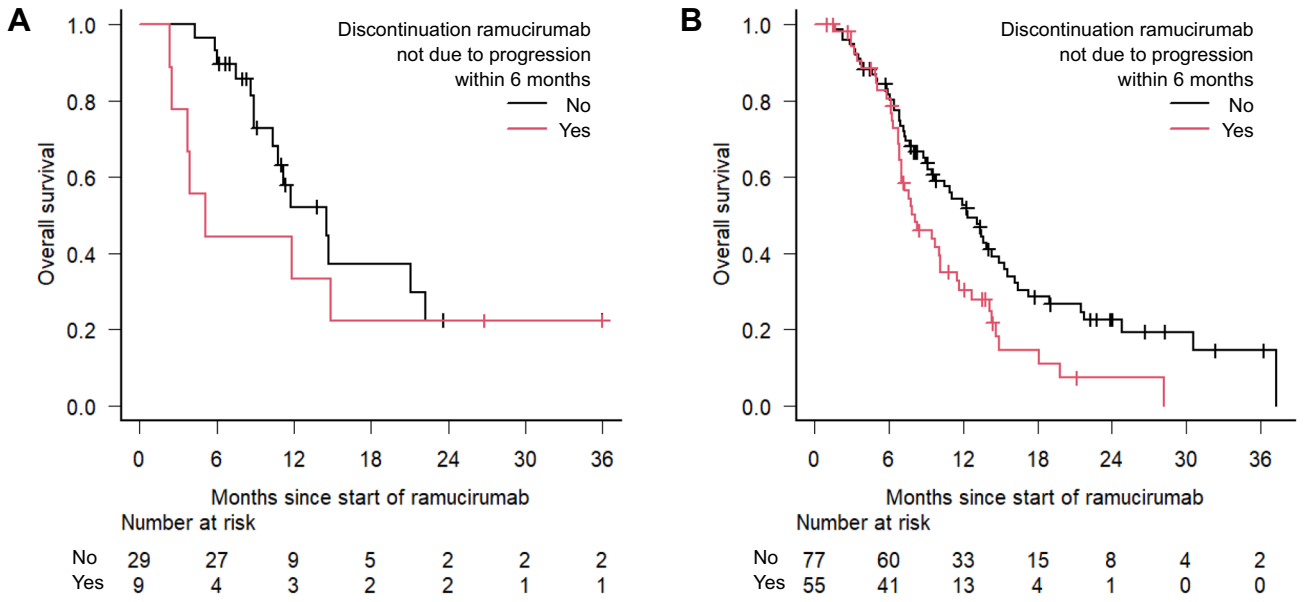

Fig. 3 Stratified analysis according to the absence (**A**) or presence (**B**) of prior bevacizumab treatment in patients treated with second-line FOLFIRI plus ramucirumab: the impact of ramucirumab discontinuation not due to progressive disease within 6 months on overall survival. Among the patients with no prior BEV treatment (**A**), the 1-year survival rates (95% CI) were 33.3% (7.8–62.3) in patients with RAM discontinuation not due to progression within 6 months and 52.1% (29.5–70.6) in those without RAM discontinuation ($P=0.29$ by log-rank test); among the patients with prior BEV treatment (**B**), the 1-year survival rates (95% CI) were 30.4% (18.0–43.7) in patients with RAM discontinuation not due to progression within 6 months and 52.7% (40.4–63.6) in those without RAM discontinuation ($P<0.01$ by log-rank test). *OS* overall survival, *CI* confidence interval, *BEV* bevacizumab, *RAM* ramucirumab

within 6 months had a survival disadvantage in both groups (Fig. 3).

Discussion

This study primarily aimed to determine whether sequential RAM after BEV treatment could exacerbate RAM-induced proteinuria in patients with mCRC receiving FOLFIRI plus RAM. The cumulative incidence of grade 2–3 proteinuria and the incidence of worst UPC ratio were significantly higher in patients with prior BEV treatment than in those without prior BEV treatment. Furthermore, a shorter interval between BEV and RAM exacerbated RAM-induced proteinuria; in particular, patients with an interval of < 28 days were at the greatest risk.

When administering sequential anti-VEGF agents after progression on first-line BEV, the following issues remains unresolved. Which strategy is the most appropriate: continuation of BEV after first-line BEV [19], sequential RAM after first-line BEV [17], or sequential AFL after first-line BEV? [18]. Two recent administrative claims database studies [24, 25] addressed this issue: among mCRC patients who failed first-line chemotherapy with fluoropyrimidines and oxaliplatin plus BEV [24], the time to treatment failure, defined as the time from initial second-line chemotherapy to treatment termination due to any cause or death, was significantly longer in the FOLFIRI plus BEV group compared with that in the FOLFIRI plus RAM (hazard ratio, 1.40; 95% CI, 1.26–1.56) and FOLFIRI plus AFL groups (hazard ratio, 1.34; 95% CI, 1.09–1.66). Among mCRC patients who were unresponsive to first-line FOLFOX plus anti-EGFR antibody [25], treatment durations of second-line irinotecan-based chemotherapy plus anti-VEGF agents were similar among the three groups (BEV, RAM, and AFL). As the duration of second-line chemotherapy concomitant with anti-VEGF agent could be affected by the presence or absence of prior BEV therapy, discontinuation of second-line anti-VEGF treatment may be due to the exacerbation of toxicities; RAM discontinuation due to the occurrence of anti-VEGF related toxicities, including proteinuria, within 6 months was likely to occur in patients who received sequential RAM after BEV. Another study also reported that the number of RAM toxicities increased in patients with advanced-stage hepatocellular carcinoma who received sequential RAM after BEV in combination with atezolizumab, compared with that reported in a pivotal phase III trial [26].

Then, with regard to the plausible mechanism of proteinuria exacerbation associated with sequential RAM after BEV, we focused on investigating the effects of dual anti-VEGF

blockades, such as VEGF-A (BEV) and VEGFR-2 (RAM). In this study, patients whose interval between final BEV and initial RAM was longer than 55 days were not at risk of developing grade 2–3 proteinuria compared with patients without prior BEV treatment. Considering that the estimated half-life of BEV is 20 days [27], the pharmacological effects of BEV and RAM could overlap if RAM is initiated prior to the completion of BEV elimination, which corresponds to four-to-five half-lives. Since the level of VEGF-A increased after BEV therapy [28], this physiological response may help maintain renal homeostasis and may be strongly inhibited by treatment with dual anti-VEGF blockade.

Second, the negative impact of RAM discontinuation, not due to progressive disease, on OS was observed in patients who received second-line FOLFIRI plus RAM, especially in patients with prior BEV treatment. Although some studies have reported an association between proteinuria/hypertension onset and good prognosis among patients treated with BEV [29, 30], the avoidance/minimization of toxicities leading to treatment discontinuation is crucial. Patients with prior BEV treatment had a higher likelihood of developing anti-VEGF toxicities leading to RAM discontinuation than those without BEV treatment. Considering that East Asian patients are at a high risk of RAM-induced grade ≥ 3 proteinuria compared with non-East Asian patients [31], the interval between final BEV and initial RAM should be longer than 55 days to avoid RAM-induced proteinuria, potentially leading to treatment discontinuation.

The limitations of this study were intrinsic to its retrospective design. For the analysis of proteinuria, the unmeasured confounders included other medications potentially decreasing proteinuria, the cumulative dose of BEV, and the time-varying covariate included hypertension and antihypertensives during RAM treatment; there may be discrepancies in the frequency of performing urinalysis in each institution. For the survival analysis, we were unable to perform a multivariable analysis of subsequent therapy and the biology of colorectal cancer owing to the exploratory nature of the analysis. Although we cannot fully exclude these limitations, the results obtained from 19 institutions in real-world practice could have high external validity.

Conclusion

In conclusion, this multi-institutional cohort study focusing on RAM-induced proteinuria among mCRC patients receiving FOLFIRI plus RAM provides additional information on the high-risk population, that is, the presence of prior BEV and the interval between final BEV and initial RAM within 55 days. Clinicians should pay attention to the timing of providing sequential RAM after BEV. In the future, an optimal sequence of anti-VEGF agents should be developed throughout the course of first- and second-line chemotherapy to avoid the development of proteinuria leading to treatment discontinuation in patients with mCRC receiving FOLFIRI plus anti-VEGF agents.

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Declarations

Conflict of interest The authors have no conflicts of interest to declare.

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