Single Center Real Life Experience with Regorafenib in Patients with Metastatic Colorectal Cancer

Metastatik Kolorektal Kanserli Hastalarda Regorafenib ile Tek Merkez Gerçek Yaşam Deneyimi

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ABSTRACT

Objective: To evaluate the clinical benefit of regorafenib in routine clinical practice.

Material and Methods: We retrospectively evaluated the data of 45 metastatic colorectal cancer (mCRC) patients who received regorafenib between January 2016 and November 2018.

Results: The median age of all patients was 54 years, and 66.7% of the patients were male. Performance status of 20 patients (44.4%) was 2, whereas in 25 patients (55.6%) it was 0-1. Thirty-six patients (80%) were performed primary tumor resection and KRAS mutation was detected in 53.3% of patients. Regorafenib was started at a dose of 160 mg in all patients, and a dose reduction was observed in 28.9% of patients. Line of regorafenib treatment was 3rd in 66.7% of patients, whereas in 33.3% of patients it was ≥ 4th. Best response was progressive disease (46.7%) and stable disease (35.6%). The median progression free survival (PFS) was 3.1 months (95% CI: 2.2-4.0) and overall survival (OS) was 6.4 months (95% CI: 3.2-9.5). Primary tumor resection status and using regorafenib ≥ 4 treatment line were significantly associated with both PFS and OS in multivariate analysis.

Conclusion: Regorafenib was associated with survival durations similar to those reported in both randomized controlled trials and in the real-life setting, and was generally well tolerated. Patients who had primary tumor resected and using regorafenib as the ≥ 4th treatment line (primary resected vs nonresected: PFS: 3.8 vs. 1.6 months, p: 0.006; OS: 6.1 vs. 3.1 months, p: 0.018, 3rd vs. 4th or more: PFS: 2.7 vs. 4.6 months, p:0.001; OS: 3.8 vs. 11.4 months, p:0.001) were associated with better PFS and OS. However, in order to explain the better survival with regorafenib in patients with primary tumor resected, this information must be confirmed with further studies.

Key Words: Regorafenib, Metastatic colorectal cancer, Survival

ÖZ

Amaç: Rutin klinik uygulamada regorafenibin klinik yararını değerlendirmektir.

Gereç ve Yöntemler: Ocak 2016 - Kasım 2018 tarihleri arasında regorafenib alan 45 metastatik kolorektal kanser hastasının verilerini retrospektif olarak değerlendirdik.

Bulgular: Tüm hastaların ortanca yaşı 54 ve %66.7'si erkek hastaydı. Yirmi hastanın (%44.4) performans durumu 2 iken, 25 hastada (%55.6) 0-1 idi. Otuz altı hastanın (%80) primer tümörü rezekeydi ve hastaların %53.3'ünde KRAS mutasyonu vardı. Tüm hastalarda regorafenib başlangıç dozu 160 mg idi ve hastaların %28.9' una doz redüksiyonu uygulanmış olduğu görüldü. Regorafenib tedavisini hastaların %66.7'si 3. basamakta almış iken, %33.3'ünde 4. basamak veya daha sonrasında almıştı. Regorafenib ile elde edilen en iyi yanıt progresif hastalık (%46.7) ve stabil hastalık (%35.6) idi. Ortanca progresyonsuz sağkalım 3.1 ay (%95 CI: 2.2-4.0) ve genel sağkalım 6.4 ay (%95 CI: 3.2-9.5) idi. Primer tümörün rezeksiyon durumu ve regorafenibin ≥ 4 basamak tedavi olarak kullanımı çok değişkenli analizde hem progresyonsuz sağkalım hem de genel sağkalım ile anlamlı şekilde ilişkiliydi.

Sonuç: Regorafenib, bizim hastalarımızda da hem randomize kontrollü çalışmalarda hem de gerçek yaşam ortamında bildirilenlere benzer hayatta kalma süreleriyle ilişkiliydi ve genellikle iyi tolere edildi. Primer tümör rezeke edilen ve regorafenibi ≥ 4 basamak tedavi olarak kullanan hastalar istatistiksel

olarak daha iyi progresyonsuz sağkalıma ve genel sağkalıma sahipti (regorafenib 3. vs ≥ 4. basamak tedavi: PFS: 2.7 vs 4.6 ay, p:0.001; OS: 3.8 vs 11.4 ay, p:0.001, primeri rezeke vs rezeke olmayan: PFS: 3.8 vs 1.6 ay, p: 0.006; OS: 6.1 vs 3.1 ay, p: 0.018). Primer tümörü rezeke edilen hastalarda regorafenib ile daha iyi sağkalım oluşunu açıklamak ve bu bilgiyi doğrulamak için başka çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: Regorafenib, Metastatik kolorektal kanser, Sağkalım

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer affecting both men and women (1). At diagnosis, approximately 20% of individuals have distant metastases. The treatment for metastatic CRC (mCRC) is palliative and not curative, and the treatment goals are to prolong survival and maintain quality of life for as long as possible. The current advances in systemic treatment have improved median survival.

Regorafenib is an oral multikinase inhibitor and inhibits VEGFR-1 to 3, RET, KIT, platelet-derived growth factor receptor (PDGFR) alpha and beta, and fibroblast growth factor receptor (FGFR) 1 and 2. In two phase III trials including the CORRECT and CONCUR trial performed in patients with mCRC who had progressed after multiple standard treatment, regorafenib demonstrated a statistically significant improvement in both median overall survival (OS) and progression-free survival (PFS) compared with placebo. Also, the disease control rate was significantly higher with regorafenib (2,3).

In this retrospective study, we evaluated the clinical benefit of regorafenib in patients with mCRC in our cohort.

MATERIALS and METHODS

We retrospectively evaluated the data of 45 mCRC patients who received regorafenib between January 2016 and November 2018 at the Medical Oncology Department of Necmettin Erbakan University Hospital. The age, sex, side of primary tumor, Eastern Cooperative Oncology Group Performance Status (ECOG PS), baseline presentation (metastatic or nonmetastatic), KRAS/NRAS/BRAF mutation results, resection status of the primary tumor, previous chemotherapy, anti-VEGF and anti-EGFR treatment, and laboratory data were recorded. In addition, we evaluated the regorafenib starting dose, the causes of withdrawal, the best response rate, the treatment line, adverse effects, and dose reduction.

The best response to regorafenib was defined with a computed tomography (CT) scan as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) based on the RECIST criteria (version 1.1). The laboratory and clinical adverse effects of regorafenib treatment were calculated using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03.

Statistical Analyses

Statistical analysis was performed by using SPSS software version 22.0. Descriptive statistics were calculated as proportions and medians. The Kaplan-Meier method was used for the survival analysis. Progression-free survival was calculated from the date of starting regorafenib till the date of radiological progression or death. Overall survival was calculated from the date of starting regorafenib till death. PFS and OS were analyzed according to sex, side of primary tumor (right vs. left), baseline presentation (metastatic vs. nonmetastatic), primary tumor resection, KRAS status, previous anti-EGFR treatment, line of regorafenib treatment (3rd vs 4th or more), and regorafenib dose reduction. A log-rank analysis was performed to compare the different subgroups. The Cox proportional hazards model was used for univariate and multivariate analysis. A p value of <0.05 was considered significant. We also calculated the 95% CI for the median time to event.

RESULTS

Patients' Characteristics

A total of 45 patients with mCRC receiving regorafenib were enrolled in this study. The median age at diagnosis was 54 years (24-81 years), and the majority of the patients was male (66.7%). ECOG PS was 2 in 44.4% of the patients. The primary tumor was left sided in 84.4% and right sided in 15.6%. Most patients had metastatic disease at initial diagnosis (55.6%), and more than half of the patients had undergone primary tumor resection (80%). Twenty four (53.3%) patients had a KRAS mutation, 1 (2.2%) patient had NRAS mutation, and 4 patients (4.4%) had a BRAF mutation. All patients had previously been treated with fluorouracil (FU), irinotecan, and oxaliplatin-based chemotherapy. The number of patients who received bevacizumab and aflibercept as an anti-VEGF treatment before regorafenib was 45 (100%) and 2 (4.4%), respectively. Also, 16 patients (35.6%) had received an anti-EGFR treatment including cetuximab and panitumumab before regorafenib (Table I).

Regorafenib Using

Regorafenib was started at the initial dose of 160 mg as recommended for all patients. The line of regorafenib treatment was 3rd for 66.7% of patients, and 4th or more 33.3% of the patients. A dose reduction was required in 28.9% of patients. The regorafenib dose during treatment was 160

Table I: Demographic and disease characteristics of patients.

Number of patients	**n (%)**
	45 (%)
Characteristic at diagnosis	
Median Age, Years	54
Age Range, Years	24-81
ECOG PS	
0	13 (28.9)
1	12 (26.7)
2	20 (44.4)
Sex	
Female	15 (33.3)
Male	30 (66.7)
Side of primary tumor	
Right	7 (15.6)
Left	38 (84.4)
Baseline presentation (at initial diagnosis)	
Metastatic	25 (55.6)
Nonmetastatic	20 (44.4)
Primary tumor resection	
Yes	36 (80)
No	9 (20)
KRAS mutation	
Wild	21 (46.7)
Mutant	24 (53.3)
NRAS mutation	
Wild	31 (68.9)
Mutant	1 (2.2)
Unknown	13 (28.9)
BRAF mutation	
Wild	30 (66.7)
Mutant	2 (4.4)
Unknown	13 (28.9)
Previous anti-VEGF treatment	
Bevacizumab	45 (100)
Aflibercept	2 (4.4)
Previous anti-EGFR treatment	
Yes	16 (35.6)
No	29 (64.4)

VEGF: Vascular endothelial growth factor receptor, **EGFR:** Epidermal growth factor receptor. **ECOG PS:** Eastern Cooperative Oncology Group Performance Status.

mg (71.1%), 120 mg (6.7%), or 80 mg (22.2%). The most common cause of regorafenib discontinuation was progressive disease (75.6%). The response rate to regorafenib was 46.7% PD, 35.6 % SD, and 2.2% PR (Table II).

Toxicity Profile

Details of all toxicities reported by patients and the laboratory abnormalities developing during regorafenib treatment were reported in Table III. The most frequent grade 1/2 and grade 3/4 adverse effect reported by patients was fatigue (15.6% vs 20%), and the most frequent grade 1/2 laboratory abnormality was hyperbilirubinaemia (22.2%), and the most frequent grade 3/4 laboratory abnormality was hypophosphataemia (24.4%).

Outcomes

The median PFS and OS were 3.1 months (95% CI: 2.2-4.0) and 6.4 months (95% CI: 3.2-9.5), respectively (Figure 1, 2).

In univariate analysis, there was no significant difference in PFS or OS according to sex (female vs. male), side of primary tumor (right vs. left), KRAS mutation (wild vs.

Table II: Regorafenib use, dose, and best response rates.

Number of patients	**n (%)**
	45
Line of regorafenib treatment	
3rd	30 (66.7)
4th or more	15 (33.3)
Regorafenib starting dose	
160 mg	45 (100)
Regorafenib dose reduction	
Yes	13 (28.9)
No	32 (71.1)
Regorafenib dose during treatment	
160 mg	32 (71.1)
120 mg	3 (6.7)
80 mg	10 (22.2)
Reasons for discontinuation of regorafenib (*n*:41)	
Progressive disease	34 (75.6)
Intolerance	7 (15.6)
Response rate to regorafenib	
Partial Response	1 (2.2)
Stable Disease	16 (35.6)
Progressive Disease	21 (46.7)
NE*	7 (15.6)

***NE:** Not evaluated because regorafenib could not be tolerated.

mutant), previous antiEGFR treatment (yes vs. no), and regorafenib dose reduction (yes vs. no). PFS and OS had statistical significance according to baseline presentation (at diagnosis) (metastatic vs. nonmetastatic, PFS: 2.7 vs. 5.4 months, p: 0.005; OS: 4 vs. 7.8 months, p: 0.085), primary tumor resection (primary resected vs. nonresected, PFS: 3.8 vs 1.6 months, p: 0.006; OS: 6.1 vs. 3.1 months, p: 0.085), and line of regorafenib (3rd vs 4th or more, PFS: 2.7 vs. 4.6 months, p:0.002; OS: 3.8 vs. 11.4 months, p:0.003) in univariate analysis (Table IV). Multivariate analysis was therefore performed, and primary tumor resection status and line of regorafenib treatment were found to be of statistical significance for both PFS (p: 0.006 and 0.001, respectively) and OS (p: 0.018 and 0.001, respectively) (Table V).

Table III: Treatment-related adverse events.

Adverse events	Grade 1/2	Grade 3/4
	n (%)	n (%)
Clinical adverse event		
Fatigue	7 (15.6)	9 (20)
Diarrhea	1 (2.2)	0
Oral mucositis	2 (4.4)	0
Laboratory abnormalities		
Anemia	7 (15.6)	0
Neutropenia	1 (2.2)	0
Thrombocytopenia	6 (13.3)	0
Hyperbilirubinaemia	10 (22.2)	3 (6.7)
AST/ALT elevation	4 (8.9)	1 (2.2)
Hypophosphataemia	4 (8.9)	11 (24.4)

DISCUSSION

In this retrospective study, we found that the median PFS was 3.1 months and median OS was 6.4 months in patients with mCRC who received regorafenib.

Phase 3 CONCUR and CORRECT trials showed the OS benefit with the addition of regorafenib to best supportive treatment in mCRC patients who had progressed with standard treatments (2,3). Overall survival was 8.8 months in the CONCUR trial and 6.4 months in the CORRECT trial. Progression-free survival was 3.2 months in the CONCUR trial and 1.9 months in the CORRECT trial. These results show that the CONCUR trial results are better than the CORRECT trial. However, no predictive factors for OS have been identified for these trials. It is thought that this difference may be related to using bevacizumab before regorafenib because all patients had previously received bevacizumab in the CORRECT trial but this was valid for 60% of the patients in the CONCUR trial. However, this has not been proven. In our study, OS was similar to that of the CORRECT trial but PFS was better than in the CORRECT trial. The ECOG PS in these trials was 0-1 but 44.4% of our patients had PS more than once and all of our patients had previously received bevacizumab as in the CORRECT trial. In the phase 3b CONSIGN study of regorafenib, median PFS was 2.7 months, ECOG PS was 0-1, and 46% of patients had a dose reduction (4). In the REBECCA study evaluating the effectiveness of regorafenib in real life, OS was 5.6 months and 92% of patients had previously received bevacizumab. Poor ECOG PS, a shorter time from initial diagnosis of metastases, an initial

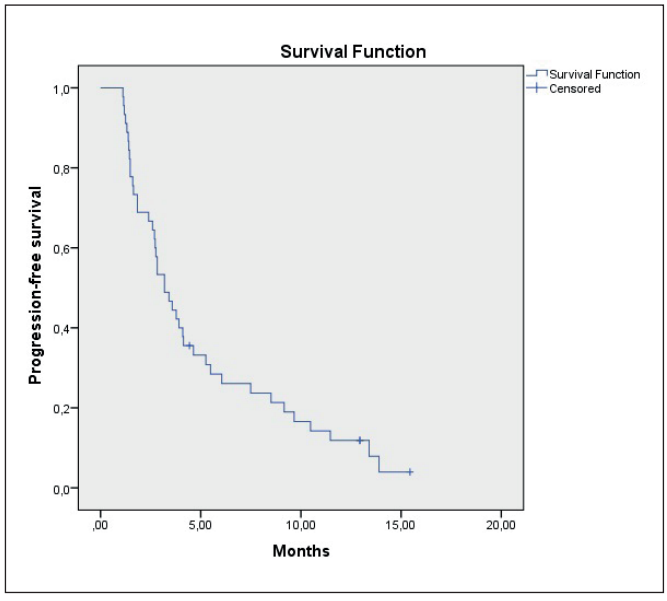


Figure 1: Kaplan-Meier curve of progression-free survival of patients treated with regorafenib.

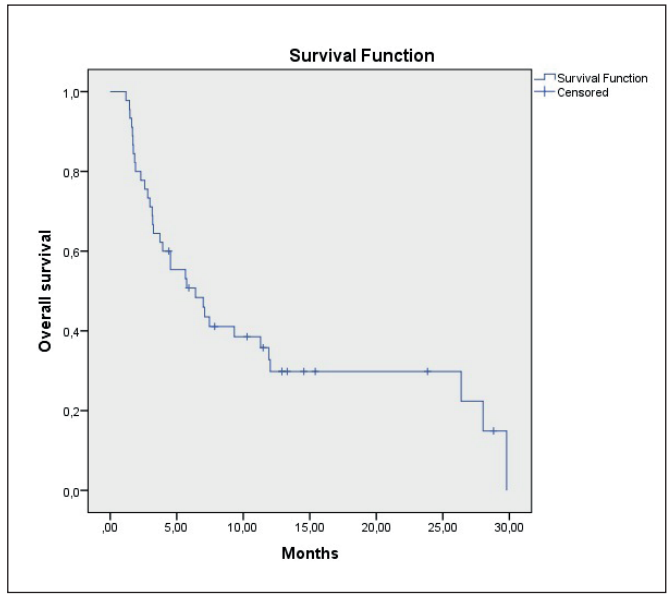


Figure 2: Kaplan-Meier curve of overall survival of patients treated with regorafenib.

regorafenib dose <160 mg, >3 metastatic sites, liver metastases, and KRAS mutations were found to be independently associated with poorer survival (5). In another multi-institutional retrospective study including patients who had previously received bevacizumab at a rate of 79%, median PFS was 2.8 months and OS was 8.0 months, and it has been found that only ECOG PS≤1 had a statistically significant impact on PFS and OS (6). In other studies evaluating real

Table IV: Univariate analysis of different variables affecting PFS and OS in patients treated with regorafenib.

Item	PFS (mo) (95% CI)	*p*	OS (mo) (95% CI)	*p*
Sex				
Female	2.7 (2.17-5.35)	0.128	3.2 (2.61-12.14)	0.212
Male	3.6 (3.73-7.13)		6.1 (6.16-11.88)	
Side of primary tumor				
Right	2.8 (1.08-8.42)	0.737	3.2 (3-3.5)	0.814
Left	3.3 (3.52-6.28)		6.1 (3.79-10.35)	
Baseline presentation (at initial diagnosis)				
Metastatic	2.7 (2.28-4.07)	0.005	4 (3.68-8.9)	0.085
Nonmetastatic	5.4 (4.55-9.08)		7.8 (6.85-15.09)	
Primary tumor resection				
Yes	3.8 (4.05-6.98)	0.006	6.1 (6.39-12.07)	0.085
No	1.6 (1.32-3.28)		3.1 (1.66-9.23)	
KRAS mutation				
Wild	2.7 (2.33-5.53)	0.167	4.4 (3.73-10.6)	0.254
Mutant	3.6 (3.8-7.6)		6.7 (6.14-13.09)	
Previous anti-EGFR treatment				
Yes	2.9 (2.21-6.28)	0.483	4.4 (3.62-12.45)	0.618
No	3.4 (3.59-6.86)		6.4 (5.72-11.7)	
Line of regorafenib treatment				
3rd	2.7 (2.52-4.60)	0.002	3.8 (3.93-8.69)	0.003
4th or more	4.6 (4.66-10.3)		11.4 (7.74-17.8)	
Regorafenib dose reduction				
Yes	3 (2.56-5.58)	0.228	5.7 (4.16-12.77)	0.885
No	3.4 (3.54-7.09)		6.4 (5.44-11.51)	

PFS: Progression-free survival, **OS:** Overall survival, **CI:** Confidence interval, **EGFR:** Epidermal growth factor receptor.

Table V: Multivariate analysis of different variables affecting PFS and OS in patients treated with regorafenib.

Item	PFS			OS		
	p	HR	95% CI	*p*	HR	95% CI
Baseline presentation (at initial diagnosis) (metastatic vs. nonmetastatic)	0.059	0.4	0.21-1.02	0.311	0.6	0.30-1.46
Primary tumor resection (yes vs. no)	0.006	3.3	1.40-7.97	0.018	3.1	1.21-8.07
Line of regorafenib treatment (3rd vs. 4th or more)	0.001	3.9	1.79-8.69	0.001	3.9	1.93-13.49

PFS: Progression-free survival, **OS:** Overall survival, **HR:** Hazard ratio, **CI:** Confidence interval.

life data, regorafenib was associated with a survival similar to that reported in the randomized controlled trials (7-11).

Having the primary tumor resected and using the regorafenib as the ≥ 4th treatment line in our patients was statistically significantly better for both PFS and OS. Among our patients, 36 (80%) had undergone primary tumor resection and 20 patients (44.4%) were not metastatic at the time of diagnosis. The primary tumor was resected in 16 patients who were metastatic at the time of diagnosis. The better survival rate in patients who regorafenib had received it as the 4th or more treatment line can be explained by the slower course of disease in these patients. However, in order to explain the better survival with regorafenib in patients with the primary tumor resected, this information must be validated by designing another study such as regorafenib activity in patients who had metastases at diagnosis with and without resection of the primary tumor.

We did not find an association between survival and sex, side of primary tumor, KRAS mutation status, and previous antiEGFR treatment. The most common cause of regorafenib discontinuation was disease progression. A response (stable disease or partial response) was seen in 37.8% of our patients and this was similar to the CORRECT trial (40%). Regorafenib was started with a standard 160 mg dose for all of our patients, and our patients tolerated regorafenib better at the starting dose as only 28.9% of patients had a dose reduction. A greater proportion of patients requiring a dose reduction was found in the CORRECT, REBECCA, and CONSIGN studies (2,5,4). In a study retrospectively evaluating response to regorafenib at an initial dose of 120 mg, disease control rates at the initial dose of 160 mg and 120 mg of regorafenib were similar (12). Furthermore, patients in an Indian exploratory analysis study were evaluated based on the initial dose of regorafenib received (80, 120, or 160 mg), and no statistically significant difference was found between the three groups for PFS (10). In another study, among 134 patients using regorafenib at initial dose of 80 mg vs. 120 mg vs. 160 mg, response rate, disease control rate, and PFS (13). Overall survival was not associated with the initial dose (≤160 mg) in a prospective observational study including 1227 patients evaluating the safety and effectiveness of regorafenib (14). In the Phase II ReDOS trial, regorafenib was started with 80 mg daily, once a week, and a dose-escalation strategy was applied when there was no treatment-related toxicity. Median OS was better in patients who underwent dose escalation, although not statistically significant, and toxicity was less (15). Also, we did not find an association between survival and regorafenib dose reduction. Based on the data in these studies, the starting lower doses for regorafenib is safe and effective.

The most common grade 1-2 treatment-related laboratory toxicity in our patients was hyperbilirubinemia (22.2%), whereas the most common grade 3-4 laboratory toxicity was hypophosphatemia (24.4%). We did not find any unexpected laboratory toxicity with regorafenib as compared with previously reported data. The most common grade 1-2 treatment-related clinical adverse effects were fatigue (15.6%), oral mucositis (4.4%), and diarrhea (2.2%). However, hand-foot skin reaction and hypertension were not reported by the patients or information was not recorded in file. Therefore, we think that it is inappropriate to make a healthy comment on clinical side effects.

CONCLUSIONS

Regorafenib was associated with survival durations similar to those reported in both randomized controlled trials and in the real-life setting. Although, most of our patients were ECOG PS 2 and all of them started with regorafenib 160 mg/day, regorafenib was generally well tolerated, and discontinuation rate of regorafenib because of intolerance or toxicity was low. As the study was a retrospective study, we thought that clinical toxicity data would not be accurate and would not be fully evaluated. Patients who had primary tumor resected and using regorafenib as the ≥ 4th treatment line had better PFS and OS. Because of our small sample, further studies involving more patients are needed to confirm this information.

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