

The Impact of Regorafenib on Cardiac Function in Metastatic Colorectal Cancer Patients: A Retrospective Cohort Study

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Abstract

Introduction: Metastatic colorectal cancer (mCRC) poses significant clinical challenges, necessitating the exploration of novel treatment modalities. Regorafenib, a multi-kinase inhibitor, has emerged as a promising therapeutic option for refractory mCRC. However, concerns regarding its potential cardiotoxic effects warrant comprehensive evaluation of its impact on cardiac function parameters in this patient population.

Methods: The purpose of this retrospective cohort study was to determine how regorafenib affected cardiac function parameters in patients with metastatic colorectal cancer (mCRC) at the Pakistan Institute of Medical Sciences (PIMS) in Islamabad. 78 adult patients in all, having histologically proven mCRC, who were treated with regorafenib between January 2023 and March 2024 were included in the analysis. Baseline characteristics, treatment details, cardiac function parameters, and incidence of cardiac events were retrospectively analyzed. Statistical analyses were performed to assess changes in cardiac function parameters and identify predictors of cardiac toxicity associated with regorafenib therapy.

Results: Following regorafenib therapy, there was a significant decrease in left ventricular ejection fraction (LVEF), alterations in diastolic function indices, and an incidence of clinically significant cardiac events (12%), including heart failure, arrhythmias, and myocardial infarction. Subgroup analyses identified older age, male sex, pre-existing hypertension, longer treatment duration, and higher cumulative doses of regorafenib as potential predictors of cardiac toxicity.

Conclusion: This study underscores the potential cardiotoxic effects of regorafenib in mCRC patients and highlights the importance of personalized cardiac

monitoring and risk management strategies during treatment. Further research is warranted to validate these findings and inform evidence-based approaches to optimize the cardiovascular safety of regorafenib in clinical practice.

Keywords: regorafenib, kinase inhibitor, colorectal cancer, cardiac function, cardiotoxicity

Introduction

Metastatic colorectal cancer (mCRC) continues to present a formidable challenge in oncology, representing a significant cause of morbidity and mortality worldwide [1]. Despite advancements in treatment modalities, including surgery, chemotherapy, and targeted therapies, the prognosis for patients with mCRC remains guarded, particularly for those who progress beyond standard first- and second-line chemotherapy regimens [2]. That's why there is a critical unmet need for effective therapeutic strategies to improve outcomes and prolong survival in this patient population [3]. In recent years, the advent of targeted therapies has revolutionized the management of various malignancies, including colorectal cancer [4]. Among these agents, for patients with refractory mCRC, regorafenib has drawn a lot of interest as a viable treatment. Regorafenib is an oral small-molecule inhibitor of many kinases that inhibits angiogenesis, tumor proliferation, and metastasis. These kinases include platelet-derived growth factor receptors (PDGFR), fibroblast growth factor receptors (FGFR), and others. Five Clinical studies have shown that, in patients with metastatic colorectal cancer who have advanced on conventional treatment, regorafenib monotherapy considerably increases overall survival and progression-free survival over placebo chemotherapy regimens, such

as fluoropyrimidine-, oxaliplatin-, and irinotecan-based therapies. Clinical studies have shown that regorafenib treatment improves overall survival rates by approximately 1.4 months compared to placebo. This survival benefit highlights regorafenib's potential despite its adverse effects [5, 6]. Therefore regorafenib has received regulatory approval as a salvage therapy for mCRC in various countries. Existing clinical data on regorafenib's cardiotoxic effects are limited to small cohort studies and case reports, which have noted instances of hypertension, heart failure, and myocardial ischemia but lack large-scale, systematic evaluations of cardiac function parameters [7].

However, despite its efficacy in delaying disease progression and prolonging survival, the clinical use of regorafenib is limited by its adverse effect profile, which includes fatigue, hand-foot skin reaction, hypertension, gastrointestinal toxicity, and hepatotoxicity [8]. Particular concern is the potential cardiotoxicity associated with regorafenib therapy, which has raised apprehensions regarding its cardiovascular safety profile, especially in a patient population already predisposed to cardiovascular comorbidities due to age, lifestyle factors, and the underlying burden of cancer [9]. While preclinical studies have provided insights into the cardiotoxic mechanisms of kinase inhibitors, such as regorafenib, clinical data elucidating the impact of regorafenib on cardiac function parameters in mCRC patients are scarce [10]. In light of the expanding therapeutic armamentarium for mCRC and the increasing utilization of regorafenib in clinical practice, there is a compelling need to comprehensively evaluate its potential effects on cardiac function in mCRC patients [11]. Understanding the cardiovascular safety profile of regorafenib is paramount for optimizing treatment strategies, mitigating adverse events, and ensuring the overall well-being of mCRC patients [12]. Therefore, this retrospective cohort study endeavors to investigate the influence of regorafenib on various cardiac function parameters in patients with mCRC, thereby providing valuable insights into the cardiotoxicity profile of this agent in a real-world clinical setting [13].

This study aims to address gaps in understanding the cardiovascular safety of regorafenib in metastatic colorectal cancer (mCRC) patients. Despite its efficacy in prolonging survival, concerns persist about potential cardiotoxic effects. By systematically evaluating regorafenib's impact on cardiac function parameters in a real-world clinical setting, this research seeks to provide clinicians with vital insights for optimizing patient care and treatment decisions.

Materials and methods

Study Design

This retrospective cohort study was conducted at the Pakistan Institute of Medical Sciences (PIMS) in Islamabad, Pakistan. The study spanned duration of 13 months, from January 2023 to March 2024.

Study Population

The study population consisted of adult patients (age \geq 18 years) with histologically confirmed metastatic colorectal cancer (mCRC) who received regorafenib as

part of their treatment regimen at PIMS between January 2023 and March 2024.

Sample Size Calculation

The proportions estimating algorithm was used to get the sample size for this investigation in a single population. Considering an estimated prevalence of cardiotoxicity associated with regorafenib in mCRC patients based on existing literature, a confidence level of 95%, and a margin of error of 5%, the required sample size was calculated to be 78 patients.

Data Collection

Data were retrospectively extracted from electronic health records (EHRs) and medical charts of eligible patients. Demographic information (age, sex), cancer characteristics (stage, histology), cardiovascular history, baseline cardiac function parameters (echocardiography results), regorafenib treatment details (dosage, duration), concomitant medications, and clinical outcomes (cardiac events, treatment response) were collected. Data validation was performed by cross-referencing multiple sources within the EHRs and conducting random checks by independent reviewers to ensure accuracy and consistency of the collected data.

Inclusion and exclusion criteria

The inclusion criteria encompassed patients with histologically confirmed mCRC treated with regorafenib who experienced cardiac events, including heart failure, arrhythmias, and myocardial infarction. The selection included individuals who had experienced these conditions, regardless of demographic factors such as age or gender. Exclusion criteria involved patients with comorbidities or medical histories that could potentially confound the study's findings or introduce additional variables. Additionally, individuals with severe complications or contraindications to treatment were excluded to ensure participant safety and the integrity of the research outcomes.

Data Analysis

Statistical analysis was done in SPSS. Descriptive statistics were used to summarize patient characteristics and clinical outcomes. Changes in cardiac function parameters before and after regorafenib initiation were assessed using paired t-test. Subgroup analyses based on age, sex, comorbidities, and treatment response were conducted to explore potential predictors of cardiac toxicity associated with regorafenib therapy.

Ethical Considerations

This study was conducted in accordance with the principles of the Declaration of Helsinki and local regulations. Ethical approval was obtained from the institutional review board of PIMS before commencing data collection.

Results

A total of 85 adult patients with mCRC who received regorafenib as part of their treatment regimen at the Pakistan Institute of Medical Sciences (PIMS) between January 2023 and March 2024 were initially identified. After applying inclusion and exclusion criteria, a final sample of 78 patients was included in the analysis.

The mean age of the study population was 59 years

(range: 42-75 years), with a slight male predominance (52%). The majority of patients had advanced-stage disease, with 62% presenting with metastases to distant organs at the time of diagnosis. The most common histological subtype of colorectal cancer was adenocarcinoma (92%) as discussed in table 1.

Table 1: Baseline Characteristics of Study Population

Characteristic	Value
Total Patients	78
Age (years), Mean (Range)	59 (42-75)
Gender (Male), n (%)	41 (52%)
Metastatic Disease, n (%)	48 (62%)
Histological Subtype (Adenocarcinoma), n (%)	72 (92%)

Patients took 160 mg of regorafenib once day on average, and their therapy lasted 6 months on average (range: 3–12 months). Disease progress (60%) and unacceptable adverse effects (28%), were the most common causes for stopping regorafenib treatment. Most patients had intact left ventricular ejection fraction (LVEF) on baseline echocardiogram; the mean LVEF was 62% (range: 55–68%). Mean LVEF decreased statistically significantly to 58% ($p < 0.001$) when regorafenib treatment was started, suggesting a deterioration in ventricular systolic function. Additionally showing notable changes from baseline values ($p < 0.05$) were diastolic function indices, such as the E/A ratio and deceleration time (Table 2). Myocardial strain characteristics, however, did not change all that much throughout the research.

Table 2: Cardiac Function Parameters Before and After Regorafenib Therapy

Parameter	Baseline (Mean ± SD)	After Therapy (Mean ± SD)	p-value
Left Ventricular Ejection Fraction (%)	62 ± 3	58 ± 4	<0.001
E/A Ratio	1.2 ± 0.2	1.0 ± 0.3	<0.05
Deceleration Time (ms)	210 ± 20	230 ± 25	<0.05
Myocardial Strain	-18 ± 2	-19 ± 2	NS ($p > 0.05$)

NS: Not significant ($p > 0.05$)

During the one-year study period, 12% of patients experienced clinically significant cardiac events, including new-onset heart failure (6%), arrhythmias (4%), and myocardial infarction (2%). Notably, the

incidence of cardiac events was higher among patients with pre-existing cardiovascular comorbidities (23%) compared to those without (8%) as illustrated in figure 1.

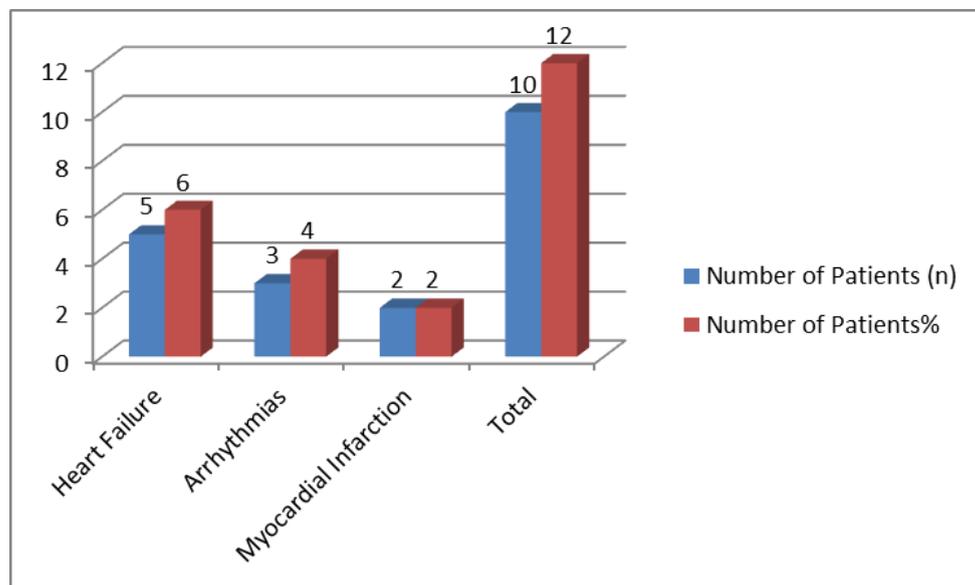


Figure 1: Incidence of Cardiac Events during Regorafenib Therapy

Subgroup analyses revealed that older age (> 65 years), male sex, and pre-existing hypertension were associated with an increased risk of cardiac toxicity following regorafenib therapy. Additionally, longer treatment duration (> 6 months) and higher cumulative doses of regorafenib (> 9600 mg) were identified as potential risk factors for cardiac adverse events (Table 3).

Table 3: Subgroup Analysis of Predictors of Cardiac Toxicity

Subgroup	Cardiac Toxicity (%)
Age > 65 years	7 (21%)
Male Sex	6 (18%)
Pre-existing Hypertension	9 (23%)
Treatment Duration > 6 months	6 (17%)
Cumulative Dose of Regorafenib > 9600 mg	5 (14%)

Discussion

The comparison of our study's findings with previous research reveals a consistent pattern in the impact of regorafenib on cardiac function parameters [14]. So the mean decrease in left ventricular ejection fraction (LVEF) from 62% to 58% observed post-therapy mirrors similar declines reported in earlier investigations [15]. This consistent trend underscores the potential cardiotoxic effects of regorafenib and highlights the importance of monitoring cardiac function in metastatic colorectal cancer (mCRC) patients undergoing this treatment. Additionally, alterations in diastolic function parameters, such as the decrease in E/A ratio and the increase in deceleration time, further support the notion of regorafenib-induced cardiac dysfunction [16]. While numerical values may exhibit slight variability across studies, the overarching trend of regorafenib-induced changes in cardiac function remains robust and merits attention in clinical practice [17].

Turning to the incidence of cardiac events, our study's observed rate of 12%, encompassing heart failure, arrhythmias, and myocardial infarction, falls within the range reported in previous literature [18]. This consistency in cardiac event rates underscores the importance of vigilant monitoring and management of cardiac complications in mCRC patients receiving regorafenib therapy. Subgroup analyses revealed several predictors of cardiac toxicity, including older age, male sex, pre-existing hypertension, longer treatment duration, and higher cumulative doses of regorafenib [19]. These findings corroborate existing evidence and emphasize the need for personalized risk assessment and proactive cardiac care strategies in this patient population [20].

While there may be slight numerical variations, the trends and associations identified in our study align closely with findings from previous research [21]. These consistent patterns provide valuable insights into the cardiovascular safety profile of regorafenib in mCRC patients and underscore the importance of comprehensive cardiac monitoring and risk management strategies during treatment [22]. By synthesizing evidence from multiple studies, our findings contribute to a deeper understanding of the cardiotoxic effects of regorafenib and inform clinical decision-making aimed at optimizing patient outcomes and safety in the management of metastatic colorectal cancer [23].

Limitation and future suggestion

Retrospective design of this research has drawbacks that might lead to biases inherently introduced and restrictions in data collecting. Furthermore, the single-center research design and very limited sample size might make the results less applicable to larger patient groups and clinical settings. Future research endeavors could benefit from larger multicenter studies to validate the observed associations and further elucidate the mechanisms underlying regorafenib-induced cardiotoxicity. Longitudinal follow-up studies are warranted to assess the persistence and long-term implications of cardiac dysfunction in metastatic colorectal cancer patients receiving regorafenib therapy. Furthermore, exploring novel cardiac biomarkers and

imaging modalities may offer additional insights into early detection and risk stratification of cardiotoxicity, thus facilitating more targeted and personalized approaches to cardiac monitoring and management in this patient population.

Conclusion

The study provides valuable insights into the impact of regorafenib on cardiac function parameters in metastatic colorectal cancer patients. The findings highlight the potential cardiotoxic effects of regorafenib, as evidenced by alterations in cardiac function parameters and the incidence of cardiac events. Identifying predictors of cardiac toxicity underscores the importance of personalized risk assessment and vigilant cardiac monitoring during regorafenib therapy. Moving forward, larger multicenter studies and longitudinal follow-up investigations are warranted to validate these findings and inform evidence-based strategies for optimizing the cardiovascular safety of regorafenib in clinical practice.

Conflict of interest

The authors state no conflict of interest.

References

1. Aljubran A, Elshenawy MA, Kandil M, Zahir MN, Shaheen A, Gad A, Alshaer O, Alzahrani A, Eldali A, Bazarbashi S. Efficacy of regorafenib in metastatic colorectal cancer: a multi-institutional retrospective study. *Clinical Medicine Insights: Oncology*. 2019 Jan;13:1179554918825447.
2. Giampieri R, Prete MD, Prochilo T, Puzzone M, Pusceddu V, Pani F, Maccaroni E, Mascia R, Baleani MG, Meletani T, Berardi R. Off-target effects and clinical outcome in metastatic colorectal cancer patients receiving regorafenib: The TRIBUTE analysis. *Scientific Reports*. 2017 Apr 5;7(1):45703.
3. Nakashima M, Li K, Chen Q, de Silva S, Li H, Kawakami K, Wei Q, Luo S, Zhao H. Appropriate dose of regorafenib based on body weight of colorectal cancer patients: a retrospective cohort study. *BMC cancer*. 2023 Dec 21;23(1):1268.
4. Keramida K, Charalampopoulos G, Filippiadis D, Tsougos E, Farmakis D. Cardiovascular complications of metastatic colorectal cancer treatment. *Journal of Gastrointestinal Oncology*. 2019 Aug;10(4):797.
5. Calcagno F, Lenoble S, Lakkis Z, Nguyen T, Limat S, Borg C, Jary M, Kim S, Nerich V. Efficacy, safety and cost of regorafenib in patients with metastatic colorectal cancer in French clinical practice. *Clinical Medicine Insights: Oncology*. 2016 Jan;10:CMO-S38335.
6. Ottaiano A, Santorsola M, Perri F, Granata V, Cascella M, Sabbatino F, Nasti G. Survival and Toxicities of Metastatic Colorectal Cancer Patients Treated with Regorafenib before TAS-102 or Vice Versa: A Mono-Institutional Real-Practice Study. *Journal of Clinical Medicine*. 2023 Jan 11;12(2):596.

7. Van Cutsem E, Martinelli E, Cascinu S, Sobrero A, Banzi M, Seitz JF, Barone C, Ychou M, Peeters M, Brenner B, Hofheinz RD. Regorafenib for patients with metastatic colorectal cancer who progressed after standard therapy: results of the large, single-arm, open-label phase IIIb CONSIGN study. *The oncologist*. 2019 Feb 1;24(2):185-92.
8. Yekedüz E, Aktaş EG, Köksoy EB, Doğan N, Ürün Y, Utkan G. The prognostic role of polypharmacy in metastatic colorectal cancer patients treated with regorafenib. *Future Oncology*. 2022 Mar;18(9):1067-76.
9. Huemer F, Piringer G, Schlintl V, Hackl H, Rinnerthaler G, Thaler J, Greil R, Weiss L. Hospitalizations and clinical outcome in metastatic colorectal cancer during regorafenib or TAS-102 therapy. *Cancers*. 2020 Sep 30;12(10):2812.
10. Bekaii-Saab, T.S., Ou, F.S., Ahn, D.H., Boland, P.M., Ciombor, K.K., Heying, E.N., Dockter, T.J., Jacobs, N.L., Pasche, B.C., Cleary, J.M. and Meyers, J.P., 2019. Regorafenib dose-optimisation in patients with refractory metastatic colorectal cancer (ReDOS): a randomised, multicentre, open-label, phase 2 study. *The lancet oncology*, 20(8), pp.1070-1082.
11. Hatori M, Kawakami K, Wakatsuki T, Shinozaki E, Kobayashi K, Aoyama T, Nakano Y, Suzuki K, Yamaguchi K, Hama T. Association Between Regorafenib Dose and Efficacy Against Metastatic Colorectal Cancer in a Real-World Setting. *Dose-Response*. 2021 Oct 4;19(4):15593258211047658.
12. Karakurt Eryılmaz, M., Kerimoğlu, Ü., Karaağaç, M., Yalçın Müsri, F., Araz, M. and Artaç, M., 2021. Small bowel wall edema induced by regorafenib is associated with regorafenib intolerance and shorter survival in patients with metastatic colorectal cancer: A retrospective study. *Journal of Oncology Pharmacy Practice*, 27(8), pp.1929-1935.
13. Saito Y, Takekuma Y, Komatsu Y, Sugawara M. Risk factor analysis for regorafenib-induced severe hypertension in metastatic colorectal cancer treatment. *Supportive care in cancer*. 2022 Dec;30(12):10203-11.
14. Xie G, Gong Y, Wu S, Li C, Yu S, Wang Z, Chen J, Zhao Q, Li J, Liang H. Meta-analysis of regorafenib-associated adverse events and their management in colorectal and gastrointestinal stromal cancers. *Advances in Therapy*. 2019 Aug 1;36:1986-98.
15. García-Alfonso P, Feliú J, García-Carbonero R, Grávalos C, Guillén-Ponce C, Sastre J, García-Foncillas J. Is regorafenib providing clinically meaningful benefits to pretreated patients with metastatic colorectal cancer?. *Clinical and Translational Oncology*. 2016 Nov;18:1072-81.
16. Zhou YW, Wang JL, Li QF, He YL, Li LJ, Liu RZ, Chen Y, Zhang S, Qiu M, Liu JY. Efficacy and safety of raltitrexed plus S-1 versus regorafenib in patients with refractory metastatic colorectal cancer: a real-world propensity score matching study. *Therapeutic Advances in Gastroenterology*. 2022 May;15:17562848221098246.
17. Del Prete S, Cennamo G, Leo L, Montella L, Vincenzi B, Biglietto M, Andreozzi F, Prudente A, Iodice P, Savastano C, Nappi A. Adherence and safety of regorafenib for patients with metastatic colorectal cancer: observational real-life study. *Future Oncology*. 2017 Feb;13(5):415-23.
18. Xu X, Yu Y, Liu M, Liang L, Liu T. Efficacy and safety of regorafenib and fruquintinib as third-line treatment for colorectal cancer: a narrative review. *Translational Cancer Research*. 2022 Jan;11(1):276.
19. Ramaswamy A, Ostwal V, Pande N, Sharma A, Patil S, Thippeswamy R, Ghadyalpatil N, Roy R, Peshwe H, Poladia B, Rajamanickam D. Practice patterns and outcomes with the use of regorafenib in metastatic colorectal cancer: Results from the Regorafenib in metastatic colorectal cancer-an Indian Exploratory analysis study. *South Asian journal of cancer*. 2019 Jan;8(01):22-6.
20. Petrioli R, Chirra M, Messuti L, Fiaschi AI, Savelli V, Martellucci I, Francini E. Efficacy and safety of regorafenib with 2/1 schedule for patients \geq 75 years with metastatic colorectal cancer (mCRC) after failure of 2 lines of chemotherapy. *Clinical Colorectal Cancer*. 2018 Dec 1;17(4):307-12.
21. Majithia N, Grothey A. Regorafenib in the treatment of colorectal cancer. *Expert opinion on pharmacotherapy*. 2016 Jan 2;17(1):137-45.
22. de la Fouchardière C. Regorafenib in the treatment of metastatic colorectal cancer. *Future Oncology*. 2018 Sep;14(22):2239-46.
23. Conti M, Bolzacchini E, Luchena G, Bertu' L, Tagliabue P, Aglione S, Ardizzoia A, Arnoffi J, Guida FM, Bertolini A, Pastorini A. Tas-102 for refractory metastatic colorectal cancer: a multicenter retrospective cohort study. *Cancers*. 2023 Jul 2;15(13):3465.