İstanbul Med J 2019
DOI: 10.4274/imj.galenos.2018.79095

Treatment Outcomes of Metastatic Colorectal Cancer Patients Treated with Regorafenib in the Third Line Setting- A Multicenter Study

3. Basamakta Regorafenib ile Tedavi Edilen Metastatik Kolorektal Kanserli Hastaların Sonuçları- Çok Merkezli Çalışma

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ABSTRACT

Amaç: Daha önce 5-florourasil (5-FU), irinotekan veya oksaliplatin temelli rejimlerle tedavi edilen ve biyolojik ajan olarak vasküler endotelyal büyüme faktörü (anti-VEGF) veya anti epidermal büyüme faktörü reseptörü (anti-EGFR) alan veya almayan metastatik kolorektal kanser (mKRK) hastalarında regorafenib tedavisinin klinik yararı daha önceki faz III çalışmalarında gösterilmiştir. Burada mKRK'li hastalarda regorafenibin etkinlik ve toksisite profilini analiz etmeyi amaçladık.

Yöntemler: Çalışmamızda Türkiye'deki iki farklı merkezden takip edilen 23 mKRK hastasının retrospektif verileri incelenmiştir. Tüm hastalar anti-VEGF veya anti-EGFR ile kombine olarak veya olmaksızın; 5-FU, irinotekan veya oksaliplatin temelli rejimler ile, iki standart ardışık tedavinin başarısızlığı sonrasında üçüncü basamakta regorafenib ile tedavi edildi. İlaç etkinliği ve güvenliği ile birlikte tedavi sonuçları retrospektif olarak analiz edildi.

Bulgular: 23 hastanın 13'ü erkekti (%56,5) ortanca yaş 62 idi (35-76). RAS wild tip tümör oranı %43,5, RAS mutant tip tümör oranı ise %56,5'ti. 18 hasta (%78,2) birinci basamakta bevasizumab tedavisi almıştı. 23 hastanın yalnızca 1'inde (%4,3) kısmi yanıt elde edilmişti. Ortanca progresyonsuz sağkalım (PSK) 3,02 (2,6-3,37) ay ve ortanca genel sağkalım (GS) ise 6,4 (2,6-10,1) aydı. Sağ kalımla ilişkili prognostik faktör saptanmadı. En sık yan etki olarak el-ayak sendromu (% 42,8) görülmekle birlikte, derece 3-4 yan etki % 30,4 hastada saptandı.

Sonuç: Önceki çalışmalarda regorafenibin klinik ve sağkalım yararı gösterilmiş olmasına rağmen, bu avantaj, çalışmamızda kullanımını zorlaştıran önemli bir toksisite profili ile şüpheli görünmektedir. Mortalite riski ile toksisite profili göz önünde bulundurularak tedavi kararı verilmelidir.

Anahtar Kelimeler: Metastatik kolorektal kanser, regorafenib, progresyonsuz sağkalım, genel sağkalım, toksisite

ÖZ

Introduction: The clinical benefit of regorafenib therapy in metastatic Colorectal Cancer (mCRC) patients who were previously treated with5-fluorouracil (5-FU), irinotecan, or oxaliplatine based regimens with or without a biologic agent as vascular endothelial growth factor (anti-VEGF) or anti epidermal growth factor receptor (anti-EGFR) has been shown in several previous phase III studies. Herein we aimed to analyze the efficacy and toxicity profile of regorafenib in patients with mCRC.

Methods: This was a retrospective study of 23 patients with mCRC followed from two different centers in Turkey. All patients were treated with regorafenib in the third line setting, after failure of two standard consecutive therapies including 5-FU, irinotecan, or oxaliplatine with or without anti-VEGF or anti-EGFR agent. Treatment outcomes along with drug efficacy and safety were retrospectively analyzed.

Results: Of the 23 patients, 13 were male (%56.5). Median age was 62 (35-76). The rates of RAS wild-type and RAS-mutated tumor were 43.5% and 56.5 %, respectively. Eighteen patients (78.2%) have received bevacizumab in the first-line setting, whereas only 5 patients (28.8%) were given a prior anti-EGFR agent. Among the 23 patients, only 1 patient (4.3%) achieved a partial response. Median progression free survival (PFS) was 3.02 (2.6-3.37) months and median overall survival (OS) was 6.4 (2.6-10.1) months. There was no prognostic factor associated with survival. Dose modification was required in 69.56% of the patients. Grade 3-4 toxicities were observed in 30.4% of the patients, with the most frequent adverse events being hand-foot skin reaction (42.8%).

Conclusion: Although previous studies showed a clinical and survival benefit of regorafenib, this advantage seems to be questionable in our study, with a significant toxicity profile making its use challenging. Treatment should be based on the risk of mortality balanced against the toxicity profile.

Keywords: Metastatic colorectal cancer; regorafenib; progression free survival; overall survival; Toxicity

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Received/Geliş Tarihi: 07.06.2018
Accepted/Kabul Tarihi: 28.10.2018

Introduction

Despite new advances in the treatment of metastatic colorectal cancer (mCRC), it is still one the most frequent gastrointestinal system cancer in the western countries, with a significant cause of cancer mortality, affecting nearly 746,000 men and 614,000 women in each year (1). Colorectal cancer is the third most common cancer worldwideand the second important cause of cancer-related death in the United States, with about 20%-30% of patients having synchronous metastatic disease at the time of presentation and morethan half of patients eventually developing metastatic disease with unresectable metastases(2). After the introduction of chemotherapeutic agents such as fluoropyrimidines, oxaliplatine, and irinotecan along with monoclonal antibodies which target the vascular endothelial growth factor (VEGF) or the epidermal growth factor receptor (EGFR), median overall survival (OS) durations of mCRC patients havebeen improved by nearly 30 months in the past 20 years (3), with a great extent of this progress being due to molecular targeted therapies, such as anti-angiogenic agent;bevacizumab orEGFR signaling pathway inhibitor; cetuximab and panitumumab(4).

Regorafenib, a novel oral multi-kinase inhibitor, has demonstrated antitumor activity in patients with mCRC who were previously treated with fluoropyrimidine-, oxaliplatine- and irinotecan-based chemotherapy +/- anti-VEGF therapy or anti-EGFR therapy through inhibiting a very diverse range of oncogenic gene products and growth factor receptors including KIT, RET, RAF1, BRAF, BRAFV600E, VEGFR, PDGFR and FGFR, hence being approved by FDA 2012 for use as monotherapy in a last-line treatment setting (5, 6). Anti-tumor activity and survival benefit of regorafenib was previously shown in two large randomized placebo-controlled trials, CORRECT (7) and CONCUR (8), which were performed in patients with mCRC progressing on standard therapies.Survival benefit and efficacy of regorafenib was also confirmed by the large European REBECCA (9) cohort study in a real-world setting, with a similar toxicity profile as seen inprevious randomized studies mentioned above.

Here in we performed a multicenter retrospective study to evaluate the efficacy and toxicity profile of regorafenib in patients with mCRC in Turkey.

Methods

From October 2015 to December 2017, a total of 23 consecutive Turkish patients from two large centers, who were treated with regorafenib monotherapy for refractory mCRCas the third-line treatment setting, were analyzed. Patients with histologically confirmed mCRC were included in the study. For this study, approval was obtained from Local Ethics Committee (Decision no. 2018/1319). This retrospective study was designed in accordance with the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013. Since it is a retrospective study, patient consent form could not be obtained. We conducted a retrospective multi-center study to assess the efficacy and toxicity profile of regorafenib in patients with mCRC, who were previously treated with fluoropyrimidine-, oxaliplatine- and irinotecan-based chemotherapy +/- anti-VEGF therapy (e.g.bevacizumab, ziv-aflibercept) or anti-EGFR (e.g. panitumumab, cetuximab) when appropriate. Baseline data of all patients including disease characteristics, patient demographics, laboratory parameters, performance status (PS), treatments, response to treatments, and toxicities were carefully recorded.

After failure of standard therapies, regorafenib was started as a monotherapy at 160 mg daily dose for 21 days, with a 28-day repeating cycle. At the discretion of physicians, a lower initial dose was allowed depending on the patient's clinical condition and dose thereafter was increased by 40 mg per week until the maximum dose of 160 mg, relying on the patient's tolerability.

The evaluation of treatment responses was performed every 3 months by computed tomography (CT) or PET-CT using the Response Evaluation Criteria in Solid Tumor (RECIST) version 1.1. National Cancer Institute Common Terminology Criteria of Adverse events (NCI CTCAE) version 4.0 was used to grade the adverse events. Dose reduction was allowed in case of drug intolerance, grade III, or higher grade oftoxicity. Regorafenib was givenuntil disease progression, unacceptable toxicity, or patient's withdrawal of treatment.

Statistical Analysis

All statistical analysis was performed using the computer program of 'Statistical Package for The Social Sciences' version 21.0 for Windows (SPSS, Inc. Chicago, IL, USA). Descriptive statistics are reported as percentages and medians. Survival data were analyzed according to the Kaplan-Meier Method and were compared using Log-rank statistics. P value less than 0.05 was considered as statistically significant. Progression-free survival (PFS) was defined as the time from the day of regorafenib initiation to the day of disease progression or death due to any reason. OS was defined as the time from the starting day of regorafenib to the day of death due to any cause.

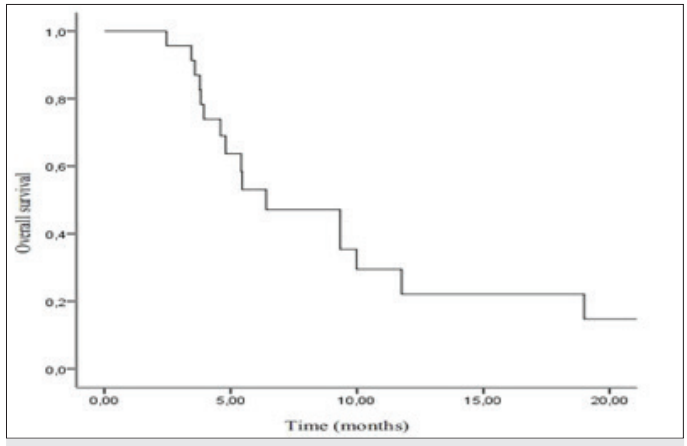
Results

A total of 23 patients were enrolled in this study. Baseline characteristics were summarized in table 1. Of the 23 patients, 13 were male (%56.5). Median age was 62 (35-76) years. The rates of RAS wild-type and RAS-mutated tumor were 43.5% and 56.5 %, respectively.

Eighteen patients (78.2%) received bevacizumab in the first-line setting, whereas only 5 patients (28.8%) were given a prior anti-EGFR agent. Primary tumor was located in left side in 17 (73.9%) patients. The number of patients who underwent palliative surgery and metastasectomy was 9 (39.1%) and 5 (21.7%), respectively. Most of the patients had a performance score of 0-1 (91.3%) at the beginning of regorafenib therapy.

With respect to survival durations, at a median follow-up time of 5.4 (2.4-23.4) months, median Progression Free Survival (PFS) was 3.02 (2.6-3.37) months and median overall survival (OS) was 6.4 (2.6-10.1) months for regorafenib therapy (figure1 and 2). Overall survival of whole population was 37 (23.9-50.4) months. The presence of comorbidity was the only prognostic factor in univariate analysis; however, no factors were found to be associated with survival (table 2).

About 73.92% of patients were commenced on lower doses than standard. Starting dose of 160 mg was administered only in 6 patients. Dose modification was required in 69.56% of the patients (table 3). Dose escalation could be performed once in 4 patients and twice in 2 patients. Dose reduction was required once in 7 patients and twice in 3 patients. About 13.04% of the patients discontinued the therapy due

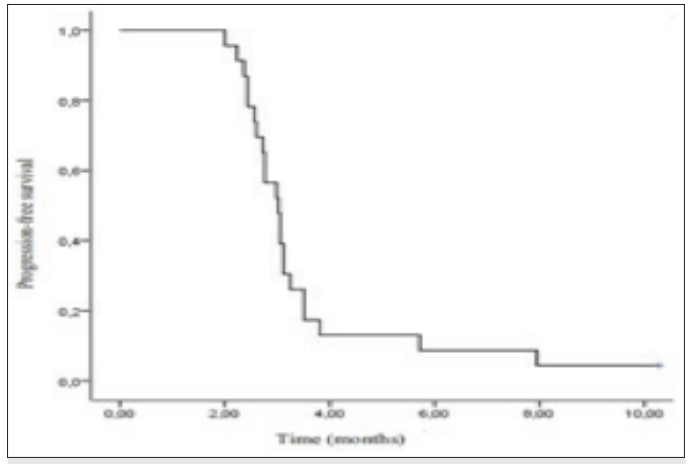


Figür 1. Overall survival curve

to toxicity. Median number of treatment cycles was 3 (1-11). The most frequent toxicities of any grade were hand-foot skin reaction (HFSR), fatigue, diarrhea, hypertension, mucositis, and thrombocytopenia. Grade 3-4 toxicities were observed in 7(30,4%) patients, with a decreasing frequency as follows; 42.8 % HFSR, 28,5%fatigue, 14,28% diarrhea, and 14,28% Hypertension (table 4).

Table 1. Baseline characteristics of patients (N=23)

N=patient	23
Median age(years)	62 (35-76)
Sex	
Male	13 (56,5)
Female	10 (43,5)
ECOG performance status	
0-1	21 (91,3)
2	2 (8,7)
Comorbidity (e.g DM, HT, Aterosclerosis)	
No	16 (69,6)
Yes	7 (30,4)
Tumorlocalization	
Right	6 (26,1)
Left	17 (73,9)
Palliativesurgery	
Yes	9 (39,1)
No	14 (60,9)
Metastasectomy	
Yes	5 (21,7)
No	18 (78,3)
RAS mutationstatus	
Mutant	13 (56,5)
Wild-type	10 (43,5)
First-linetherapy	
Folfox/xelox+ Beva	9 (39,1)
Folfox/xelox+ Pan/Cet	2 (8,7)
Folfiri+B	9 (39,1)
Folfiri+ Pan/Cet	3 (13,0)
Responsetofirst-linetherapy	
Partialresponse	11 (47,8)
Stabledisease	4 (17,4)
Progression	8 (34,8)
Second-linetherapy	
Folfox	2 (8,7)
Folfiri	3 (13,0)
Folfox/B	8 (34,8)
Folfox+C/P	1 (4,3)
Folfiri+B	4 (17,4)
Folfiri+C/P	3 (13,0)
Other	2 (8,7)
Responsetosecond-linetherapy	
Partialresponse	8 (34,8)
Stabledisease	8 (34,8)
Progression	7 (30,4)
Responseto Third-lineRegorefenib	
Partialresponse	1 (4,3)
Progression	22 (95,6)



Figür 2. Progression-free survival curve

Table 2. Univariate analysis

parameters	n (%)	Overallsurvival (month) Univariate analysis	P value
Age (years)			
≤60	10 (43,5)	37.1	0.46
>60	13 (56,5)	32.1	
Sex			
Male	13 (56,5)	45.7	0.12
Female	10 (43,5)	25.7	
ECOG performance status			
0-1	21 (91,3)	41.0	0.20
2	2 (8,7)	25.7	
Comorbidity (DM, HT, Atherosclerosis)			
No	16 (69,6)	45.7	<0.001
Yes	7 (30,4)	22.3	
Tumor localization			
Right	6 (26,1)	52.4	0.85
Left	17 (73,9)	37.1	
Palliative surgery			
Yes	9 (39,1)	45.7	0.15
No	14 (60,9)	32.1	
Metastasectomy			
Yes	5 (21,7)	45.7	0.69
No	18 (78,3)	32.1	
RAS mutation status			
Mutant	13 (56,5)	45.7	0.24
Wild-type	10 (43,5)	31.7	
First-line therapy			
Folfox/xelox+ Beva	9 (39,1)	37.1	0.17
Folfox/xelox+ Pan/Cet	2 (8,7)	31.7	
Folfiri+B	9 (39,1)	57.1	
Folfiri+ Pan/Cet	3 (13,0)	26.7	

Response to first-line therapy	11 (47,8)	52.4	0.34
Partial response	4 (17,4)	32.1	
Stable disease	8 (34,8)	25.7	
Progression			
Second-line therapy			
Folfox	2 (8,7)	18.1	
Folfiri	3 (13,0)	26.1	0.12
Folfox/B	8 (34,8)	41.0	
Folfox+C/P	1 (4,3)	25.7	
Folfiri+B	4 (17,4)	NR not reached	
Folfiri+C/P	3 (13,0)	37.1	
Other	2 (8,7)	32.1	
Response to second-line therapy	8 (34,8)	45.7	0.01
Partial response	8 (34,8)	37.1	
Stable disease	7 (30,4)	23.0	
Progression			
Response to third-line Regorafenib	1 (4,3)	31.7	0.53
Partial response	22 (95,6)	37.1	
Progression			

Table 3. Regorafenib administration

Median number or treatment cycles	3 (1-11)
Starting dose	N (%)
160 mgr	6 (26.08)
120 mgr or lower	17 (73.92)
Treatment discontinuation	3 (13.04)
Dose escalation	6
Once	4 (66.6)
twice	2 (33.3)
Dose reduction	10
once	7 (70)
twice	3 (30)

Table 4. Adverse Events

	Any Grade N=18 (78,26%)	Grad 3-4 N=7 (30,4%)
Hand-foot skin reaction	6 (33,3)	3 (42,8)
Fatique	4 (22,2)	2 (28,5)
Diarrhea	3 (16,6)	1 (14,28)
Hypertension	2 (11,1)	1 (14,28)
Mucositis	2 (11,1)	-
Thrombocytopenia	1 (5,5)	-

Discussion

In the past 10 years, the availability of many drugs and the advent of new anti-angiogenic agents such as bevacizumab combined in standard regimens in the first-line, second-line, or beyond progression setting has offered a considerable survival benefit withimproved prognosis in patients with mCRC. Angiogenic regulation is consisted of a range of pathways, and inhibiting a single target, such as VEGF, results in up regulation of a diversity of pro-angiogenic factors (10), suggesting thata salvage treatment setting which includes a multi-kinaseinhibitor with anti-angiogenic activity may be a plausibletreatment option(11). Regorafenib, a novel agent, is a multi-kinase inhibitor targeting a range of receptors including VEGF 1–3, platelet-derived growth factor, tyrosine receptor kinase-2, fibroblast growth factor, BRAF, KIT, and RET (12).

Herein we aimed to evaluate the efficacy and safety of this new kinase inhibitor, although not including a representative sample. Median OS and median PFS in our study were 6.4 and 3.02 months, respectively. These findings were comparable tothose reported in previous randomized studies. The CORRECT study was an international, randomized, and placebo-controlled phase-III trial, including 760 patients who were randomized 2:1 to receive either regorafenib 160 mg daily or placebo, demonstrating an improved median OS for regorafenib group compared to the placebo (6.4 months vs 5.0 months, p = 0.0052)(7), showing similar results to our findings.One another international phase III trial, CONCUR, which also confirmed the OS benefit of regorafenib in 204 Asian patients who were randomized 2:1 ratio to receive either regorafenib or placebo (8.8 months vs 6.3 months, p = 0.00016) (8), had a better median OS than that observed in our study.Median PFS durations for CORRECT and CONCUR trial were 1.9 and 3.2 months in the regorafenib arm, gaining only 0.2 and 1.5 months, respectively, compared to placebo group. The median PFS in our study was similar to that reported in CONCUR trial and higher than that found in the CORRECT trial. The REBECCA trial, a cohort of 1178 patients with mCRC, wasan open-label and single-arm studyof654 patients (in full analyze) treated with regorafenib after a failure on standard therapies.This study demonstrated a median OS of 5.6 months and median PFS of 2.9 months with 12-month survival rate of 22 % (9), indicating a similar median PFS but a lower median OS duration compared to those reported in our study, despite the higher number of patients starting the lower dose of regorafenib in our study (73.9% in our study vs. 18% in REBECCA).

The most frequent toxicities of any grade in our cohort were HFSR, fatigue, diarrhea, hypertension, mucositis, and thrombocytopenia. HFSR, fatigue, diarrhea, and hypertension were the most common grade 3-4 toxicities. This toxicity profile was substantially consistent with the adverse events which were reported in the REBECCA real-world cohort(9), the CORRECT trial (7), and in the CONCUR trial(8). Most adverse events weresimilar in the CONCUR(8) and CORRECT(7) trial, with the only exception of any-gradeHFSR (74% vs47%, respectively) and impaired liver function tests (37% vs20%, respectively), which were more frequent in CONCUR trial(8). The most common reason leading to drug-discontinuation in our study was the toxicitywhich was similar to that observed in the REBECCA cohort(9).Most patients (69.56%) in our cohort required dose modifications, and this was higher than those reported in the CORRECT(7) (in which 20% of patients required a dose reduction) and CONCUR trial(8) (in which 40% of patients required a dose reduction). Compared with the REBECCA (9) cohort, greater proportion in cohort started at a lower dose of regorafenib (18% vs. 73,9%, respectively). In order to minimize the incidence of adverse events and enable patients to fully benefit from regorafenib therapy to optimize the treatment results, patients need to be informed regarding the prophylaxis and management of regorafenib-related adverse events prior to treatment. Therefore, the most common adverse events should be discussed with the patient before the treatment.

The REBECCA real-world analysis(9)reported that high ECOG PS, a shorter time from the initial diagnosis of metastasis, starting a lower initial dose of regorafenib, more than 3 metastatic sites, the presence of liver metastasis, and KRAS mutation were the factors associated with shorter OS. However, there were no predictive factors associated with survival in our cohort, which might be due to the small sample size of our cohort.

So far, certain studies have explored some biomarkers of efficacy for regorafenib, but no pretreatment useful biomarker in clinical practice

has yet been determined (13, 14). Indeed, no predictive biomarker to allow selection of patients most likely to benefit from regorafenib has been available (11). However, Komori et.al reported that serum CA19–9 response was an early predictive marker of efficacy of regorafenib in mCRC (15).

The major limitation in our analysis was its small sample size, resulting in a suboptimal evaluation of predictors of outcome in cox regression analysis. Hence, the results of this study should be interpreted with caution. In addition, selection bias and absence of independent monitoring were the other limitations inherent in retrospective studies, which might affect our results. Moreover, identifying patients who will tolerate full-dose or a reduced dose of regorafenib is pretty important to optimize the study design. Nevertheless, our findings support the available data in literature and provide usefull information regarding the results of mCRC patients treated with regorafenib.

Conclusion

Regorafenib, a novel agent, is a multi-kinase inhibitor for use as monotherapy at the last-line treatment setting in mCRC. Despite regorafenib showing a small, but significant survival benefit in patients with mCRC who do not have any further treatment options after the failure over standard therapies, its toxicity profile along with the absence of predictive factors suggests a careful evaluation for the benefit/risk ratio before its use in clinical practice.

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