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ORIGINAL ARTICLE

Second-line FOLFIRI plus ramucirumab with or without prior bevacizumab for patients with metastatic colorectal cancer

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Abstract

Purpose Few data of folinic acid, fluorouracil, and irinotecan (FOLFIRI) plus ramucirumab (RAM) obtained in bevacizumab-naïve patients in clinical trials or routine clinical practice are available. The purpose of this retrospective study was to report the results of FOLFIRI plus RAM treatment as second-line chemotherapy for metastatic colorectal cancer (mCRC).

Methods Seventy-four patients with mCRC who received second-line FOLFIRI + RAM mCRC therapy were stratified by previous first-line therapy to groups that had (PB) or had not (NPB) been given bevacizumab. The overall survival (OS), progression-free survival (PFS), and objective response were evaluated.

Results The overall median PFS was 6.2 months (95% CI 4.6–9.3) and median OS was 17.0 months (95% CI 11.6–NA). Median PFS was 8.0 months (95% CI 4.9–11.2) in NPB patients and 5.0 months (95% CI 3.1–7.3) in PB patients (hazard ratio = 0.72, 95% CI 0.40–1.30, $p = 0.28$). The response rates were 23% and 3% in NPB and PB patients, respectively. The disease control rates were 85% and 69% in NPB and PB patients, respectively.

Conclusions The effectiveness of FOLFIRI + RAM as a second-line chemotherapy in patients with mCRC was in line with that reported in the previous RAISE phase III trial. The response was better in bevacizumab-naïve patients than those with first-line treatment that had included bevacizumab.

Keywords Anti-VEGF · RAM · Bevacizumab-naïve · EGFR · Colorectal cancer

Introduction

Colorectal cancer is responsible for approximately 880,000 deaths worldwide, making it the second leading cause of cancer-related deaths [1]. Despite recent therapeutic advances, the prognosis remains poor, especially in patients with advanced clinical disease [2]. The first-line treatment of metastatic colorectal cancer (mCRC) includes triplet combination therapy which includes both oxaliplatin and irinotecan or doublet combination therapy which includes oxaliplatin or irinotecan with cytotoxic agents plus bevacizumab (BEV) [3–8]. Doublet combination of cytotoxic agents plus an anti-epidermal growth factor receptor (anti-EGFR) antibody (cetuximab/panitumumab) is recommended for RAS wild-type [9–14] mCRC [15, 16]. If the first-line treatment includes combination therapy with fluoropyrimidine and oxaliplatin, then 5-fluorouracil (5-FU) and irinotecan (FOLFIRI) plus an anti-vascular endothelial growth factor (anti-VEGF) antibody or an (anti-EGFR) antibody (cetuximab/panitumumab) are recommended as second-line chemotherapy [15–17].

Ramucirumab (RAM) is a complete human IgG1 monoclonal antibody that binds to VEGF receptor-2 [18]. In RAISE phase III trial, over 1000 patients were randomized to FOLFIRI + RAM or FOLFIRI + placebo, and the addition of RAM to FOLFIRI lead to improve OS for the patients

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with mCRC previously treated with bevacizumab, oxaliplatin and fluoropyrimidine [19]. The median overall survival (OS) was 13.3 months with FOLFIRI-RAM and 11.7 months with FOLFIRI + placebo. Progression-free survival (PFS) was 5.7 months with FOLFIRI–RAM and 4.5 months with FOLFIRI + placebo. Whether the results of the RAISE trial can be generalized to clinical practice evidence remains to be unclear.

The efficacies of regimens with anti-VEGF antibodies combined with fluoropyrimidine-based doublet cytotoxic agents as a second-line chemotherapy for mCRC have been described for RAM, bevacizumab (BEV) and aflibercept (AFL). The efficacy of BEV and AFL regimens were validated in the E3200 trial of folinic acid, fluorouracil, oxaliplatin (FOLFOX) + BEV [3], the EAGLE trial of FOLFIRI + BEV [20], the ML18147 trial of FOLFIRI + BEV [21], and the VELOUR trial of FOLFIRI + AFL [22] These four phase III trials support the adoption of these regimens as standard of second-line chemotherapy for mCRC. The percentages of patients with prior exposure to BEV-containing first-line treatment were 0% (0/577 pts) in the E3200 trial, 100% (369/369 pts) in the EAGLE trial, 100% (819/819 pts) in the ML18147 trial, 100% (1072/1072 pts) in the RAISE trial, and 30.4% (373/1226) in the VELOUR trial. There has been almost no prospective evidence of FOLFIRI + RAM for second-line mCRC chemotherapy in patients without prior BEV. This retrospective study reports the results of FOLFIRI + RAM treatment as second-line chemotherapy for mCRC in clinical practice in our institution as used in patients with or without prior BEV exposure.

Materials and methods

Patients

This retrospective single-center cohort study included 74 patients with FOLFIRI + RAM treatment for mCRC as a second-line chemotherapy between September 15, 2016 and May 5, 2018 at the Cancer Institute Hospital of the Japanese Foundation for Cancer Research. Clinical characteristics including patient background, laboratory and imaging data, toxicities, and prognosis were collected retrospectively, and follow-up ended on August 31, 2018.

Treatment

FOLFIRI + RAM was given intravenously every 2 weeks and consisted of ramucirumab 8 mg/kg over 1 h, folinic acid 400 mg/m^2 over 2 h, and irinotecan 150 mg/m^2 over 150 min on day 1, followed by bolus fluorouracil 400 mg/m^2 on day 1; next, continuous fluorouracil 2400 mg/m^2 over 46 h on days 1–3. Dose reduction or interruption was performed based on the institutional standards of clinical practice. Adverse events (AEs) were graded by the Common Terminology Criteria for Adverse Events, version 4.0 [23]. Objective responses were evaluated using the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [24]. Imaging evaluation, mainly by computed tomography, was performed every 2 months following a standard institutional practice, which corresponded to once every four treatment cycles.

Statistical analysis and endpoints

R Statistics (The *R* Project for Statistical Computing, https://www.r-project.org) was used for the statistical analysis [25]. Differences in patients without prior exposure to BEV (NPB) and those with prior exposure to BEV (PB) and the differences among other subgroups were evaluated for significance. PFS was the time from the start of FOLFIRI + RAM treatment to the date of disease progression, and OS was the time from the start of FOLFIRI + RAM treatment to the date of death. Cumulative survival was estimated by the Kaplan–Meier method and Cox proportional hazard regression. The response rate (RR) was calculated as the proportion of patients with complete response (CR) plus partial response (PR). Disease control rate was calculated as the proportion of sum of RR plus stable disease (SD). If the RECIST evaluation differed from the judgment of the attending physician, then the latter were included in the evaluation. Multivariate analysis and a Cox proportional hazard model were used to estimate the differences in each explanatory variable. $P < 0.05$ was considered significant. The occurrence of AEs during the first two cycles after starting FOLFIRI + RAM were collected retrospectively and included neutropenia, hypertension, proteinuria, thrombosis, and gastrointestinal perforation. These AEs were concerned to be associated with RAM treatment.

Results

Patient characteristics

Eighty patients with FOLFIRI + RAM treatment for mCRC were reviewed. Six were excluded because of lack of early follow-up after starting FOLFIRI + RAM or receiving FOLFIRI + RAM that was not regarded as second-line therapy. FOLFIRI + RAM administered after early recurrence following oxaliplatin-containing treatment was considered as second-line. Thirty-nine received first-line chemotherapy without BEV (NPB); 35 received first-line treatment including BEV (PB, Fig. 1). The patient and tumor of the 74 patients included in both study groups are shown in Table 1. The median age was 63 (range 31–82) years, 39 (53%) patients

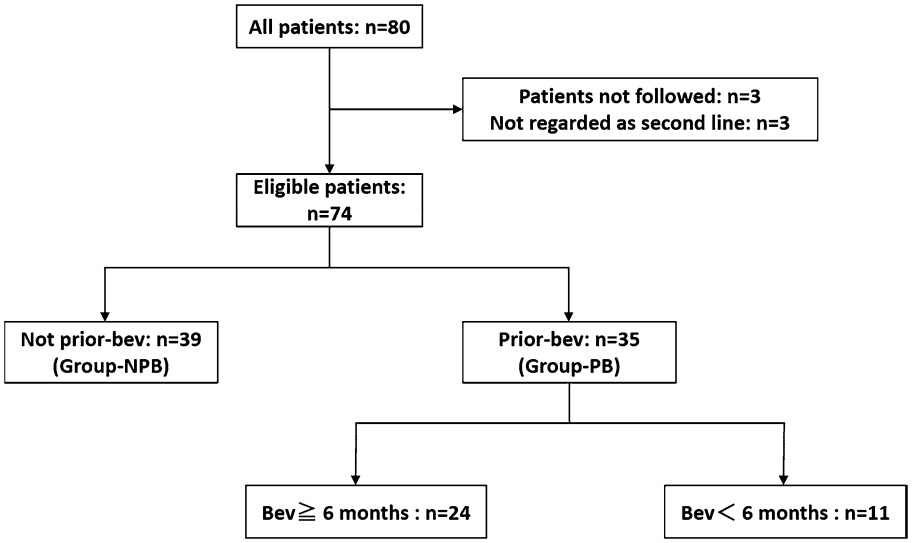

Fig. 1 Flow diagram of patient selection and analysis sorted by usage of BEV

were women, 35 (47%) were ECOG performance status 0 and 16 (22%) pts were performance status 1. Twenty-five patients (34%) had right-side, cecum–transverse colon primary tumors, 31 (42%) had RAS mutations, and 18 (24%) had 3 or more metastatic sites. The median ages and range and male:female ratio, CEA levels, tumor location, and the number of metastatic sites in the two groups were similar. Nine NPB patients (23%) and 22 PB patients (63%) had RAS mutations (KRAS exon 2–4 or NRAS exon 2–4). Eight NPB patients (21%) had received adjuvant chemotherapy; 22 (56%) had had received only palliative systemic chemotherapy. None of the PB patients had received adjuvant chemotherapy; 30 (86%) had received only systemic chemotherapy. Twenty-four patients (69%) had received BEV for more than 6 months. Twenty-five NPB patients (64%) had received anti-EGFR antibody (cetuximab or panitumumab).

Survival

The overall median follow-up was 8.9 (range 1.0–23.4) months, 10.6 (range 3.7–23.4 months) in NPB patients, and 7.0 (range 1.0–16.8 months) in PB patients. Overall median PFS was 6.2 months (95% CI 4.6–9.3) and overall median OS was 17.0 months (95% CI 11.6–NA) (Fig. 2). The median PFS was 8.0 months (95% CI 4.9–11.2) in NPB and 5.0 months (95% CI 3.1–7.3 months) in PB patients (HR = 0.72, 95% CI 0.40–1.30; $p = 0.28$; Fig. 3). Median PFS was significantly better in patients with left-side than with right-side tumors (8.0 months vs. 4.0 months; HR = 0.40 95% CI 0.22–0.74, $p = 0.0026$; Supplemental Fig. 1). The difference was also observed in the multivariate analysis of PFS (Supplemental Table 1). The evaluation of PFS including previous BEV exposure and tumor location is shown in Fig. 4. NPB patients with left-side tumors had the best of prognosis of the four cohorts. PB patients with right-side tumors had the worst prognosis (HR = 0.76, 95% CI 0.59–0.98; $p = 0.037$). The PFS of PB patients with more than 6 M of BEV was significantly better than that of those with BEV of less than 6 M (median 7.3 vs. 3.6 months; HR = 0.24, 95% CI 0.087–0.66, $p = 0.0059$; Supplemental Fig. 2).

Tumor response

The clinical responses of NPB and PB patients are shown in Table 2. There were no CRs in either NPB or PB patients. NPB patients had significantly better clinical responses than PB patients ($p = 0.0286$). PRs were achieved in nine NPB patients (23%) and in one PB patient (3%). SD was seen in 24 NPB patients (62%) and 23 PB (66%) patients. Six NPB patients (15%) and 10 PB patients (29%) had PD, and more NPB patients (21 of 39, 54%) than PB patients (10 of 35, 29%) experienced tumor shrinkage (Supplemental Fig. 3).

Safety

Fifty-seven of the 74 study patients (77%) experienced treatment-related toxicities during the first 2 cycles of FOLFIRI + RAM chemotherapy (Supplemental Table 2). All grades of severity were reported. The most frequent grade 3 or higher toxicity was neutropenia in 27 patients (36%). Grade 3 or higher hypertension and proteinuria were observed in four patients (5%). The frequencies of toxicities of all grades in each group were similar, 29 NPB patients (74%) and 28 PB patients (80%). Fourteen NPB patients (36%) and 15 PB patients (43%) experience grade 3 or higher toxicities. Neutropenia was reported in 16 NPB (41%) and 11 PB (31%) patients. Hypertension was reported in 2 NPB (5%) and 2 PB (6%) patients. Proteinuria was not reported in any PB patients and in three PB patients (9%).

Table 1 Patient characteristics in Group-NPB and Group-PB

Characteristics ($N=74$)	Group-NPB ($N=39$) *N* (%)	Group-PB ($N=35$) *N* (%)
Sex		
Female	20 (51%)	19 (54%)
Male	19 (49%)	16 (46%)
ECOG PS		
0	26 (67%)	9 (26%)
1	10 (26%)	6 (17%)
Unknown	3 (8%)	20 (57%)
CEA		
< 10	14 (36%)	10 (29%)
> 10	25 (64%)	25 (71%)
Tumor location		
Right side (cecum ~ transverse colon)	12 (31%)	13 (38%)
Left side (descending colon)	27 (69%)	22 (63%)
RAS mutation		
Wild	30 (77%)	12 (34%)
Mutant	9 (23%)	22 (63%)
Unknown	0 (0%)	1 (3%)
Number of metastatic sites		
1	15 (38%)	19 (54%)
2	14 (36%)	8 (23%)
3+	10 (26%)	8 (23%)
Previous chemotherapy		
Adjuvant	8 (21%)	0 (0%)
Adjuvant + systemic	9 (23%)	5 (14%)
Systemic	22 (56%)	30 (86%)
Duration of bev		
< 6 months	–	11 (31%)
> 6 months		24 (69%)
Prior anti-EGFR antibody		
Yes	25 (64%)	–
No	14 (36%)	

PS performance status, *CEA* carcinoembryonic antigen, *EGFR* epidermal growth factor receptor

Intestinal perforation was not reported in NPB patients, but occurred in one PB patient (3%). Grade 3 or higher thrombosis was not observed in any patients.

Discussion

This retrospective analysis reports the outcomes achieved with FOLFIRI + RAM as second-line chemotherapy of mCRC in clinical practice and includes a comparison of cohorts with and without previous exposure to BEV. We believe this is the first report of the results of FOLFIRI + RAM as second-line therapy for mCRC in bevacizumab-naïve patients. Both PFS and tumor response were better in NPB than in PB patients. BEV administration might be predictive of the efficacy of FOLFIRI + RAM in such patients. The median PFS of the entire population (6.2 months) and of the PB patients (5.0 months) were comparable to that reported in the RAISE study (5.7 months). The occurrence of RAM-related AEs, such as neutropenia, hypertension, and proteinuria observed in the first two treatment cycles were similar to the rates observed in the RAM group of the RAISE trial. Patients treated in clinical practice may be in relatively poor condition compared with those included in clinical trials. However, there were no significant differences in the toxicities observed in NPB and PB patients. The follow-up duration available for the evaluation of OS was relatively short. The overall RR was similar to that in the RAISE trial (13.5% vs. 13.4%); RR in NPB patients (23%) was higher than that in PB patients.

An anti-EGFR antibody (cetuximab or panitumumab) administered in combination with fluoropyrimidine-based doublet regimens is recommended for first-line treatment of RAS and wild-type and left-side colorectal cancer [9–11]. As a result, the number of BEV-naïve patients who require second-line systemic chemotherapy has been increasing. Preliminary studies support the use of anti-VEGF antibodies following treatment with an anti-EGFR antibody. Increased

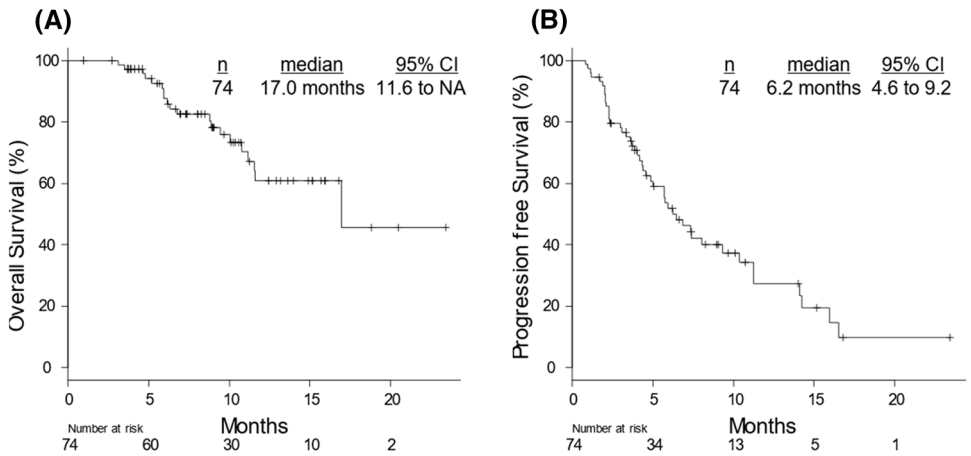

Fig. 2 OS (**a**) and PFS (**b**) in the all included study population

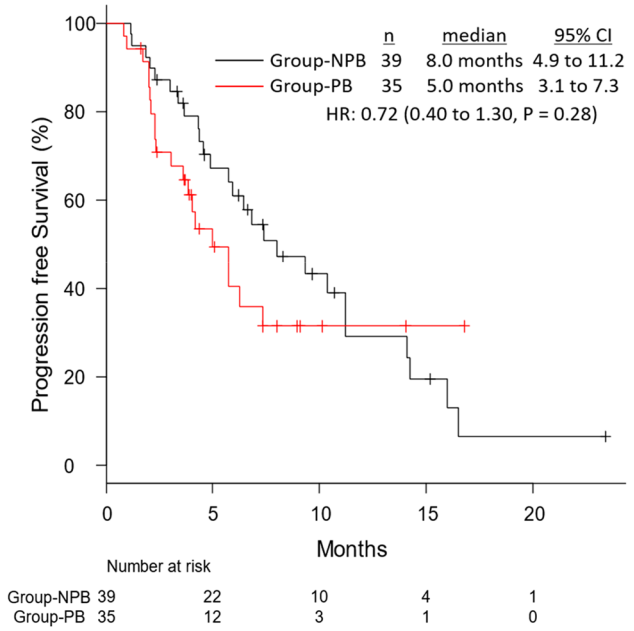

Fig. 3 PFS curves in patients with prior BEV exposure (group-PB) and without prior BEV exposure (group-NPB)

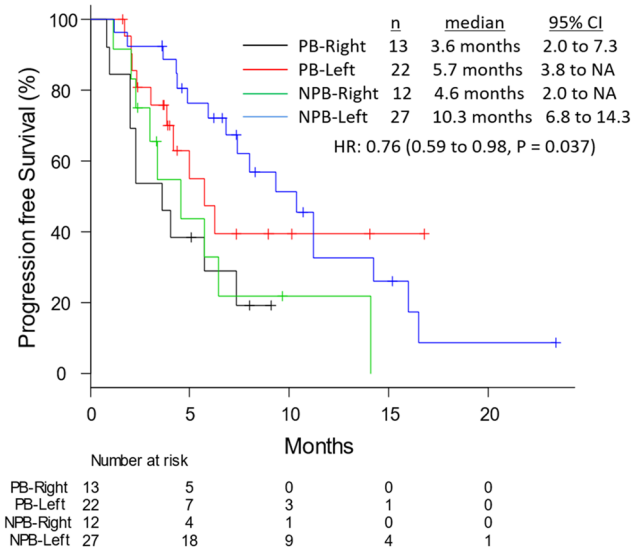

Fig. 4 PFS curves in patients stratified by with or without prior BEV exposure and tumor location (sideness)

VEGF expression was reported in five of six EGFR-resistant tumor xenografts [26], and some human cancer cell lines that are resistant to EGFR express VEGFR [27]. A translational study of xenografts treated with panitumumab followed by BEV described potential anti-tumor mechanisms that derived from differential gene and protein expression and protein phosphorylation associated with panitumumab followed by BEV and BEV followed by panitumumab [28].

Table 2 Clinical response in Group-NPB and Group-PB

	Group-NPB *N* (%)	Group-PB *N* (%)
Complete response (CR)	0 (0)	0 (0)
Partial response (PR)	9 (23)	1 (3)
Stable disease (SD)	24 (62)	23 (66)
Progressive disease (PD)	6 (15)	10 (29)
Not evaluable (NE)	0 (0)	1 (3)
Response rate (RR)	9 (23)	1 (3)
Disease control rate (DCR)	33 (85)	24 (69)

The applicability of FOLFIRI + RAM for BEV-naïve patients is uncertain owing to lack of prospective and retrospective clinical data. Also, the RAISE trial included only patients who had been given first-line chemotherapy that included BEV. A subset analysis of the VELOUR trial revealed better outcomes of BEV-naïve than the BEV-exposed cohort in response to FOLFIRI + AFL (HR = 0.788 vs. 0.862), which is in line with the results of this study. In addition, the median OS and PFS of the FOLFOX + BEV cohort in E3200 trial (7.3 and 12.9 months, respectively) were longer than those in response to chemotherapy plus BEV in the ML18147 trial (5.7 and 11.2 months, respectively). Differences in the study design made comparison difficult, but it is possible that initiation of BEV in second- rather than first-line therapy could contribute to an improved outcome of the second-line therapy.

Other subset analyses have found significantly better prognoses for left-side tumor location and long-term BEV administration in PB patient cohorts. Although the result does not conflict with the previous reports that the addition of BEV was more effective if first line was given for > 9 months, the results could be strongly affected by the characteristics of the tumor itself. The use of anti-EGFR antibodies tends to be avoided in patients with right-side mCRC [29]. Tumor location (sidedness) remained independently associated with PFS on multivariate analysis, and location often affects the selection an anti-EGFR antibody or BEV for first-line therapy. A four-arm analysis was conducted in this study, including tumor location and previous BEV exposure. Consequently, NPB patients had better PFS than PB patients in both right- and left-sided tumors. This result suggests NPB may have a favorable prognosis independent of tumor location or anti-EGFR antibody pre-exposure in the first-line therapy. The main study limitations are its single-center, retrospective design, and relatively small sample size.

Conclusion

The efficacy of FOLFIRI + RAM as a second-line chemotherapy in mCRC patients was in line with that reported in the previous RAISE phase III trial. The response was

better in bevacizumab-naïve patients than in those with first-line treatment that had included bevacizumab. Prospective studies, including patients without prior BEV, are needed to investigate the use of anti-VEGF antibody in second-line therapy.

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Compliance with ethical standards

Conflict of interest Honoraria from Takeda, Merck Serono, Taiho, Chugai, Lily, Sanofi, Yakult.

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