European Review for Medical and Pharmacological Sciences 2021; 25: 3470-3477

Treatment options after regorafenib failure in metastatic colorectal cancer

E. ERASLAN, M. DOĞAN, F. YILDIZ, A. İLHAN, Ö.B. ÖKSÜZOĞLU

Medical Oncology, University of Health Sciences Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Ankara, Turkey

Abstract. – OBJECTIVE: In the treatment of metastatic colorectal cancer (mCRC), there is a need for a treatment option in patients who have received regorafenib (RGR) therapy and progressed, especially in patients fit enough to receive a new therapy. We aimed to compare the role of rechallenge chemotherapy (RCH CTx) with best supportive care (BSC) in mCRC patients after standard CTx and subsequent RGR treatment in terms of survival benefit.

PATIENTS AND METHODS: Patients with progressive mCRC who received at least one month of subsequent RGR therapy after standard CTx treatments were included in the study. Patients were divided into two groups: receiving RCH CTx or BSC (without antitumoural therapy) after RGR failure. There were 26 patients in the RCH CTx group and 30 patients in the BSC group. The RCH CTx and BSC groups were compared for demographic and clinical features, laboratory parameters, and survival rates.

RESULTS: After the RGR failure, the median overall survival (OS) for the RCH CTx (n = 26) and BSC (n = 30) groups were 7.5 (95% CI, 6.3-8.7) months and 1.2 (95% CI, 0.9-1.5) months, respectively ($p < 0.001$). The median OS was 7.5 (95% CI, 6.3-8.7) months for the RCH CTx (n = 26) and 1.4 (95% CI, 0.3-2.4) months for the BSC (n = 14) groups when only the patients with an Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≤ 2 at progression with RGR treatment were compared, respectively (p < 0.001).

CONCLUSIONS: After the RGR failure, mCRC patients, especially those with a better ECOG-PS (≤ 2) and adequate organ function, should be considered candidates for RCH CTx instead of BSC.

Key Words:
Metastatic colorectal cancer, Regorafenib, Rechallenge chemotherapy, Chemosensitizing effect.

Abbreviations

mCRC: Metastatic colorectal cancer; EGFR: Epithelial growth factor receptor; VEGF: Vascular endothelial growth factor; RGR: Regorafenib; RCH CTx: Rechallenge chemotherapy; BSC: Best supportive care; ECOG PS: Eastern Cooperative Oncology Group Performance Status; CTC-AE: Common Terminology Criteria for Adverse Events; LDH: Lactate dehydrogenase; CEA: Carcinoembryonic antigen; CA 19-9: Cancer antigen 19-9; KRAS: Kirsten Rat Sarcoma viral oncogene homolog; NRAS: neuroblastoma RAS viral oncogene homolog; BRAF: v-raf murine sarcoma viral oncogene homolog B; WT: Wild-type; PFS: Progression-free survival; TTP: Time to progression; OS: Overall survival.

Introduction

Colorectal cancer is the fourth most common cancer and constitutes approximately 9% of cancer-related deaths[1]. Despite novel treatment approaches in the systemic treatment of metastatic colorectal cancer (mCRC) in recent years, it is still an incurable disease with a five-year overall survival of 14%[1]. Systemic treatment options such as 5-fluorouracil (5FU)-based chemotherapy (CTx) (5-fluorouracil, folinic acid, capecitabine, oxaliplatin, and irinotecan combinations) and targeted therapies (anti-epithelial growth factor receptor [EGFR] or anti-vascular endothelial growth factor [VEGF] agents) form the basis of systemic treatment in mCRC with an overall survival (OS) of more than 30 months[2-5].

Regorafenib (RGR) is a small molecule multikinase inhibitor targeting some angiogenic and stromal factors, mainly VEGF. In phase III, CORRECT and CONCUR trials and salvage therapy with RGR showed an OS benefit over placebo in the patients diagnosed with progressive mCRC after standard therapies[6,7]. Thus, RGR has become one of the standard treatment options in heavily pretreated patients. Furthermore, RGR may have a chemosensitizing effect since it has been shown that some patients may respond to CTx after RGR despite progressive disease with

Corresponding Author: Ermrah Eraslan, MD; e-mail: dremraheraslan@gmail.com

previous CTx regimens[8]. Under current treatment guidelines, there is no standard treatment option after RGR in progressive mCRC[9,10]. Therefore, the need for any treatment option is evident in patients who have received all standard treatment options, especially for those who are fit enough to tolerate a subsequent treatment line with sufficient organ function.

In our study, we aimed to compare the role of rechallenge (RCH) CTx consisting of the chemotherapeutics in previous treatment lines with best supportive care (BSC) in mCRC patients after standard CTx and subsequent RGR in terms of survival benefit.

Patients and Methods

Patients

There were 92 patients diagnosed with mCRC between July 2010 and March 2020 that received RGR after standard CTx lines at the University of Health Sciences Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital that were evaluated retrospectively. All patients had a histopathologically-confirmed diagnosis of adenocarcinoma. Patients who received at least one cycle of subsequent RGR therapy after standard treatments (CTx with or without targeted agents) and progressed with RGR were included in the study. Those who had received RGR treatment for less than one month (i.e., discontinuation of RGR due to treatment intolerance, Eastern Cooperative Oncology Group Performance Status [ECOG PS] deterioration, toxicity, liver, and kidney function deterioration) were excluded from the study. The patients who were lost to follow-up or had insufficient medical records were also excluded. The patients eligible for the study were subgrouped into RCH CTx and BSC groups. The RCH CTx group included the patients who received at least one of the chemotherapeutic agents they had received in the previous lines, while the BSC group included those who received the best supportive care without any antineoplastic agent.

Methods

Patient characteristics, ECOG PS values, pathological features, treatment responses, treatment toxicities, dose reduction rates, and laboratory parameters (serum albumin, LDH, CEA, CA 19-9) at progression with RGR treatment were obtained by reviewing the medical records. Treatment-related toxicities were assessed according to the Common Terminology Criteria for Adverse Events (CTC-AE) version 4.0; grade III-IV toxicities were recorded. Progression-free survival (PFS) for RGR and RCH CTx was calculated as the time from treatment initiation to the time of progression. The time from the day of diagnosis of metastatic disease to progression with RGR treatment was calculated as the time to progression (TTP). OS was calculated as the time from the diagnosis of metastatic disease to death or the last day the patient was known to be alive. Overall survival after RGR (OS-AR) was calculated as the time elapsed from progression with RGR to death or the last day known to be alive. We compared the RCH CTx and BSC groups for demographic and clinical features, laboratory parameters, and survival rates (PFS, TTP, OS).

The study was conducted after approval by the local Ethics Committee.

Statistical Analysis

Descriptive statistics were used to show the distribution of the main characteristics of the population. The groups' differences in categorical and ordinal parameters were evaluated using chi-square and Mann-Whitney U-tests, respectively. Survival rates were estimated using the Kaplan-Meier method, and the groups were compared using the log-rank test for differences in survival. Statistical analysis was performed using SPSS software (SPSS for Windows, version 24.0, SPSS Inc., Chicago, IL, USA). All statistical tests were two-sided, and a p-value of < 0.05 was considered statistically significant.

Results

There were 92 mCRC patients that received RGR treatment after the frontline therapies (CTx with or without targeted agents). 18 (19.6%) patients were excluded since they received the RGR treatment for less than one month. Of the 74 (80.4%) patients who received RGR treatment for at least one month, 5 (5.4%) discontinued follow-up, 5 (5.4%) were currently receiving RGR, and 8 (8.7%) patients with insufficient medical data were excluded from the study. 56 (60.9%) patients with a progressive disease with at least one month of RGR treatment and sufficient medical data were eligible for the study.

Patients

There were 56 patients with a median age of 59.4 (31.1-75.0) years included in the study, 22 (39.3%) female and 34 (60.7%) males. The median follow-up period was 33.1 (6.8-88.7) months. There were 47 (83.9%) patients diagnosed with a left-sided tumour. The rates for the wild type (WT), mutant, and unknown mutation status were 60.7% (n = 34), 37.5% (n = 21), and 1.8% (n = 1) for the KRAS mutation and 55.4% (n = 32), 3.6% (n=2), and 41.1% (n = 23) for the NRAS, respectively. No patients had a BRAF mutation. Of the patients who progressed with RGR treatment, 26 (46.4%) patients received RCH CTx, and 30 (53.6%) patients were followed up with BSC. The patients in both groups were similar in terms of demographic features (age and gender) and tumour characteristics (tumour localization, metastasis-related features, the proportions of patients with KRAS-WT, NRAS-WT, BRAF-WT tumours, and treatment responses to RGR). The groups had no difference in TTP. The rate of patients with better ECOG PS (≤ 2) was significantly higher in the RCH group (100% *vs.* 46.7%, $p < 0.001$). However, when we compared the patients with ECOG-PS (≤ 2) at progression with RGR treatment, we found that the patients in RCH CTx had a longer OS after progression with RGR ($p < 0.001$). The BSC group patients had significantly lower serum albumin levels and higher CEA and CA 19-9 levels than the RCH CTx group at the time of progression with RGR treatment ($p = 0.013$, $p = 0.037$, and $p = 0.023$, respectively). The comparison of patient and tumour characteristics are shown in Table I.

Rechallenge Chemotherapy (RCH-CTx)-Associated Features

There were 3 (11.5%), 22 (84.6%), and 1 (3.8%) patients in the RCH CTx group (n = 26) who received RCH CTx at the third, fourth, and fifth lines, respectively. There were 16 (61.5%) patients that received FOLFIRI (a combination of 5-fluorouracil, folinic acid, and irinotecan) or irinotecan CTx. Stable disease was obtained with RCH CTx in 7 (26.9%) patients. None of the patients had complete or partial remission. Grade 3-4 toxicity was observed in 4 (15.4%) patients, and the treatment was discontinued in 2 (7.7%) patients due to severe adverse effects. There was no toxic death. A chemotherapy dose reduction from 10% to 50% was performed in 5 (19.2%) patients. The features associated with RCH CTx are shown in Table II.

Survival

The median PFS for RGR treatment (n = 56) was 3.7 months (95% CI, 3.0-4.3). The median PFS for the RCH CTx treatment (n = 26) was 3.7 months (95% CI, 3.1-4.3).

The median OS for the RCH CTx (n = 26) and BSC (n = 30) groups were 40.4 (95% CI, 33.8-47.0) months and 26.7 (95% CI, 17.4–36.1) months, respectively ($p = 0.084$) (Figure 1A). The median OS-AR for the RCH CTx (n = 26) and BSC (n = 30) groups was 7.5 (95% CI, 6.3-8.7) and 1.2 (95% CI, 0.9-1.5) months, respectively ($p < 0.001$) (Figure 1B). The median OS-AR was 7.5 (95% CI, 6.3-8.7) months for the RCH CTx (n = 26) and 1.4 (95% CI, 0.3-2.4) months for the BSC (n = 14) groups when only the patients with an ECOG PS of ≤ 2 at progression with RGR treatment were compared, respectively ($p < 0.001$) (Figure 1C). Six (42.9%) of the 14 patients who progressed with RGR treatment and had an ECOG PS ≤ 2 could not receive RCH CTx due to hyperbilirubinemia. There were 8 (57.1%) out of 14 patients that did not receive RCH CTx due to other reasons (physician choice [n = 3, 37.5%], patient choice [n = 2, 25.0%], intrusive infection [n = 2, 25.0%] and urgent operation for kidney stones [n = 1, 12.5%]). When we compare these patients with those who received RCH CTx, the median OS-AR for the RCH CTx (n = 26) and BSC (n = 8) groups was 7.5 (95% CI, 6.3-8.7) and 2.3 (95% CI, 0.6-4.0) months ($p = 0.023$), respectively (Figure 1D).

Discussion

Under current treatment guidelines, RGR is recommended as a subsequent treatment option after standard treatment lines in mCRC, and there is no standard recommendation after RGR failure in this setting[9,10]. The median OS is around three years in mCRC; therefore, there is a need for the patients who have progressed after RGR therapy and are still candidates due to their good ECOG-PS for a new treatment option. Currently, insufficient literature data is matching this situation. Rechallenge treatment strategies may be considered as an option for mCRC patients, especially for those whose treatment options are exhausted after standard management. Our study evaluated whether RCH CTx with any previous chemotherapeutics had an OS benefit over BSC after standard lines of treatment for this popula-

Table I. The patient and tumor characteristics after progression with regorafenib (RGR) treatment.

Characteristic	RCH CTx n = 26 (39.3%)	BSC n = 30 (60.7%)	Total n = 56 (100%)	*p*-value
Age, median (IQR)	57.1 (52.9-64.2)	59.6 (51.0-65.1)	59.4 (51.3-64.3)	0.742
Gender				
Male	19 (73.1%)	15 (50.0%)	34 (60.7%)	0.103
Female	7 (26.9%)	15 (50.0%)	22 (39.3%)	
ECOG PS				
≤ 2	26 (100.0%)	14 (46.7%)	40 (71.4%)	< 0.001
> 2	0 (0.0%)	16 (53.3%)	16 (28.6%)	
Localization				
Right	4 (15.4%)	5 (16.7%)	9 (16.1%)	1.0
Left	22 (84.6%)	25 (83.3%)	47 (83.9%)	
Metastasis features				
Denovo metastatic	18 (69.2%)	15 (50.0%)	33 (58.9%)	0.176
Recurrence with metastasis	8 (30.8%)	15 (50.0%)	23 (41.1%)	
Number, median (range)[§]	2 (1-4)	2 (1-4)	2 (1-4)	0.813
Single Organ	4 (15.4%)	5 (16.7%)	9 (16.1%)	1.0
Multi Organ	22 (84.6%)	25 (83.3%)	47 (83.9%)	
KRAS-WT	17 (65.4%)	18 (60.0%)	35 (62.5%)	0.785
NRAS-WT	17 (65.4%)	14 (46.7%)	31 (55.4%)	0.187
Pan-RAS-WT	17 (65.4%)	16 (53.3%)	33 (58.9%)	0.422
BRAF-WT	13 (50.0%)	13 (43.3%)	21 (37.5%)	0.099
Previous Treatment Agents				
5FU/Capecitabine	26 (100.0%)	30 (100.0%)	56 (100.0%)	
Oxaliplatin	23 (88.5%)	25 (83.3%)	48 (85.7%)	0.712
Irinotecan	26 (100.0%)	30 (100.0%)	56 (100.0%)	
Cetuximab/Panitumumab	17 (65.4%)	16 (53.3%)	31 (55.4%)	0.422
Bevacizumab	23 (88.5%)	24 (80.0%)	47 (83.9%)	0.481
Ziv-Aflibercept	4 (15.4%)	3 (10.0%)	7 (12.5%)	0.693
Regorafenib	26 (100.0%)	30 (100.0%)	56 (100.0%)	
Laboratory parameters, median (IQR)[¶]				
Albumin (g/dL)	3.6 (3.0-4.0)	3.0 (2.6-3.6)	3.3 (2.8-3.8)	0.013
LDH (U/L)	353 (238-420)	427 (297-1231)	359 (251-454)	0.215
CEA (µg/L)	24 (15-288)	417 (55-1234)	107 (19-512)	0.037
CA 19-9 (U/mL)	65 (13-434)	1978 (125-5069)	148 (29-2371)	0.023
Response to regorafenib				
Clinical Benefit Rate	8 (30.7%)	9 (30.0%)	17 (30.4%)	1.0
PD	17 (69.4%)	21 (70.0%)	38 (67.9%)	
Total TTP[δ]	30.3 (26.3-34.4)	25.9 (17.4-33.7)	29.0 (23.9-34.1)	0.672

RCH CTx, rechallenge chemotherapy; BCS, best supportive care; ECOG PS, Eastern Cooperative Oncology Group Performance Status; [§]Number of metastatic organs; WT, wild type; [¶]Laboratory values at the time of progression with regorafenib treatment; LDH, lactate dehydrogenase; CEA, carcinoembryonic antigen; CA, cancer antigen; PD, progressive disease; [δ]Survival from the time of diagnosis of metastatic disease to the time of progression under regorafenib treatment.

tion. We found that in fit patients (an ECOG PS ≤ 2), a better OS was obtained with RCH CTx than with BSC.

The CORRECT study demonstrated that RGR provided approximately 1.5 months of OS benefit over placebo for mCRC patients after progression with standard chemotherapy regimens[6]. It was mentioned that the PFS curve in this study indicated the possibility of achieving different RGR treatment responses in different patient subgroups[6]. Moreover, 26% of the patients who progressed after RGR treatment received another treatment in the next line, although their outcomes were not published[6]. Thus, it can be considered that some patients may receive another treatment line after disease progression under RGR. It was reported that 83 patients with heavily pretreated mCRC might have responded to treatment with re-administration of oxaliplatin-containing CTx, and a time to treatment failure of approximately six months[11]. Kajitani et al[12] reported stable disease in seven of 13 patients with chemorefractory mCRC by re-administration of previous treatment schemes containing

Table II. Features associated with rechallenge chemotherapy.

Parameter	Number of Patients, n (%)
Chemotherapy scheme	
FOLFIRI	11 (42.3%)
FUFA/Capecitabine	7 (26.9%)
Irinotecan	5 (19.2%)
FOLFOX/CapeOx	3 (11.5%)
Treatment Response	
SD	7 (26.9%)
PD	17 (65.4%)
N/E	2 (7.7%)
Grade 3-4 toxicity	4 (15.4%)
Dose reduction	5 (19.2%)
Dose reduction ratio, median (range)	30 (10-50)

FOLFIRI, a combination of 5-fluorouracil, folinic acid, and irinotecan; FUFA, a combination of 5-fluorouracil and folinic acid; FOLFOX, a combination of 5-fluorouracil, folinic acid, and oxaliplatin; CapeOx, a combination of capecitabine and oxaliplatin; SD, stable disease; PD, progressive disease; N/E, not evaluated.

anti-EGFR antibodies in a prospectively designed study. They also noted that an anti-EGFR antibody re-administration could have provided a modest survival benefit with a median OS of approximately 7.5 months[12]. In a phase II study, a 21% (95% CI, 10%-40%) response rate and a 54% (95% CI, 36%-70%) rate of disease control were achieved by RCH of cetuximab plus irinotecan treatment as a third-line treatment in 28 patients with RAS and BRAF WT mCRC with acquired resistance to first-line cetuximab and irinotecan treatment[13]. These studies show that RCH treatment strategies can provide clinical benefits for some patients. However, it should be noted that the patients in these studies did not receive RGR, so these results may differ in the RGR era.

Ergun et al[14] compared RGR and capecitabine plus temozolomide treatment in the third-line treatment of mCRC and found that both treatment responses and OS were similar in the RGR and CTx groups. In contrast, Köstek et al[15] reported better OS with RCH CTx when compared to RGR as a third-line setting (12.0 [95% CI, 8.1-15.9] months *vs.* 6.6 [95% CI, 6.0-7.3] months, $p < 0.001$). However, it was not clear whether the patients in this study received any subsequent treatment or whether there was a difference between these two groups in this re-

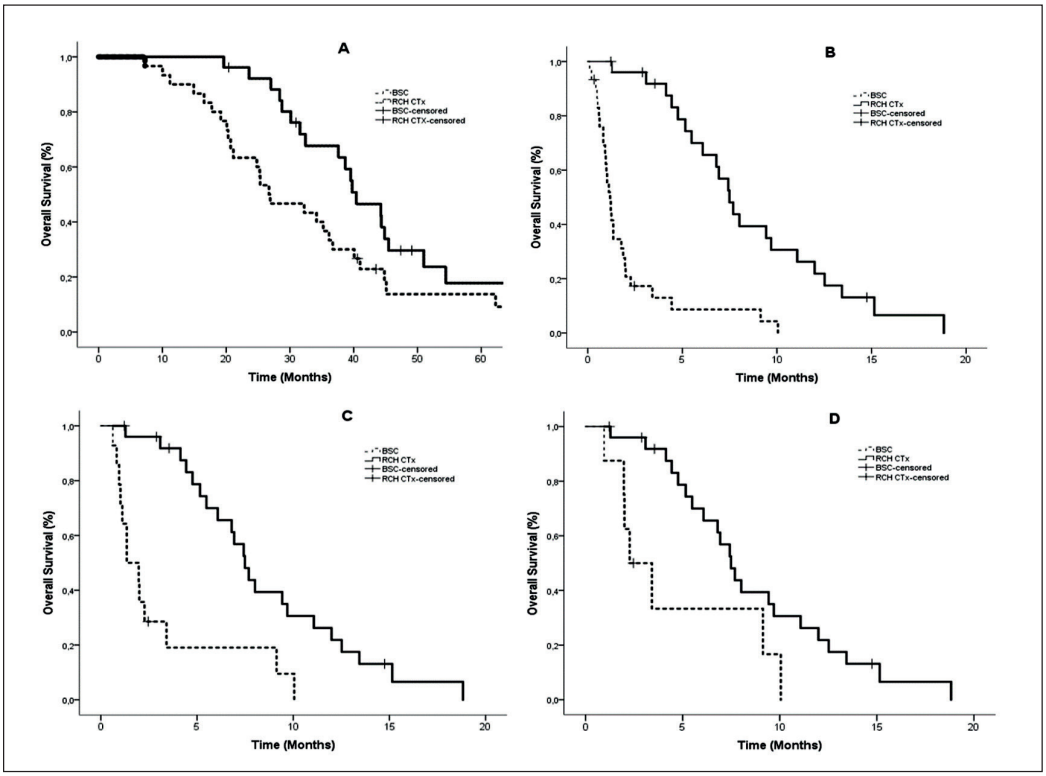

Figure 1. Overall survival. **A,** OS for patients receiving RCH CTx (n = 26) and BSC (n = 30). **B,** OS-AR for patients receiving RCH CTx (n = 26) and BSC (n = 30). **C,** OS-AR for patients receiving RCH CTx (n = 26) and BSC (n = 14) in patients with ECOG PS ≤2. **D,** OS-AR for patients receiving RCH CTx (n = 26) and BSC (n = 8) in patients fit enough to receive chemotherapy.

spect. Moreover, there was a difference between the two groups in terms of metastatic sites (i.e., liver metastasis [73.8% *vs.* 58.6%], lung metastasis [27.8% *vs.* 13.8%], and RAS mutation rates [60.6% *vs.* 26.7%]) and this suggests that the compared groups are not similar at baseline[15]. Currently, no robust literature data shows that RCH CTx is better than RGR in pretreated mCRC patients. Although treatment guidelines mention RCH therapies, they do not recommend it as a treatment option[9,10]. For this reason, RCH treatments before RGR seem not to be accurate. We consider that there might be a rationale for RCH therapies after standard treatment options, including RGR.

In a retrospective analysis, 14 (84%) of 17 mCRC patients who were given post-RGR standard treatments (regardless of whether the patient has had it before) were found to have a stabilized disease or treatment response[8]. Objective response to RCH CTx even with the previous progression with this chemotherapeutic in 2 (12%) of these patients suggests that RGR may be a chemosensitizing agent, probably due to a multikinase inhibitor effect on signalling pathways[8]. It has been discussed that treatment holidays or RCH treatment approaches might have reversed the epigenetic changes that might have had roles in drug resistance or breakdown of resistance through clonal selection mechanism, and so on for a long time[16,17]. A combination of RGR with fluoropyrimidine might lead to disease stabilization[18]. The authors reported that the combination of RGR and 5-FU had a synergistic antitumoural effect on colorectal cancer cells with KRAS, BRAF, and P53 mutations as well as mismatch repair-deficient cells in cell culture experiments[18]. These findings suggest that RGR treatment may help to overcome CTx resistance. Parseghian et al[19] evaluated the circulating tumour DNA profile in the post-progressive period of 135 patients who had RAS and/or EGFR mutations after anti-EGFR therapy though they had RAS/BRAF WT mCRC at diagnosis. This study supported the anti-EGFR RCH treatment rationale by showing that the relative mutant allele frequency of RAS and EGFR decreased exponentially with a cumulative half-life of 4.4 months[19]. However, there are limited data for RCH CTx after RGR though it is clearer for anti-EGFR RCH after RGR[20]. We consider that RCH CTx is an option for developing countries where rechallenging targeted agents are not reimbursed, as in Turkey.

The median PFS with previous RGR was also similar for both groups, eliminating the contribution of RGR response to subsequent RCH CTx survival outcomes compared to the BSC group. The RCH CTx group had a longer OS-AR despite no difference in previous PFS being achieved by RGR. We report a better OS in the RCH CTx group when compared to the BSC group in our study. The patients in the BSC group had worse ECOG PS and laboratory values as expected. These factors might be suspected as poor prognostic factors for OS. Therefore, we compared the patients according to ECOG PS in both groups. When we compared only the patients with an ECOG-PS ≤ 2 at progression receiving RGR in both groups, again the patients with an ECOG-PS ≤ 2 in the RCH CTx group had a significantly longer OS after progression when receiving RGR ($p < 0.001$). Thus, RCH CTx is an effective treatment for these patients.

Bertocchi et al[21] evaluated the role of RGR as a sensitising agent for CTx, and they reported the median OS as 2.1 months and a clinical benefit rate of 18.2% with CTx after progression when receiving RGR. Though their study design was similar to our study, we report better OS and response rates with a higher number of patients. In this study, 4 (36.4%) patients received RGR as the third-line treatment, and other patients received RGR at further lines[21]. However, in our study, only 1 (3.8%) patient received RGR in the fourth line, and none of our patients received it in further lines. The difference in survival and clinical benefit might be attributed to the difference in RGR treatment lines. We consider that RGR should not be used in further lines, and RCH CTx might be an option after progression with RGR.

The ECOG PS is a prognostic factor in cancer. The patients with a lower ECOG PS tolerate systemic treatment well, even in metastatic disease. Therefore, we compared the patients with a better ECOG PS (≤ 2) in the RCH CTx and BSC groups for OS. We considered that the patients with a better ECOG PS should be given RCH CTx after progression, with RGR as a subsequent treatment option. The conclusions of Takeuchi et al[22] support our study. They evaluated mCRC patients with an ECOG PS ≤ 2 after failure of the RGR treatment, and they reported that the patients who were given CTx after RGR had better OS than the BSC group (23.3 weeks *vs.* 9 weeks, $p = 0.0003$)[22]. Similarly, in our study, eight patients with a good ECOG PS (≤ 2) were also followed up with BSC though they could have had received RCH CTx.

We consider that this subgroup (i.e., BSC in the patients with an ECOG PS ≤ 2) might have been the ideal subgroup to be compared with those of an ECOG PS ≤ 2 in the RCH CTx group. However, this comparison was not possible due to the small number of patients.

We consider that RGR may be a chemosensitizer, and our hypothesis is supported by Tai et al[23]. They compared the sequential use of RGR and reduced-intensity FOLFOXIRI treatments in chemorefractory mCRC patients, and they reported a better OS (13.8 *vs.* 10.7 months, $p = 0.038$) with RGR as the first procedure rather than the reduced-intensity FOLFOXIRI as the first approach[23].

Conclusions

Rechallenge chemotherapy may be a treatment option in mCRC after standard treatment options, including RGR with a survival benefit and an acceptable toxicity profile. We consider that mCRC patients, especially those with a better ECOG-PS (≤ 2) and adequate organ function, should be considered candidates for RCH CTx instead of BSC. However, randomized clinical trial data are certainly.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020; 70: 7-30.
2) Heinemann V, von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran SE, Heintges T, Lerchenmüller C, Kahl C, Seipelt G, Kullmann F, Stauch M, Scheithauer W, Hielscher J, Scholz M, Müller S, Link H, Niederle N, Rost A, Höffkes HG, Moehler M, Lindig RU, Modest DP, Rossius L, Kirchner T, Jung A, Stintzing S. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. Lancet Oncol 2014; 15: 1065-1075.
3) Venook AP, Niedzwiecki D, Lenz HJ, Innocenti F, Fruth B, Meyerhardt JA, Schrag D, Greene C, O'Neil BH, Atkins JN, Berry S, Polite BN, O'Reilly EM, Goldberg RM, Hochster HS, Schilsky RL, Bertagnolli MM, El-Khoueiry AB, Watson P, Benson AB 3rd, Mulkerin DL, Mayer RJ, Blanke C. Effect of first-line chemotherapy combined with cetuximab or bevacizumab on overall survival in patients with KRAS wild-type advanced or metastatic colorectal cancer: a randomized clinical trial. JAMA 2017; 317: 2392-2401.
4) Schwartzberg LS, Rivera F, Karthaus M, Fasola G, Canon JL, Hecht JR, Yu H, Oliner KS, Go WY. PEAK: a randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type KRAS exon 2 metastatic colorectal cancer. J Clin Oncol 2014; 32: 2240-2247.
5) Van Cutsem E, Tabernero J, Lakomy R, Prenen H, Prausová J, Macarulla T, Ruff P, van Hazel GA, Moiseyenko V, Ferry D, McKendrick J, Polikoff J, Tellier A, Castan R, Allegra C. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. J Clin Oncol 2012; 30: 3499-3506.
6) Grothey A, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, Humblet Y, Bouché O, Mineur L, Barone C, Adenis A, Tabernero J, Yoshino T, Lenz HJ, Goldberg RM, Sargent DJ, Cihon F, Cupit L, Wagner A, Laurent D. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013; 381: 303-312.
7) Li J, Qin S, Xu R, Yau TC, Ma B, Pan H, Xu J, Bai Y, Chi Y, Wang L, Yeh KH, Bi F, Cheng Y, Le AT, Lin JK, Liu T, Ma D, Kappeler C, Kalmus J, Kim TW. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Oncol 2015; 16: 619-629.
8) Kidd MT, Wilcox RE , Rogers J, Eng C, Saadat S, Lenz HJ, Hubbard JM, Grothey A. Efficacy of chemotherapy after treatment with regorafenib in metastatic colorectal cancer (MCRC). Ann Oncol 2014; 25: ii85.
9) NCCN Clinical Practice Guidelines in Oncology, Colon Cancer Version 1.2021 https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf [Last accessed 17.01.2021]
10) Van Cutsem E, Cervantes A, Nordlinger B, Arnold D. Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014; 25: iii1-9.
11) Costa T, Nuñez J, Felismino T, Boente L, Mello C. REOX: Evaluation of the efficacy of retreatment with an oxaliplatin-containing regimen in metastatic colorectal cancer: a retrospective single-center study. Clin Colorectal Cancer 2017; 16: 316-323.
12) Kajitani T, Makiyama A, Arita S, Shimokawa H, Oda H, Shirakawa T, Baba E, Esaki T. Anti-epi-

dermal growth factor receptor antibody readministration in chemorefractory metastatic colorectal cancer. Anticancer Res 2017; 37: 6459-6468.

13) Cremolini C, Rossini D, Dell'Aquila E, Lonardi S, Conca E, Del Re M, Busico A, Pietrantonio F, Danesi R, Aprile G, Tamburini E, Barone C, Masi G, Pantano F, Pucci F, Corsi DC, Pella N, Bergamo F, Rofi E, Barbara C, Falcone A, Santini D. Rechallenge for patients with RAS and BRAF wild-type metastatic colorectal cancer with acquired resistance to first-line cetuximab and irinotecan: a phase 2 single-arm clinical trial. JAMA Oncol 2019; 5: 343-350.
14) Ergun Y, Bal O, Dogan M, Uncu D. Capecitabine plus temozolomide (CapTem): an alternative regimen to regorafenib as third-line setting in metastatic colorectal cancer? J BUON 2019; 24: 2435-2441.
15) Köstek O, Hacıoğlu MB, Sakin A, Demir T, Sarı M, Ozkul O, Araz M, Doğan AF, Demircan NC, Uzunoğlu S, Çiçin İ, Erdoğan B. Regorafenib or rechallenge chemotherapy: which is more effective in the third-line treatment of metastatic colorectal cancer? Cancer Chemother Pharmacol 2019; 83: 115-122.
16) Tonini G, Imperatori M, Vincenzi B, Frezza AM, Santini D. Rechallenge therapy and treatment holiday: different strategies in management of metastatic colorectal cancer. J Exp Clin Cancer Res 2013; 32: 1-8.
17) Kuczynski EA, Sargent DJ, Grothey A, Kerbel RS. Drug rechallenge and treatment beyond progression--implications for drug resistance. Nat Rev Clin Oncol 2013; 10: 571-587.
18) Marks EI, Tan C, Zhang J, Zhou L, Yang Z, Scicchitano A, El-Deiry WS. Regorafenib with a fluoropyrimidine for metastatic colorectal cancer after progression on multiple 5-FU-containing combination therapies and regorafenib monotherapy. Cancer Biol Ther 2015; 16: 1710-1719.
19) Parseghian CM, Loree JM, Morris VK, Liu X, Clifton KK, Napolitano S, Henry JT, Pereira AA, Vilar E, Johnson B, Kee B, Raghav K, Dasari A, Wu J, Garg N, Raymond VM, Banks KC, Talasaz AA, Lanman RB, Strickler JH, Hong DS, Corcoran RB, Overman MJ, Kopetz S. Anti-EGFR-resistant clones decay exponentially after progression: implications for anti-EGFR re-challenge. Ann Oncol 2019; 30: 243-249.
20) Sartore-Bianchi A, Siena S, Tonini G, Bardelli A, Santini D. Overcoming dynamic molecular heterogeneity in metastatic colorectal cancer: Multikinase inhibition with regorafenib and the case of rechallenge with anti-EGFR. Cancer Treat Rev 2016; 51: 54-62.
21) Bertocchi P, Aroldi F, Prochilo T, Meriggi F, Beretta GD, Zaniboni A. Chemotherapy rechallenge after regorafenib treatment in metastatic colorectal cancer: still hope after the last hope? J Chemother 2017; 29: 102-105.
22) Takeuchi N, Koike K, Yoshida S, Kudo A, Sekiguchi N, Nakayama A, Kubota K, Rokuhara T, Kitahara M. Treatment of metastatic refractory colorectal cancer following regorafenib failure. Mol Clin Oncol 2017; 7: 308-312.
23) Tai CC, Chen WS, Jiang JK, Yang SH, Wang HS, Chang SC, Lan YT, Lin CC, Lin HH, Huang SC, Cheng HH, Chao Y, Teng HW. Comparing lateline treatment sequence of regorafenib and reduced-intensity FOLFOXIRI for refractory metastatic colorectal cancer. Am J Clin Oncol 2020; 43: 28-34.