CLINICAL FACTORS PREDICTING RESPONSE TO REGORAFENIB IN METASTATIC COLORECTAL CANCER

Özlem Nuray Sever*[1], Gökmen Aktaş[1], Başar Aksoy[2], Mustafa Yıldırım[1]

[1]Sanko University School of Medicine, Department of Medical Oncology, Gaziantep, Turkey.

[2]Sanko University School of Medicine, Department of General Surgery, Gaziantep, Turkey.

** Corresponding author: ozlem.sever@hotmail.com*

Geliş Tarihi / Received: 15.01.2022
Kabul Tarihi / Accepted: 12.03.2022

Araştırma Makalesi/Research Article
DOI: 10.38065/euroasiaorg.924

ABSTRACT

Colorectal cancer (CRC) is a common disease with high mortality. Regorafenib (Stivarga ®) is an oral small molecule, multiple kinase inhibitor approved worldwide for use in metastatic colorectal cancer. In our study, clinical factors predicting response to regorafenib were investigated.

Patients who applied to Gaziantep Medical Park Hospital and Sanko University Medical Faculty Hospital Medical Oncology outpatient clinic between 2010-2021 with the diagnosis of mCRC and using regorafenib were included in the study. Electronic medical records of the patients were reviewed retrospectively. Statistical analyzes were performed using SPSS version 15.0 software.

A total of 20 patients with metastatic colorectal cancer using regorafenib in the third or fourth line therapy were included in the study. Overall, 15 (75%) patients had liver metastases. The median overall survival of the patients was 25.5 months (95% Confidence Interval (CI), 24.1-26.8). Overall survival was not significantly associated with sex, ECOG performance status score, de novo metastatic disease status, smoking status and weight loss history (p=0.139, p=0.240, p=0.173, p=0.911, p=0.923, respectively). A significant association was found between the presence of liver metastasis and survival (p=0.036). The median overall survival was 40.3 months (95% CI, 0-92.6) in patients without liver metastases, and 25 months (95% CI: 13.8-36.2) in patients with liver metastases.

In this retrospective study investigating the factors affecting the survival of patients using regorafenib with the diagnosis of mCRC, the presence of liver metastasis was found to be associated with a poor prognosis.

Keywords: Metastatic Colorectal Cancer, Regorafenib, Overall Survival

INTRODUCTION

Colorectal cancer (CRC) is a common disease with a high mortality rate. Although the parameters determining the pathological stage are the strongest predictors of the postoperative outcome, other clinical, molecular and histological features may affect the prognosis regardless of the stage. The prognosis in patients with stage IV disease is more closely related to the location and extent of distant metastatic disease.

In patients who present with advanced disease and do not receive treatment, the average life expectancy is 9 months and 5-year survival is 3% [1]. Advances in treatment over the past 15 to 20 years have led to better outcomes, and currently, the average life expectancy of patients who are treated with chemotherapy is 30 months [2]. In addition, in some cases, multimodal treatments may even provide cure in the setting of metastatic disease. Understanding the natural history of metastatic CRC in the context of patient- and tumor-specific factors is crucial for making treatment decisions when there are several options [1].

Regorafenib (Stivarga ®) is an oral small-molecule inhibitor of multiple kinases, approved worldwide for use in metastatic colorectal cancer [3]. Regorafenib shows an antiangiogenic effect by inhibiting

VEGFR1-3 receptors. In the multicenter CORRECT Study, regorafenib was demonstrated to be associated with significantly longer median progression-free survival (mPFS) (3.2 versus 1.7 months) and median overall survival (mOS) (8.8 versus 6.3 months) compared to placebo. The disease control rate was also significantly higher with regorafenib (51 vs 7 %), but only 6 patients (4 %) achieved a partial response [4]. The most common adverse reactions with regorafenib were pain, hand-foot skin reaction (HFSR), asthenia/fatigue, diarrhea, decreased appetite and food intake, hypertension, and infection. The most common serious adverse events with regorafenib are severe liver injury, bleeding, gastrointestinal (GI) perforation, and infection [5].

The treatment outcome of patients with metastatic CRC (mCRC) has improved in recent years, but it is unclear what changes in treatment and management strategies have led to better prognosis. Tumor and disease-related factors influence the choice of treatment. In our study, clinical factors that predicted response to regorafenib were investigated.

METHODS

Patients with an histopathologically confirmed diagnosis of secondary metastatic or de novo metastatic colorectal cancer who presented to Gaziantep Medical Park Hospital and Sanko University Medical Faculty Hospital Medical Oncology outpatient clinic between 2010-2021 were included in the study. Electronic medical records of the patients were reviewed retrospectively, and information on age, sex, histopathological subtype, radiological imaging results, tumor stage and recurrence during follow-up, and survival were retrieved for each patient.

Statistical analyses were performed using the SPSS Statistics for Windows, version 15. 0 (SPSS Inc., Chicago, Ill., USA) software. Evaluation of overall survival (OS) by univariate analyses was conducted using the log-rank test. OS was calculated by Kaplan-Meier survival analysis method. Statistical significance was considered when the type-1 error level was below 5%.

RESULTS

A total of 20 patients with metastatic colorectal cancer receiving third- or fourth-line treatment with regorafenib were included in the study. Of the patients, 11 (55%) were male and 9 (45%) were female. Seven of the patients (35%) had comorbid conditions. Essential hypertension (HT) was present in 3 (15%) patients, type 2 diabetes mellitus (DM) in 1 (5%) patient, DM and HT in 1 (5%) patient, benign prostatic hyperplasia in 1 (5%) patient, and DM, HT and atherosclerotic heart disease in 1 (5%) patient. When the patients were evaluated according to the ECOG performance status score, 14 (70%) patients had an ECOG score of 0 and an ECOG score of 1 was found in 6 (30%) patients. None of the patients had a family history of colorectal cancer . Only 2 (10%) of the patients had a history of smoking.

Looking at the site of metastasis in CRC patients, liver metastases were detected in 9 (45%) patients, lung metastases in 1 (5%), liver and lung metastases in 3 (15%), peritoneal metastases in 4 (20%), liver, ovary, omentum and peritoneal metastases in 1 (5%), lung and bone metastases in 1 (5%), and liver, lung and bone metastases in 1 (5%) patient. Overall, 15 (75%) patients had liver metastases.

Six (30%) of the patients had secondary metastatic disease and 14 (70%) had de novo metastasis. Of these patients, 2 received adjuvant FOLFOX therapy and 4 received adjuvant CAPOX therapy. For metastatic disease, FOLFOX in combination with bevacizumab was used in 6 patients, FOLFIRI + bevacizumab in 2 patients, FOLFOX + panitumumab in 4 patients, and FOLFIRI + cetuximab in 2 patients. These patients received a median of 6 cycles of chemotherapy.

Among patients with secondary metastatic disease, 3 (50%) patients received FOLFIRI plus bevacizumab, 2 (33.3%) patients received FOLFIRI + panitumumab and 1 (16.7%) patient received FUFA + bevacizumab as second-line treatment. In patients with primary metastatic disease, FOLFOX plus bevacizumab was used in 2 (14.5%) patients, FOLFIRI + bevacizumab in 4 (28.6%) patients,

FOLFOX + panitumumab in 1 (7.1%) patient, FOLFIRI panitumumab in 1 (7.1%) patient, FOLFOX + cetuximab in 1 (7.1%) patient, FOLFIRI + aflibercept in 4 (28.6%) patients, and FOLFIRI + cetuximab in 1 (7.1%) patient were used as second-line treatment. Patients with secondary metastatic disease received a median of 8 chemotherapy cycles, and patients with primary metastatic disease received 6 cycles of chemotherapy.

In patients with secondary metastatic disease, third-line therapies included FOLFOX in 1 patient (16.7%), FOLFOX plus bevacizumab in 3 (50%) patients, and regorafenib in 2 patients (33.3%). In patients with primary metastatic disease, FOLFOX was used in 1 (7.1%) patient and regorafenib was used in 13 (92,9%) patients as third-line therapy. Patients with secondary metastatic disease received a median of 2.5 cycles, and patients with primary metastatic disease received 3.5 cycles of treatment.

Four of the patients with primary metastasis received regorafenib as fourth-line therapy. Among patients with secondary metastatic disease, 1 patient received regorafenib, 2 patients received capecitabine, and one patient each received irinotecan and nivolumab and raltitrexed. Patient characteristics are shown in Table 1.

The median overall survival of the patients was 25.5 months (95% Confidence Interval (CI), 24.1-26.8) (Figure 1). There was no difference in survival between primary and secondary metastatic disease (p=0.173, Figure 2). Overall survival was not significantly associated with sex, ECOG performance status score, smoking status and weight loss history (p=0.139, p=0.240, p=0.911, p=0.923, respectively). A significant association was found between the presence of liver metastasis and survival (p=0.036, Figure 3). The median overall survival was 40.3 months (95% CI, 0-92.6) in patients without liver metastases, and 25 months (95% CI: 13.8-36.2) in patients with liver metastases.

The median survival was 9 months (95% CI, 6.47-10.64) in patients receiving regorafenib as third-line therapy. When the median survival was assessed according to the presence of liver metastases, it was 27.2 months in the group without liver metastasis and 4.69 months in the group with liver metastases (p=0.424) (Figure 4).

Regarding the grade 3 and higher side effects associated with the use of regorafenib, hand-foot-skin reaction was experienced by 4 (20%) patients, and fatigue occurred in 6 (30%) patients. While there were 8 (40%) patients who underwent dose reduction due to treatment-related side effects, there were no patients who required permanent discontinuation of treatment.

DISCUSSION

In this retrospective study investigating the factors affecting the survival of patients with mCRC who were treated with regorafenib, the presence of liver metastasis was found to be associated with poor prognosis. In our study, the median survival was 25 months in 15 patients with liver metastases and 40.3 months (p=0.036) in patients with extrahepatic metastases. When we looked at the patients receiving regorafenib as third-line therapy, the median survival was significantly shorter in the patient group with liver metastases compared to those without liver metastases (27.2 months vs. 4.69 months; p=0.424), although the difference was statistically non-significant.

In metastatic colorectal cancer, optimal therapeutic options after second-line therapy are limited. NCCN guidelines recommend regorafenib, trifluridine-tipiracil (TAS102), nivolumab or pembrolizumab (in dMMR/MSI-H patients only), trastuzumab + pertuzumab or lapatinib, or fam-trastuzumab deruxtecan-nxki (in HER2 amplified and RAS and BRAF wild-type patients), and encorafenib+ cetuximab or panitumumab (in BRAF V600E mutant patients) [6].

The efficacy and side effect profile of regorafenib in the treatment of chemorefractory mCRC have been investigated in many studies. In the phase III, randomized CORRECT trial, regorafenib showed advantages for both OS (HR 0.77; 95% CI, 0.64-0.94) (p=0.0052) (median OS 6.4 vs 5.0 months) and PFS (HR 0 .49; 95% CI, 0.42-0.58) (p<0.0001) (mPFS 1.9 vs 1.7 months) in comparison to

placebo [4]. The efficacy of regorafenib was assessed in Asian mCRC patients in the Phase III, randomized CONCUR study, showing results similar to those obtained in the CORRECT study in terms of efficacy and outcome [7]. In light of these studies, the NCCN and ESMO guidelines recommend regorafenib for the treatment of patients with mCRC who have progressed after first- and second-line chemotherapy regimens based on fluoropyrimidine, oxaliplatin, and irinotecan.

In our study, the median OS was 9 months (95% CI, 6.47-10.64) in patients with mCRC who received regorafenib as third- line treatment. This may be related to the small sample size and the inclusion of patients who could receive regorafenib in the third- or fourth- line treatment only (selection bias).

There are a number of studies available in the literature investigating the effectiveness of TAS102, capecitabine-temozolamide and SIRT treatments in combination with regorafenib for the treatment of chemorefractory mCRC. In a retrospective, single-center study, Ergun Y. et al. compared the efficacy of regorafenib versus capecitabine-temozolamide (Cap-Tem) in patients with chemorefractory mCRC. mOS and mPFS were found to be similar between the two treatment arms (mOS: 7 months in the Regorafenib arm versus 6.5 months in the Cap-Tem arm; HR 0.60; 95% CI, 0.28-1.27; p=0.18) and mPFS: 3.3 months in the Regorafenib arm versus 3.2 months in the Cap-Tem arm (HR 0.68; 95% CI, 0.34 -1.33; p=0.25)). The authors stated that it was not possible to determine predictive and prognostic markers due to the retrospective design of the study and the small number of patients (n=27 in the regorafenib arm and n=15 in the Cap-Tem arm, total n=42) [8].

In a study conducted by Arai H. et al., the predictive importance of early morphological changes observed with the use of regorafenib in the treatment of mCRC was investigated. They reported that cavity formation in lung metastasis and morphological response in liver metastasis may be predictive markers associated with good outcomes in patients with mCRC treated with regorafenib, and therefore may guide the clinician in deciding whether to continue treatment [9].

In the REBECCA study involving 656 patients in which real-life data were analyzed, mOS was reported to be 5.6 months in the regorafenib arm. In that study, ECOG PS score, delay in starting treatment, initial regorafenib dose, number of metastatic foci, and presence of liver metastases were determined as prognostic factors [10].

Consistently, in our study, liver metastasis was statistically significantly associated with worse prognosis in terms of overall survival (p=0.036), and non-significantly associated with worse prognosis in terms of survival after treatment with regorafenib in the patient group with liver metastasis compared to the patient group without liver metastasis.

In a network meta-analysis evaluating the efficacy of regorafenib, TAS102 and SIRT using Y-90 resin microspheres in the third- line treatment, all 3 treatments were found to be more effective in the treatment of mCRC compared to BSC. Although it was mentioned that heterogeneous studies were compared, it was reported that SIRT could be preferred over regorafenib and TAS-102 in the appropriate patient group due to its more favorable side effect profile [11]. Since our study was a single-arm study, it was not possible to make such a comparison.

In the phase IIIb CONSIGN study investigating treatment-related side effects encountered with regorafenib, the most frequently observed grade 3 and higher side effects were hypertension (15%), hand-foot-skin reaction (14%), fatigue (13%), diarrhea (5%). and hypophosphatemia (5%) [12]. It was reported that dose reduction was required in 46% of patients due to treatment-related adverse events. Although this study was not designed to evaluate survival data, on exploratory analysis, PFS was better in patients with better PS, no liver metastases, and a longer time from diagnosis to metastatic disease. These findings are also consistent with the findings of the REBECCA study. In that multicenter study, which included more than 2,800 patients, the high rates of dose reduction and treatment interruption were emphasized and the importance of optimal patient selection was stated. In our study, the most common treatment-related side effects were hand-foot-skin reaction and fatigue. The number of patients requiring dose reduction due to treatment-related side effects was 8

(40%). However, due to the retrospective design of our study, it should be kept in mind that there may be patients who were not adequately evaluated for side effects.

CONCLUSION

As a conclusion; regorafenib is a viable therapeutic option for the treatment of chemorefractory mCRC in the appropriate patient population. However, considering the frequency of treatment-related side effects and the high number of patients requiring dose reduction, it is important to demonstrate predictive markers.

REFERENCES

1. Kopetz S, Chang G.J., Overman M.J., et al. ; Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. J Clin Oncol 2009; 27: pp. 3677-3683

2. Van Cutsem E, Cervantes A, Adam R, et al. ; ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol. 2016 Aug;27(8):1386-422.

3. Carter NJ. Regorafenib: a review of its use in previously treated patients with progressive metastatic colorectal cancer. Drugs Aging. 2014;31(1):67–78.

4. Grothey A, Van Cutsem E, Sobrero A, et al. ; Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet. 2013 Jan 26;381(9863):303-12. doi: 10.1016/S0140-6736(12)61900-X. Epub 2012 Nov 22. PMID: 23177514.

5. Dhillon S. Regorafenib: A Review in Metastatic Colorectal Cancer. Drugs. 2018 Jul;78(11):1133-1144.

6. https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf, Version 2.2021, 01/21/21.

7. Li J, Qin S, Xu R, et al. ; 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 Jun;16(6):619-29.

8. 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 Nov-Dec;24(6):2435-2441. PMID: 31983117.

9. Arai H, Miyakawa K, Denda T, et al. ; Early morphological change for predicting outcome in metastatic colorectal cancer after regorafenib. Oncotarget. 2017 Nov 30;8(66):110530-110539. doi: 10.18632/oncotarget.22807. PMID: 29299166; PMCID: PMC5746401.

10. Adenis A, de la Fouchardiere C, Paule B, et al. ; Survival, safety, and prognostic factors for outcome with Regorafenib in patients with metastatic colorectal cancer refractory to standard therapies: results from a multicenter study (REBECCA) nested within a compassionate use program. BMC Cancer. 2016 Jul 7;16:412. doi: 10.1186/s12885-016-2440-9. Erratum in: BMC Cancer. 2016 Jul 25;16(1):518. PMID: 27389564; PMCID: PMC4936193.

11. Walter T, Hawkins NS, Pollock RF, Colaone F, Shergill S, Ross PJ. Systematic review and network meta-analyses of third-line treatments for metastatic colorectal cancer. J Cancer Res Clin Oncol. 2020 Oct;146(10):2575-2587. doi: 10.1007/s00432-020-03315-6. Epub 2020 Jul 27. PMID: 32715436; PMCID: PMC7467965.

12.Van Cutsem E, Martinelli E, Cascinu S, et al. ; Regorafenib for Patients with Metastatic Colorectal Cancer Who Progressed After Standard Therapy: Results of the Large, Single-Arm, Open-Label Phase IIIb CONSIGN Study. Oncologist. 2019 Feb;24(2):185-192. doi: 10.1634/theoncologist.2018-0072. Epub 2018 Sep 6. PMID: 30190299; PMCID: PMC6369948.