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Does the efficacy of regorafenib differ in chemotherapy refractory metastatic colorectal cancer patients who had mucinous pathology compared to those who had non-mucinous pathology?

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ABSTRACT

Purpose: To investigate the importance of mucinous histopathology on the assessment of tumor response in patients with metastatic colorectal cancer (mCRC) receiving regorafenib. *Materials and method*: All patients diagnosed with histologically confirmed mCRC in 2 oncology centers between 2013 and 2018 were retrospectively analyzed. Among 678 patients diagnosed with mCRC, 103 patients were treated with regorafenib. Ninety-four of these patients who had used at least 2 cycles of regorafenib and evaluable for treatment response were included in the analysis. Histopathologically, 18 patients with mucinous adeno-

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carcinoma and 76 patients with nonmucinous adenocarcinoma were compared in terms of response rate and survival durations. *Results*: Median follow-up duration of 6 months, median age of the patients was 61 (34-77) years. While 19.1% of the patients had mucinous histology, 80.9% had nonmucinous histology. The overall response rate was significantly lower in the mucinous subgroup than the nonmucinous subgroup (5.6% vs 43.4%, respectively, $P = 0.003$). Similarly, both progression-free survival (3.0 vs 4.0 months, respectively, $P = 0.011$) and overall survival duration were shorter in the mucinous subgroup (3.0 vs 7.0 months, $P = 0.016$, respectively) compared with the nonmucinous subgroup. *Conclusion*: The histological subgroup may predict tumor response in mCRC patients receiving regorafenib. Its efficacy on nonmucinous histology had significantly more favorable than mucinous subtype.

ARTICLE INFO

Keywords: Metastatic colorectal cancer; Regorafenib; Mucinous adenocarcinoma; Response rate

Introduction

Colorectal cancer (CRC) is one of the leading causes of cancer-related deaths.[1] Approximately 25% of the patients are metastatic at the time of diagnosis, while half of the remaining become metastatic at later stages.[2] According to the World Health Organization, mucinous adenocarcinoma (characterized by containing 50% or more mucin) constitutes 10%-20% of CRCs.[3] Despite being a controversial issue, increasing evidence suggests that mucinous histology is an independent prognostic factor,[4-6] which have different oncogenic and molecular pathways.[7-9] Additionally, mucinous adenocarcinoma has been recently shown to be pharmacogenomically distinct subtype of CRC.[9] However, the National Comprehensive Cancer Network has not ascribed mucinous histology as a risk factor which may influence therapeutic decision making.

It has been shown that mucinous adenocarcinoma is associated with inferior survival time when compared with nonmucinous subgroup.[10-12] Furthermore, mucinous adenocarcinomas appeared to be less responsive to fluoropyrimidines, irinotecan, and oxaliplatin-based chemotherapy.[10-13] Although the mechanism of this relative resistance to cytotoxic chemotherapy in comparison with nonmucinous colorectal adenocarcinoma remains poorly understood, it is thought to be associated with different pattern of genetic mutations between mucinous and nonmucinous subgroups.[8] Additionally, in patients with RAS and BRAF wild type mucinous mCRC, it has been shown that the tumor does not benefit from antiepidermal growth factor receptor (EGFR) inhibitors regardless of whether the tumor originates from the right or left colon.[14] On the other hand, although the response rate with bevacizumab, an antivascular endothelial growth factor (VEGF) agent, in mucinous subgroup was reported to be significantly lower, it was found to be similar in mucinous and nonmucinous subgroup in terms of progression-free survival (PFS) and overall survival (OS) contribution.[15]

Regorafenib, an oral multikinase inhibitor has received FDA approval in patients who developed progression after standard chemotherapy regimens have been depleted in patients with mCRC.[16] There is no information on whether treatment response and survival durations are different in mucinous and nonmucinous subgroups in patients receiving regorafenib. Therefore, the present study was planned to investigate whether histopathological subgroups could predict the treatment response in patients receiving regorafenib.

Material and method

Patients

The files of all consecutive patients who were treated with the diagnosis of mCRC between January 2013 and December 2019 in Health Sciences University, Kartal Dr. Lutfi Kirdar Train-

ing and Research Hospital were reviewed retrospectively. In addition, laboratory, clinical, and pathological data were obtained from the medical records in the hospital automation system, when needed. Out of 678 patients with mCRC identified, 103 patients who were detected to be using regorafenib were evaluated. However, a total of 94 patients were analyzed after 9 patients were excluded from the study for different reasons (4 patients were lost to follow-up after the first visit, 3 patients received irregular regorafenib due to toxicity, and 2 patients were not evaluated for treatment response). According to government reimbursement program in our country fluorouracil, oxaliplatin, and irinotecan should have been used before regorafenib. The regorafenib dose could be reduced, or interrupted to manage treatment-related toxicities. The patients were categorized into 2 subgroups as mucinous (adenocarcinoma with a mucinous component of more than 50 percent of tumor volume) and nonmucinous adenocarcinoma. Response rate, PFS, and OS were recorded according to the subgroups. In addition, patients were divided into subgroups according to right colon and left colon involvement (right colon from cecum to splenic flexure, left colon from splenic flexure to rectum) and RAS status (wild vs mutant type). The study was conducted in accordance with the Helsinki Declaration Principles and ethics committee approval was obtained from the Ethics Committee of Kartal Dr. Lutfi Kirdar Training and Research Hospital.

Statistical analysis

For statistical analysis, SPSS version: 22.0 (Armonk NY, IBM Corp. 2013) was used. PFS was defined as the time elapsed after regorafenib was administered up to radiological progression or death for any reason. OS was defined as the time elapsed after regorafenib was administered up to death. Numerical variables between 2 independent statuses were analyzed by student *t* test under normal distribution and by Mann-Whitney *U* test if otherwise. Response rates between mucinous and nonmucinous groups were analyzed by chi-square test and Fisher-Exact test. Kaplan-Meier was used for survival analysis.

Findings

Of the 94 patients included in the analysis, 39.4% were female and 60.6% were male, with a median age of 61 (34-77). Primary tumor was located in the left colon in 81.9% of the patients and in the right colon in 18.1% of the patients. RAS mutation was RAS wild (NRAS wild and KRAS wild) in 61.7% of the patients, RAS mutant (NRAS mutant or KRAS mutant) in 37.2%, and in 1.1% RAS status was not known. When evaluated according to histopathological subgroup, 80.9% were nonmucinous and 19.1% were mucinous. In terms of differentiation degree, 11.7% of the cases were grade 1, 62.8% were grade 2 and 25.5% were grade 3.

Regarding the line of regorafenib administration, 72.3% used it in the third line, 22.3% used it in the fourth line and 5.4% used it in the fifth line. All patients received 5-fluorouracil (5-FU) and irinotecan-based treatment, while 98.9% of patients received 5-FU and oxaliplatin-based chemotherapies. Around 97.9% of patients received anti-VEGF treatment besides 61.7% of patients received anti-EGFR treatment as targeted treatments. Detailed demographic data of the patients are shown in Table 1.

Regorafenib-related adverse events were fatigue (48.9%), diarrhea (35.2%), hand-foot skin reaction (34%), anorexia (19.1%), nausea (18.1%), and thrombocytopenia (12.7%). The most common grade 3-4 adverse reactions with the drug were fatigue (14.9%), hand-foot skin reaction (5.3%), and diarrhea (4.3%). In addition, dose reductions due to the drug toxicities required in 40.4% of patients, but the drug was permanently discontinued in only 2 patients. Treatment-related adverse events are listed in Table 3.

When all patients were taken into consideration, median PFS was 3 months (95% confidence interval [CI] 2.6-3.4), while the median OS was 6 months (95% CI 4.5-7.5) (Fig 1 A, B). With

Table 1
Patients' characteristics.

Variables	All patients n = 94 (%)	Nonmucinous n = 76 (%)	Mucinous n = 18 (%)	*P*-value
Age				
>60 years	50 (53.2)	39 (51.3)	11 (61.1)	0.454
Gender				
Male	57 (60.6)	47 (61.8)	10 (55.6)	0.789
ECOG PS at the time of diagnosis				
0	27 (28.7)	24 (31.6)	3 (16.7)	
1	47 (50.0)	39 (51.3)	8 (44.4)	0.123
2	20 (21.3)	13 (17.1)	7 (38.9)	
Primary sidedness				
Right	17 (18.1)	11 (14.5)	6 (33.3)	0.087
Primary tumor resected				
Yes	83 (88.3)	68 (89.5)	15 (83.7)	0.466
Grading				
1	11 (11.7)	10 (13.2)	1 (5.6)	
2	59 (62.8)	49 (64.5)	10 (55.6)	0.295
3	24 (25.5)	17 (22.4)	7 (38.9)	
K-ras or N-ras				
Wild	58 (61.7)	47 (62.7)	11 (61.1)	
Mutant	35 (37.2)	28 (37.3)	7 (38.9)	0.903
Unknown	1 (1.1)			
Braf				
Wild	54 (54.0)	46 (60.5)	1 (5.6)	
Mutant	3 (3.2)	2 (2.6)	8 (44.4)	0.431
Unknown	37 (39.4)	28 (36.8)	9 (50.0)	
Previous chemotherapy regimens				
Fluoropyrimidine	94 (100)	76 (100)	18 (100)	
Oxaliplatin	93 (98.9)	75 (98.7)	18 (100)	
Irinotekan	94 (100)	76 (100)	18 (100)	NA
Anti-VEGF	92 (97.9)	75 (98.7)	17 (94.4)	
Anti-EGFR	58 (61.7)	47 (62.7)	11 (61.1)	
Which lines of treatment				
3	68 (72.3)	56 (73.7)	12 (66.7)	
4	21 (22.3)	16 (21.1)	5 (27.8)	0.82
5	5 (5.3)	4 (5.3)	1 (5.6)	

EGFR, epidermal growth factor receptor; NA, not applicable; VEGF, vascular endothelial growth factor.

respect to the histological subgroup, median PFS (mPFS) was 4 months (95% CI 3.4-4.6) in the nonmucinous subgroup, while mPFS was 3 months (95% CI 2.6-3.4) in the mucinous subgroup ($P = 0.011$) (Fig 1-C). Similarly, median OS (mOS) was observed to be 7 months (95% CI 5.2-8.8) in the nonmucinous subgroup and 3 months (95% CI 2.0-4.0) in the mucinous subgroup ($P = 0.016$) (Fig 1-D).

When compared according to regorafenib response, the best response rate in the mucinous subgroup was 5.6%, while this rate was 43.4% in the nonmucinous group (odds ratio [OR], 13.05; 95% CI, 1.65-104.0; $P = 0.003$). When the response rates were analyzed in detail, response was obtained in only 1 patient (as stable disease) in the mucinous subgroup while response was obtained in 33 patients (partial response in 3 patients and a stable disease in 30 patients) in the nonmucinous subgroup (Table 2). When the patients in the mucinous and nonmucinous groups were evaluated in terms of demographic and clinicopathologic characteristics, no significant difference was found between the groups except that the frequency of right colon tumor was slightly higher in the mucinous subgroup ($P > 0.05$).

The patients were recategorized according to RAS status to determine whether RAS mutation status affected response to histopathological subgroups. When the response rates of muci-

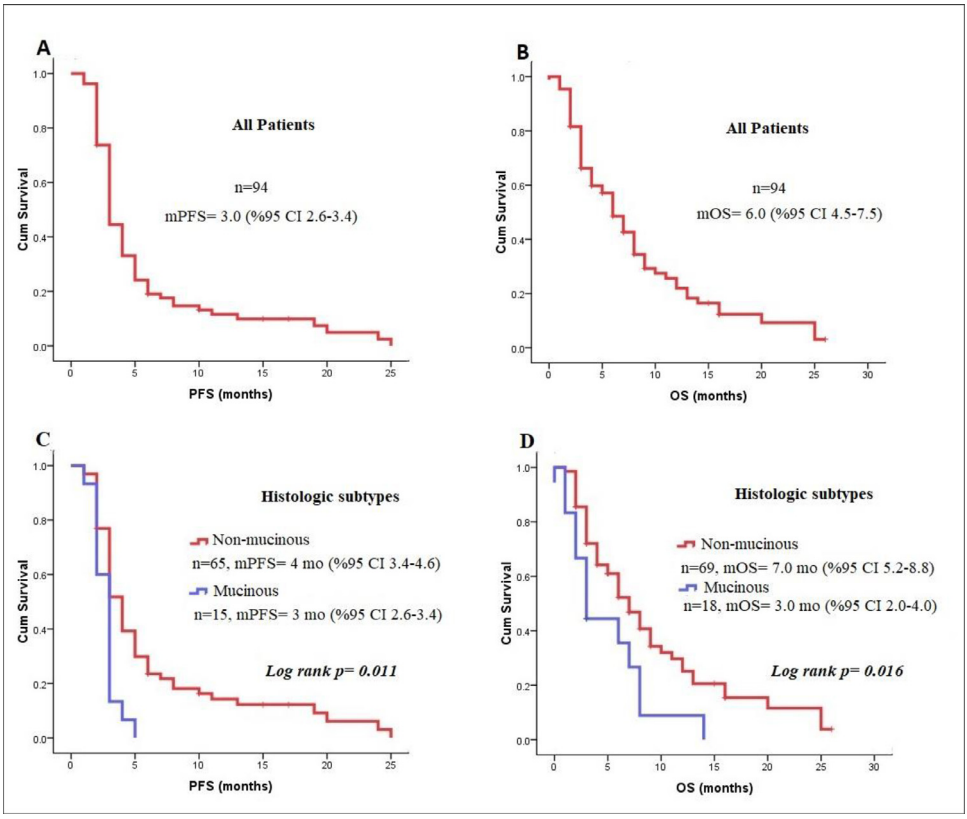

Fig. 1. Kaplan-Meier analyses of progression-free survival and overall survival in all patients (A, B) and histologic subtypes (C, D) metastatic colorectal cancer. (Color version of figure is available online.)

Table 2
Response and survival parameters.

	Mucinous	Nonmucinous	Overall population
Evaluable for response, n (%)	N = 18	N = 76	N =94
CR	0 (0)	0 (0)	0 (0)
PR	0 (0)	3 (3.9)	3 (3.2)
SD	1 (5.6)	30 (39.5)	31 (33.0)
PD	17 (94.4)	43 (56.6)	60 (63.8)
ORR, %	5.6	43.4	36.2
OR (95% CI)	13.05 (1.65-104.0)		
P	0.003		
PFS	N = 15	N = 65	N = 80
Events, n	15	59	74
Median PFS, mos	3,0	4,0	3,0
HR (95% CI)		2.16 (1.19-3.94)	
P		0.011	
OS	N = 18	N = 69	N = 87
Events, n	15	51	66
Median OS, mos	3,0	7,0	6,0
HR (95% CI)		2.06 (1.14-3.72)	
P		0.016	

CI, confidence interval; CR, complete response; OR, odds ratio; ORR, overall response rate; OS, overall survival; PD, progression disease; PFS, progression-free survival; PR, partial response; SD, stable disease.

Table 3
Ragorafenib-related adverse events.

	Grade ½ n (%)	Grade 3/4 n (%)
Fatigue	32 (34.0)	14 (14.9)
Anemia	7 (7.4)	1 (1.1)
Hand-food skin reaction	27 (28.7)	5 (5.3)
Nausea	15 (16.0)	2 (2.1)
Oral mucositis	12 (12.8)	2 (2.1)
Diarrhea	29 (30.9)	4 (4.3)
Increased liver enzymes	13 (13.8)	2 (2.1)
Neutropenia	7 (7.4)	1 (1.1)
Anorexia	15 (17.0)	2 (2.1)
Hypertension	10 (10.6)	0 (0)
Voice changes	9 (9.6)	0 (0)
Thrombocytopenia	10 (10.6)	2 (2.1)

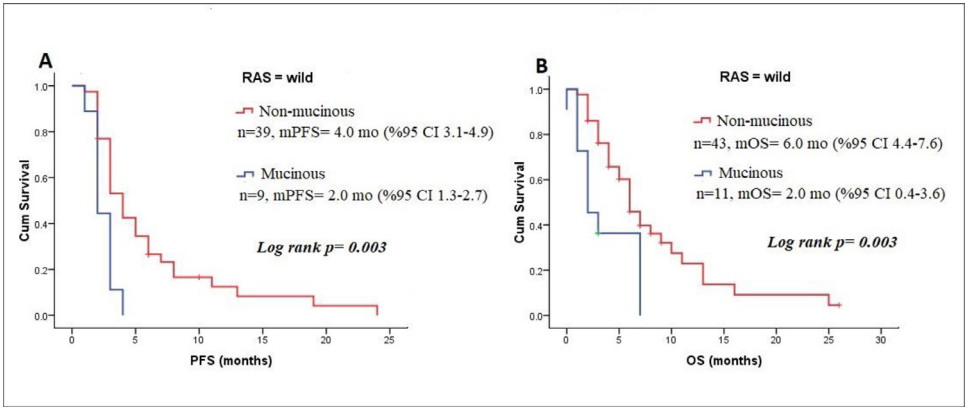

Fig. 2. Kaplan-Meier analyses of progression-free survival (A) and overall survival (B) in Ras-wild patients. (Color version of figure is available online.)

nous and nonmucinous groups were evaluated in RAS wild patients, both mPFS (nonmucinous: 4 months, mucinous: 2 months, ($P = 0.003$) (Fig 2-A) and mOS (nonmucinous: 6 months, mucinous: 2 months, ($P = 0.003$) (Fig 2-B) were higher in nonmucinous group. In the RAS mutant subgroup, it could not be analyzed separately because the number of mucinous patients was very low.

Discussion

Regorafenib, showed survival contribution[16-18] in patients who progressed following 5-FU, irinotecan, oxaliplatin, and monoclonal targeted therapies in mCRC patients and received FDA approval in 2012 for this indication. It is not known whether there is a relationship between tumor response and histological subgroup in patients with mCRC who use regorafenib. Therefore, we investigated the relationship between tumor response and histological subgroup in patients with mCRC using regorafenib who progressed after using 5-FU, irinotecan and oxaliplatin-based combination regimens.

Studies suggest that patients with mucinous subgroup have a poorer response rate than nonmucinous subgroup.[10-13] For example, in the study of Catalano V et al[11] in which irinotecan or oxaliplatin based regimens were used, mucinous and nonmucinous subgroups were compared

and response rate in the mucinous subgroup was 18.4%, while the response rate in the nonmucinous subgroup was 49% ($P = 0.0002$). In addition, similar response rates were reported by Maisano R et al.[12] Although, the reason for this relative resistance to chemotherapy is not clear, it may be in part due to a different pattern of genetic mutations between mucinous and nonmucinous subgroups.[8] Furthermore, the study of Reynolds IS et al[9] suggests that mucinous adenocarcinoma is a pharmacogenomically distinct subtype of CRC.

In the setting of targeted therapy, it was reported from a RAS and BRAF wild type study that anti-EGFR agents were not beneficial in the mucinous subgroup when compared with nonmucinous subgroup in terms of both survival time and response rates.[14] In another mCRC study in which only mucinous subgroup patients were evaluated, a better PFS and OS contribution were shown with bevacizumab compared with cetuximab.[19]

To the best of our knowledge, there has been no study comparing treatment response as mucinous and nonmucinous in patients with mCRC using regorafenib, so the present study is the first in this respect. In the present study, the median OS and PFS obtained with regorafenib were similar to the durations reported in randomized trials[16,17] and meta-analyzes.[20] When patients were categorized according to the histologic subgroup, worse PFS and OS were detected in the mucinous subgroup compared to the nonmucinous subgroup. It can be argued that this difference in survival between the 2 subgroups is due to the fact that the number of patients with right colon tumors known to be worse prognostic is slightly higher in the mucinous subgroup, rather than histologic subtype. However, although the number of patients with right colon cancer was slightly higher in the mucinous subgroup, the *P* value did not reach significance level ($P = 0.087$). In addition, since location of the tumor in the right or left colon did not affect the prognosis in RAS mutant patients according to a recently published study,[21] RAS mutant patients were excluded, and RAS wild patients were reanalyzed. In this new comparison, it was found that the value of "*P*" became more insignificant (data not shown). Therefore, it seems unlikely that this unwanted potential bias could alter our analysis. On the other hand, when the response rate of mucinous and nonmucinous subgroups was compared, the response rate in the mucinous subgroup was significantly low. In addition, when the patients were categorized according to RAS mutation status and reevaluated in terms of response rate, the difference in response between mucinous and nonmucinous groups became more prominent in the RAS wild group against the mucinous group. In the RAS mutant subgroup, it could not be analyzed separately because the number of mucinous patients was very low. This result shows that the histological subtype may predict regorafenib response in mCRC patients.

Compared to the nonmucinous subgroup, the mucinous subgroup was recently shown to be associated with both high microsatellite instability (MSI)[21] and high tumor mutation burden.[22] Considering that the response to cytotoxic treatment is relatively low in the mucinous subgroup, it is expected that immunotherapy may find application in this patient group. Moreover, the greater expression of PDL-1 expression[23] which is a predictive biomarker for immunotherapy, in the mucinous subgroup compared to the nonmucinous subgroup, increased interest in this subject. In the mucinous subgroup, data on efficacy of immunotherapy are very limited. In an immunotherapy study in patients with high MSI CRC, the response rate in the mucinous subgroup was observed to be lower than in the nonmucinous group.[24] Although a combination of regorafenib and anti-PD-1 has been shown to be effective in a preclinical CRC study,[25] the number of clinical studies on this subject is very limited. In a small clinical immunotherapy study,[26] combination of nivolumab and regorafenib showed strong antitumoral efficacy in both CRC patients and stomach cancers, but there was no information regarding the mucinous subgroup in this study.

In REBECCA study grade 3 or 4 treatment-related adverse events (TRAE) were observed in 37% of patients.[27] In CORRECT trial, grade 3 or 4 TRAEs occurred in 54% of patients and adverse event leading to dose modification was 38% of patients.[16] Our TRAE findings were consistent with the previous studies. In our study, TRAEs were most commonly fatigue, diarrhea, hand-foot skin reaction, anorexia, nausea, and thrombocytopenia. Grade 3 or 4 TRAEs were observed in 37.2% of patients. TRAEs led to dose modifications in 40.4% of patients, but the drug was

permanently discontinued in only 2 patients. This data suggest that TRAEs were managed with dose modifications, allowing patients to stay on therapy.

The limitations of the current study were its retrospective nature, the small number of patients, not knowing the BRAF status in most of the patients, MSI status, and not having the information of consensus molecular subtypes that have been shown to have prognostic significance. In addition, analysis of dose intensity between subgroups is also not available in our study.

In summary, in the light of current information, regorafenib is a safe and effective agent in mCRC patients who have progressed after 5-FU, oxaliplatin, irinotecan, and anti-EGFR treatments. Manageable side effects and survival contribution increase the importance of the drug. When analyzed according to subgroups, usage of regorafenib in the mucinous subgroup may not have clinical contribution when compared to the nonmucinous subgroup. However, because of small sample size and retrospective nature of the study, our conclusions should be interpreted with caution.

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