ÖZGÜN ARAŞTIRMA ORIGINAL RESEARCH

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SALVAGE TREATMENT OPTION FOR METASTATIC COLORECTAL CANCER: REGORAFENIB

METASTATİK KOLOREKTAL KANSERDE KURTARMA TEDAVİSİ: REGORAFENİB

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Öz

Giriş
Kolorektal kanser (KRK), kanser ölümünün önde gelen nedenlerinden biridir. Bu çalışmanın amacı, metastatik KRK hastalarında regorafenib tedavisinin etkinlik ve toksisite profilini değerlendirmektir.

Gereç ve Yöntem
Bu çalışmada tek merkezde takip edilen 25 mKRK hastasının retrospektif verileri incelendi. Tüm hastalarda biyolojik ajanlar olan anti-epidermal büyüme faktörü reseptörü (anti-EGFR) ve anti-vasküler endotelyal büyüme faktörü (anti-VEGF) ile kombine olarak veya olmaksızın 5-fluorourasil, irinotekan ve okzaliplatin ile progresyon saptanmıştı.

Bulgular
Ortanca yaş 58 (dağılım 27-84) idi, ve 14 erkek ve 11 kadın vardı. Hastalar regorafenib başlangıcından önce ortanca 3 sıra sistemik tedavi aldı. En sık görülen 3. veya 4. derece toksisiteler yorgunluk %20, daire %16 ve mukozit %16 idi. Ortanca PFS 2.07 ay (0.43-5.13) ve ortanca OS 4.14 ay (0.62-19.88) idi. Tek değişkenli analizde hiçbir faktör PFS ve OS ile ilişkili bulunmadı.

Sonuç
Regorafenib, standart tedavilerdeki başarısızlıktan sonra başka tedavi seçeneği bulunmayan metastatik KRK hastalarında küçük fakat önemli bir sağkalım yararı göstermektedir. Prediktif faktörlerin olmamasıyla birlikte toksisite profili klinik uygulamada kullanılmadan önce dikkatli bir değerlendirme yapılmalıdır.

Anahtar Kelimeler: Kolorektal kanser, regorafenib, yan etki

Abstract

Objective
Colorectal cancer (CRC) is an important cause of cancer-related deaths. The aim of this study was to evaluate the efficacy and toxicity profile of regorafenib treatment in metastatic CRC patients.

Materials and Methods
This was a retrospective study of 25 mCRC patients from a single center. All patients had previously progressed fluorouracil, irinotecan, and oxaliplatin with or without biologic agents such as epidermal growth factor receptör (anti-EGFR) or vascular endothelial growth factor receptor (anti-VEGF).

Results
The median age was 58 years (range, 27 to 84 years), and there were 14 males and 11 females. Patients had received a median of 3 lines of systemic therapy before regorafenib initiation. The most common grade 3 or 4 toxicities were fatigue 20%, daire 16% and mucositis 16%. Median PFS was 2.07 months (0.43-5.13) and median OS was 4.14 months (0.62-19.88).

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No factors were significantly associated with PFS and OS in the univariate analysis.

Conclusion
Regorafenib shows a small but significant survival benefit in patients with metastatic CRC who do not have any further treatment options after the failure over standard therapies. Its toxicity profile along with the absence of predictive factors suggest a careful evaluation before its use in clinical practice.

Keywords: Colorectal cancer, regorafenib, toxicity

Introduction

Colorectal cancer is an important cause of cancer-related deaths (1). 20-30% of patients have synchronous metastasis at the presentation and more than half of them eventually developing metastatic disease (2). Chemotherapy is important in the treatment of metastatic colorectal cancer (mCRC) patients. After the introduction of chemotherapeutic agents such as fluoropyrimidines, oxaliplatine, and irinotecan along with vascular endothelial growth factor (VEGF) or epidermal growth factor receptor (EGFR) pathway inhibitors, median overall survival duration of mCRC patients has reached approximately 30 months over the last 20 years (3). Until September 2012, there was no standard treatment except for these agents and thus, regorafenib was approved by the Food and Drug Administration (FDA) as salvage treatment for mCRC according to the results of the international multicenter phase 3 CORRECT study (4). Regorafenib is a potent inhibitory activity against vascular endothelial growth factor receptors 1-3 (VEGFR1-3), platelet-derived growth factor receptor-β (PDGFR- β), fibroblast growth factor receptor 1 (FGFR1) and the mutant oncogenic kinases suc as BRAF, KIT and RET (5). Anti-tumor effect and survival benefit of regorafenib were previously shown in two studies, CORRECT (4) and CONCUR (6), which were performed in mCRC patients progressing on standard therapies. In this study, evaluating the efficacy and toxicity profile of regorafenib treatment in mCRC patients was aimed.

Materials and Methods

Study Design and Patient Characteristics

Totally, 25 patients receiving regorafenib monotherapy for refractory mCRC between October 2015 and November 2018 at the Gaziantep University Faculty of Medicine, Oncology Department enrolled in this study. The study was approved by the Ethics and Clinical Research Committees of Gaziantep University (Decision No: 2019/108, 13.03.2019). Therapy was given upon informed consent. The inclusion criteria were: (1) confirmed by pathologically of colon and rectum adenocarcinoma, (2) patients received and demonstrated radiologically progression with or unacceptable toxicity to standard systemic therapies, which include fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab and anti-EGFR therapy (cetuximab and panitumumab, only for RAS wild tumors). After the failure of standard therapies, regorafenib was initiated as a monotherapy at 160 mg daily dose for 21 days with a 28-day repeating cycle. Dose reduction was performed in cases of intolerable adverse events (AEs). Evaluation of treatment responses was performed every 2-3 months by positron emission tomography (PET-CT) or computed tomography (CT) using the Response Evaluation Criteria in Solid Tumor (RECİST) version 1.1. Adverse events (AE) were gradeded by Common Terminology Criteria of Adverse events version 4.0. The treatment was given until disease progression, occuring of unacceptable AE or patient's refused of therapy.

Statistical Analysis

Descriptive statistics were showned as percentage and median. The outcomes of treatment were progression-free survival (PFS), overall survival (OS), response rates and toxicities. OS was described as the time interval between regorafenib initiation and death of any cause. PFS was defined as the time interval from regorafenib initiation to disease progression or death due to any reason. Survival analysis was performed with the Kaplan-Meier Method and was compared by Log-rank statistics. P value less than 0.05 was defined as statistically significant. Statistical Package for Social Sciences version 22.0 for Windows (SPSS, Inc. Chicago, IL, USA) was performed for all statistical analyzes .

Results

Regorafenib was offered to 34 patients and in this, 25 (73.5%) patients were started treatment. Reasons for not starting regorafenib were patient's request (n=7, 77.7%) and unknown (n=2, 22.2%). Patients who did not receive regorafenib therapy were not reported. Patient's baseline characteristics were showned in Table 1. The median age was 58 years (range, 27-84 years). 14 patients were male and 11 were female.

Table 1 Baseline characteristics of patients (n:25)

	Number (%)
Age-Median (range)	58 (27-84)
Gender	
Female	11(44)
Male	14(56)
ECOG PS	
0-1	23(92)
>1	2 (8)
Co-morbidity	
Yes	7 (28)
No	18 (72)
Tumor sidedness	
Right	7(28)
Left	15(72)
Palliative surgery	
Yes	4(16)
No	21(84)
Metastasectomy	
Yes	2(8)
No	23(92)
Number of organs involved	
1	5(20)
>1	20 (80)
Metastasic Region	
Liver	17(68)
Lung	18(72)
Lymph nodes	4(16)
Bone	3(12)
Peritoneum	4(16)
RAS mutation status	
Wild-type	11 (44)
Mutant	14(56)
Prior bevacizumab	
Yes	25 (100)
No	0
Prior anti-EGFR agents	
Cetuximab	9(36)
Paitumumab	2 (8)
No	14 (56)
Dose reduction	
Yes	10 (40)
No	15 (60)
Treatment line	
3	10 (40)
4	11(44)
≥ 5	4 (16
Response to Regorafenib	
Stable	1(4)
Progression	24 (96)

The median performance score according to Eastern Cooperative Oncology Group (ECOG) was 1 (range, 0 to 2). The primary site was colon in the majority of patients (60%). The primary tumor was located on the left side (left colon and rectum) in 18 patients (72%). In terms of metastasis localization, 80% of the patients had >1 metastatic site and the most common sites of metastasis were lung (72%), liver (68%), lymph nodes (16%) and peritoneum (16%). The number of patients who underwent palliative surgery and metastasectomy was four (16%) and two (8%), respectively.

The rates of RAS wild-type and RAS mutated tumor were 11 (44%) and 14 (56%), respectively. B-raf mutation results of patients were unknown. Of the RAS wild-type patients, 2 were treated with panitumumab and 9 were treated with cetuximab. All of them patients were treated with bevacizumab.

Before regorafenib treatment, patients received a median of 3 lines of systemic therapy. The initial dose was 160 mg in all patients. Dose reduction was performed in 15 (60%) patients due to grade 3-4 side effects. The median number of treatment cycles was 3 (1-5). The most common reasons for termination of regorafenib therapy were progression of the disease (84%) and toxicity (12%).The treatment of one patient was still ongoing.

The most common AE of any grade were fatigue 80%, hand and foot skin reaction (HFSR) 72%, diare 60% and mucositis 60%. The most common grade 3 or 4 AE were fatigue 20%, daire 16% and mucositis

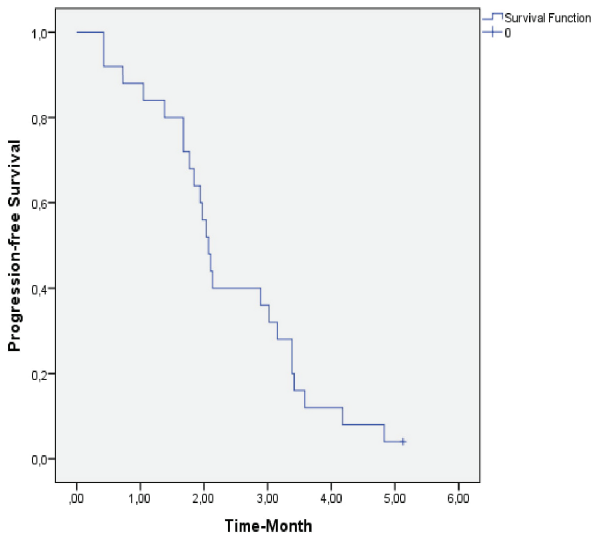
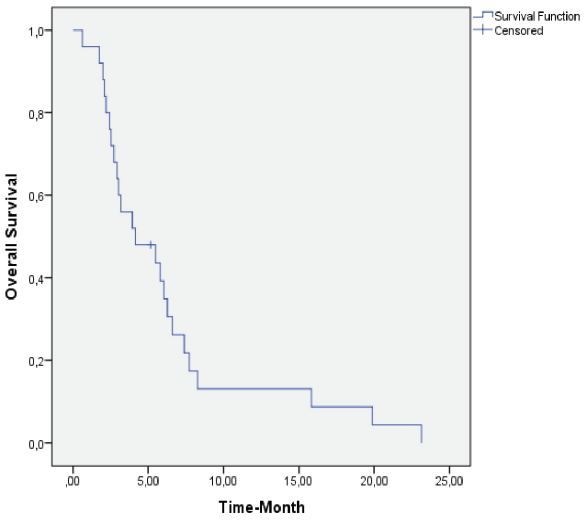


Figure 1: Kaplan-Meier curve of progression-free survival (Median 2.07 month, 0.43 to 5.13)



16% (Table 2). None of the patients had a complete response and a partial response. The best treatment response was stable disease in 1 patients; 96% experienced progression.

Regarding survival, median PFS was 2.07 months (0.43 to 5.13) and median OS was 4.14 months (0.62 to 19.88) for regorafenib therapy. PFS and OS curves were showned in figure 1 and figure 2 in patients receiving regorafenib treatment. The OS was 41.88 months (10.38 to 133.98 months). According to univariate analysis, none of the factors were associated with PFS and OS (Table 3).

Figure 2: Kaplan-Meier curve of overall survival (Median OS 4.14 month, 0.62 to 19.88)

Table 2 Adverse events

	Any grade (Number)	Grade 3-4 (Number)
Fatigue	20	1
Hand foot skin reaction	18	5
Diare	15	4
Mucositis	15	4
Hypertension	3	0
Trombocytopenia	4	1

Table 3 Univariate analysis of progression-free survival (PFS) and overall survival (OS)

Parameters	N(%)	PFS	p	OS	p
Age					
<65	15 (60)	2.07	0.748	3.18	0.056
≥65	10 (40)	2.03		6.04	
Gender					
Female	11 (44)	3.02	0.070	5.78	0.831
Male	14 (56)	1.93		2.92	
Co-morbidity					
Yes	7 (28)	2.03	0.570	2.53	0.820
No	18 (72)	2.07		4.14	
Tumor sidedness					
Right	6 (24)	1.97	0.321	2.53	0.506
Left	19(76)	2.07		5.48	
RAS status					
Wild	10 (40)	2.13	0.629	3.18	0.774
Mutant	15 (60)	1.84		5.78	
Metastasis at diagnosis					
Yes	12 (48)	2.07	0.743	3.18	0.549
No	13 (52)	2.03		5.48	

Discussion

The most patients with colorectal cancer develop resistance to standart treatments and as a result progression of the disease occurs. Some of the patients who have progressed after cytotoxic chemotherapy and/or biological agent treatments have good performance and need new treatment. Unluckily, therapy options of patients who do not respond to treatment are limited. Several pathways exist in colorectal cancer progression, and the tyrosine kinase signaling pathway is one of them. Regorafenib, a small multikinase inhibitor molecule, blocks protein kinase activities (7).

Here, it was aimed to assess the efficacy and safety of this new kinase inhibitor, although it did not include a representative sample. The median OS and PFS in our study were 4.14 and 2.07 months, respectively. These findings were comparable to those reported in previous randomized studies. In the CORRECT and CONCUR studies, it was reported that regorafenib remarkably extended the duration of survival in intensively pretreated mCRC patients as against to plasebo. In the CORRECT study, the median OS was 6.4 months in the regorafenib group versus 5.0 months in the plasebo (4). Subsequently, CONCUR trial revealed that OS was better with regorafenib (median OS was 8.8 months versus 6.3 months in favor of regorafenib) (6). In our experience, the OS time was shorter in our patients than was reported in the CORRECT and CONCUR trials. 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 CORRECT trial and lower than in the CONCUR trial. Survival and response to treatment are highly related to patient compliance (8,9). A recent study of mCRC reported that compliance rate was < 80% with chemotherapy regimens (10). Multiple studies have shown that cancer patients prefer oral treatment rather than intravenous treatment because of low incidence of hospital admission, applicable in home environment and problems about intravenous administation (11). In our study, the treatment compliance of our patients was poor compared to previous publications. They were perceived as a feeling of hopelessness and an end to end feeling if oral treatment was started after intravenous therapy. After than, they distrupted the treatment and did not receive adequate therapy. The decrease in OS and PFS values was thought to be due to this situation. Therefore, the physicians should inform patient and patient's relatives about the importance of treatment when starting oral treatment.

The characteristics of intensivly pretreated patients in daily practice differ from in clinical trials. In CONCUR (6) study, the mean age was 57.5 (range 50 to 66), and in CORRECT (4) study was 61 (range 54 to 67). In our study, although the average age was similar, there were younger patients, such as 27, and older age, 84 years. This could have affected the treatment toxicity and survival outcomes.

The biological rationale of anti-VEGF therapy post-progression on prior the same pathway in mCRC is a largely unexplored arena. A close look at the CORRECT (4) study reveals that 100% of patients had previously received bevacizumab, while only sixty percent received bevacizumab in the CONCUR (6) study. In our study, all of the patients recevied bevacizumab. Whether such lower use of prior bevacizumab resulted in slightly improved PFS in the CONCUR study compared with CORRECT study is a point of debate (3.2 vs 1.9 months) (4,6). Such hypothesis brings to focus the possibility of using regorafenib earlier in the treatment sequencing of mCRC as it has also been postulated in the REVERCE study with cetuximab (12).

The toxicity profile of regorafenib may be severe. It affects predominantly the skin (with hand-foot skin reaction(HFSR) and rash), patient's general status (fatigue and loss of appetite) and the gastrointestinal (diarrhea) and cardiovascular systems, needing both prevention and close management in everyday clinical practice (13,14). The characteristic of these side effects is to occur mainly during cycles 1 and 2 and to decrease over following cycles, requesting a frequent and close monitoring especially during the 2 months (15). The most common side effects of any grade in our cohort were fatigue (80%), HFSR (72%), diare (60%) and mucositis (60%). HFSR, diarrhea and mucositis were the most common grade 3-4 toxicities. This toxicity profile is substantially consistent with the adverse events reported in the REBECCA real-world cohort (16). The rate of therapy related adverse events of any grade was lower in REBACCA (80 %). This rate was 97% in CORRECT and 93% in CONCUR study.

None of factors with predictive of PFS or OS were founded in our patients. Analysis of the REBECCA study demonstrated several factors associated with shorter OS: low performans status, a shorter time between the initial diagnosis and metastasis, low initial dose of regorafenib compared to standart dose, detection of RAS mutation, presence of more than 3 metastatic sites and presence of liver metastasis (16).

Caused by the small number of patients, these findings were not supported in our study.

There were some restrictive aspects of the study. First, retrospective design of the study was a disadvantage. It was difficult to control the factors affecting mortality. Therefore, it might had caused a bias in the study. The data about toxicity profile might have missing information and for this reason there was an incomplete identification of adverse events. Secondly, this study was developed a single center and the number of patients was small. This might be a problem to adapt the results to all colorectal cancer patients.

Conclusion

In patients with mCRC, palliative chemotherapy improves survival, regression of symptoms and improves quality of life. In case of progression to standart therapy, oncologists should be careful about the side effect profile and degree of treatment when planning treatment. Regorafenib shows 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 suggest a careful evaluation before its use in clinical practice.

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