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The Relationship between Bevacizumab and Body Mass Index in Metastatic Colorectal Cancer

Metastatik Kolorektal Kanserli Hastalarda Bevacizumab ile Vücut Kitle İndeksi Arasındaki İlişki

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ÖZET

Amaç: Bevacizumab dolaşımdaki vasküler endotelyal büyüme faktörüne(VEGF) karşı monoklonal bir antikordur. Serum VEGF'ün yüksek seviyeleri, artan visseral ve abdominal yağ kütlesi ile ilişkilidir. Sistemik kemoterapi ile birlikte bevacizumab alan metastatik kolorektal kanserli hastalarda vücut kitle indeksinin (VKİ) sağkalım ile ilişkisini değerlendirmeyi amaçladık.
Yöntemler: Çalışmaya birinci basamak tedavide bevacizumab bazlı sistemik kemoterapi alan metastatik kolon kanserli 90 hasta dahil edildi. VKİ <25 kg/m^2 olanlar 1. grup ve VKİ ≥25 kg/m^2 olanlar 2. grup olarak belirlendi. Gruplar arasında klinik, laboratuvar parametreleri, tedavi cevap oranı, genel sağkalım (GS) ve progresyonsuz sağkalım (PFS) sonuçları kıyaslandı.
Bulgular: Grup 1 ve grup 2'nin medyan PFS'si sırasıyla 15,8 (%95CI: 10,1-21,5) ve 15,6 (%95CI:10,1-21,5) ay idi (p=0,4). Medyan GS grup 1 için 22,6 (%95CI: 20,1-28,8) ay ve grup 2 için 27,61 (%95CI: 21,81-29,92) ay idi (p=0,02). Çok değişkenli analizde VKİ'nin (HR: 0,89, %95CI: 0,69-0,96, p=0,024) GS için risk faktörü olduğu belirlendi.
Sonuç: VKİ yüksek olan hastalarda bevacizumab kullanımı metastatik kolon kanserli hastalarda uzun sağkalım ile ilişkili idi ve artmış VKİ uzun GS için bagımsız bir prediktif belirteç olarak bulundu.

Anahtar Kelimeler: Bevacizumab, VEGF, vücut kitle indeksi, sağkalım, kolorektal kanser

ABSTRACT

Aim: Bevacizumab is a target therapy drug inhibiting vascular endothelial growth factor (VEGF). High serum VEGF levels are related to increased visceral and abdominal fat mass. We aim to observe the relation of body mass index (BMI) with survival in metastatic colorectal cancer (mCRC) receiving bevacizumab with cytotoxic therapy.
Methods: The study included 90 metastatic colon cancer patients receiving bevacizumab-based systemic chemotherapy in first-line treatment. Study population was stratified into two according to the BMI. Group 1 was consisted of patients with a BMI lower than 25 kg/m^2, Group 2 was consisted of patients with a BMI higher than 25 kg/m^2. Overall survival (OS), progression free survival (PFS), clinic characteristics, laboratory parameters, and response rates were compared between the groups.
Results: The mPFS of group 1 and group 2 were 15.8 (95% Conf. Int: 10.1-21.5) and 15.6 (95% Conf. Int:10.1-21.5) months (p=0.4), respectively. The mOS was 22.6 (95% Conf. Int: 20.1-28.8) months for group 1 and 27.61 (95% Conf. Int: 21.81-29.92) months for group 2 (p=0.02). In multivariate analysis, BMI (Hazard Ratio: 0.89, 95% Conf. Int: 0.69-0.96, p=0.024) was determined to be a risk factor for OS.
Conclusion: Increased BMI was related with more prolonged survival in patients with mCRC receiving bevacizumab. Increased BMI was found to be an independent predictive marker for improved OS.

Key words: Bevacizumab, VEGF, body mass index, survival, colorectal cancer

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INTRODUCTION

Colorectal cancer is one of the top three most common cancers worldwide (1). For most metastatic colorectal cancer patients (mCRC), treatment is generally palliative and usually consists of systemic chemotherapy. However, survival rates of mCRC have increased with the discovery of new drugs targeting epidermal or vascular endothelial growth factor (VEGF) (2). The treatment of Ras mutant mCRC is usually bevacizumab in combination with chemotherapy (3, 4). Bevacizumab targets circulating VEGF ligand and inhibits tumor growth by inhibiting the development of tumor angiogenesis and provides regression of tumor vascularity (3, 4). Bevacizumab plus cytotoxic chemotherapy have improved survival outcomes in mCRC (3, 5, 6).

VEGF functions in normal blood vessel development and vascular pathologies (7). It also causes of pathogenic neovascularization and tumor growth (7). It has been reported that serum VEGF concentrations are increased by visceral fat accumulation and may affect vascular endothelial function (8). The body mass index (BMI) has an effect on survival both progression-free (PFS) and overall (OS) survival in mCRC (9). In addition, although BMI does not affect the effect of fluoropyrimidine-based treatment (10), high VEGF levels have mostly been seen in patients with excessive abdominal and visceral adipose tissue, which may alter the efficacy of anti-VEGF (8, 11, 12).

If high serum VEGF levels are related to increased visceral and abdominal fat mass, bevacizumab treatment may be more beneficial for patients with high BMI. Therefore, we aimed to observe the relation of BMI with survival in mCRC receiving bevacizumab with systemic chemotherapy.

METHODS

The study included 90 patients with mCRC receiving bevacizumab-based systemic chemotherapy in first-line treatment. Patient data were obtained retrospectively from the patient files and hospital database between January 2014 and December 2022 in the department of medical oncology. Patients with malnutrition, active infection, and a second cancer diagnosis were excluded. Study population

Table 1. Comparison of clinical data between group 1 and group 2

		Study population	Group 1 (BMI<25 kg/m²)	Group 2 (BMI≥25 kg/m²)	p
Gender (n)	Female	39 (43.3%)	14 (34.1%)	25 (51%)	0.1
	Male	51 (56.7%)	27 (65.9%)	24 (49%)	
Age (n)	<65	63 (70%)	28 (68.3%)	35 (71.4%)	0.74
	≥65	27 (30%)	13 (31.7%)	14 (28.6%)	
ECOG-PS (n)	0	24 (26.7%)	13 (31.7%)	11 (22.4%)	0.29
	1	41 (45.6%)	15 (36.6%)	26 (53.1%)	
	2	13 (27.8%)	13 (31.7%)	12 (24.5%)	
Comorbidity (n)	Yes	53 (58.9%)	26 (63.4%)	27 (55.1%)	0.42
	No	37 (41.1%)	15 (36.6%)	22 (44.9%)	
Surgery to primary tumor (n)	Yes	40 (44.4%)	22 (53.7%)	18 (36.7%)	0.1
	No	50 (55.6%)	19 (46.3%)	31 (63.3%)	
Tumor side (n)	Left	70 (77.8%)	30 (73.2%)	40 (81.6%)	0.33
	Right	20 (22.2%)	11 (26.8%)	9 (18.4%)	
Chemotherapy backbone (n)	Folfox	66 (73.3%)	29 (70.7%)	37 (75.5%)	0.72
	5-FU/ Capecitabine	21 (23.3%)	10 (24.4%)	11 (22.4%)	
	Folfiri	3 (3.4%)	2 (4.9%)	1 (1.1%)	
Number of metastatic sites (n)	1	24 (26.7%)	13 (31.7%)	11 (22.4%)	0.32
	≥2	66 (73.3%)	18 (68.3%)	38 (77.6%)	
CEA (n)	<5 mg/dl	31 (34.4%)	12 (29.3%)	19 (38.8%)	0.34
	≥5 mg/dl	59 (65.6%)	29 (70.7%)	30 (61.2%)	
Ras mutation status (n)	Wild	50 (%)	24 (58.2%)	26 (54.2%)	0.6
	Mutant	40 (%)	18 (41.5%)	22 (45.8%)	
Braf mutation status (n)	Wild	75 (83.3%)	37 (90%)	38 (77.5%)	0.07
	Mutant	7 (7.9%)	1 (2.5%)	6 (12.3%)	
	Unknown	8 (8.8%)	3 (7.5%)	5 (10.2%)	
Mismatch repair (n)	dMMR	20 (22.2%)	8 (21%)	12 (24.5%)	0.91
	pMMR	24 (26.6%)	10 (26.3%)	14 (28.6%)	
	Unknown	46 (51.2%)	20 (52.7%)	23 (46.9%)	
Best response to treatment (n)	Complete	10 (11.2%)	7 (17.1%)	3 (6.1%)	0.2
	Partial	40 (44.4%)	18 (43.9%)	22 (44.9%)	
	Stable	28 (31.1%)	15 (36.6%)	13 (26.5%)	
	Progression	12 (13.3%)	1 (2.4%)	11 (22.5%)	

was stratified into two according to the BMI. Group 1 was consisted of patients with a BMI lower than 25 kg/m^2, Group 2 was consisted of patients with a BMI higher than 25 kg/m^2. Clinicopathological characteristics, response rates, PFS, and OS were compared between the groups.

SPSS software (SPSS 20.0; IBM Inc.) was used to analyze the data. The chi-square or fisher exact test used in comparison of categorical variables between group 1 and group 2. Survival analyses were performed by Kaplan-Meier analysis. PFS was referred as the time from the date of treatment initiation until the disease's radiological progression. OS was referred as the time from the date of diagnosis until the patient's death from any reason. Risk factors for survival outcomes were established by univariate and multivariate cox regression analysis. The p values lower than 0.05 were accepted statistically significant.

RESULTS

Among the 90 patients in the study, 51 (56.7%) of the patients were male and 39 (43.3%) were female. There was no significant difference between group 1 and group 2 in terms of clinical characteristics (p>0.05 for all) (Table 1). In groups 1 and 2, the most commonly used chemotherapy was the backbone Folfox regimen. The least commonly used chemotherapy was the Folfiri regimen (p=0.72) (Table 1).

The best response with treatment was a partial response in group 1 and group 2, however statistical significance was not reached (p=0.02) (Table 1). Additionally, there were no significant difference in terms of primary surgery, tumor side, number of metastatic sites, CEA level, Ras, Braf, and MMR status compared between the groups (p>0.05 for all) (Table 1). The mPFS was 15.8 months (95% Conf. Int: 10.1-21.5)

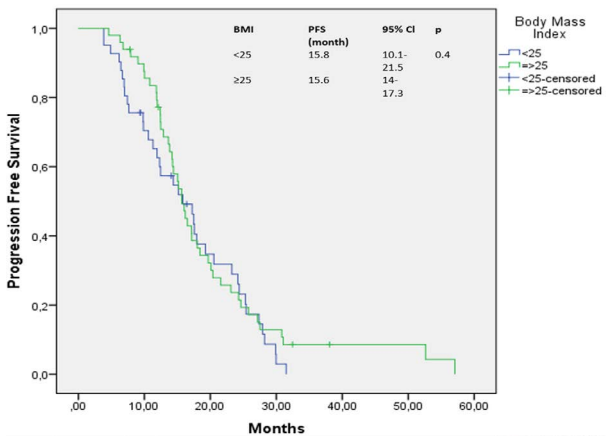

Figure 1. Progression free survival in study group according to Body Mass Index

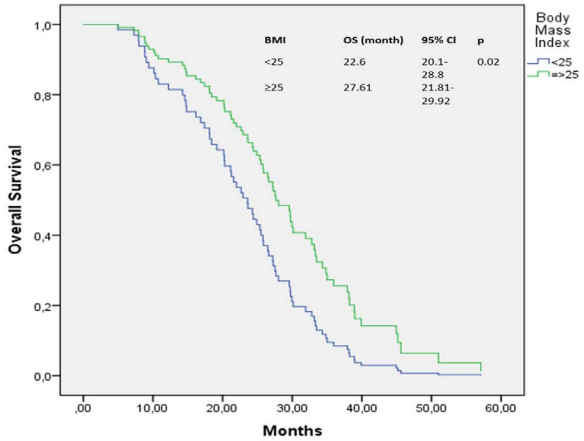

Figure 2. Overall survival in study group according to Body Mass Index

Table 2. Cox regression analyzes of various factors related to progression free survival (PFS)

PFS	Multivariate analysis	Univariate analysis					
		Hazard Ratio	95% Conf. Int.	p	Hazard Ratio	95% Conf. Int.	p
Age (n)	<65 vs ≥65	-	-	-	0.67	0.46-1.28	0.12
BMI (n)	≥25 vs <25	0.70	0.45-1.21	0.16	1.2	0.65-1.84	0.4
Gender (n)	Male vs female	-	-	-	1.52	0.99-1.92	0.06
Comorbidity (n)	No vs Yes	-	-	-	1.35	0.87-1.54	0.17
ECOG-PS (n)	0	-			Reference		0.26
	1	-	-	-	0.72	0.45-1.32	0.24
	2	-	-	-	0.60	0.41-1.05	0.1
Tumor side (n)	Left vs right	0.84	0.65-1.32	0.5	0.9	0.84-1.12	0.72
CEA (n)	<5 vs ≥ 5	0.62	0.51-1.02	0.052	0.62	0.32-0.89	0.04
Number of metastatic sites (n)	≥2 vs 1	1.09	0.74-1.54	0.72	0.81	0.74-1.24	0.4
Ras mutation (n)	Wild vs Mutant	0.98	0.89-1.18	0.76	0.93	0.78-1.42	0.74
Braf mutation (n)	Mutant vs Wild	2.11	1.11-2.87	0.09	1.69	1.02-1.91	0.19
MMR (n)	dMMR vs pMMR	-	-	-	0.95	0.84-1.25	0.87

Table 3. Cox regression analyzes of various factors related to overall survival (OS)

OS		Multivariate analysis			Univariate analysis		
		Hazard Ratio	95% Conf. Int.	p	Hazard Ratio	95% Conf. Int.	p
Age (n)	<65 vs ≥65	-	-	-	0.95	0.79-1.12	0.4
BMI (n)	≥25 vs <25	0.89	0.69-0.96	0.024	0.66	0.34-0.94	0.01
Gender (n)	Female vs male	-	-	-	1.02	0.85-1.11	0.9
ECOG-PS (n)	0		-		Reference	0.95	
	1	-	-	-	0.95	0.84-1.15	0.85
	2	-	-	-	0.91	0.89-1.24	0.76
Tumor side (n)	Left vs right	0.89	0.64-1.21	0.71	1.12	0.78-1.32	0.66
CEA (n)	<5 vs ≥5	0.55		0.019	0.74	0.59-0.92	0.018
Number of metastatic sites (n)	≥2 vs 1	1.39	0.95-1.87	0.22	0.62	0.46-1.62	0.06
Ras mutation (n)	Wild vs Mutant	1.09	0.89-1.35	0.73	1.01	0.91-1.21	0.94
Braf mutation (n)	Mutant vs Wild	1.80	1.1-2.25	0.20	0.77	0.65-1.15	0.53
MMR (n)	dMMR vs pMMR	-	-	-	1.4	0.99-1.84	0.31

for group 1 and 15.6 months (95% Conf. Int:10.1-21.5) for group 2 (p=0.4), (Figure 1). The mOS was 22.6 (95% Conf. Int: 20.1-28.8) months for group 1 and 27.61 (95% Conf. Int: 21.81-29.92) months for group 2 (p=0.02) (Figure 2). Age (<65 vs.≥65), BMI (<25 vs.≥25 kg/m^2), gender (female vs. male), comorbidity (no vs. yes), ECOG-PS (0.1 vs. 2), tumor side (left vs. right), CEA (<5 vs.≥ 5 ug/l), number of metastatic sites (≥2 vs. 1), Ras, Braf, and MMR status were evaluated for mPFS. Univariate and multivariate analyses revealed no risk factors for mPFS (Table 2).

CEA (<5 vs.≥5 ug/l) (Hazard Ratio: 0.74, 95% Conf. Int: 0.59-0.92, p=0.018) and BMI (≥25 vs. <25) (Hazard Ratio: 0.66, 95% Conf. Int: 0.34-0.94, p=0.01) were identified as risk factors for mOS in univariate analysis. In multivariate analysis, only BMI (Hazard Ratio: 0.89, 95% Conf. Int: 0.69-0.96, p=0.024) was found to be a risk factor (Table 3). Age (<65 vs.≥65), gender, ECOG-PS, tumor side, metastatic site number, Ras, Braf, and MMR status were not detected as risk factors (Table 3).

DISCUSSION

We found that high BMI (≥25 kg/m^2) is associated with longer OS in mCRC receiving bevacizumab plus systemic chemotherapy. However, there was no significant relation between response rate or PFS and BMI. The impact of BMI on cancer patient survival and response to treatment is controversial (13, 14). Increased BMI is related with both good and poor survival outcomes in CRC (9, 13). It has been reported that high VEGF levels are observed in patients with abdominal and visceral adipose tissue (12). In this context, it has been reported that bevacizumab may alter the efficacy of bevacizumab in patients with excess adipose tissue (8, 11). Hopitean et al. found that BMI <27 kg/m^2 was related with shorter PFS and OS (15). In our study, OS was shorter in patients with BMI <25 kg/m^2; however, no significant relation was found between PFS and BMI. The most critical problem in interpreting these results is the need for a specific cut-off value for BMI.

There are many prognostic factors determined in patients with cancer. Apart from well known risk factors, many new risk factors have investigated in different cancer types (16). In this study, a CEA level <5 ug/l was related with shorter OS. The prognostic significance of CEA level is controversial; in some studies, a high CEA level was found to be favorable prognostic, whereas, in some studies, it was found unfavorable prognostic (17, 18). In colon cancer patients, radiological imaging methods are used to detect metastases and determine treatment response (19, 20). However, the standardized uptake value (SUV) value is used as a prognostic marker in positron emission tomography. SUV value above ten is reported to be associated with poor prognosis (21).

Our study has some limitations. Firstly, our study is retrospective. Secondly, it is a single-center study; thirdly, the number of patients is relatively small. Fourthly, there is no specific cut-off value to compare the association of BMI with survival outcomes.

CONCLUSION

Increased BMI was related with more prolonged survival in mCRC receiving bevacizumab. Studies including larger populations are needed to confirm these results.

Etik Kurul: The local ethics committee approved the study (Approval number: 2023/4408).

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