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Prognostic factors influencing regorafenib treatment outcomes in metastatic colorectal cancer

Metastatik kolorektal kanserde regorafenib tedavi sonuçlarını etkileyen prognostik faktörler

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Abstract

Aim: We aimed to determine the efficacy and prognostic factors of Regorafenib in advanced colorectal cancer patients.

Materials and Methods: This study was designed as single-center and retrospective. The study included 72 patients with metastatic colorectal cancer treated with Regorafenib. Univariate and multivariate analyses of factors affecting survival were generated by Cox Regression Models.

Results: Twenty-three (31.9%) of the patients were female, the median age was 65 years. The median progression-free survival (PFS) and overall survival (OS) were 4.13 and 8.7 months, respectively. The carcinoembryonic antigen (CEA) level (p=0.001), and Eastern Cooperative Oncology Group (ECOG) score (p<0.001) were found to be prognostic in the multivariate model for PFS. ECOG (p<0.001), CEA level (p<0.001), dose reduction (p=0.003), and side of the primary tumor (p=0.037) were prognostic for OS.

Conclusion: Our study revealed that ECOG, requiring dose reduction during the treatment, and lower baseline CEA levels were found to be prognostic.

Keywords: Regorafenib; Advanced colorectal cancer; Survival.

Öz

Amaç: Metastatik kolorektal kanserli hastalarda Regorafenib'in etkinliğini ve prognostik faktörlerini belirlemeyi amaçladık.

Gereç ve Yöntem: Bu çalışma tek merkezli ve retrospektif olarak tasarlandı. Çalışmaya Regorafenib ile tedavi edilen 72 metastatik kolorektal kanserli hasta dahil edildi. Sağkalımı etkileyen faktörlerin tek değişkenli ve çok değişkenli analizleri Cox Regresyon Modelleri ile oluşturuldu.

Bulgular: Hastaların yirmi üçü (%31,9) kadındı ve medyan yaş 65 idi. Hastalara ait medyan progresyonsuz sağkalım (PFS) ve toplam sağkalım (OS) sırasıyla 4,13 ay ve 8,7 aydı. Karsinoembriyonik antijen (CEA) seviyesi (p=0.001) ve Eastern Cooperative Oncology Group (ECOG) Skoru (p<0,001) PFS için çok değişkenli Cox-regresyon modelinde prognostik bulunmuştur. OS için yapılan çok değişkenli modelde ECOG (p<0,001), CEA (p<0,001), doz azaltımı (p=0,003), primer tümörün olduğu taraf (p=0,037) prognostik olarak bulundu.

Sonuç: Çalışmamız, ECOG skoru, tedavi sırasında doz azaltımı, ve daha düşük başlangıç CEA seviyelerinin OS için prognostik olduğunu ortaya koydu.

Anahtar Kelimeler: Regorafenib; İleri-Evre kolorektal kanser; Sağkalım.

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Introduction

Colorectal cancer (CRC) is a common and lethal disease. According to 2023 cancer statistics data, CRC is the third most diagnosed cancer in men and the second most common in women.[1] Incidence and mortality rates are substantially higher among men than among women. In the United States and many other countries, CRC mortality rates have steadily declined since the mid-1980s. This improvement can be attributed to the earlier detection of CRC and the increased efficacy of primary and adjuvant therapies.[2,3] However, approximately a quarter of newly diagnosed colorectal cancers have an advanced-stage disease at presentation, and some others may develop metastatic disease after potentially curative treatment of localized disease. In the era of fluorouracil as the only active agent, overall survival was approximately 11 to 12 months, but nowadays the average median survival is approaching three years.[4]

Regorafenib is an alternative treatment for metastatic colorectal cancer (mCRC) patients who have been previously treated and failed with chemotherapy, and who are willing to receive additional cancer treatment. Regorafenib provides anti-angiogenesis by activating multi-kinase VEGF receptor inhibition.[5,6] For patients with treatment-refractory mCRC, advanced gastrointestinal stromal tumors after imatinib and sunitinib, and unresectable hepatocellular carcinoma following sorafenib, Regorafenib is an approved alternative medication.[7] Effectiveness in refractory mCRC was first reported in the CORRECT study, where patients who progressed after multiple standard therapies were assigned to regorafenib (160 mg orally once daily, three times every four weeks) or placebo in addition to best supportive care.[8] As shown in the CORRECT study, the efficacy of regorafenib was subsequently verified in the multicenter CONCUR study, in which 204 Asian patients with mCRC who had progressed after standard therapies were randomly assigned to regorafenib or placebo.[9]

We aimed to elucidate the effect of regorafenib on survival as well as prognostic factors affecting the duration of response in mCRC.

Materials and Methods

This study was designed as a single-center and retrospective study. The study included patients with metastatic colorectal cancer who were treated with Regorafenib between 2012 and 2022. The following patients were included in the study: *1)* patients with pathologically proven colorectal cancer; *2)* 18 years of age or older; *3)* with at least one comparable metastatic site confirmed using imaging methods; *4)* no history of concomitant or prior malignancy. Patients receiving immunotherapy were excluded.

All patients received standard chemotherapy for metastatic disease and disease progression during or after the last treatment. Standard imaging modalities (computed tomography, magnetic resonance imaging, and positron emission tomography) used in the center were considered to assess response to treatment. Patients' characteristics such as age, sex, side of the primary tumor, Eastern Cooperative Oncology Group Performance (ECOG) score, initial presentation (de-novo or recurrent), RAS mutation results, anti-vascular endothelial growth factor (VEGF), and anti-epidermal growth factor receptor (EGFR) treatment, carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19.9) measurement prior the Regorafenib treatment were recorded from the hospital electronic data record system. The institutional ethics committee approved this study, which was conducted in accordance with the ethical standards of the Declaration of Helsinki.

Statistics

Progression-free survival (PFS) was defined as the time from the start of Regorafenib until any documented clinical progression, relapse, or death from any cause. Overall survival (OS) was defined as the time from the start of Regorafenib treatment until death from any cause. SPSS version 26.0 package program was used for statistical analyses. Survival plots were performed using the Kaplan-Meier curves. Univariate and multivariate analyses of factors affecting

survival were generated by Cox Regression Models. CEA and CA 19.9 levels prior to the Regorafenib treatment were categorized into two groups according to median level. Statistical significance was defined as a *p-value* <0.05.

Results

A total of 72 patients with mCRC were included in this study. Twenty-three (31.9%) of the patients were female, the median age was 65 years and the number of patients with ECOG score ≥2 was 18 (25%). Colon cancer and rectal cancer rates in the patient population were equal. While 8 patients (11.1%) had right-side tumors, the rate of ras mutant patients was 47.2%. Thirty-one patients (43.1%) were de-novo metastatic at baseline, while 52 patients (72.2%) underwent surgery for the primary tumor. The number of patients receiving anti-VEGF therapy was 59 (81.9%), while the percentage of patients receiving anti-EGFR therapy was 52.8%. Patients who received regorafenib treatment at the 4th line or more were 10 (13.9%). Prior to Regorafenib treatment, the median CEA value was 58 mg/dL, while the median CA 19.9 level was 74 mg/dL (Table 1).

Table 1. Clinical-pathological characteristics.

Variable	n (%)
Age	
<65	35 (48.6)
≥65	37 (51.4)
Sex	
male	49 (68.1)
female	23 (31.9)
ECOG	
0-1	54 (75)
≥2	18 (25)
Type of tumor	
colon	36 (50)
rectum	36 (50)
Side of primary tumor	
right side	8 (11.1)
left side	64 (88.9)
Ras Mutation	
yes	34 (47.2)
no	38 (52.8)
Presentation at initial diagnosis	
de-novo metastatic	31 (43.1)
recurrent metastatic	41 (56.9)
Surgery for primary tumor	
yes	52 (72.2)
no	20 (27.8)
Radiotherapy for primary tumor	
yes	18 (25)
no	54 (75)
Anti-VEGF treatment	
yes	59 (81.9)
no	13 (18.1)
Anti-EGFR treatment	
yes	38 (52.8)
no	34 (47.2)
Line of regorafenib treatment	
3rd	62 (86.1)
4th or above	10 (13.9)
Best response to Regorafenib	
Partial Response	2 (2.8)
Stable Disease	22 (30.6)
Progressive Disease	48 (66.7)
Dose reduction	
yes	33 (45.8)
no	39 (54.2)
CEA	
≥58	35 (48.6)
<58	37 (51.4)
CA 19.9	
≥74	36 (50)
<74	36 (50)

%: percent, ECOG: Eastern Cooperative Oncology Group, VEGF: Vascular endothelial growth factor receptor, EGFR: Epidermal growth factor receptor

Progression and survival time

The median PFS and OS for regorafenib-treated patients were 4.13 months and 8.7 months, respectively (Figure 1).

In the univariate analysis for PFS; age (<65 vs. ≥65), sex (female vs male), type of tumor (colon vs rectum), side of the primary tumor (right vs left), Ras mutation (yes vs no), anti-VEGF treatment (yes vs no), anti-EGFR treatment (yes vs no), line of regorafenib treatment (3rd vs 4th or above), dose reduction (yes vs no) showed no significant difference, while ECOG PS (p<0.001), presentation at initial diagnosis (p=0.015), surgery for primary tumor (p=0.033), CEA level (p=0.014), CA 19.9 level (p=0.024) were found to be statistically significant (Table 2). The CEA level {Hazard Ratio (HR)=5.70, 95% Confidence Interval (CI): 1.46-10.60, p=0.001}, and ECOG score (HR=2.46, 95% CI: 1.46-4.16, p<0.001) remained statistically prognostic in the multivariate Cox-regression model for PFS (Table 3).

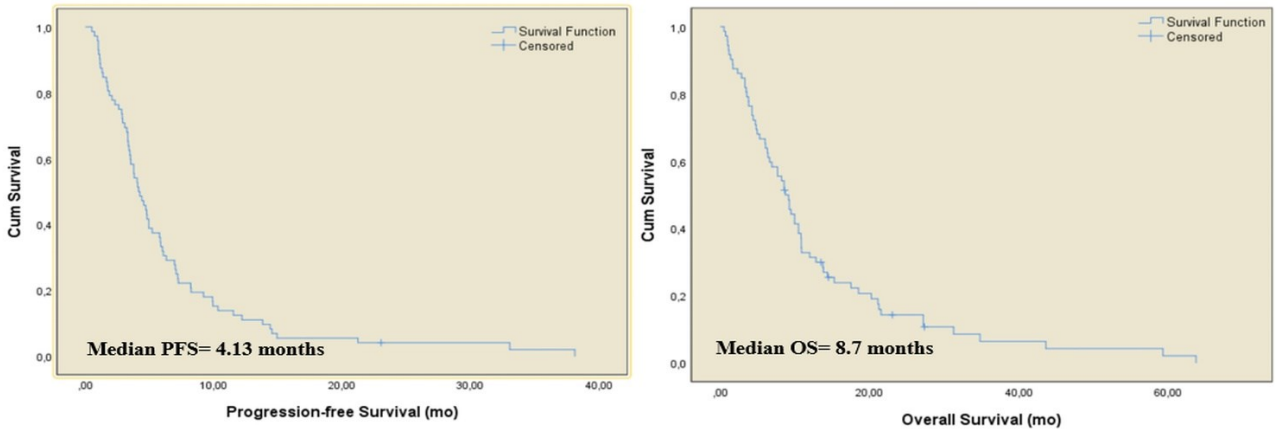

Figure 1. Kaplan-Meier curve of progression-free survival and Overall Survival.

Table 2. Univariate analysis of factors for Progression Free Survival and Overall Survival.

Variable	Progression Free Survival (months)	*p*	Overall Survival (months)	*p*
Age				
<65	4.53 (3.80-5.27)	0.814	9.13 (7.19-11.08)	0.520
≥65	3.77 (2.81-4.72)		8.70 (4.85-12.55)	
Sex				
female	4.70 (2.51-6.89)	0.866	9.23 (4.28-14.19)	0.230
male	4.07 (3.20-4.93)		8.70 (6.60-10.80)	
ECOG PS				
0-1	4.93 (3.65-6.21)	**<0.001**	10.47 (9.06-11.87)	**<0.001**
≥2	1.63 (0.94-2.33)		1.70 (0.31 - 3.09)	
Type of tumor				
colon	3.80 (3.02-4.58)	0.771	7.67 (5.12-10.22)	0.456
rectum	4.77 (3.44-6.09)		10.7 (8.06-12.87)	
Side of primary tumor				
right side	3.40 (2.01-4.79)	0.334	4.93 (2.08-10.75)	**0.047**
left side	4.23 (3.25-5.21)		9.23 (7.08-11.38)	
Ras Mutation				
yes	4.23 (2.81-5.66)	0.717	8.53 (5.96-11.11)	0.442
no	4.03 (2.99-5.08)		9.13 (6.85-11.42)	
Presentation at initial diagnosis				
de-novo metastatic	4.23 (2.92-5.54)	**0.015**	6.60 (2.34-10.86)	0.212
recurrent metastatic	4.13 (1.54-6.73)		9.23 (7.48-10.99)	
Surgery for primary tumor				
yes	4.13 (2.45-5.82)	**0.033**	9.23 (7.78-10.69)	0.720
no	3.80 (2.78-4.82)		6.07 (3.66- 8.48)	
Anti-VEGF treatment				
yes	4.07 (3.14-5.00)	0.220	8.53 (6.37-10.70)	0.222
no	6.00(3.61-8.39)		10.47 (2.56-18-37)	
Anti-EGFR treatment				
yes	4.53 (3.58-5.49)	0.382	8.53 (5.18-11.89)	0.227
no	3.77 (2.96-4.57)		8.70 (6.72-10.68)	
Line of regorafenib treatment				
3rd	4.07 (3.07-5.06)	0.563	8.53 (6.53-10.53)	0.053
4th or above	5.83 (2.58-9.09)		10.83 (2.80-24.91)	
Dose reduction				
yes	4.77 (2.85-6.68)	0.398	10.83 (8.68-12.99)	**0.003**
no	3.77 (2.99-4.54)		6.37 (3.02 - 9.71)	
CEA				
≥58	3.77 (2.92-4.62)	**0.014**	6.37 (4.47 - 8.26)	**0.001**
<58	4.77 (2.46-7.07)		12.80 (8.35-17.25)	
CA 19.9				
≥74	3.77 (3.18-4.35)	**0.024**	6.30 (4.34 - 8.26)	**0.001**
<74	4.77 (3.59-5.94)		10.47 (9.10-11.84)	

ECOG PS: Eastern Cooperative Oncology Group Performance Score, VEGF: Vascular endothelial growth factor receptor, EGFR: Epidermal growth factor receptor, CEA: Carcinoembryonic antigen, CA 19.9: Cancer antigen 19-9

Table 3. Multivariate analyses of factors for Progression Free Survival and Overall Survival

		Progression Free Survival (months)		Overall Survival (months)	
Variable	**Category**	HR (95% CI)	***P*** [f]	HR (95% CI)	***P*** [f]
CEA	<58 vs ≥58	5.70 (1.46-10.60)	**0.001**	3.16 (1.80-5.52)	**<0.001**
ECOG	0-1 vs ≥*2*	2.46 (1.46-4.16)	**<0.001**	6.17 (3.27-11.64)	**<0.001**
Side of primary tumor	right vs left	-	-	0.44 (0.20-0.95)	**0.037**
Dose reduction	yes vs no	-	-	0.43 (0.25-0.75)	**0.003**

[s] Significant values are indicated in bold. P[f]: Forward: LR method.

In univariate analysis established for OS; ECOG score (p<0.001), side of the primary tumor (p=0.047), dose reduction (p=0.*003*), CEA level (p=0.001), and CA 19.9 level (*p=0.001*) were found to be statistically significant (Table 2). The multivariate Cox-regression model revealed that the ECOG score (HR=6.17, 95% CI: 3.27-11.64, p<0.001), the CEA level (HR=3.16, 95% CI: 1.80-5.52, p<0.001), the dose reduction (HR=0.43, 95% CI: 0.25-0.75, p=0.003), the side of the primary tumor (HR=0.44, 95% CI: 0.20-0.95, p=0.037) were found to be prognostic for OS (Table 3).

Discussion

This study elaborated on the survival effect of Regorafenib in mCRC patients and the prognostic factors affecting the duration of response to Regorafenib treatment as a real-life, single-center experience. In our study, we found that Regorafenib can be the preferable treatment for patients who have used prior therapies. Our analyses showed that ECOG score and CEA levels were independently prognostic for PFS, while ECOG score and CEA levels as well as the side of the primary tumor, and the dose reduction were prognostic for OS.

In the CORRECT study, which included 760 patients who progressed after multiple therapies, demonstrated the efficacy of regorafenib in mCRC and received approval, the median OS was 6.4. This study also showed a statistically modest statistically significant improvement in PFS (1.9 months) in patients receiving Regorafenib compared to placebo. In the phase 3 CONCUR study, which evaluated the CORRECT study in a larger Asian patient population, the mOS was 8.8 months. This study, too, demonstrated the OS benefit of Regorafenib vs. placebo. In another large randomized trial, patients receiving regorafenib in later-line therapy for mCRC had a mOS of 5.6 months, and the 12-month survival rate was 22% (10). In our study, median OS and PFS in patients receiving Regorafenib were 4.13, and 8.7 months, respectively.

The REBECCA study, which is one of the real-life studies evaluating the efficacy of Regorafenib used in later-line treatment for mCRC, revealed that OS was unfavorably associated with the following factors: poorer performance status, a shorter time from diagnosis to start of regorafenib treatment, lower regorafenib dose (< 160 mg), > 3 metastatic sites, having liver metastases, and presence of KRAS mutations.[10] In another real-world study, OS was significantly different in subgroups according to ECOG score (ECOG 0/1 vs. 2) and time since initial diagnosis (<18/≥18 months).[11] With the OS benefit of treatment with regorafenib, several studies have been conducted to identify predictive/prognostic markers. In one of these studies, Komori et al. determined CEA and CA19-9 as prognostic markers of PFS. Relationships between treatment outcomes and other laboratory parameters such as high platelet count/high neutrophil/lymphocyte ratio (related to worse OS), or higher lymphocyte count (related to better OS) were also reported in the literature.[12,13] In our study, however, ECOG score, the side of the primary tumor, the dose reduction, CEA, and CA 19.9 were shown as independent prognostic factors for Overall Survival.

Regorafenib can cause adverse events in using mCRC similar to its use in other indications.[14,15] In the CORRECT study, side effects were reported in 93% of patients, which generally improved with dose reduction and drug interruption. Adverse reactions usually seen with regorafenib were hand-foot skin reaction (HFSR), asthenia/fatigue, diarrhea, decreased appetite and food intake,

hypertension, and infections; however, side effects such as severe liver damage, bleeding, and gastrointestinal perforation may also occur.[16] Regorafenib as a small-molecule multiple kinase inhibitor, as can be seen with other drugs in this class, side effects may also be associated with better OS.[17] The CORRECT study suggested that patients who had hand-foot skin reactions had a greater OS. A study of 102 patients with mCRC treated with Regorafenib found that better OS was significantly ($p<0.05$) associated with HFSR and rash, neutropenia, and AST elevations.[18]

Study limitation

This study has several limitations. The main limitation of our study is the retrospective design and the smaller patient population than other studies in the literature. The strength of the study is that it shows real-life data on patients receiving Regorafenib for mCRC.

Conclusion

Regorafenib treatment is a preferable medication in resistant mCRC. Our study revealed that patients with better ECOG score, requiring dose reduction during the treatment, and lower levels of initial CEA were found to be prognostic for OS. It can be used in patients with mCRC who have failed after standard therapies and are willing to receive treatment.

Ethics Committee Approval

The present study was performed in line with the principles of the Declaration of Helsinki. The Tekirdag Namik Kemal University Ethics Committee granted formal approval to this study (approval no: 2023.72.08. 20 on April 25th, 2023).

Informed Consent

Not Applicable.

Authors' contributions

All of the authors contributed at every stage of the study.

Acknowledgments

Not Applicable.

Conflicts of interest/Competing interests

There is no conflict of interest to declare.

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