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ORIGINAL ARTICLE

Regorafenib or rechallenge chemotherapy: which is more effective in the third-line treatment of metastatic colorectal cancer?

Osman Köstek[1] · Muhammet Bekir Hacıoğlu[2] · Abdullah Sakin[3] · Tarık Demir[4] · Murat Sarı[5] · Ozlem Ozkul[6] · Murat Araz[7] · Aysun Fatma Doğan[1] · Nazım Can Demircan[1] · Sernaz Uzunoğlu[1] · İrfan Çiçin[1] · Bülent Erdoğan[1]

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Abstract

Purpose To assess the efficacy and safety of regorafenib versus rechallenge chemotherapy in previously treated mCRC patients in third-line setting.

Materials and methods The data of 104 patients diagnosed with mCRC enrolled from 2010 to 2017 in six oncology centers were analyzed. Tumor treatment options were obtained from follow-up and treatment files. Rechallenge chemotherapy was identified as the re-use of the regimen which was previously administered to patients in one of the therapy lines and obtained disease control, these were the patients whose disease did not progress within 3 months.

Results A total of 104 patients had received previously two lines of chemotherapy regimens for mCRC. Of these, 73 patients with mCRC who received regorafenib and 31 those who received rechallenge chemotherapy in third-line therapy were analyzed. Overall survival was better with rechallenge than it was with regorafenib (HR 0.29 95% CI 0.16–0.54, $p < 0.001$). Median OS was 12.0 months (95% CI 8.1–15.9) in rechallenge versus 6.6 months (95% CI 6.0–7.3) in regorafenib group ($p < 0.001$). Progression-free survival in the rechallenge group showed a higher median value of 9.16 months (95% CI 7.15–11.18) versus with that recorded in the regorafenib group of 3.41 months (95% CI 3.01–3.82), in favor of rechallenge chemotherapy. The most common adverse events of regorafenib was liver function test abnormality and hand–foot syndrome. Although grade 3 or 4 adverse events were similar, non-hematologic toxicities were more common than those of rechallenge.

Conclusions Rechallenge is still a valuable option against regorafenib in patients who achieved disease control in one of the first two lines of therapy. Even though mCRC patients treated with regorafenib benefited clinically from this treatment, we revealed that chemotherapy rechallenge compared to regorafenib was more effective in the third-line treatment for mCRC patients.

Keywords Rechallenge · Regorafenib · Metastatic colorectal cancer · Overall survival · Progression-free survival · Third-line

Introduction

Colorectal cancers (CRC) are one of the most common cancers worldwide. De novo metastatic patients constitute approximately 25% of newly diagnosed colorectal cancer patients. Within 5 years, approximately 25–30% of stages 2 and 3 disease have became metastatic [1]. In general, fluorouracil-based doublet regimens (5-fluorouracil/leucovorin + irinotecan and 5-fluorouracil/leucovorin + oxaliplatin) combined targeted therapies including either anti-endothelial

✉ Osman Köstek
osmankostek@hotmail.com

[1] Department of Medical Oncology, Trakya University, Edirne, Turkey

[2] Clinic of Medical Oncology, Konya Training and Research Hospital, Konya, Turkey

[3] Okmeydanı Training and Research Hospital, Clinic of Medical Oncology, Istanbul, Turkey

[4] Department of Medical Oncology, Bezmi Alem Vakıf University, Istanbul, Turkey

[5] Department of Medical Oncology, Istanbul University, Istanbul, Turkey

[6] Department of Medical Oncology, Sakarya University, Sakarya, Turkey

[7] Department of Medical Oncology, Afyon Kocatepe University, Afyon, Turkey

growth factor receptor (EGFR; cetuximab or panitumumab) treatment for patients with rat sarcoma viral oncogene (RAS) wild type or vascular endothelial growth factor (VEGF; bevacizumab) have been routinely used in first- and second-line standard therapies, and the overall survival (OS) among these patients has reached up to 30 months [2–4]. Unfortunately, metastatic stage CRC patients' disease are progressing after first and second line chemotherapy. For third-line therapy, a new targeted treatment (Regorafenib, TAS-102, Apatinib) seems to be an option for patients with metastatic CRC refractory to standard first- and second-line therapy.

Regorafenib is an oral multikinase inhibitor which inhibits proangiogenic signaling pathways. CORRECT and CONCUR studies have shown that regorafenib is effective compared to placebo in OS in patients with metastatic CRC who have received chemotherapy (5-FU-oxaliplatin/irinotecan or anti-VEGF or anti-EGFR) [5, 6]. It is a preferable option for chemotherapy refractory patients who have previously received various chemotherapy regimens. On the other hand, rechallenge of previously given therapy is another option, especially in those regimens which were discontinued before progression. Rechallenge of drugs which patients developed resistance may also be feasible, although evidence for this strategy is limited. In this retrospective study, we aimed to assess the efficacy and safety of regorafenib versus rechallenge chemotherapy in previously treated mCRC patients in the third-line setting.

Materials and methods

Study patients

This was a retrospective study. The data of 104 patients diagnosed with mCRC from 2010 to 2017 enrolled in six oncology centers were analyzed. Patients who had another malignancy were excluded. The demographic and clinical characteristics of the patients and the pathological features of tumors, metastasis sites, types of chemotherapy, treatment schedules, Eastern Cooperative Oncology Group (ECOG) performance status and survival data were evaluated using the medical records of the patients.

Mutant RAS status was detected if either KRAS or NRAS or both had a mutation. The analyses were performed in our molecular pathology laboratories, and the following mutations were analyzed: CAA > CTA Q61L, CAA > CAT Q61H, CAA > CGA Q61R, GGT > GTT G12V, GGC > GAC G13D, GGT > GAT G12D, GGT > TGT G12C, GGT > AGT G12S, GGT > GCT G12A, GGT > CGT G12R, and GGT > c.34_35GG > TT G12F. DNA was extracted from the primary tumor tissue samples using QIAamp DNA FFPE Tissue Kit (Qiagen, Hilden, Germany). The Pyro Kit 24 V1 (Qiagen, Hilden, Germany) was used for K-RAS and N-RAS analyses, and the point mutations were analyzed with the PyroMark Q24 Software System (Qiagen, Hilden, Germany).

Treatment

Patients with mCRC who were treated in third-line after progression or recurrence beyond the second-line, received 5-fluorouracil/leucovorin plus irinotecan and 5-fluorouracil/leucovorin plus oxaliplatin combined targeted therapies including either EGFR (cetuximab or panitumumab) treatment for patients with RAS wild type or VEGF (bevacizumab) in first- and second-line were analyzed. Of these, 73 patients received regorafenib and others received rechallenge chemotherapy. Tumor treatment options were obtained from follow-up and treatment files. Rechallenge chemotherapy was identified as the re-use of the regimen which was previously administered to patients in one of the therapy lines and obtained disease control; these were the patients whose disease did not progress within 3 months.

Response assessment

Data about efficacy and safety of rechallenge and regorafenib in patients whose disease progress or reoccur beyond the second line were obtained from medical files. According to RECIST 1.1 criteria, complete response was disappearance of all target lesions; at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters; progressive disease as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study, recorded since treatment started; and stable disease as less than 30% reduction, or less than 20% increase from baseline [7]. The primary endpoint was overall survival (OS) and secondary efficacy endpoints were progression-free survival and ratio of patients who achieved disease control (defined as a complete or partial response, or stable disease recorded ≥ 6 weeks after beginning of treatment). In subgroup analysis, patients were categorized into three groups: patients with partial response or stable disease after both, first- and second-line therapy, were defined as Group A; patients with partial response or stable disease after only one-line therapy were defined as Group B; and patients with progressive disease after both first- and second-line therapies were defined as Group C. OS, PFS, response and disease control rates were analyzed among group A, B and C.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 15.0 for Windows (SPSS Inc., Chicago, IL). Overall survival and PFS were compared

between treatment groups with a stratified log-rank test; HRs (with 95% CI) were calculated with the Cox model; and Kaplan–Meier survival estimates were calculated for each treatment group. Disease control rates were compared between treatment groups with Chi square test, adverse events were reported by treatment group, category, and grade. A p value of <0.05 was considered statistically significant.

Results

Patient characteristics

A total of 104 patients had received previously two lines of chemotherapy regimens for mCRC. Of these, 73 patients with mCRC who received regorafenib and 31 those who received rechallenge chemotherapy in third-line therapy were analyzed. Table 1 shows clinical and demographic characteristics of the patients. Overall, the median age was 61 and female:male ratio was 47:57. There was no difference in terms of age and gender between groups. In addition, primary tumor localization, tumor grade, metastatic status were similar between regorafenib and rechallenge group. RAS mutation (60.6%) in patients who treated with regorafenib were significantly higher than those who treated with rechallenge (26.7%) group.

The first- and second-line treatment

Oxaliplatin-based regimens (FOLFOX and XELOX) were mostly used as first-line therapy in both groups. Of these, 53.4% were combined with bevacizumab. The first-line bevacizumab combined with chemotherapy were significantly higher in regorafenib (72.6%) than rechallenge (48.3%) group. FOLFIRI regimen was commonly used in the second-line therapy in both groups. Combination chemotherapy, anti-VEGFR and anti-EGFR therapies were similarly used in both groups for the second-line. The profile of the first- and second-line chemotherapies and combined anti-VEGF and anti-EGFR treatment regimens are shown in Table 2. On the other hand, rechallenge chemotherapy regimens consisted of eight patients (21.7%) FOLFOX + cetuximab, six patients (17.4%) FOLFOX + bevacizumab, four patients (17.4%) FOLFOX, two patients (8.7%) FOLFIRI, two patients (8.7%) capecitabine, three patient (4.3%) FOLFIRI + cetuximab, one patient (4.3%) FOLFOX + panitumab, one patient FOLFIRI + bevacizumab, one patient (4.3%) FUFA + bevacizumab, one patients (4.3%) capecitabine + bevacizumab, one patient (4.3%) XELOX + bevacizumab and one patient (4.3%) FOLFIRINOX, respectively.

Table 1 Demographic and clinical characteristics of study subjects

	Regorafenib ($N=73$)	Rechallenge group ($N=31$)
Age		
Median (range) years	58 (48–64)	62 (54–67)
<50 years, no. (%)	21 (28.8)	4 (12.9)
50–65 years, no. (%)	34 (46.6)	15 (48.4)
≥65 years, no. (%)	18 (24.7)	12 (38.7)
Gender, no. (%)		
Female	33 (45.2)	14 (45.2)
Male	40 (54.8)	17 (54.8)
Primary tumor localization		
Left/right	54/19	24/7
Rectal cancer, no. (%)	25 (34.2)	12 (38.7)
Sigmoid-descending colon, no. (%)	29 (39.7)	12 (38.7)
Transverse colon, no. (%)	2 (2.7)	2 (6.5)
Cecum-ascending colon, no. (%)	17 (23.3)	5 (16.1)
Tumor grade, no. (%)		
Grade 1	17 (23.3)	14 (45.2)
Grade 2	43 (58.9)	12 (38.7)
Grade 3	8 (11.0)	3 (9.7)
Unknown	5 (6.8)	2 (6.5)
RAS mutation status, no. (%)*		
Wild type	28 (39.4)	22 (73.3)
K- or N-RAS mutation	43 (60.6)	8 (26.7)
Metastatic status, no. (%)		
After adjuvant therapy	15 (20.5)	8 (25.8)
De novo metastatic	58 (79.5)	23 (74.2)
Metastatic site, no. (%)		
Liver	53 (73.6)	17 (58.6)
Lung	20 (27.8)	4 (13.8)
Other	11 (15.1)	10 (32.3)
Metastasectomy, no. (%)	13 (18.8)	6 (21.4)

*p value <0.05, others were not significantly associated between-group differences in the characteristics listed here

Efficacy and toxicity

Among 104 patients, disease control rate was 85.6% (partial response 60.6% and stable disease 25.0%) in first-line and 69.2% (partial response 39.4% and stable disease 29.8%) in second-line. Table 3 shows the response rates of the study subjects in the first-, second- and third-line therapies. In third-line, disease control rate was higher in rechallenge (58.1%) group than those in regorafenib (37.0%) group ($p=0.04$). Subsequently, subgroup analysis of disease control rate is shown in Table 4.

Patients in rechallenge group were on treatment longer than those in regorafenib group, with a median treatment

Table 2 The first and second regimens of the patients

	Regorafenib ($N=73$)	Rechallenge group ($N=31$)	p
First-line chemotherapy, no. (%)			
FOLFIRI	35 (47.9)	10 (32.3)	0.17
FOLFOX/XELOX	35/3 (52.1)	13/7 (64.5)	
Capecitabine	–	1 (3.2)	
First-line bevacizumab, no. (%)	53 (72.6)	15 (48.3)	0.008
FOLFIRI	30 (56.6)	6 (40.0)	
FOLFOX/XELOX	23 (43.4)	8 (53.3)	0.11
Capecitabine	–	1 (6.7)	
First-line anti-EGFR, no. (%)	9 (17.6)	2 (8.3)	0.28
Panitumab/cetuximab	3/6	–/2	0.33
FOLFIRI	4 (44.4)	1 (100)	0.15
FOLFOX	5 (55.6)	–	
Second-line chemotherapy, no. (%)			
FOLFIRI/XELIRI	40/1 (56.2)	24/– (77.4)	0.07
FOLFOX/XELOX	28/3 (42.5)	5/1 (19.4)	
FUFA/capecitabine	–/1 (1.4)	1/– (3.2)	
Second-line bevacizumab, no. (%)	40 (54.8)	16 (51.6)	0.76
FOLFIRI/XELIRI	21/1 (55.0)	12/– (75.0)	0.07
FOLFOX/XELOX	16/2 (45.0)	3/– (18.8)	
FUFA/capecitabine	–	1 (6.3)	
Second-line anti-EGFR, no. (%)	16 (21.9)	11 (35.5)	0.14
Panitumab/cetuximab	6/10	3/8	0.58
FOLFIRI	9 (56.3)	10 (90.9)	0.09
FOLFOX	7 (43.8)	1 (9.1)	

Table 3 Response rates of the study subjects in the first-, second- and third-lines

	Regorafenib ($N=73$)	Rechallenge group ($N=31$)	p
First-line, no. (%)			
Partial response	42 (59.2)	21 (67.7)	0.68
Stable disease	19 (26.8)	7 (22.6)	
Second-line, no. (%)			
Partial response	24 (33.8)	17 (54.8)	0.12
Stable disease	23 (32.4)	8 (25.8)	
Third-line, no. (%)			
Partial response	–	6 (19.4)	0.04
Stable disease	27 (37.0)	12 (38.7)	

duration of 5.01 months (IQR 3.25–7.39) for those in rechallenge group versus 3.17 months (IQR 2.41–4.73) for those in regorafenib group ($p<0.001$). Overall, 42 (57.5%) of regorafenib patients and 16 (51.6%) of rechallenge patients had an adverse events leading to dose modification (dose reduction or dose interruption, $p=0.31$).The most common reason for treatment discontinuation was disease progression in both groups.

Overall survival was significantly better with rechallenge than it was with regorafenib (HR 0.29 95%CI 0.16–0.54, $p<0.001$, Fig. 1) in third-line. Median OS was 12.0 months (95% CI 8.1–15.9) in rechallenge and 6.6 months (95% CI 6.0–7.3) in regorafenib group ($p<0.001$, Fig. 1). Subsequently, subgroup analysis of OS is shown in Table 5. Group

Table 4 Efficacy outcomes of subgroups in third-line

	Group A ($n=68$)		Group B ($n=26$)		Group C ($n=10$)	
	Regorafenib	Rechallenge	Regorafenib	Rechallenge	Regorafenib	Rechallenge
Count (%)	46 (67.6)	22 (32.4)	17 (65.3)	9 (34.7)	10 (100)	–
RR, no. (%)	–	5 (22.7)	–	1 (11.1)	–	–
DCR, no. (%)	24 (52.2)	16 (72.7)	1 (5.9)	2 (22.2)	2 (20.0)	–

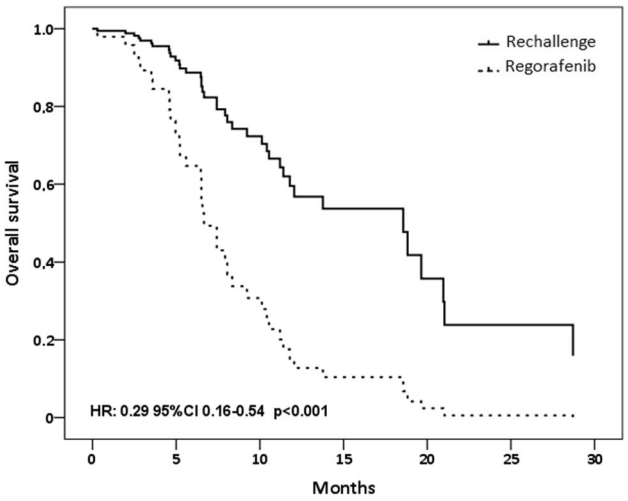

Fig. 1 Overall survival of the patients in the third-line

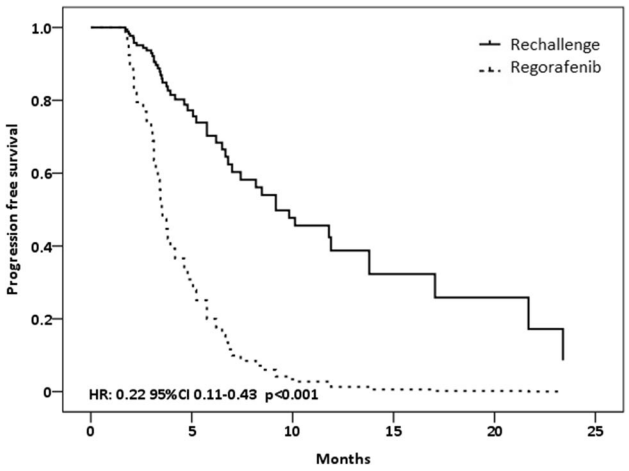

Fig. 2 Progression-free survival of the patients in the third-line

Table 5 OS and PFS of the study subjects

	Overall survival	Progression-free survival
Group A (months) (95% CI)		
Overall	10.4 (6.9–13.8)	6.21 (2.87–9.54)
Regorafenib	7.3 (6.7–7.8)	3.54 (2.42–4.67)
Rechallenge	18.6 (7.2–29.9)	9.82 (6.58–13.10)
p value	< 0.001	0.001
Group B (months) (95% CI)		
Overall	6.4 (5.1–7.8)	3.81 (3.11–4.51)
Regorafenib	5.2 (4.3–6.1)	3.41 (2.19–4.64)
Rechallenge	8.3(3.3–13.4)	6.81 (6.20–7.39)
p value	0.04	< 0.001
Group C (months) (95% CI)		
Overall/regorafenib	5.6 (2.7–8.5)	2.99 (1.85–4.13)

A and B patients had better OS with rechallenge compared to regorafenib.

Progression-free survival was also significantly better with rechallenge than it was with regorafenib (HR 0.22 95% CI 0.11–0.43, $p < 0.001$), with a median PFS of 9.16 months (95% CI 7.15–11.18) in rechallenge and 3.41 months (95% CI 3.01–3.82) in regorafenib group ($p < 0.001$, Fig. 2). Subsequently, subgroup analysis of PFS is given in Table 5. Group A and B patients had better PFS with rechallenge chemotherapy.

Regarding RAS status, group A (RAS wild: 53.8% vs RAS mutant: 46.2%, $p = 0.24$) and B (RAS wild: 53.8% vs RAS mutant: 46.2%, $p = 0.61$) patients had similar mutation. About 90% of group C patients was RAS mutant ($p = 0.02$). Overall, DCR, PFS and OS values in the third-line were similar between RAS wild and RAS mutant groups ($p = 0.69$, $p = 0.06$ and $p = 062$, respectively).

All patients had treatment related toxicity. Grade 3 or 4 adverse events were seen in 27 patients (36.9%) in regorafenib group and in eight patients (25.8%) in rechallenge group ($p = 0.50$). These are (33.3%) patients with liver function test abnormality, 7 (25.9%) patients with hand-foot syndrome, 4 (14.8%) patients with hypertension, 4 (14.8%) patients with fatigue and 3 (11.1%) patients with thrombocytopenia who received regorafenib. On the other hand, grade 3 or 4 toxicities were 4 (50%) patients with thrombocytopenia, 3 (37.5%) patients with neutropenia and 1 (12.5%) patient with hypertension who received rechallenge chemotherapy. In addition, grade 1 or 2 toxicities were gastrointestinal (57.1% vs. 43.5%), hand and foot syndrome (62.5% vs. 52.4%), fatigue (75.6% vs. 86.4%), hypertension (31.7% vs. 33.3%), anorexia (63.4% vs. 52.4%), mucositis (53.7% vs. 68.2%), and liver functional abnormalities (22.0% vs. 19.0%) in patients who received regorafenib versus those who received rechallenge, respectively (all $p > 0.05$).

Discussion

The third-line therapy, after first- and second-line therapies, whether rechallenges chemotherapy or regorafenib in terms of optimal therapy is still unclear, even if the patient's condition is suitable [8]. Especially regorafenib is the standard option in chemotherapy refractory patients/where therapy options are exhausted [5]. Progression is always inevitable in the treatment of metastatic colorectal cancer after two series of chemotherapy. If the tumor continues to be susceptible to chemotherapy, it is up to the clinician to choose which option to use. As for the third-line therapy, a multitargeted tyrosine kinase inhibitor regorafenib, or, alternatively, rechallenge chemotherapy are among the treatment options [6]. At this point, critical questions for the future

are to determine which patients can benefit from rechallenge treatment, and which patients need regorafenib treatment. In this study, we suggested that rechallenge is still a valuable option against regorafenib in patients with at least disease control in one of the first two lines of therapy. Even though patients treated with regorafenib benefited clinically from this treatment, we saw that rechallenge as third-line therapy compared to regorafenib was more efficient with regard to disease control for patients with partial response or stable disease after both, first- and second-line therapies (Group A) and in patients with partial response or stable disease after only one-line therapy (Group B).

Regorafenib is a novel oral multikinase-inhibitor that is involved in the regulation of tumor angiogenesis (VEGFR1, VEGFR2, VEGFR3, TIE2), oncogenesis (KIT, RET, RAF1, BRAF and $BRAF^{V600E}$), and the tumor microenvironment (PDGFR and FGFR) [9]. In the CORRECT study, it was shown that regorafenib has survival benefits (HR, 0.77; 95% CI 0.64–0.94; $p=0.005$) compared to placebo; median survival was 6.4 months in the regorafenib group versus 5.0 months in the placebo group [5]. Subsequently, second phase 3, CONCUR trial revealed that overall survival (HR 0.55; 95% CI 0.40–0.77; $p=0.0001$) was better with regorafenib than it was with placebo; median survival was 8.8 months (95% CI 7.3–9.8) in the regorafenib group versus 6.3 months (95% CI 4.8–7.6) in the placebo group [6]. On the other hand, data about rechallenge chemotherapy for patients who received previously two lines of chemotherapy (oxaliplatin and irinotecan) is insufficient in third-line setting. In the explanatory trial of Matsuda et al., it was revealed that patients who had received previous oxaliplatin and irinotecan at first- and second-line therapies had been treated with capecitabin plus oxaliplatin ± bevacizumab in 14-day cycles, median OS was 12.1 months versus capecitabin plus oxaliplatin ± bevacizumab in 21-day cycles, median OS was 9.2 months, (HR 0.672; 95% CI 0.316–1.428) in third-line [10]. In other non-randomized trials, there were heterogenous therapy regimens with different OS values. First, Hartmann et al. showed that median OS was 7.9 months (95% CI 6.1–11.1) with only irinotecan administration in the third line for patients who had previously received two series of chemotherapy [11]. Then, phase II trial of Suenaga et al. demonstrated that patients who had received oxaliplatin and irinotecan in first- and second-lines and had been treated with FOLFOX-6 regimen, median OS was 300 days (95% CI 229–370 days) in third-line [12]. In real-world studies, Gebbia et al. reported a median OS of 6 months, giving two cycles of chemotherapy regimen with three series of cetuximab plus irinotecan in patients receiving irinotecan and oxaliplatin [13]. Finally, in the study where the treatment regimen was similar to our study group, Lievre et al. revealed that patients who had previously undergone fluoropyrimidine plus irinotecan and/or oxaliplatin regimens in two lines, median OS was 18.4 months (95% CI 13.6–not reached) with FOLFOX4 plus bevacizumab or FOLFIRI plus bevacizumab in the third-line [14]. In our study, overall survival was better with rechallenge than it was with regorafenib (HR 0.29 95% CI 0.16–0.54, $p<0.001$). Median OS was 12.0 months (95% CI 8.1–15.9) in rechallenge versus 6.6 months (95% CI 6.0–7.3) in regorafenib group ($p<0.001$). Median OS of both regorafenib and rechallenge treatment were compatible with the literature. Different OS values in patients can be explained due to various heterogeneous treatment options for the rechallenge group. In our study, anti-EGFR or anti-VEGFR combinations were more commonly used in the first line. This was similar to the study of Lievre et al. In subgroup analysis, we found that median OS values (18.6 months, 95% CI 7.2–29.9) obtained with rechallenge in Group A patients were significantly higher than those with regorafenib (7.3 months, 6.7–7.8) ($p<0.001$) and Group B patients had higher median OS (8.3, 95% CI 3.3–13.4) in the rechallenge group than in regorafenib group (5.2, 95% CI 4.3–6.1) ($p=0.04$).

Patients whose disease earlier progressed after the first- and second-line chemotherapies (chemotherapy refractory; Group C) had similar OS (5.6 months, 95% CI 2.7–8.5) values compared with that recorded (6.4 months, 95% CI 3.6–11.8) in the CORRECT study [5]. In our study, we showed that the rechallenge chemotherapy option had better OS values compared to regorafenib, especially in those patients who had achieved disease control with the first two lines of therapy and did not have any earlier progression. On the other hand, the OS values obtained with regorafenib as third-line treatment in patients defined as chemotherapy refractory were also in accordance with the literature. Progression-free survival in the rechallenge group showed a higher median value of 9.16 months (95% CI 7.15–11.18) versus with that recorded in the regorafenib group of 3.41 months (95% CI 3.01–3.82), in favor of rechallenge chemotherapy. In the CONCUR study, patients received regorafenib who eventually achieved a similar PFS of 3.2 months [6]. In subgroup analysis, the rechallenge median PFS value ofGroup A patients (9.82 months, 95% CI 6.58–13.10), was significantly higher than the value obtained with regorafenib (3.54 months, 2.42–4.67) ($p=0.001$) and Group B patients had also higher median PFS (6.81, 95% CI 6.20–7.39) value in rechallenge group than that recorded (3.41, 95% CI 2.19–4.64) in regorafenib group ($p<0.001$). Median PFS time of Group C patients was 2.99 (95% CI 1.85–4.13) months. In this study, even though Group A and Group B benefited from regorafenib therapy as third line treatment, the benefit was higher with rechallenge therapy. These data showed that median OS and PFS values achieved with rechallenge treatment seem better than those achieved with regorafenib, not only in our study but also in both CORRECT and CONCUR trials (in the CORRECT study with a

median PFS of 1.9 months, median OS of 6.4 months, and in the CONCUR study with a median PFS of 3.2 months, median OS of 8.8 months in the regorafenib group) [5, 6].

There was no complete response in both groups, but 6 (19.4%) patients in the rechallenge group had a partial response. Disease control rate (DCR) was higher in rechallenge (58.1%) group than in the regorafenib (37.0%, all SD) group ($p = 0.04$). Our disease control rate achieved with regorafenib was slightly lower than the one achieved with regorafenib both in CORRECT (41%) and CONCUR (51%) trials [5, 6]. On the other hand, real-world studies on rechallenge as third-line therapy are limited. Lievre et al. reported that disease control rate with FOLFOX-4 plus bevacizumab or FOLFIRI plus bevacizumab was 67.8% (PR 29% and SD 38.8%) in patients who received previous fluorouracil, oxaliplatin and irinotecan as first- and second-line therapy [14]. Then, Chaix et al. reported their DCR was 73% with FOLFIRINOX plus bevacizumab in third-line therapy in patients who were treated with ≥ 2 previous regimens, including fluorouracil, irinotecan, oxaliplatin plus bevacizumab [15]. Although there are some studies about the efficacy of chemotherapy in third-line in patients with mCRC, their third-line regimens were different than previous regimens, as a rechallenge strategy. First, Larsen et al. showed that disease control rate was 71% (SD 62%, PR 9%) in 34 patients who were treated with capecitabine plus bevacizumab in third-line who previously received fluorouracil, oxaliplatin and irinotecan in the first and second-lines [16]. In addition, Jimenez-Fonseca et al. demonstrated that disease control rate with gemcitabine and capecitabine was 43.7% (SD 37.8, PR 5.9%) in 119 rechallenge patients who were treated previously with oxaliplatin and irinotecan-based fluoropyrimidine and/or bevacizumab or cetuximab or panitumab [17]. Moreover, Yoshida et al. revealed that DCR with bevacizumab and S-1 was 67.9% (all SD) in 31 patients who treated > 2 previous regimens including oxaliplatin and irinotecan regimens [18]. Kwon et al. revealed that patients whose disease progressed after oxaliplatin and irinotecan and for whom bevacizumab plus infusion 5-FU/LV and irinotecan was allowed as third-line therapy achieved a 28.5% response rate with 57% of stabilized patients [19]. These results were also heterogeneous and not demonstrating enough data regarding rechallenge for third-line therapy. On the other hand, there are no data about comparing the rechallenge and regorafenib treatment in third-line setting. It is unlikely to compare rechallenge with regorafenib in terms of efficacy and safety in randomized trials. Therefore, real-world studies which compare the efficacy of rechallenge and regorafenib regimens may provide guidance in the third-line setting. Our results (19.4% response rate with 38.7% of stabilized patients) are valuable due to the demonstration of the efficacy of rechallenge and comparison against those of regorafenib in third-line.

On the basis of the efficacy findings, treatment with either rechallenge chemotherapy or regorafenib is an appropriate first choice beyond the second-line; thus, performance status and the safety profiles of each are likely to be determinant in the choice of treatment. Treatment modification rate in patients treated with rechallenge chemotherapy was similar to those treated with regorafenib. On the other hand, previously administered rechallenge chemotherapy to patients may be a benefit in the side effect management of the drug. The most common adverse events of regorafenib was liver function test abnormality and hand–foot syndrome. Although grade 3 or 4 adverse events were similar, non-hematologic toxicities were more common than those of rechallenge. Especially, grade 3 or 4 hematologic toxicity profiles consisted of thrombocytopenia and neutropenia.

There are some major limitations. First, retrospective clinical data of the patients from medical records have disadvantages to control for all potential confounding bias that may influence the mortality. Secondly, the number of patients was small, which hampered the present results to be applied to all mCRC patients. On the other hand, disease control rates are assessed with RECIST criteria. Since it is not known whether the RECIST criteria are applied optimally in different centers, the response rate to the radiological response evaluation is evaluated as expressed in the reports. Also, data about toxicity profile may have missing data due to incomplete identification of adverse events considering the limitation of the retrospective study.

In conclusion, although regorafenib might be a preferable option in the third-line treatment for patients with mCRC, chemotherapy rechallenge is more effective option against regorafenib formCRC patients who achieved disease control in one of the first two lines of treatment. To our best knowledge, this study is the first to compare regorafenib with rechallenge in third-line setting of mCRC. Further studies should aim to identify which patients are likely to benefit from regorafenib or from rechallenge chemotherapy regimens.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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