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ORIGINAL ARTICLE

Prognostic importance of tumor location and anti-EGFR therapy in patients with K-RAS wild type metastatic colorectal cancer

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Summary

Purpose: *To compare anti-EGFR and anti-VEGF agents in patients with K-RAS wild-type metastatic colorectal cancer (mCRC) with regards to tumor location.*

Methods: *450 patients diagnosed with mCRC, who applied to our center were included in this retrospective study. Of 450 patients, 303 underwent K-RAS mutation tests, assessed as having right-sided or left-sided mCRC and grouped according to localization of right and left colon. Sixty-five patients with K-RAS wild-type mCRC, who were treated with first-line anti-EGFR or anti-VEGF containing combination therapies of fluorouracil with leucovorin and either irinotecan or oxaliplatin were compared.*

Results: *393 (87%) out of 450 mCRC patients had left-sided colon cancers, and 57(13%) had right-side colon cancers. K-RAS analysis was performed in 303 of 450 patients with mCRC, 186 (61.4%) patients had K-RAS wild-type and 117 (38.6%) had K-RAS mutant. Median survival for right-sided cancers was 23.3 months and 29.4 months for left-sided cancers (p=0.309). Median progression-free survival (PFS) was 10.4 months (95% CI 7.3–13.4) in the anti-EGFR containing regimens group and 9.7 months (8.2–11.1) in the anti-VEGF containing regimens group (p=0.037); however, median overall survival (OS) was 18.4 months (95% CI 11.7–25.1) in the anti-EGFR containing regimens group and 19.3 months (95% CI 15.7–22.9) in the anti-VEGF containing regimens group (p=0.635).*

Conclusion: *Addition of anti-EGFR in left sided K-RAS wild-type mCRC regarding PFS was beneficial, however there was no difference in terms of OS.*

Key words: *colorectal cancer, tumor location, K-RAS wild type, anti-EGFR therapy*

Introduction

Colorectal cancer (CRC) is now considered a heterogeneous disease. CRCs arising from right-side and left-side of the colon are molecularly and clinically different. During embryologic development, the right colon arises from the midgut and the left colon from the hindgut [1,2]. Right-sided tumors are more frequently characterized with BRAF mutation positivity, the existence of microsatellite instability; moreover, left-sided tumors more frequently have gene expression profiles characteristic of an epidermal growth factor receptor (EGFR) and HER2-neu amplifications [1,3]. The RAS/RAF/MAPK pathway is downstream of EGFR; mutations of this pathway are predictive markers for efficacy of anti-EGFR therapies [4,5]. Randomized studies firstly demonstrated that adding anti-EGFR monoclonal antibody to fluorouracil with irinotecan or oxaliplatin-based therapies significantly improved

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PFS in the first-line treatment of patients with K-RAS wild-type mCRC [6,7]. Additional studies with extended analyses (with Pan RAS analyses) also showed a positive difference in survival with the addition of anti-EGFR monoclonal antibodies [8]. There has been consensus that the left colon cancer indicates better survival than the right colon cancer in studies conducted over the last years [9-12]. In terms of primary tumor location in CRCs, treatment results with biologic agents (especially anti-EGFR agents) recent studies indicate differences [9,13]. A meta-analysis of FIRE-3/AIO KRK0306, CALGB/SWOG 80405 and PEAK studies shows that patients with RAS wild-type left-sided mCRC had a notably greater survival benefit from anti-EGFR therapy compared with anti-VEGF therapy when added to standard chemotherapy [11].

The studies showing that CRC localization is predictive of anti-EGFR or anti-VEGF therapies are retrospective, and the guidelines are not strongly suggestive about treatment preference according to tumor location [14,15]. Until now, there has been no prospective study of stratification according to primary CRC localization. The aim of this study was to contribute to this controversial issue. We aimed to compare anti-EGFR and anti-VEGF agents in patients with K-RAS wild-type mCRC with regards to tumor location.

Methods

Four hundred fifty patients diagnosed with mCRC, who applied to the Medical Oncology Department of Dicle University Medical Faculty were included in the study between January 2011 and December 2017. This study included adult patients aged ≥18 years with diagnosed metastatic colorectal adenocarcinoma. The patients underwent K-RAS analysis tests, identified tumor location, Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 and adequate organ function. Patients with K-RAS mutation or unknown were excluded from the study. Patients having K-RAS wild-type were assessed as having right-sided or left-sided mCRC and grouped according to localization of right and left CRC.

Of 450, 303 patients underwent K-RAS mutation tests, 65 patients with K-RAS wild-type mCRC, who were treated with first-line anti-EGFR (Cetuximab) or anti-VEGF (Bevacizumab) containing combination therapies of fluorouracil with leucovorin and either irinotecan (FOLFIRI regimen) or oxaliplatin (FOLFOX regimen) were compared in this study.

FOLFIRI was administered as 180 mg/m^2 of irinotecan and 400 mg/m^2 of leucovorin followed by a 400 mg/m^2 bolus of fluorouracil and a 48-h infusion of 2400 mg/m^2 of fluorouracil repeated every 2 weeks. FOLFOX6 was administered as 85 mg/m^2 of oxaliplatin and 400 mg/m^2 of leucovorin, followed by a 400 mg/m^2 bolus of fluorouracil, followed by 48-h infusion of 2400 mg/m^2 of fluorouracil repeated every 2 weeks. Cetuximab was administered as 400 mg/m^2 i.v. on day 1, then 500 mg/m^2 every 2 weeks. Bevacizumab was administered as 5 mg/kg every 2 weeks. Treatment was continued until disease progression or unacceptable toxic effects. The median treatment duration was planned as 6 months.

Factors affecting first-line treatment of patients with mCRC were investigated; moreover, survival outcomes between patients with right- and left-sided tumors were studied. PFS was defined and calculated from the initiation of treatment until disease first progression. OS was defined as the time from the date of diagnosis to the date of the last control or death from any cause.

Left-sided tumors were determined those arising from the splenic flexure, descending colon, sigmoid colon or rectum. Right-sided tumors were determined those arising from the appendix, cecum, ascending colon, hepatic flexure, or transverse colon.

DNA was extracted from formalin-fixed, paraffin-embedded blocks. DNA concentration was determined by the cobas K-RAS Kit. K-RAS (exons 2, 3, and 4) mutational status was tested by cobas-z (RT-PCR).

This study was approved by the Ethics Committee for Clinical Research of Dicle University (Permission number: 195-Date: 23 June 2017). Response Evaluation Criteria in Solid Tumors (RECIST) version 1.09 was used accordingly. Adverse events were recorded continuously from enrollment to the end of the final study visit and were classified and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0.

Statistics

SPSS software version 18.0 was used for statistical analysis. OS and PFS were determined with Kaplan-Meier method and their curves were compared with log-rank test. The chi-square test or Fisher's exact test (when chi-square test assumptions did not hold due to low expected cell counts) were used where appropriate to compare these proportions in different groups. P value less than 0.05 was considered to show a statistically significant difference.

Results

Study diagram and patient characteristics at baseline are summarized in Figure 1 and Table 1. All patients were distributed according to tumor location and K-RAS analysis. Out of 450 mCRC patients, 393 (87%) had left-sided colon cancers, and 57(13%) had right-sided colon cancers. K-RAS analysis was performed in 303 of 450 patients with mCRC; 186 (61.4%) patients had K-RAS wild-type and 117 (38.6%) patients had mutant K-RAS. Patients with K-RAS wild-type treated with biological agent in first-line were selected from all the patients. Sixty five patients with KRAS wild-type tumors were administered first-line chemotherapy regimen. Thirty one (47%) patients out of 65 were administered anti-EGFR containing regimen, and

34 (53%) anti-VEGF. The median duration of treatment was 5.2 months in the anti-EGFR group versus 5.4 months in the anti-VEGF group (p>0.05). The median number of cycles was 10 in the anti-EGFR group versus 11 in the anti-VEGF group.

Median OS was 28.8 (25.2-32.3) months. Median OS for right-sided cancers was 23.3 months and 29.4 months for left-sided cancers (p=0.309). No significant differences between anti-EGFR containing regimens and anti-VEGF containing regimens

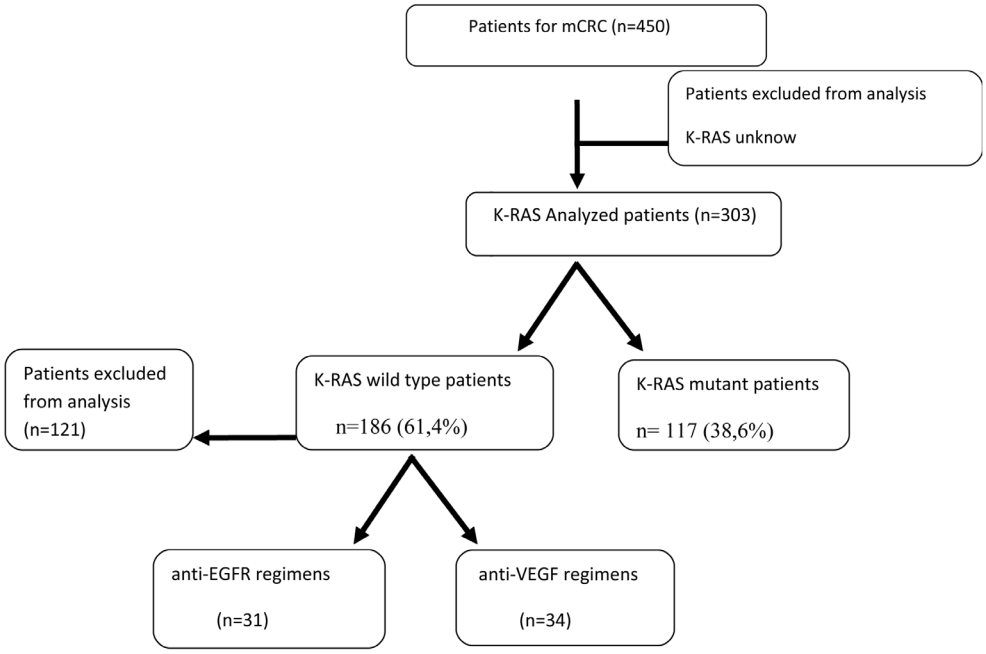

Figure 1. Flow diagram of the study.

Table 1. Patient characteristics at baseline between groups

Patient characteristics	*Anti-EGFRs containing regimens* (n=31) n (%)	*Anti-VEGF containing regimens (n=34)* n (%)	*p value*
Sex			0.951
Male	13 (41.9)	14 (41.2)	
Female	18 (58.1)	20 (58.8)	
ECOG score			0.600
0	7 (22.5)	10 (29.4)	
1-2	24 (78.5)	24 (70.6)	
Age (years)			0.501
<65	25 (80.6)	30 (88.2)	
>65	6 (19.4)	4 (11.8)	
Site of primary tumor			0.611
Left	26 (83.9)	30 (88.2)	
Right	5 (16.1)	4 (11.8)	
Previous adjuvant therapy			0.306
Yes	9 (30)	14 (41)	
No	22 (70)	20 (59)	
Primary tumor resected			0.115
Yes	17 (54)	25 (73)	
No	14 (46)	9 (27)	
Combination treatment			0.063
Irinotecan-based	18 (58.1)	27 (79.4)	
Oxaliplatin-based	13 (41.9)	7 (20.6)	

Table 2. Efficacy results for K-RAS wild-type mCRC on treatment arms

	K-RAS wild type All patients (n=65)		*Left-sided tumors (n=56)*		*Right-sided tumors (n=9)*	
	Anti-EGFR containing regimens (n=31)	Anti-VEGF containing regimens (n=34)	*Anti-EGFR containing regimens (n=26)*	*Anti-VEGF containing regimens (n=30)*	*Anti-EGFR containing regimens (n=5)*	*Anti-VEGF containing regimens (n=4)*
PFS Median, months	10.4	9.7	10,3	10.4	7.7	9.9
p value	0.037		0.755		0.110	
OS Median, months	18.4	19.3	19.02	16.3	19.02	20.4
p value	0.635		0.755		0.438	

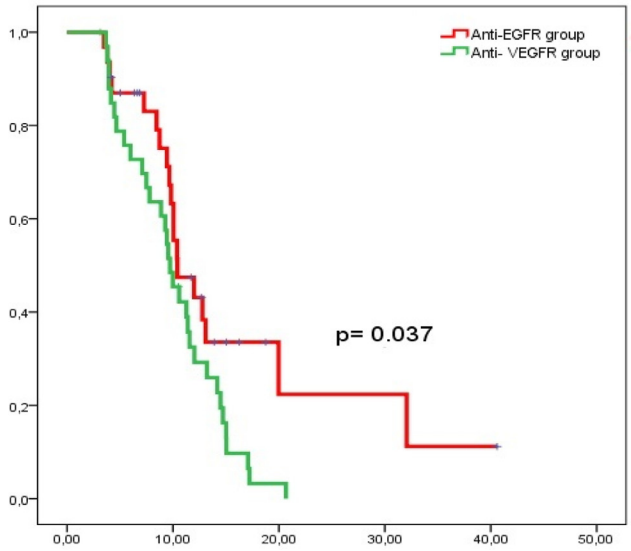

Figure 2. Kaplan-Meier analysis of PFS comparing with K-RAS wild type patients with left-sided tumors anti-EGFR and anti-VEGFR containing regimens.

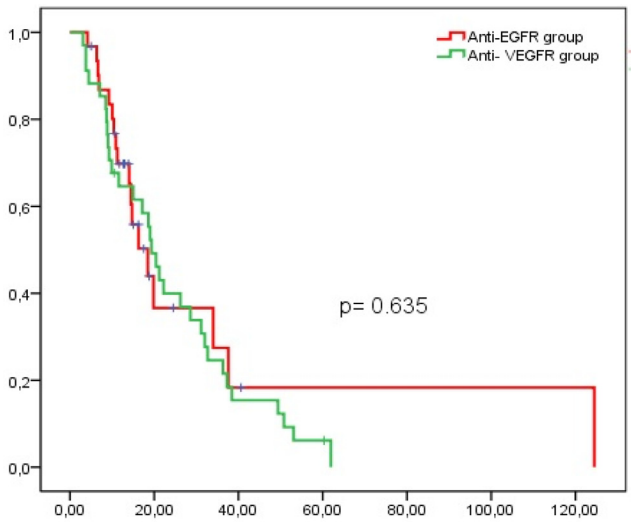

Figure 3. Kaplan-Meier analysis of OS comparing with K-RAS wild type patients withh left-sided tumors ant EGFR and anti-VEGFR containing regimens.

groups were observed in terms of sex (p= 0.951), ECOG score 0/1-2 (p=0.600), age groups (p=0.501), site of primary tumor (p=0.611), receiving or not receiving previous adjuvant therapy (p=0.306), resecting or not resecting primary tumor (p=0.115), which combination treatment regimen with biologic agent was administered (p=0.063).

Survival parameters are listed in Table 2 and Figures 2 and 3. Median PFS was 10.4 months (95% CI 7.3–13.4) in the anti-EGFR containing regimens group and 9.7 months (8.2–11.1) in the anti-VEGF containing regimens group (p=0.037); however, median OS was 18.4 months (95% CI 11.7–25.1) in the anti-EGFR containing regimens group and 19.3 months (95% CI 15.7–22.9) in the anti-VEGF containing regimens group (p=0.635). Among K-RAS wild-type patients with left sided tumors, those treated with anti-EGFR containing regimens had significantly longer PFS than patients receiving anti-VEGF containing regimens.

In the primary analysis, complete or partial responses were reported in 16 (52%) of 31 patients receiving anti-EGFR containing regimens group and 15 (46%) of 34 patients receiving anti-VEGF containing regimens group. Objective response rates were similar between the two treatment groups.

The safety profiles in both treatment groups were similar. The incidence of grade 3 or worse adverse events was similar between treatment groups, and was noted in 23 (68%) of 34 patients in the anti-EGFR containing regimens group and 20 (64%) of 31 in the anti-VEGFR group.

Discussion

In this study, we assessed the predictive importance of primary tumor location in patients with K-RAS wild-type mCRC treated with first-line anti-EGFR or anti-VEGF therapies in combination with

fluorouracil with leucovorin and either irinotecan or oxaliplatin regimens. In this retrospective analysis involving patients with K-RAS wild-type mCRC, there was no significant difference in OS with treatment using anti-EGFR versus anti-VEGF added to FOLFOX or FOLFIRI chemotherapeutic regimens as first-line treatments. However, for K-RAS wild-type patients with left sided tumors, those treated with anti-EGFR containing regimens had significantly longer PFS than patients receiving anti-VEGF containing regimens. This result was similar with previously published trials that anti-EGFR treatment in K-RAS wild-type mCRC was more effective on the left-sided colon cancers.

An important development in recent years has been that "sidedness" is considered crucial. Multiple factors must be considered when making treatment choices for patients with mCRC, including patient characteristics, molecular characteristics, tumor characteristics, and patient preferences [16,17]. These characteristics are already known factors, but the tumor localization must not be ignored. Patients with right-sided colon tumors tend to experience a much worse response to treatment and have a different treatment paradigm than those with left-sided tumors [18]. In the studies conducted so far, right-sided mCRC was associated with a remarkably worse prognosis compared with left-sided mCRC (hazard ratio [HR] for OS: 1.56: 1.43-1.70 p<0.0001) [11]. In other words, patients with left-sided tumors had markedly superior PFS and OS compared with patients with right-sided tumors [19].

In mCRC patients, although important steps have been taken regarding the selection of biologic agent in first-line therapy, the optimal options are still unclear. In recent years the predictive importance of K-RAS, N-RAS and BRAF mutations has been established. Also, there have been studies emphasizing the predictive and prognostic importance of tumor localization in CRC. However, no prospective study exists in which the biologic agents were compared in K-RAS wild-type mCRC patients stratified according to tumor localization.

Although this study is retrospective, it compared the effect of biologic agents on survival in first-line therapy with K-RAS wild-type mCRC patients stratified according to tumor localization, whereas its limitation is that it does not have all the extended K-RAS analyses.

A recent randomized phase 3 trial compared first-line FOLFIRI plus anti-EGFR vs FOLFIRI plus anti-VEGF in patients with K-RAS wild-type mCRC. PFS was similar between treatment arms; however, OS was significantly improved in anti-EGFR treated patients [20].

In combined analyses of the CRYSTAL and FIRE-3 trials, to assess the prognostic and predictive importance of primary tumor location in patients with K-RAS wild-type mCRC, first-line FOLFIRI plus anti-EGFR regimen versus FOLFIRI anti-VEGF was compared [19]. Among the patients with left-sided wild-type K-RAS tumors, the median PFS was similar between anti-VEGF and anti-EGFR treatment (10.3 months vs 10.0 months with anti-EGFR; (p=0.55). In this study, the median OS was longer with anti-EGFR treatment at 38.3 months vs 28.0 months with anti-VEGF (p=0.002). In a retrospective analysis of the FIRE-3 study, among the patients with right-sided wild-type K-RAS tumors, the median PFS was slightly longer with anti-VEGF treatment: 9.0 months vs 7.6 months with anti-EGFR [20].

A meta-analysis of PRIME and CRYSTAL studies suggests that when stratified by tumor location, patients had a better survival benefit from the addition of anti-EGFR antibody to standard chemotherapy in patients with K-RAS wild-type tumor (overall survival, HR for left-sided mCRC: 0.69; 95% CI: 0.58-0.83; p< 0.0001 and HR for right-sided mCRC: 0.96; 95% CI: 0.68-1.35; p=0.802) [11]. In this meta-analysis of FIRE-3/AIO KRK0306, CALGB/SWOG 80405 and PEAK studies showed that patients with K-RAS wild-type left-sided tumors had a markedly longer survival benefit from anti-EGFR treatment compared with anti-VEGF treatment when added to standard chemotherapy (HR 0.71; p=0.0003) [11].

Similarly, Wang et al found that adding anti-EGFR to first-line or second-line chemotherapy significantly improved PFS and OS in patients with left-sided mCRC, but had limited benefit in patients with right-sided tumors [21].

Likewise, other studies indicate that OS was significantly longer in K-RAS wild-type patients with left-sided tumors treated with first-line chemotherapy (FOLFOX or FOLFIRI) plus anti-EGFR vs those receiving chemotherapy (FOLFOX or FOLFIRI) plus anti-VEGF, whereas there was no significant difference between treatment arms among patients with right-sided tumors [13]. Conversely, patients with right-sided mCRC treated with anti-EGFR therapies tended to have shorter survival (p=0.081).

This data is similar to our observations regarding the prognostic and predictive relevance of primary tumor location in patients with K-RAS wild-type mCRC. The meta-analysis of Holch et al shows that tumor location is prognostic and predictive in mCRC [11].

Our study revealed that addition of anti-EGFR in left-sided K-RAS wild-type mCRC regarding PFS was beneficial, whereas there was no difference in

terms of OS because of the limited number of the sampling.

Conclusions

The studies carried out up to date indicate that patients with left-sided K-RAS wild-type mCRC should preferentially be treated with an anti-EGFR antibody, but optimal treatment has yet to be defined. For this, we will need to wait for prospective studies whose colon localization and K-RAS state is stratified and classified.

Conflict of interests

The authors declare no conflict of interests.

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