ORIGINAL RESEARCH

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Investigation of Regorafenib Efficacy in Patients with Metastatic Colorectal Carcinoma in Relation to the Delivered Dose Intensity/Body Surface Area

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ABSTRACT Objective: Regorafenib is an orally active inhibitor of angiogenic receptor tyrosine kinases, used to treat metastatic colorectal cancer (mCRC) refractory to standard therapy. The significance of relative dose intensity (RDI) in the treatment of various types of solid cancers has been studied. Nevertheless, RDI may not accurately reflect the treatment intensity of regorafenib, where the standard dose cannot be tolerated by most patients. We aimed to investigate the efficacy of the delivered dose intensity/body surface area (BSA) ratio at 2 months (2M-DBR) by comparing the relationship between 2M-DBR, RDI at 2 months, and the therapeutic response. **Material and Methods:** The therapeutic response to regorafenib was studied in 53 patients retrospectively from 2015 to 2020. Computed tomography scans were performed at 8-12 weeks after the initiation of treatment. We also investigated the clinical factors associated with high 2M-DBR and BSA. **Results:** Patients with high 2M-DBR achieved significantly better objective response rates than those with low 2M-DBR ($p<0.064$). Patients with high 2M-DBR experienced longer overall survival ($p=0.445$) and progression-free survival ($p=0.524$) than those with low 2M-DBR but the difference was not statistically significant. Tolerance to 160 mg regorafenib was found to be better in patients with high BSA (22%) than in a patient with low BSA (0%) ($p=0.011$). **Conclusion:** BSA is crucial in determining the tolerance dose of regorafenib. 2M-DBR plays a key role in reflecting treatment intensity and is a useful tool for predicting the response to regorafenib in mCRC.

Keywords: Regorafenib; body surface area; colorectal cancer

Colorectal cancer (CRC) is the third most frequently diagnosed cancer in men and the second most commonly diagnosed cancer in women worldwide.[1]

Regorafenib is an orally administered tyrosine kinase receptor inhibitor that targets angiogenic [including the vascular endothelial growth factor (VEGF) receptors 1 to 3], stromal, and oncogenic cells. It inhibits a variety of kinases located within angiogenic and tumor growth-promoting pathways and is structurally similar to sorafenib.[2]

The activity of regorafenib in metastatic CRC (mCRC) patients not responding to standard chemotherapy and targeted therapy was initially shown in the CORRECT trial. In this trial, 760 patients were randomized to receive the best supportive care and regorafenib (160 mg orally once daily for the first three of every four weeks cycle).[2]

Findings of phase 2 ReDOS study support that regorafenib is an option in eligible patients with mCRC who develop disease progression despite treatment with fluoropyrimidine, irinotecan, and ox-

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aliplatin-based chemotherapy plus anti-epidermal growth factor receptor (EGFR) agent (if RAS wild-type) or anti-VEGF agent. In this trial, regorafenib was administered with a starting dose of 80 mg per day rather than 160 mg (the approved dose), escalating the dose weekly in the absence of toxicity, and ending at 160 mg daily for 21 days of each 28-day cycle.[3]

It is essential to evaluate the patient's condition before initiating treatment, especially in anticancer therapy aimed at optimizing the therapeutic effects of the drug. It is also crucial to closely monitor patient performance to adequately manage adverse effects (AEs) and administer optimum dose intensity (DI).

The relative DI (RDI) is an index of the treatment intensity of anticancer drugs and is calculated as the percentage of the delivered DI divided by the standard DI.[4]

In various types of cancers, including breast cancer, pancreatic ductal adenocarcinoma, renal cell carcinoma, malignant lymphoma, and hepatocellular carcinoma (HCC), the relationship between RDI and therapeutic efficacy has been reported.[5-9]

RDI may not show the correct treatment exposure, as depicted in the following formula. If the patient started to take 160 mg/day for one month followed by 120 mg/day for one month then RDI at 60 days (2M-RDI) will be calculated as (160 mg×21 days+120 mg×21 days)/(160 mg×42 days)=0.8125 (81.25%).

The delivered dose intensity/body surface area (BSA) ratio at 2 months (2M-DBR) will be calculated as (160 mg×21 days+120 mg×21 days)/BSA.

Thus, we hypothesize that 2M-DBR represents treatment exposure of regorafenib more accurately than 2M-RDI. We aimed to investigate the benefit of DBR usage by studying the correlation between DBR or RDI and drug efficacy. In addition, we evaluated the clinical factors that were related to 2M-DBR.

MATERIAL AND METHODS

STUDY DESIGN

We retrospectively evaluated 53 patients with advanced mCRC, including RAS wild-type and RAS mutant-type treated with regorafenib, between January 2015 and December 2020, across 3 Turkish institutions (Mersin City Training and Research Hospital, Mersin University Hospital, and Mersin Medical Park Hospital). Histological diagnosis and staging of mCRC based on the World Health Organization tumor-node-metastasis (TNM) staging and classification system. The recruitment criteria included patients with cytologically or histologically confirmed stage IV mCRC who underwent regular treatment with regorafenib and who harbored RAS wild-type or RAS mutant-type mCRC. The patients with the absence of a measurable lesion as per the latest version of Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 criteria were excluded from the study.[10] We conducted the study in accordance with the Principles of the Declaration of Helsinki. Our study was approved by Mersin University Ethics Committee on January 20, 2021, with the decision number 2021/50.

THE TREATMENT PROTOCOL OF REGORAFENIB

The starting dose of regorafenib was 160 mg in most patients and 80 or 120 mg in the rest of the patients. The dose was then gradually increased. As per the manufacturer's guidelines, the dose of regorafenib was reduced, or the treatment was stopped when the patient underwent any intolerable drug-related AEs. National Cancer Institute Common Terminology Criteria for AEs, version 4.0 was employed when AEs occurred. Dose de-escalation or temporary cessation of regorafenib was exercised till the AEs were recovered to Grade 1 or 2, according to the manufacturer's guideline.

To determine the TNM stage, all patients underwent a colonoscopy, physical examination, positron emission tomography using 18F-fluorodeoxyglucose or computed tomography plus bone scintigraphy before the initiation of therapy. Patients' characteristics such as clinical stage, age at diagnosis, sex, Eastern Cooperative Oncology Group (ECOG) performance status at the initiation of regorafenib treatment, RAS mutation status, body weight, height, and the number of regimens before regorafenib were determined, by a retrospective chart review. We used the following formula to calculate BSA: BSA (m^2)=[body weight (kg)]0.425×[height (cm)]0.725×0.007184.[11]

DETERMINATION OF 2M-DBR AND 2M-RDI CALCULATION

2M-RDI was calculated as the percentage of delivered DI (total delivered dose for the first 60 days) divided by the standard DI of regorafenib for 60 days (6,720 mg). The standard DI of regorafenib for 60 days was calculated as follows: 160 mg×42 days=6,720 mg.

2M-DBR was calculated as the delivered DI for the first 60 days divided by BSA. BSA was calculated based on the patient's height and body weight just before starting the treatment with regorafenib.

RECIST v1.1 was used for defining radiographic tumor responses [progressive disease (PD), an increase of at least 20% in the sum of the target lesion diameters compared with the smallest sum during the study; complete response (CR), the disappearance of all target lesions; partial response (PR), a decrease in the sum of the target lesion diameters of at least 30% compared with baseline; stable disease (SD), insufficient shrinkage or expansion to qualify as PR or PD].[10] Differences in the response rates (RRs) according to the patient's characteristics were compared by using Fisher's exact test. The time from the day of starting regorafenib to PD or until death from any cause was defined as PFD (progression free death), and the time from the first day of treatment to death or until the last follow-up date was evaluated as overall survival (OS). Kaplan-Meier method was used for plotting the survival curves, and the log-rank test was used for analyzing the differences in survival times. The p value <0.05 was considered to be statistically significant.

RESULTS

BASELINE CHARACTERISTICS

The baseline clinical characteristics of patients according to BSA are demonstrated in Table 1. Our study included 22 females and 31 males (age range 37-87 years; median age 62.0 years). The median BSA was 1.78. The difference of high BSA ratio in males and females was statistically significant (71% vs. 22.7% p: 0.001). Overall, 27 patients had BSA≥1.78, and 26 patients had BSA<1.78. There were two patients with ECOG: 0, 40 patients with ECOG: 1, and 11 patients with ECOG: 2. TNM stages of the patients were IVA (n=9), IVB (n=30), and IVC (n=14). Out of 53 patients, 33 underwent primary surgery, while 20 patients did not. The primary tumor sites of the patients were predominantly the right colon (n=13) followed by the left colon (n=40). Among all the patients, 28 patients had RAS-mutant type, 24 had RAS-wild type, and one patient harbored *BRAF* mutant type of mCRC. Of all the patients included, 26 patients had <3 chemotherapy line before regorafenib therapy, 16 patients had 3 lines, and 11 patients had ≥4 lines. Regarding a standard dose of regorafenib, 9 patients tolerated 80 mg, 38 patients tolerated 120 mg, and 6 patients tolerated 160 mg. The high BSA group tolerated 160 mg better than the low BSA group (22% vs. 0%, p=0.011). The last biologic agent used was anti-EGFR in 9 patients, anti-VEGF in 39 patients, and any agent in 5 patients. The standard dose of regorafenib was started in 31 patients, while the reduced dose of regorafenib was started in 22 patients.

The baseline clinical characteristics of enrolled patients according to 2M-DBR are shown in Table 2. Cut-off 2M-DBR was 3,657 mg, and area under the receiver operating characteristic (AUROC) was 0.776. There was no statistically significant difference in baseline characteristics of low 2M-DBR and high 2M-DBR groups.

TREATMENT RESPONSE TO REGORAFENIB IN AS PER 2M-DBR

In the first 2 months, 7 of 53 patients temporarily discontinued the dosage, while a dose reduction was introduced in 25 of them. According to modified RECIST guidelines compatible computed tomography (8-12 weeks) evaluations, PD, PR, and SD were noted in 28, 4, and 1 patient, respectively, while CR was not observed in any patient.

To find the cut-off values that distinguish responders from non-responders, ROC curve analysis of 2M-RDI and 2M-DBR was done, and the AUROC values were compared to predict the objective response (CR or PR) (Figure 1). When the objective RR (ORR) (CR+PR) of the high 2M-DBR group (20.0%, CR=0, PR=3) and the low 2M-DBR group (2.6%, CR=0, PR=1) were compared at 8-12 weeks, no significant difference was found (2-sided Fischer's

TABLE 1: he baseline characteristics according to BSA.

	BSA<1.78	BSA≥1.78	p value
Sex			
Male	9 (34.6%)	22 (81.5%)	**0.001**
Female	17 (65.4%)	5 (18.5%)	
Median age: 62.0			
Age <65	14 (53.8%)	15 (55.6%)	0.901
Age ≥65	12 (46.2%)	12 (44.4%)	
ECOG			
0-1	20 (76.9%)	22 (82.6%)	0.682
2	6 (23.1%)	5 (7.4%)	
1 metastasis	5 (19.2%)	4 (14.8%)	0.711
≥2 metastasis	14 (53.9%)	16 (59.3%)	
Periton metastasis	7 (26.9%)	7 (25.9%)	
Time from diagnosis of metastasis			
<18 months	9 (34.6%)	8 (29.6%)	0.697
≥18 months	17 (65.4%)	19 (70.4%)	
Primer surgery (+)	17 (65.4%)	16 (59.3%)	0.646
Primer surgery (-)	9 (34.6%)	11 (40.7%)	
Tumor side, n (%)			
Right	6 (23.1%)	7 (25.9%)	0.810
Left	20 (76.9%)	20 (74.1%)	
RAS status			
RAS wild	10 (38.5%)	15 (55.6%)	0.827
RAS mutant	16 (61.5%)	12 (44.4%)	
Prior chemotherapy line			
<4	20 (76.9%)	18 (66.7%)	0.407
≥4	6 (23.1%)	9 (33.3%)	
Regorafenib toleration dose			
80-120 mg	26 (100%)	21 (77.8%)	**0.011**
160 mg	0 (0%)	6 (22.2%)	
Prior biologic agent			
Anti-EGFR	4 (16.0%)	5 (20.8%)	
Anti-VEGF	21 (84.0%)	19 (79.2%)	0.725
PFS	4.8 (0.8-8.7)	4.1 (2.5-5.6)	Logr: 0.231
OS	12.6 (8.3-17.0)	14.8 (4.5-23.6)	Logr: 0.608

BSA: Body surface area; ECOG: Eastern Cooperative Oncology Group; EGFR: Epidermal growth factor receptor; VEGF: Vascular endothelial growth factor; PFS: Progression-free survival; OS: Overall survival.

exact test p=0.064). Also, the disease control rates (disease control rate, CR+PR+SD) of the high 2M-DBR group (33.3%, CR=0, PR=3, SD=2) and the low 2M-DBR group (52.6%, CR=0, PR=1, SD=19) at 8-12 weeks did not reveal any significant difference (2-sided Fischer's exact test p=0.150, see Table 3).

ADVERSE EFFECTS OF REGORAFENIB TREATMENT

AEs of regorafenib therapy are shown in Table 4. We divided the side effects into three grades as follows: any grade, grade ≥3, potential grade ≥3.

Relationship between survival [progression-free survival (PFS) and OS] and 2M-RDI or 2M-DBR of regorafenib (Table 5).

TABLE 2: The baseline characteristics according to the 2M-DBR.

	2M-DBR<3,657	2M-DBR≥3,657	p value
Sex			
Male	25 (65.8%)	6 (40.0%)	0.086
Female	13 (34.2%)	9 (60.0%)	
Median age: 62.0			
Age <65	19 (50.0%)	10 (40.0%)	0.272
Age ≥65	19 (50.0%)	15 (60.0%)	
ECOG			
0-1	28 (73.6%)	14 (93.3%)	0.149
2	10 (26.4%)	1 (6.7%)	
No periton metastasis	25 (65.8%)	13 (86.7%)	0.182
Periton metastasis	13 (34.2%)	2 (13.3%)	
Time from diagnosis of metastasis			
<18 months	12 (31.6%)	5 (33.3%)	0.902
≥18 months	26 (68.4%)	10 (66.7%)	
Primer surgery (+)	14 (36.8%)	6 (40.0%)	0.831
Primer surgery (-)	24 (63.2%)	9 (60.0%)	
Tumor side, n (%)			
Right	8 (21.1%)	5 (33.3%)	0.480
Left	30 (78.9%)	10 (66.7%)	
RAS status			
RAS wild	15 (39.5%)	9 (60.0%)	0.176
RAS mutant	23 (60.5%)	6 (40.0%)	
Prior chemotherapy line			
<4	29 (76.3%)	9 (60.0%)	0.313
≥4	9 (23.7%)	6 (40.0%)	
Regorafenib toleration dose			
80-120 mg	35 (92.1%)	12 (80.0%)	0.334
160 mg	3 (7.9%)	3 (20.0%)	
Prior biologic agent			
Anti-EGFR	6 (16.7%)	3 (23.1%)	0.683
Anti-VEGF	30 (83.3%)	10 (76.9%)	

2M-DBR: The delivered dose intensity/body surface area ratio at 2 months; ECOG: Eastern Cooperative Oncology Group; EGFR: Epidermal growth factor receptor; VEGF: Vascular endothelial growth factor.

The median OS of all the patients studied was 12.6 months (7.5-17.8), and PFS was 4.1 months (2.83-5.36 months).

The PFS of the high 2M-RDI group (≥81.25%, n=30) and the low 2M-RDI group (<81.25%, n=23) demonstrated no significant difference between the two groups (Figure 2a). Furthermore, the group with high 2M-DBR (≥3,657, n=15) had higher PFS than the group with low 2M-DBR (<3,657, n=38) though it was not statistically significant (Figure 2b).

When the OS of the high 2M-RDI group (≥81.25%, n=30) and the low 2M-RDI group (<81.25%, n=23) were compared, no significant difference was observed between the two groups (Figure 3a). Furthermore, the group with high 2M-DBR (≥3,657, n=15) had higher OS than the group with low 2M-DBR (<3,657, n=38), but it was not statistically significant (Figure 3b).

DISCUSSION

As per the Phase III CORRECT study, regorafenib, a tyrosine kinase inhibitor, is used in the treatment of mCRC refractory to standard therapy.[2] OS in Phase III CORRECT trial and Phase III CONCUR trial was

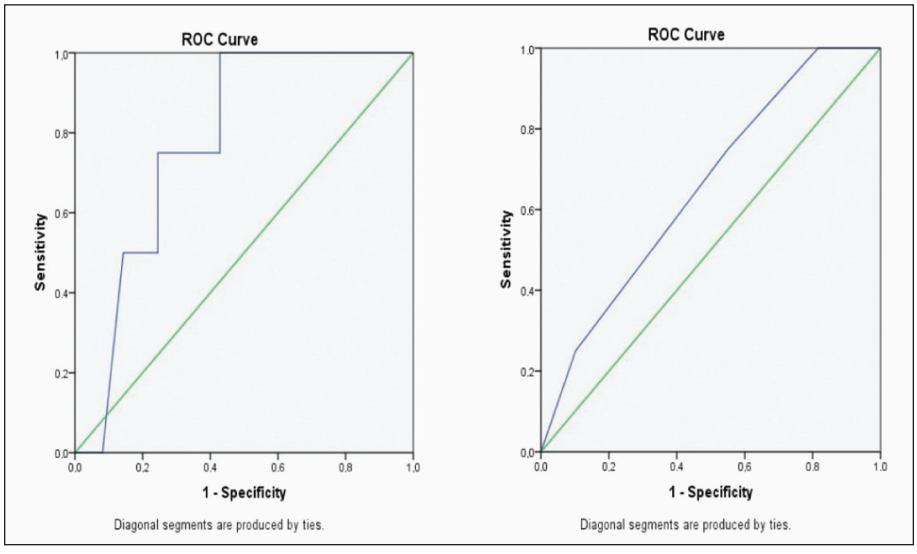

FIGURE 1: ROC curve analyses of the 2M-RDI and 2M-DBR to predict the objective response to lenvatinib at 8-12 weeks. **a)** The AUROC of 2M-DBR was 0.776 at an optimal cut-off value of 3,657 (sensitivity, 75.0%; specificity, 75.5%), which was higher than that of 2M-RDI. **b)** The AUROC of 2M-RDI was 0.653 at an optimal cut-off value of 81.25% (sensitivity, 75.0%; specificity, 55.1%). **a:** 2M-DBR: Cut-off: 3,657; AUROC: 0.776; **b:** 2M-RDI: Cut-off: 81.25; AUROC: 0.653.
ROC: Receiver operating characteristic; AUROC: The area under the receiver operating characteristic; 2M-RDI: Relative dose intensity at 2 months; 2M-DBR: The delivered dose intensity/body surface area ratio at 60 days.

TABLE 3: Tumor response evaluation according to delivered dose intensity/body surface area at 60 days (2M-DBR).

Response	2M-DBR <3,657	2M-DBR≥3,657	p value
Complete response	0	0	
Partial response	1 (2.6%)	3 (20.0%)	
Stable disease	19 (50.0%)	2 (13.3%)	
Progressive disease	18 (47.4%)	10 (66.7%)	
ORR	1 (2.6%)	3 (20.0%)	0.064
DCR	20 (52.6%)	5 (33.3%)	0.150

ORR: Overall response rate; DCR: Disease control rate. DBR: 2M-DBR (The delivered dose intensity/body surface area at 60 days).

6.4 months and 8.6 months, respectively, and PFS was 1.9 months and 3.2 months, respectively. In our study, we observed better PFS (4.1 months) and OS (12.6 months), which can be attributed to the better understanding of this drug currently than it was five years ago.[3] With enhanced knowledge of the pharmacodynamics and pharmacokinetics of the drug, we can better manage its side effects and drug dosage.

RDI is a useful index for investigating the applicability of pharmacotherapy, especially anticancer

TABLE 4: Adverse events (>10%).

Adverse events	Any grade (94.3%)	Grade ≥3 (52.83%)	Potential grade ≥3 (88.7%)
Fatigue	43.4	18.8	26.4
Hand foot skin reaction	41.5	15.1	22.6
Diarrhea	28.3	1.8	5.6
Appetite loss	26.4	7.5	15.1
Hypertension	22.6	3.7	3.7
Oral mucositis	18.8	1.8	7.5
Rash or desquamation	16.9	7.5	9.4
Nausea	16.9	3.7	7.5
Weight loss	11.32	0	0
Thrombocytopenia	11.32	1.8	3.7

TABLE 5: PFS and OS, according to 2M-DBR).

	2M-DBR<3,657	2M-DBR≥3,657	p value	Overall
Median PFS (months)	4.4 (3.84-4.96)	4.0 (2.29-5.70)	0.524	4.1 (2.83-5.36)
Median OS (months)	10.74 (5.43-16.05)	16.82 (11.09-22.54)	0.445	12.68 (7.53-17.83)

2M-DBR: The delivered dose intensity/body surface area ratio at 2 months; PFS: Progression-free survival; OS: Overall survival.

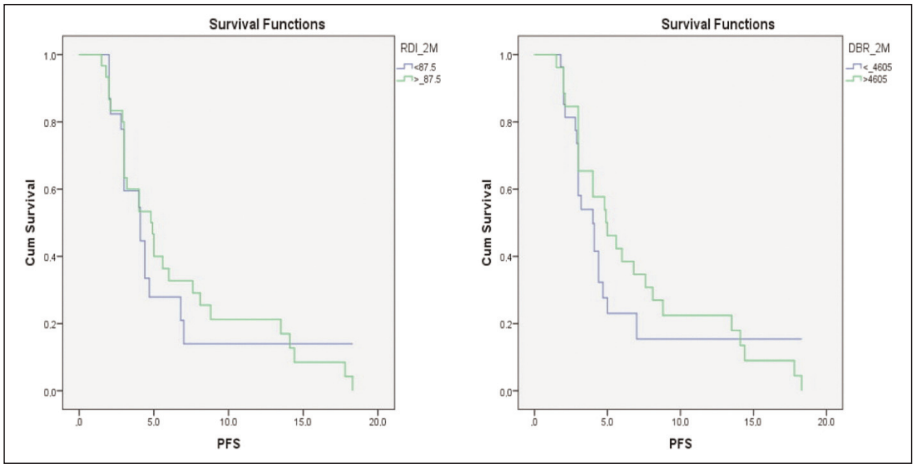

FIGURE 2: PFS according to the 2M-RDI levels or 2M-DBR. **a)** No significant difference was noted in PFS between the high 2M-RDI group and the low 2M-RDI group (4.8 months, 4.1 months respectively, log-rank test, p=0.933). **b)** No significant difference was noted in PFS between the high 2M-DBR group and the low 2M-DBR group (4.9 months, 4.0 months respectively, log-rank test, p=0.115).
PFS: Progression-free survival; 2M-RDI: Relative dose intensity at 2 months; 2M-DBR: The delivered dose intensity/body surface area ratio at 60 days.

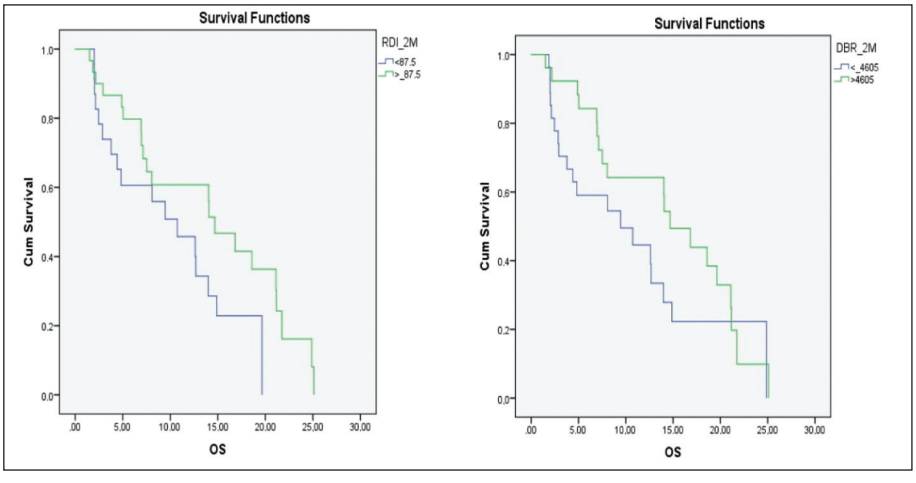

FIGURE 3: OS according to the 2M-RDI levels or 2M-DBR. **a)** No significant difference was noted in OS between the high 2M-RDI group and the low 2M-RDI group (14.6 months, 10.7 months respectively, log-rank test, p=0.088). **b)** No significant difference was noted in OS between the high 2M-DBR group and the low 2M-DBR group (14.6 months, 9.6 months respectively, log-rank test, p=0.115).
OS: Overall survival; 2M-RDI: Relative dose intensity at 2 months; 2M-DBR: The delivered dose intensity/body surface area ratio at 60 days.

drug therapy.[4] The importance of molecular targeted therapy and the RDI relationship in HCC has been demonstrated.[9,12] In a study where the importance of regorafenib RDI for the first month (1M-RDI) in HCC was studied, it was observed that patients with 1M-RDI≥50 had significantly better PFS and OS than patients with 1M-RDI<50.[9] However, in this study, the cut-off value was determined according to quartiles rather than ROC analysis. Hence, the results had high specificity, but sensitivity was low.[9] In a study conducted on lenvatinib, 2M-RDI was found to be ineffective on PFS, and ROC analysis was used to determine the cut-off value similar to our study.[12] Regardless of body weight, 160 mg once daily dose is the standard dose of regorafenib for mCRC and HCC.[2,13]

In this study, we demonstrated for the first time that similar to 2M-RDI, 2M-DBR can also reflect treatment intensity of regorafenib in mCRC. Patients with high 2M-DBR depicted better ORR and longer PFS than those with low 2M-DBR though it was not statistically significant. Comparing patients with high and low DBRs, the tolerance of the group with high BSA was better but not statistically significant.

In our study, the BSA had a statistically significant effect on the drug tolerance dose. Regorafenib has a very high potential for side effects when used at the standard dose of 160 mg. Only six patients were able to tolerate the standard dose. The high level of drug tolerance in patients with high BSA indicates that BSA plays an important role in the pharmacodynamics of regorafenib. In patients with low BSA, the drug dose needs to be reduced due to intolerance, and hence the amount of drug per square meter is balanced. Therefore, a statistically significant difference between BSA and PFS or OS could not be observed. The relationship between BSA and PFS or OS was statistically significant in tyrosine kinase inhibitors such as gefitinib, which are relatively easy to tolerate.[14] Since the majority of patients in our study could not tolerate the standard dose of regorafenib, the effect of BSA on PFS and OS was not found to be statistically significant.

High 2M-DBR was associated with longer PFS, but it was not statistically significant.

2M-DBR is an important factor in demonstrating treatment intensity and predicting response to regorafenib. Hence, utilizing it may be beneficial to develop a personalized regorafenib dose strategy. In this study, it was found that PFS and objective response (CR or PR) were better in the group with high DBR (≥3,657 mg). To devise the strategy that balances treatment efficacy and AE management, the use of a 2M-DBR target dose for each patient before starting treatment seems to be promising. A statistically significant effect of 2M-DBR on PFS was demonstrated in the study with lenvatinib.[12] This may be attributed to varying the dose of administration of lenvatinib according to weight.[12]

Our study is novel because it evaluates the relationship between 2-month dose exposure and BSA in patients using regorafenib in mCRC.

Based on the results of our data, it can be concluded that 2M-DBR is important in predicting response to regorafenib in mCRC, and clinical findings are valuable in determining treatment intensity. But there are some limitations in our study. It is a retrospective study, designed in three-centers in a single city, and has a limited sample size. For these reasons, the possibility of selection bias cannot be ruled out. In addition, a large cohort study needs to be conducted to determine the optimal cut-off value and set period of DBR. Therefore, our findings should be interpreted with caution. Further studies are needed to verify the outcomes of this study and investigate the relationship between 2M-DBR and parameters that demonstrate the therapeutic efficacy of Regorafenib, such as ORR, disease control rate, PFS, and OS.

CONCLUSION

BSA is effective in determining the tolerance dose of regorafenib, 2M-DBR could be an important factor that reflects treatment intensity and useful for predicting the response to regorafenib in mCRC.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Kadir Eser, Emel Sezer;* ***Design:*** *Kadir Eser, Vehbi Erçolak;* ***Control/Supervision:*** *Kadir Eser, Ali İnal;* ***Data Collection and/or Processing:*** *Kadir Eser, Hakan Basır;* ***Analysis and/or Interpretation:*** *Kadir Eser, Alper Ata, Mustafa Berkeşoglu;* ***Literature Review:*** *Emel Sezer;* ***Writing the Article:*** *Kadir Eser, Vehbi Erçolak;* ***Critical Review:*** *Kadir Eser, Alper Ata, Ali İnal;* ***References and Fundings:*** *Kadir Eser, Hakan Basır;* ***Materials:*** *Kadir Eser, Emel Sezer.*

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