Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Research Article

J Exp Clin Med
2022; 39(4): 1112-1119
doi: 10.52142/omujecm.39.4.34

Use of monoclonal antibodies (Bevacizumab, Cetuximab, and Panitumumab) in patients with metastatic colorectal cancer: A single center experience

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Received: 19.02.2022 • **Accepted/Published Online:** 12.07.2022 • **Final Version:** 29.10.2022

Abstract

Despite all the advances in therapeutic modalities such as targeted therapies and immunotherapies that have recently been used in cancer treatment, Colorectal Cancer (CRC) continues to be the fourth most common cause of cancer-related deaths. The introduction of targeted monoclonal antibodies (mAbs) and their use in cancer treatment led to revolutionary advances in oncology. The aim of this study was to share our experiences regarding the usage rates of mAbs (Bevacizumab, Cetuximab, and Panitumumab), Overall Survival (OS) and progression-free survival (PFS) in patients with mCRC followed up in our hospital. This retrospective study included 210 patients with mCRC who were followed up in our hospital's oncology clinic between January 2010 and October 2020 and who received mAb treatment, regardless of their stage at the time of diagnosis. Fifty-two (24.8%) of the patients received a treatment regimen with Cetuximab and 46 with Panitumumab mAb. 29 patients (17.8%) received Cetuximab and Bevacizumab mAb treatment at different times, and 22 patients received Panitumumab and Bevacizumab mAb treatment, 112 of the patients received only Bevacizumab treatment. Panitumumab and Cetuximab mAb treatment was mostly taken in the 1st lines (69.6%, 76.9%, respectively). A statistically significant difference was found between the OSs of the cases according to the mAb treatment received ($p = 0.001$). Administration of Panitumumab and Cetuximab mAb in the 1st or 2nd series did not make a significant difference to PFS. When the retrospective data were evaluated, the distribution of Panitumumab and Cetuximab mAb treatments was seen to be balanced. Panitumumab and Cetuximab mAb therapy were not preferred for K-RAS mutant patients. They were preferred to give it in the first line. Patients who received anti EGFR mAb treatment had longer OS and PFS duration than those who received anti VEGF mAb only. It can be said that taking anti EGFR mAb treatment (being KRAS WT) has a positive effect on prognosis.

Keywords: Colorectal cancer, bevacizumab, cetuximab, panitumumab, prognosis

1. Introduction

Despite all the advances in therapeutic modalities such as targeted therapies and immunotherapies that have recently been used in cancer treatment, Colorectal Cancer (CRC) continues to be the fourth most common cause of cancer-related deaths after lung, stomach, and liver cancer. While the primary goal of early-stage colorectal cancer treatment is to provide a cure, the goal of stage IV CRC treatment is to reduce tumor-related symptoms and to prolong overall survival (OS) by minimizing the adverse effects of drug toxicities on patient quality of life parameters (1, 2).

In the 1990s, the primary treatment for CRC was fluoropyrimidine-based chemotherapy (5-fluorouracil [5-FU] or capecitabine), and the OS benefits of this therapy were proven (3, 4). Irinotecan and oxaliplatin are widely used in combination with 5-FU and Leucovorin (folinic acid) as first or second-line therapy for metastatic CRC (mCRC) (5, 6). While this combination has been shown to prolong survival by an average of 2–4 months, the presence of severe side effects and toxicities affecting the quality of life have also emerged (7).

The introduction of targeted monoclonal antibodies (mAbs) and their use in cancer treatment led to revolutionary advances in oncology. The abnormal over-expression of the Epidermal Growth Factor Receptor (EGFR) is associated with many human malignancies, one of the most common of which is CRC (8, 9). Drugs targeting EGFR have become a focus of interest in the treatment of mCRC. Currently, there are two anti-EGFR mAbs in clinical use, Cetuximab, and Panitumumab. These two drugs received Food and Drug Administration (FDA) approval for the treatment of mCRC in 2004 and 2007, respectively (10, 11).

Angiogenesis is a crucial stage for the development of tumors, and antiangiogenic agents inhibit the growth of new blood vessels, opening a new approach to cancer therapy (12). Bevacizumab is an angiogenic inhibitor that targets tumor vascularization and acts primarily on vascular endothelial growth factor (VEGF) or its receptors and was approved by the FDA in 2004 (13).

In this article we share our experiences regarding the

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usage rates of mAbs (Bevacizumab, Cetuximab, and Panitumumab), OS, and progression-free survival (PFS) in patients with mCRC followed up in our hospital.

2. Material and Method

This retrospective study included patients with mCRC who were followed up in our hospital's oncology clinic between January 2010 and October 2020 and who received mAb treatment, regardless of their stage at the time of diagnosis. Patients who started oncological treatment in another hospital or did not continue their treatment in our hospital were not included in the study. Clinical retrospective data were obtained from the electronic medical records, including demographic characteristics, medical history, clinical features, laboratory findings, treatments, and radiological images.

2.1. Compliance with ethical standards

This retrospective study was approved by the Ethics Committee of Bakirköy Sadi Konuk Training and Research Hospital, and the National Ethics Committee. All procedures were applied in accordance with the Helsinki Declaration and its later amendments or comparable ethical standards (No:2020/403).

2.2. Outcome measures

The primary outcome measures of the study were OS and PFS. The assessment of OS, as the time between diagnosis and death for any reason, is the most accepted method for evaluating the outcomes of cancer treatments. American and European oncology groups also agree that OS should be the primary outcome measure in clinical trials. It should be noted that PFS, the time until a disease progresses, is used as a measure to evaluate the direct effect of a treatment in patients with metastatic cancer (14).

2.3. Statistical analysis

NCSS (Number Cruncher Statistical System) program was used for statistical analysis. The Mann-Whitney U test was applied to inter-group comparisons of quantitative variables that did not show normal distribution, and the Kruskal-Wallis test and Dunn-Bonferroni test were used in the comparisons of more than two groups of quantitative variables that did not show normal distribution. The relationships between quantitative variables were evaluated with Spearman correlation analysis. Statistical significance was accepted as $p < 0.05$.

3. Results

The median age of 210 CRC patients included in the study was 63 years, and 57.6% (n = 121) of the patients were male. The prevalence of males decreased as the age decreased, and 50% of the patients in the ≤40 years age group (young patients) (n = 10) were male.

In 75.7% of the patients (n = 159), the tumor was located on the left side, and this tumor location was similar in the young patient group (70% on the left side).

The majority of the patients (64.8%) had metastatic disease at presentation, and the most common metastasis region was the liver at 87.7%, followed by the lung at 6.1%. In the young patient group, 70% had liver metastasis. Surgery was applied as the first treatment in 48.1% of the patients (n = 101), chemotherapy alone was given to 41.4%, neoadjuvant chemotherapy to 10.5%, and then surgical resection was performed.

The median OS in the whole patient population was found to be 23.05 months. In the subgroup analysis of patients aged ≤40 years (n = 10), the median OS was found to be significantly lower at 17.2 months. ($p < 0.001$). Mortality developed in 57.1% of the patients (n = 120) due to disease progression, and 90 patients are still alive and receiving treatment. Thirty-one patients (14.8%) presented with intestinal obstruction and 14 with intestinal perforation. Approximately half of the patients (45.2%) had lymphovascular invasion, while 37.1% had perineural invasion. During the first surgical treatment, a total of 27 patients underwent metastasectomy. The time to median metastasis in patients was found to be 6.65 months. (Table 1).

Table 1. Clinical characteristics of patients

Age *year*	*Median (Range)*	63 (26-89)
		N (%)
Gender	**Female**	89 (42.4)
	Male	121 (57.6)
Gender of 40 years and under	**Female**	5 (50)
	Male	5 (50)
Location of tumor	**Right**	51 (24.3)
	Left	159 (75.7)
Initial stage	**Metastatic**	136 (64.8)
	Limited	74 (35.2)
Site of metastasis	**Liver**	186 (87.7)
	Lung	13 (6.1)
	Intraperitoneal local	6 (2.9)
	Brain	3 (1,4)
	Bone	2 (0.9)
	Bladder	1 (0.5)
	Gastric	1 (0.5)
First type of treatment	**Surgical resection**	101 (48.1)
	Chemotherapy	87 (41.4)
	Neoadjuvant chemotherapy	22 (10.5)
Overall survival *months*	*Median (Range)*	23.05 (1-99)
OS in the ≤ 40 years age group *months*	*Median (Range)*	17.02 (8-32)
Survival	**Alive**	90 (42.9)
	Dead	120 (57.1)
Obstruction	*Median (Range)*	31 (14.8)
Perforation		14 (6.7)
Lymphovascular invasion presence		95 (45.2)
Perineural invasion presence		78 (37.1)
Metastasectomy		27 (12.9)
Metastasis free survival *months*		6.65 (1-62)

Patients most frequently received 1 and 2 lines of treatments (41.4%, 32.9%, respectively), fifty-two (24.8%) patients received a treatment regimen with Cetuximab and 46 with Panitumumab mAb. Twenty-nine patients (17.8%) received Cetuximab and Bevacizumab mAb treatment at different times, and 22 patients received Panitumumab and Bevacizumab mAb treatment. One hundred twelve patients received only Bevacizumab treatment. Panitumumab and Cetuximab mAb treatment was mostly taken in the 1st lines (69.6%, 76.9%, respectively). The distribution of the treatments is shown in Table 2.

Table 2: Distribution of treatments received and side-effects, n (%)

Number of treatment lines received	**1**	87 (41.4)
	2	69 (32.9)
	3	38 (18.1)
	4	16 (7.6)
Treatment	**Bevacizumab**	112 (53.3)
	Cetuximab	52 (24.8)
	Panitumumab	46 (21.9)
Bevacizumab	**Bevacizumab**	112 (68.7)
	Cetuximab+ Bevacizumab	29 (17.8)
	Panitumumab+ Bevacizumab	22 (13.5)
Panitumumab	**1st line**	32 (69.6)
	2nd line	13 (28.3)
	3rd line	1 (2.2)
Cetuximab	**1st line**	40 (76.9)
	2nd line	10 (19.2)
	3rd line	2 (3.8)
Rash/Dermatitis acneiform	**No**	191 (91)
	Yes	19 (9)
Grade of Rash/ Dermatitis acneiform	**2**	17 (89.5)

In 9% of the patients (n = 19), rash/dermatitis was observed during the treatment, which was mostly (89.5%) grade 2 severity (Table 2). The treatments and mAbs taken by the cases in the 1st, 2nd, 3rd, and 4th lines are shown in Table 3. The response rates of the cases distributed according to the lines are shown in Table 4. The frequency of progressive disease in the 1st, 2nd and 3rd lines of treatments was seen to be similar at 78.6%, 78.9%, and 74.1%, respectively.

Table 3. Preferred treatments in 1st, 2nd, 3rd, and 4th series

• 1st line treatment	**FOLFOX**	101 (48.1)
	FOLFIRI	71 (33.8)
	XELOX	35 (16.7)
	Capecitabine	3 (1.4)
	Monoclonal Antibodies	
	Bevacizumab	80 (52.6)
	Combination with Cetuximab	40 (26.3)
	Combination with Panitumumab	32 (21)
• 2nd line treatment	**FOLFIRI**	69 (57.5)
	FOLFOX	37 (30.8)
	XELOX	8 (.7)
	Capecitabine	6(5)
	Monoclonal Antibodies	
	Bevacizumab	60 (67.4)
	Combination with Panitumumab	14 (15.7)
	Combination with Cetuximab	12 (13.4)
	Regorafenib	3 (3.4)
• 3rd line treatment	**Regorafenib**	28 (51.8)
	FOLFIRI	13 (24.1)
	FOLFOX	10 (18.5)
	Capecitabine	3 (5.5)
	Monoclonal Antibodies	
	Bevacizumab	12 (60)
	Combination with Panitumumab	4 (20)
	Combination with Cetuximab	4 (20)
•4th line treatment	**Regorafenib**	6 (37.5)
	FOLFOX	3 (18.7)
	FOLFIRI	3 (18.7)
	Capecitabine	3 (18.7)
	XELOX	1 (6.2)
	Monoclonal Antibodies	
	Bevacizumab	3 (60)
	Combination with Cetuximab	1 (20)
	Combination with Panitumumab	1 (20)

FOLFIRI= Fluorouracil, Leucovorin plus Irinotecan, FOLFOX= 5-Fluorouracil plus Oxaliplatin, XELOX= Capecitabine plus Oxaliplatin

Table 4. Response to Treatment and Progression-free survival (PFS) results

Treatment	**Response**	**n(%)**
1st line	**stable**	45 (21.5)
	progression	165 (78.6)
2nd line	**stable**	26 (21.1)
	progression	97 (78.9)
3rd line	**stable**	14 (25.9)
	progression	40 (74.1)
4th line	**stable**	6 (37.5)
	progression	10 (62.5)
1st line PFS *months*	*Median (Range)*	12.92 (1-130)
2nd line PFS *months*	*Median (Range)*	6.94 (1-57)
3rd line PFS *months*	*Median (Range)*	6.89 (1-38)
4th line PFS *months*	*Median (Range)*	7.83 (2-28)

The 1st line median PFS was 12.92 months, which was longer than the 2nd, 3rd, and 4th series PFS duration (6.94, 6.89, 7.83, respectively) (Table 4). There was no significant difference in OS according to gender and location (right,

left) of the tumor (p> 0.05). OS was found to be significantly lower in patients with metastatic disease at the time of diagnosis (p = 0.001). A statistically significant difference was found between the OS of the cases according to the first treatment method. The OS of the patients who received only chemotherapy treatment (patients without surgical resection) was found to be significantly lower than those who underwent surgical resection after diagnosis or underwent surgical resection after receiving neoadjuvant chemotherapy treatment (p = 0.001; p = 0.001; p <0.01). A statistically significant difference was found between the OSs of the cases according to the mAb treatment received (p = 0.001; p <0.01). According to the results of the paired comparisons made to determine the difference, the OS of the patients who received only Bevacizumab mAb treatment was found to be significantly lower than those who received Panitumumab and Cetuximab mAb (p = 0.004; p = 0.011; p <0.05). The number of treatment lines received made a significant difference to OS. (p = 0.001; p <0.01). According to the results of the paired comparisons made to determine the difference, the survival time of patients who received 1 line of treatments was found to be significantly lower than those who received 3 and 4 lines of treatments (p = 0.008; p = 0.001; p <0.01). The survival time of the patients who received 2 lines of treatments was found to be significantly lower than those who received 4 lines of treatments (p = 0.001; p <0.01). The administration of Panitumumab and Cetuximab mAb on the 1st or 2nd line did not have a statistically significant effect on OS durations (p> 0.05).

The OS of patients who developed rash/dermatitis during treatment was found to be higher than those without (p = 0.020; p <0.05). While the OS of the cases presenting with obstruction was found to be statistically significantly lower (p = 0.044; p <0.05), the presence of perforation did not have a significant effect on OS (p> 0.05). The OS of cases with lymphovascular invasion was found to be statistically significantly lower than cases without (p = 0.001; p <0.01), but the presence of perineural invasion did not have a significant effect on OS (p> 0.05). There was no significant difference in OS of the patients with and without metastasectomy (p> 0.05) (Table 5).

Table 5. Overall survival and comparison of parameters

		Overall survival *months*		
		Range	Median	*p*
Gender	**Female (n=89)**	2-99	25.9	[a]***0.971***
	Male (n=121)	1-90	26.8	
Location of tumor	**Right (n=51)**	2-66	22.3	[a]***0.079***
	Left (n=159)	1-99	27.7	
Initial stage	**Metastatic (n=136)**	1-71	20.5	[a]***0.001****
	Limited (n=74)	7-99	37.2	
First type of treatment	**Neoadjuvant chemotherapy (n=22)**	12-77	34.7	[b]***0.001****
	Surgical resection (n=101)	6-99	31.6	
	Chemotherapy (n=87)	1-66	18.2	
Treatment	**Bevacizumab (n=112)**	1-99	22.5	[b]***0.001****
	Panitumumab (n=46)	3-90	32.6	
	Cetuximab (n=52)	8-71	29.4	
Number of treatment lines received	**1 (n=87)**	1-90	22.1	[b]***0.001****
	2 (n=69)	2-99	26.3	
	3 (n=38)	9-66	30.1	
	4 (n=16)	22.8-65	41.1	
Panitumumab	**1st line treatment (n=32)**	3-90	29.5	[a]***0.244***
	2nd line treatment (n=13)	11-77	37.7	
	Φ 3rd line treatment (n=1)	63	63	
Cetuximab	**1st line treatment (n=40)**	8-71	29.1	[a]***0.467***
	2nd line treatment (n=10)	15-59	32.7	
	Φ 3rd line treatment (n=2)	18-20	18.8	
Rash/Dermatitis acneiform	**No (n=191)**	1-99	25.6	[a]***0.020****
	Yes (n=19)	12-69	34.9	
Obstruction	**No (n=179)**	1-99	27.5	[a]***0.044****
	Yes (n=31)	6-50	20.1	
Perforation	**No (n=196)**	1-99	26.2	[a]***0.522***
	Yes (n=14)	9-71	28.6	
LVI presence	**No (n=115)**	6-84	30.2	[a]***0.001****
	Yes (n=95)	1-99.63	23.3	
PNI presence	**No (n=132)**	1-99	25.3	[a]***0,090***
	Yes (n=78)	2-66	22.3	
Metastasectomy	**No (n=183)**	1-99	27.7	[a]***0.082***
	Yes (n=27)	1-71	20.5	

[a]Mann Whitney U Test, [b]Kruskal Wallis Test, *p<0.05, **p<0.01, included in comparison due to insufficient number of patients, LVI=Lymphovascular invasion, PNI= Perineural invasion

There was no statistically significant relationship between the age of the patients and OS (p> 0.05), but OS was significantly shorter in the ≤40 years age group, the young patients. A moderate negative correlation was observed between the carcinoembryonic antigen (CEA) levels at the time of diagnosis and OS (OS decreased with increasing CEA value at the time of diagnosis) (r = -0.411; p = 0.001; p <0.01). A moderate positive correlation (OS increased with increasing PFS) between PFS and OS was observed (r = 0.509; p = 0.001; p <0.01). (Spearman's Correlation analysis) (Table 6).

Table 6. Relationship between overall survival and age, initial CEA, and Progression-Free Survival

		Overall survival
Age	**r**	0.112
	p	***0.105***
Initial CEA ng/ml	**r**	-0.411
	p	***0.001****
PFS	**r**	0.509
	p	***0.001****

r=Spearman's correlation coefficient, **p<0,01 PFS=Progression-free survival, CEA: carcinoembryonic antigen

Administration of Panitumumab and Cetuximab mAb in the 1st or 2nd series did not make a significant difference to PFS (p> 0.05) (Table 7).

There was no statistically significant difference in OS and PFS according to the disease location (right / left) of the patients who received Bevacizumab mAb treatment (p> 0.05) (Table 8).

A significant difference was found in OS and PFS when Bevacizumab mAb was administered single or sequentially with other mAbs (p = 0.001; p <0.01). According to the results of the pairwise comparisons, the OS of patients who received only Bevacizumab mAb treatment was found to be significantly lower than that of patients with Bevacizumab and Panitumumab mAb at different times (p = 0.001; p <001). The PFS of the patients who received Bevacizumab and Panitumumab mAb treatment at different times was significantly higher than those who received Bevacizumab alone and those who received Bevacizumab and Cetuximab mAb at different times (p = 0.004; p = 0.005; p <001) (Table 9).

Table 7. Comparisons related to Progression-free Survival

		Progression-free survival (month)		
		Range	Median	*p*
Panitumumab	**1st line treatment (n=32)**	1-62	8.9	[a]***0.412***
	2nd line treatment (n=13)	1-26	8.7	
	ϕ 3rd line treatment (n=1)	15	15.5	
Cetuximab	**1st line treatment (n=40)**	1-39	5.6	[a]***0.186***
	2nd line treatment (n=10)	1-44	14	
	ϕ 3rd line treatment (n=2)	1	1	

[a]Mann Whitney U Test *p<0,05, ϕNot included in comparison due to insufficient number of patients

Table 8. Overall survival and progression-free survival in Bevacizumab treated patients by tumor location

		Location of tumor		
		Right (n=29)	Left (n=83)	*p*
OS (months)	*Median (Range)*	20.3 (2-66)	23.2 (1-99)	[a]***0.347***
PFS (months)	*Median (Range)*	3.9 (1-31)	5.6 (1-64)	[a]***0.845***

[a]Mann Whitney U Test OS=Overall survival, PFS= Progression-free survival

Table 9. Overall survival and progression-free survival by monoclonal antibodies treatment

		Treatment			
		Beva (n=112)	Beva + Pan (n=22)	Beva + Cet (n=29)	*p*
OS (months)	*Range*	1-99	11-77	8-50	[b]***0.001****
	Median	22.5	38	25.9	
PFS (months)	*Range*	1-63	1-46	1-32	[b]***0.002****
	Median	5.2	11.8	4.3	

[b]Kruskal Wallis Test **p<0,01 OS=Overall survival, PFS= Progression-free survival

4. Discussion

The annual incidence of CRC worldwide is higher in males than in females, with reported rates of just over was equal. Most studies have shown that the incidence of CRC diagnosed at a young age is more common, mainly in the distal colon and rectum, and is at an advanced stage at diagnosis. Similarly, 70% of the currently studied young patients were determined to have CRC originating from the left colon. Although this issue is controversial, it is thought that CRC in young patients has 1 million for males and 79,500 for females (15). In the current study patient population, the frequency of male patients was higher in the general group, while the ratio of female and male patients aged 40 years and younger a more aggressive biological behavior and worse prognosis (16-18). Also supporting this view, the median OS was significantly lower in the ≤ 40 years age group of this study.

In CRC, the most common and generally first metastasis site is the liver, and liver metastasis is one of the most important factors determining survival (19). Similarly, in the current study patient population, the liver was the most common metastasis site in both the general group and the young patients, and the median OS was found to be longer in patients who underwent metastasectomy compared to those who did not. As expected, patients who underwent surgical resection at the time of initial diagnosis or after

receiving neoadjuvant chemotherapy had a longer median OS than those who had no surgical resection. It can also be said that operability affects overall survival. Patients with metastases that could not be resected at the time of diagnosis were treated with systemic chemotherapy only.

There was a negative correlation between the CEA level at the time of diagnosis and the median OS in the current study patients. Although studies have been carried out on the availability of new methods such as new parameters, personalized analysis, and mutation analysis to predict OS, CEA still continues to provide an idea about OS. Other advantages of CEA are that the levels change with treatment, it provides guidance in response to treatment, and it is relatively inexpensive compared to new parameters (20).

Bevacizumab, which acts as an anti-VEGF, inhibits VEGF function in vascular endothelial cells and inhibits tumor angiogenesis and has been shown to result in a significant increase in OS and PFS when co-administered with chemotherapy in most randomized controlled mCRC studies (21). The current study patient group consisted of CRC patients who received only mAb treatment, and the most common mAb treatment administered in the study was Bevacizumab. Anti-EGFR mAb (Panitumumab and Cetuximab) treatment was given to patients with wild-type Kirsten Rat Sarcoma viral oncogene mutation (WT K-RAS), and combination therapies with Bevacizumab mAb were given in progressive series to patients with progression. The administration of Bevacizumab mAb to patients who could not be given anti-EGFR mAb treatment (such as being K-RAS mutant or the lack of reimbursement of anti-EGFR treatment by health insurances in the early 2000s) may have had an effect on Bevacizumab being the leading treatment (22).

Biological and clinical evidence supports that carcinogenesis follows different molecular pathways in proximal (right side) and distal (left side) CRCs and may have different expression profiles due to their different embryonic origins (23-26). Nevertheless, the results obtained in studies evaluating the effect of primary tumor location on OS in mCRC are complicated due to the heterogeneity in molecular and pathological features and treatments received (27-29). Although different levels of efficacy of Bevacizumab mAb have been reported in cancers located in the right and left colon, in the current study, no relationship was found between tumor location and OS in patients who received Bevacizumab mAb.

An important factor for adding Cetuximab or Panitumumab to conventional therapy in mCRC patients is the K-RAS mutation status. Mutation in the K-RAS gene is a negative predictor of response to Cetuximab and/or Panitumumab, and in a meta-analysis, the response to anti-EGFR mAb therapy in K-RAS mutant patients was reported to be significantly lower than in those with WT K-RAS (30). In the current study patient group, only WT K-RAS patients received anti-EGFR mAb treatment. The fact that only this group is reimbursed by the national health insurance system was also influential in this choice.

In most clinical trials, anti-EGFR mAbs have been used in the treatment protocol in patients with mCRC resistant to conventional chemotherapy. In this regard, anti-EGFR mAbs are generally used in second or third line therapy for treatment and often in combination with some chemotherapeutic agents. However, in some studies, anti-EGFR mAbs have been used as monotherapy due to chemotherapy failure or intolerable toxicity (21). In the current study, anti-EGFR mAbs were given more frequently to mCRC patients in the first lines. Although there were patients who underwent dose reduction due to chemotherapy toxicity, none of the patients were given anti-EGFR mAb therapy as a monotherapy. It was seen that the lines in which anti-EGFR mAb was given did not affect PFS, which was observed to be similar when anti-EGFR mAb was given in the 1st or 2nd lines.

In general, targeted agents and monoclonal antibodies do not induce many of the systemic side effects that are typically associated with conventional cytotoxic agents and are difficult to tolerate. However, a number of specific toxicities of these agents have been reported, which can be severe and impair quality of life (31). A wide range of skin-related side effects can occur, ranging from mildly dry skin to widespread and life-threatening rashes, which can sometimes seriously affect patients' physical, psychological, and social well-being (32, 33). In the current study, patients who developed grade 2 and 3 rash/dermatitis were recorded, and OS was found to be better in patients with skin toxicity. In a previous trial conducted on mCRC patients receiving anti-EGFR mAb treatment, there was determined to be a relationship between the skin inflammatory response associated with the development of skin rash and the efficacy of the treatment (34).

A series of meta-analyses have shown that Panitumumab and Cetuximab mAb therapy in mCRC patients have similar efficacy in terms of OS and PFS, and even the side-effect profiles were similar (35). In the current study, OS was similar in mCRC patients who received Panitumumab and Cetuximab mAb treatment. However, a detail that drew attention was that the OS and PFS of those who received Panitumumab and Bevacizumab mAb treatment at different times were significantly longer than those who received only Cetuximab or Cetuximab and Bevacizumab mAb at different times.

In conclusion, our patients' treatments are planned considering the OS advantage obtained by adding mAb treatments to conventional chemotherapy in mCRC patients that have been followed up in our clinic for the last ten

years. When the retrospective data were evaluated, the distribution of Panitumumab and Cetuximab mAb treatments was seen to be balanced.

Panitumumab and Cetuximab mAb therapy was not preferred for K-RAS mutant patients because of its low contribution to OS and the lack of reimbursement from health insurance. It was noticed that there was no significant difference in terms of efficacy when anti-EGFR mAb therapy was given in the 1st or 2nd lines for mCRC patients. Generally, it was preferred to give it in the first line. Patients who received anti-EGFR mAb treatment had longer OS and PFS duration than those who received anti-VEGF mAb only. It can be said that taking anti-EGFR mAb treatment (being KRAS WT) has a positive effect on prognosis.

Acknowledgment

The authors have no conflict of interests to declare.

Funding

No funding was received from any source for this study.

Authors' contributions

Gulcin SAHINGOZ ERDAL, Ilkay GULTURK, Aykut OZMEN, Mesut YILMAZ, Seher Yıldız TACAR, and Deniz TURAL contributed to the design and implementation of the research, to the analysis of the results and the writing of the manuscript.

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