Original Article

Relationship between prognostic nutritional index and neutrophil lymphocyte ratio with overall survival in patients with metastatic colorectal cancer receiving regorafenib

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ABSTRACT

Aim: In this study, we aimed to analyze the effect of prognostic nutritional index and neutrophile lymphocyte ratio on the overall survival (OS) in patients treated with regorafenib.

Materials and Methods: Metastatic colorectal cancer (CRC) patients who treated with regorafenib between 2016 and 2020 in a single center were evaluated retrospectively. ROC analysis was used for neutrophile lymphocyte ratio (NLR's) and prognostic nutritional index (PNI's) optimum cut-off value. The relationship between OS with PNI and NLR was investigated.

Results: Fifty-two patient's data were analyzed. The median age was 57 years, 22 (41.5%) of the patients were female. The optimal cut-off value of PNI for OS was 45.7 according to ROC curve analysis. The median NLR value was accepted as 2.7. Median OS was 8.3 months. Patients who have high PNI value than 45.7 had longer OS (12.09 months vs. 6.31 months hazard ratio [HR]: 0.37 95% confidence interval [CI]: 0.19–0.73 $P = 0.003$) and there was a tendency for longer OS with low NLR value then median (12.05 months vs. 6.14 months HR: 0.54 95% CI: 0.29–1.23 $P = 0.057$). Primary tumor resected patients had longer OS than nonresected patients (12.05 months vs. 6.30 months HR: 0.34 95% CI: 0.17–0.66 $P = 0.001$). In multivariate analysis, high PNI value more than 45.7 (HR: 0.40 95% CI: 0.18–0.88 $P = 0.02$) and resection of the primary tumor (HR: 0.40 95% CI: 0.21–0.80 $P = 0.01$) were the only independent factors for longer OS.

Conclusion: Metastatic CRC patients with high pretreatment PNI and primary tumor resected are more likely to have longer OS with regorafenib. PNI is more reliable index than NLR to predict OS in metastatic CRC patients treated with regorafenib.

KEY WORDS: Disease control, neutrophil-lymphocyte ratio, prognostic nutritional index

INTRODUCTION

Colorectal cancers (CRCs) are one of the most common cancers in both sex. Approximately 25% of new CRC patients are metastatic at the time of diagnosis and approximately 25%–30% of stages 2 and 3 CRC patients expected to develop metastasis within 5 years.[1] As standard first- and second-line treatments fluorouracil-based chemotherapy regimens that include oxaliplatin, irinotecan or both combined with monoclonal antibodies directed against vascular endothelial growth factor against (bevacizumab or aflibercept) or endothelial growth factor receptor (cetuximab or panitumumab) for patients with RAS wild type tumors or have been routinely used.[2] For MSI-H patients checkpoint inhibitors and BRAF mutated patients BRAF inhibitors with anti-EGFR monoclonal antibody are new emerging treatment option.[3,4]

With these standard therapies, in metastatic patients, the overall survival (OS) has reached up to 30 months.[5,6] For patients with metastatic

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CRC (mCRC) that have developed progression after standard first-and second-line therapy regorafenib and TAS-102 are approved treatment options in the third or later line of therapy.[2]

Regorafenib is an oral small-molecule multikinase inhibitor which inhibits signaling pathways that promote tumor development and angiogenesis.[7] In two placebo-controlled phase 3 trials, CORRECT and CONCUR efficacy and safety of regorafenib have been assessed after failure of all standard therapies.[8,9] Regorafenib showed a significant OS benefit in both studies against placebo. In CORRECT study, OS was 6.4 months versus 5.0 months (hazard ratio [HR] 0.77; 95% confidence interval [CI] 0.64–0.94; one-sided $P = 0.0052$) and in CONCUR study it was 8·8 months versus 6·3 months (HR 0.55, 95% CI 0.40–0.77, one-sided $P = 0.00016$). In CORRECT and CONCUR trials objective response rates were 1% and 4%, and disease control rates were 41% and 51%, respectively. Despite these absolute low survival benefit and low response rates grade 3 or higher drug-related adverse events (most commonly hand-foot syndrome, fatigue, nausea, hypertension, anemia, and thrombocytopenia) occurred in 51% of patients who randomized to regorafenib in both trials. Therefore, it is needed to define new factors that predict benefit from regorafenib.

Prognostic nutritional index (PNI) and neutrophile lymphocyte ratio (NLR) are two parameters that could be easily calculated with using routine blood counts and albumin levels. It is known that these two parameters show the nutritional and immunologic status of the patients.[10-12] In this study, we aimed to analyze the impact of PNI and NLR on the OS in patients treated with regorafenib after progressing standard regimens.

MATERIALS AND METHODS

Patients

Metastatic colorectal cancer patients who treated with regorafenib at Trakya University Medical Oncology Clinic between 2016 and 2021 were evaluated retrospectively. Patients older than 18 years, who received at least two lines of standard chemotherapy (or FOLFOXIRI), one including anti-VEGF, before regorafenib treatment, who have normal liver and kidney function are included. Patients who had ECOG PS 2 or more, cachexia, bone marrow suppression, massive liver metastasis, AST, ALT elevation more than 2.5 times upper limit of normal, renal failure; patients whom pretreatment blood count or albumin levels could have not been reached; excluded from the analysis. All patients received regorafenib 3/4 week drug dose was 120 mg/day at the beginning then escalated to 160 mg/day if patients tolerated.

Clinical data collection

We examined patients' demographic and clinic data, laboratory parameters, data about previous treatment, and radiological responses from archive files. Albumin was measured using an automatized chemistry analyzer (Roche Hitachi Cobas 8000, Rotkreuz, Switzerland), and lymphocyte counts were calculated using a hematology analyzer (Sysmex SE-9000, Kobe, Japan).

For calculating PNI and NLR we used laboratory values that were measured one to seven days before treatment. PNI was calculated by (10 × serum albumin value [gr/dL]) + (0.005 × total lymphocyte count [per mm^3]).[10] Neutrophil lymphocyte ratio calculated by dividing neutrophil counts to lymphocyte counts of the patients.

OS is defined as the time from initiation of regorafenib till death or last follow-up for living participants. Progression-free survival (PFS) is defined as time from initiation of regorafenib till progression event. Disease control is defined as objective response or stabile disease per RECİST 1.1 at the radiologic imaging with computed tomography at least 2 months after initiating regorafenib.[13]

The local ethical committee of Trakya University Hospital approved the trial that conducted in compliance with the postulates of the Declaration of Helsinki.

Statistics

Chi-square and Fisher's exact tests were used to compare categorical variables. Numeric variables were written as median (IQR; Inter Quartile Range). Numeric variables were compared with independent-sample *t*-test or Mann–Whitney *U* test. Median OS estimated made by Kaplan–Meier method. Median OS differences were evaluated by log-rank test. A multivariate survival analysis was performed using the Cox regression method. A $P < 0.05$ was considered statistically significant.

The receiver operating characteristic (ROC) analysis was used for NLR's and PNI's optimum cut-off value for OS assuming more than estimated OS of whole population months as a classification variable. If optimum cut-off cannot be found median values will be used as cut-off value.

RESULTS

Study population

A total of 98 patients treated with regorafenib between 2016 and 2020. Forty-six patients were excluded, 52 patients' data were analyzed. All patients had already treated with fluorouracil based, oxaliplatin irinotecan, bevacizumab, and anti-EGFR monoclonal antibody, for RAS wild-type tumor, including chemotherapy regimens. The median age was 57 (IQR 49.5–65) years, 22 (41.5%) of the patients were female. ECOG PS of all patients was 0 or 1. Most of the tumors were located at the left colon (78.8%), 28 (53.8%) patients were RAS mutant, none of the patients was BRAF mutated. The rate of primary tumor resected patients was 61.5%. The median duration of regorafenib treatment was 3.3 months (IQR 2.61–5.50). Nearly two-third of the

patients (69.2%) received regorafenib at the third line. Disease control achieved in 18 (33.9%) patients; (2 partial response, 16 stable disease). 13 (25%) patients received subsequent treatment with TAS102 or rechallenge. Other clinical features and laboratory results of the patients are given in Table 1.

Prognostic nutritional index and neutrophil-lymphocyte ratio cut-off value and characteristics of groups

A total of 10 patients (19.2%) were alive at the time of analysis. Median OS was 8.3 months (95% CI: 3.29–13.45). Median PFS was 3.1 months (95% CI: 2.55–4.08). The optimal cut-off value of PNI was 45.7 (sensitivity 69%, specificity 76%, AUC 0.803, 95% CI: 0.68–0.91, $P < 0.001$) assuming more than 8.3 months of OS as classification variable. We could not find optimal cut-off value of NLR for OS (AUC 0.367, 95% CI: 0.20–0.53, $P = 0.11$) therefore median NLR value, 2.7 accepted as cut-off value. 22 (42.3%) patients had a PNI value more than 45.7.

Table 1: Characteristics and demographic features of study subjects

	All patients (*n*=52)
Age (years)	
<65	38 (73.1)
≥65	14 (26.9)
Gender, *n* (%)	
Female	22 (42.3)
Male	30 (57.7)
Tumor location, *n* (%)	
Left	41 (78.8)
Right	11 (21.2)
RAS mutation, *n* (%)	
Wild	24 (46.2)
Mutant	28 (53.8)
Denovo metastasis, *n* (%)	
Yes	35 (67.3)
No	17 (32.7)
Primary tumor resection, *n* (%)	
Yes	32 (61.5)
No	20 (38.5)
Number of metastatic sites, *n* (%)	
1	16 (30.8)
≥2	36 (69.2)
Disease control first line, *n* (%)	
Yes	43 (82.7)
No	9 (17.3)
Disease control second line, *n* (%)	
Yes	15 (28.8)
No	37 (71.2)
Regorafenib treatment line, *n* (%)	
3rd line	36 (69.2)
4th line and beyond	16 (30.8)
Regorafenib dose (mg), *n* (%)	
160	20 (38.5)
<160	32 (61.5)
Disease control with regorafenib, *n* (%)	
Yes	18 (34.0)
No	35 (66.0)
Pretreatment albumin (g/L), median (IQR)	3.8 (3.3-4.1)
Pretreatment lymphocyte (per mm^3), median (IQR)	1500 (1190-1990)
Pretreatment neutrophile (per mm^3), median (IQR)	4500 (3100-6500)
Pretreatment PNI, median (IQR)	45 (40.97-50.0)
Pretreatment NLR, median (IQR)	2.7 (1.74-4.72)

IQR=Interquartile range, PNI=Prognostic nutritional index, NLR=Neutrophile lymphocyte ratio, RAS=Rat sarcoma virus

Comparison of patients according to PNI value showed that patients who have high PNI value than 45.7 were significantly primary tumor resected patients ($P = 0.01$). In addition, disease control with regorafenib significantly more achieved in patients with high PNI-value than 45.7 ($P = 0.04$). Other factors were similar in both groups. In NLR low and high groups, patient and disease features were not different except gender ($P = 0.005$) [Table 2].

Survival analysis

Patients who have high PNI value than 45.7 also had longer OS (12.09 months vs. 6.31 months HR: 0.37 95% CI: 0.19–0.73 $P = 0.003$) [Figure 1]. There was a tendency for longer OS with low NLR value than median (12.05 months vs. 6.14 months HR: 0.54 95% CI: 0.29–1.23 $P = 0.057$). Primary tumor resected patients had longer OS than nonresected patients (12.05 months vs. 6.30 months HR: 0.34 95% CI: 0.17–0.66 $P = 0.001$) Other factors; age, gender, tumor location, RAS mutational status, de-novo metastasis, number of metastatic sites, disease control at the first and the second line, regorafenib treatment line, regorafenib dose was not related with longer OS. In multivariate analysis high PNI value more than 45.7 (HR: 0.40 95% CI: 0.18–0.88 *P*: 0.02) and resection of the primary tumor (HR: 0.40 95% CI: 0.21–0.80 $P = 0.01$) was the only independent factor for longer OS [Table 3].

DISCUSSION

According to our knowledge, this is the first paper that evaluates PNI in mCRC patients treated with regorafenib. We found that high PNİ (45.7 or more) and resection of the primary tumor are two independent predictors of longer OS in metastatic CRC patients treated with regorafenib. NLR is not a predictor of OS.

In general, patients progressing after second-or third-line therapy have low-performance score. Safety became important in patients who will be treated with third or later line of therapy because usually drugs that advised at later lines of cancer treatment have minimal absolute survival benefit and low response rates. Grade 3 or more drug-related adverse events are 41%–51% with regorafenib.[8,9] The identification of predictive markers to specific agents may improve efficacy and protects patients from unnecessary treatment and treatment-related toxicities. Lee *et al.*[14] examined tumor tissues of mCRC patients with next-generation sequencing-based cancer panel tests treated with regorafenib to find relationship between molecular profiling and efficacy of regorafenib. They found that APC mutations are significantly associated with response ($P < 0.05$) and all tumors (3 patients) with FGFR1 amplification had a partial response. Patients with BRAF and/or SMAD4 mutation have poor PFS. Signaling pathway analysis also showed that patients with a TGF-beta pathway have a

Table 2: Distribution of patient characteristics by prognostic nutritional index and neutrophile lymphocyte ratio

	PNI <45.7 (*n*=30)	PNI ≥45.7 (*n*=22)	*P*	NLR <2.71 (*n*=26)	NLR ≥2.71 (*n*=26)	*P*
Age (years), *n* (%)						
<65	22 (73.3)	16 (72.7)	0.96	19 (73.1)	19 (73.1)	1
≥65	8 (26.7)	6 (27.3)		7 (29.6)	7 (29.6)	
Gender, *n* (%)						
Female	12 (40.0)	10 (45.5)	0.69	16 (61.5)	6 (23.1)	0.005
Male	18 (60.0)	12 (54.5)		10 (38.5)	20 (76.9)	
Tumor location, *n* (%)						
Left	24 (80.0)	17 (77.3)	0.81	21 (80.8)	20 (76.9)	0.73
Right	6 (20.0)	5 (22.7)		5 (19.2)	6 (23.1)	
RAS mutation, *n* (%)						
Wild	16 (53.3)	8 (36.4)	0.22	13 (50.0)	11 (42.3)	0.57
Mutant	14 (46.7)	14 (63.6)		13 (50.0)	15 (57.7)	
Denovo metastasis, *n* (%)						
Yes	10 (33.3)	7 (31.8)	0.90	8 (30.8)	9 (34.6)	0.76
No	20 (66.7)	15 (68.2)		18 (69.2)	17 (65.4)	
Primary tumor resection, *n* (%)						
Yes	14 (46.7)	18 (81.8)	0.01	9 (34.6)	11 (42.3)	0.56
No	16 (53.3)	4 (18.2)		17 (65.4)	15 (57.7)	
Number of metastatic sites, *n* (%)						
1	11 (36.7)	5 (22.7)	0.28	6 (23.1)	10 (38.5)	0.22
≥2	19 (63.3)	17 (77.3)		20 (76.9)	16 (61.5)	
Disease control first line, *n* (%)						
Yes	27 (90.0)	16 (72.7)	0.12	20 (76.9)	23 (88.5)	0.46
No	3 (10.0)	6 (27.3)		6 (23.1)	3 (11.5)	
Disease control second line, *n* (%)						
Yes	22 (73.3)	15 (68.2)	0.68	18 (69.2)	19 (73.1)	0.76
No	8 (26.7)	7 (31.8)		8 (30.8)	7 (26.9)	
Regorafenib treatment line, *n* (%)						
3rd line	21 (70.0)	15 (68.2)	0.88	18 (69.2)	18 (69.2)	1
4th line and beyond	9 (30.0)	7 (31.8)		8 (30.8)	8 (30.8)	
Regorafenib dose (mg), *n* (%)						
160	12 (40.0)	8 (36.4)	0.79	12 (46.2)	8 (30.8)	0.25
<160	18 (60.0)	14 (63.6)		14 (53.8)	18 (69.2)	
Disease control with regorafenib, *n* (%)						
Yes	7 (23.3)	11 (50.0)	0.04	10 (38.5)	8 (30.8)	0.56
No	23 (76.7)	11 (50.0)		16 (61.5)	18 (69.2)	

PNI=Prognostic nutritional index, NLR=Neutrophile lymphocyte ratio, RAS=Rat sarcoma virus

Table 3: Univariate and multivariate survival data

	Univariate analysis			Multivariate analysis	
	Median OS (months)	HR (95% CI)	*P*	HR (95% CI)	*P*
Age (years), <65 versus ≥65	12.05 versus 7.29	0.82 (0.38-1.73)	0.60		
Gender, female versus male	8.37 versus 6.66	0.98 (0.48-1.68)	0.75		
Tumor location, right versus left	11.79 versus 6.66	0.76 (0.36-1.57)	0.45		
RAS mutation, wild versus mutant	8.24 versus 7.45	0.74 (0.39-1.38)	0.34		
Denovo metastasis, *n* (%), yes versus no	6.50 versus 12.1	1.38 (0.69-2.72)	0.35		
Primary tumor resection, *n* (%), yes versus no	12.05 versus 6.30	0.34 (0.17-0.66)	0.001	0.40 (0.21-0.80)	0.01
Number of metastatic sites, *n* (%), 1 versus ≥2	10.7 versus 6.6	0.71 (0.34-1.46)	0.35		
Disease control first line, yes versus no	8.24 versus 6.67	0.70 (0.31-1.52)	0.36		
Disease control second line, yes versus no	10.74 versus 6.50	0.69 (0.35-1.35)	0.28		
Regorafenib treatment line, 3rd line versus 4th line and beyond	8.24 versus 7.3	0.71 (0.35-1.43)	0.34		
Regorafenib dose (%), <160 mg versus 160 mg	8.37 versus 6.67	0.79 (0.42-1.50)	0.48		
Pretreatment PNI, ≥45.7 versus <45.7	12.09 versus 6.31	0.37 (0.19-0.73)	0.003	0.43 (0.21-0.88)	0.02
NLR, <2.7 versus ≥2.7	12.05 versus 6.14	0.54 (0.29-1.02)	0.057	0.59 (0.29-1.21)	0.16

PNI=Prognostic nutritional index, NLR=Neutrophile lymphocyte ratio, HR=Hazard ratio, CI=Confidence interval, OS=Overall survival, RAS=Rat sarcoma virus

significantly poor PFS than those without a TGF-beta pathway. Despite these encouraging results it is not possible to detect these factors in routine practice. There is a need to define easy to reach markers to predict response and survival.

Unfortunately, the inflammatory response against tumor may promote tumor growth, metastasis and angiogenesis.[15,16] Neutrophiles are important sources of inflammatory cytokines and proangiogenic factors, including the vascular endothelial growth factors.[17] Lymphocytes are another important component of the adaptive immune system and take crucial role in cancer immunosurveillance and immunoediting.[18] High levels of tumor infiltrating lymphocytes are associated with better OS in CRC.[18] In cancer patients, lymphopenia is

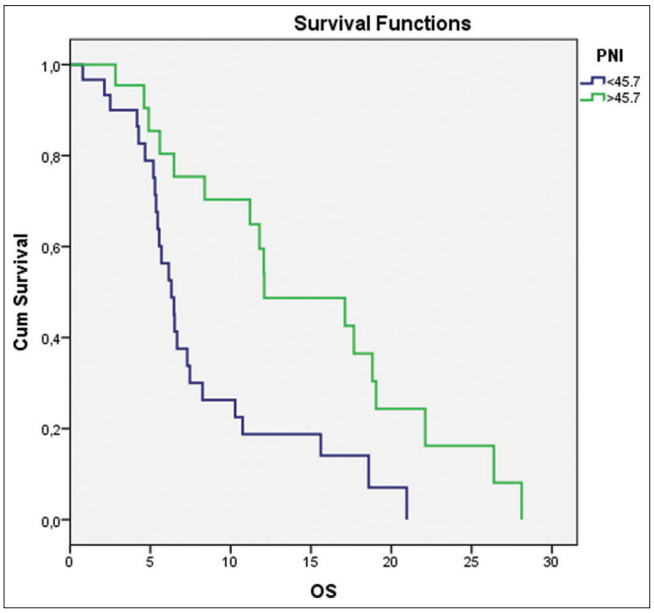

Figure 1: Survival functions in PNI groups

associated with worse OS because it reflects an inadequate immune response against cancer.[19,20] NLR is the reflection of the immune status of the host. Many studies have shown that high NLR is associated with poor prognosis in CRCs.[21-23] Prete *et al*.[20] showed that pretreatment high NLR, platelet and neutrophil count, and low lymphocyte count significantly associated with worse outcome in regorafenib-treated patients. To the best of our knowledge, their study is the only study that analyze NLR in regorafenib treated mCRC patients in English literature. They assumed PFS more than 2 months as a classification variable to find optimal cut-point. We assumed OS more than 8.3 months as classification variable and could not find optimal cut point. We found that there is a tendency for OS to be longer in NLR-low group than NLR-high group ($P = 0.056$). We could not find any significant relation with between NLR and OS in multivariate analysis ($P = 16$).

The PNI is another simple prognostic score that can be easily calculated with lymphocyte count and serum albumin level.[10] First, Onodera *et al*. suggested that PNI can predict post-operative complications after gastrointestinal cancer surgery.[10] In the last decade, it is a well-studied in gastrointestinal cancers as well as all cancer types.[24-27] Generally, it is accepted, that PNI is a parameter that reflects the nutritional and immunological status of the patient. It is well known that malnutrition impairs immunity therefore nutritional support improves treatment outcome in malnourished cancer patients.[28,29] In our study despite the exclusion of cachexic, ECOG PS 2 or low patients, we found that high PNI was associated with longer OS. According to PNI formula main determinant is albumin level, therefore patients with low albumin levels have probably low PNI. Malnutrition is not the only cause of low albumin levels in cancer patients, it is also due to excess production of proinflammatory cytokines, mainly tumor necrosis factor-α, interleukin-1, interleukin-6 and which regulate the production of albumin in the liver therefor low albumin level is also a sign of systemic inflammation.[30] According to our analysis, patients with high PNI have longer OS ($P = 0.02$) and high disease control rate ($P = 0.04$). We suggest that low PNI might reflect the aggressive, resistant disease rather than malnutrition. In a study that evaluated the significance of preoperative PNI in 1321 CRC patients, they found that patients with low PNI significantly have poorly differentiated tumor and have aggressive clinicopathological characteristics.[31] Results of this study also support our suggestion.

Resection of primary tumor recommended for mCRC patients with fatal complications, for example, total obstruction and major bleeding. However, in several studies, it has been shown that resection of the primary tumor is associated with better results in mCRC patients after chemotherapy.[32,33] Primary tumor resection reduces tumor burden and may prevent primary tumor-related morbidity and mortality. We found that primary tumor resection is an independent prognostic factor for OS even in the patients who received regorafenib at the third or later lines of treatment ($P = 0.01$).

A major limitation of our study is being retrospective and relatively less patient number that may raise suspicion about multivariate analysis. However to get the most accurate results, patients who have any condition that may interfere PNI result excluded from the analysis.

CONCLUSION

In this first study than analyze PNI in mCRC patients treated with regorafenib, we found that high pretreatment PNI and primary tumor resection are independent predictive factors for longer OS. Patients with high PNI are also more likely to have disease control. PNI is more reliable index than NLR to predict response and OS in mCRC patients treated with regorafenib.

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Conflicts of interest
There are no conflicts of interest.

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