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Araştırma

Folfiri Plus Panitumumab as the First-Line Treatment in Patients with KRAS Wild-Type Metastatic Colorectal Cencer. A Single Center Experience

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ABSTRACT

Objective: *FOLFIRI is widely used in clinical practice for mCRC patients. Panitumumab is used in patients with KRAS wild-type mCRC.This study investigated the efficacy and safety of first-line panitumumab plus FOLFIRI for patients with KRAS wild-type mCRC.*

Material and Methods: *In our retrospective study, patients with RAS wild-type mCRC were enrolled into the medical oncology department in Okmeydanı Training and Research Hospital, İstanbul, between April 2014 and September 2016.*

Results: *A total of 47 patients were enrolled. The median age was 60 years old (range of 35-78). Twenty-seven patients were male, and 20 were female. The median follow-up was 16.4 months, and the median PFS was 11.6 months. Median OS was 26 months in patients with KRAS wildtype mCRC. In wild-type KRAS and NRAS, mCRC patients' median PFS was 14 months, median OS was 27 months, 90.7% for six-month OS, 82.6% for one-year OS, 82.6% for two-year OS, and 66.1% for three-year OS. The most frequent grade 1/2 toxicities were diarrhea (34.1%), acne-like rash (46.7%), and neutropenia (35.1%). The most frequent grade 3/4 toxicities were diarrhea (7.3%), acne-like rash (6.7%), and neutropenia (11.1%).*

Conclusion: *First-line panitumumab and FOLFIRI was associated with favorable efficacy in patients with RAS WT mCRC and was well tolerated.*

Keywords: *metastatic colorectal cancer, FOLFİRİ, Panitumumab*

ÖZ

RAS Wild Tip Metastatik Kolorektal Kanser Hastalarının İlk Seri Tedavi Olarak Folfiri Panitumumab. Tek Merkez Deneyimi

Amaç: *FOLFİRİ kemoterapi rejimi metastatik kolorektal kanser tedavisinde yaygın şekilde kullanılmaktadır. Panitumumab RAS wild tip metastatik kolorektal kanser tedavisinde kullanılan monoklonal bir antikordur. Bu çalışmada RAS wild tip matastatik kolorektal kanserli hastaların ilk seri tedavisinde FOLFİRİ Panitumumab rejiminin etkinlik ve tolerabilitesini araştırmak istedik.*

Gereç ve Yöntem: *Bu çalışma retrospektif olarak dizayn edildi.İstanbul Okmeydanı eğitim ve araştırma hastanesi onkoloji bölümündeki nisan 2014 ila eylül 2016 tarihleri arasındaki hasta dosya kayıtlarından veriler elde edildi.*

Bulgular: *Toplam 47 hasta alındı. Median yaş 60 (37-78) idi. 27 hasta erkek olup, 20 hasta kadındı. Median takip süresi 16.4 aydı. KRAS wild tip olan kolorektal kanserli hastalarda median PFS 11.6 ay ve median OS 26 aydı. RAS wild tip olan kolorektal kanserli hastalarda median PFS 14 ay ve median OS 27 ay olarak bulundu. 6 aylık OS %90,7, 1 yıllık OS %82,6, 2 yıllık OS %82,6 ve 3 yıllık OS %66,1 olarak bulundu. En sık görülen grade 1/2 yan etkiler ishal %34,1, akne benzeri raş %46,7 ve nötropeni %35,1 olarak tespit edildi. En sık grade 3/4 yan etki olarak ishal %7,3, Akne benzer raş %6,7 ve nötropeni %11,1 bulundu.*

Sonuç: *RAS wild tip metastatik kolorektal kanserli hastaların ilk seri tedavisinde FOLFİR Panitumumab rejimi etkili olduğu tespit edilmiş ve toksisite açısından tolere edilebilir olarak bulunmuştur.*

Anahtar kelimeler: *metastatik kolorektal kanser, FOLFİRİ, Panitumumab*

INTRODUCTION

FOLFIRI (folinic acid, infusional 5-fluorouracil, and irinotecan) is a regimen recommended to be used both as the first- and second-line treatments of metastatic colorectal cancer (mCRC) [(1)]. EGFR inhibitors (panitumumab, cetuximab) are used in combination with the FOLFOX (folinic acid, infusional 5-fluorouracil, and oxaliplatin) and FOLFIRI regimens in the treatment of wildtype KRAS (Kirsten rat sarcoma vi-

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ral oncogene homolog) and NRAS mCRC patients [2]. The combination of EGFR inhibitors (panitumumab, cetuximab) with the FOLFOX or FOLFIRI regimens improved survival in the first- and second-line treatments [2-7]. Initially, the combination of panitumumab and FOLFOX was used in the treatment of mCRC patients, and it was found to be effective without impairing quality of life [8,9]. For the second-line treatment of wild-type RAS mCRC patients, the panitumumab plus FOLFIRI regimen was found to be superior to the FOLFIRI regimen alone regarding the disease-free survival [10]. In a few studies, the FOLFIRI plus panitumumab regimen was used and found to be effective and safe as the firstline treatment of wild-type KRAS mCRC patients [11-13]. Here, we would like to present our single center experience regarding the efficacy and safety of the FOLFIRI plus panitumumab regimen as the first-line treatment in wild-type KRAS mCRC patients.

MATERIALS and METHODS

Wild-type KRAS mCRC patients, who had been followed up in the medical oncology department of Okmeydanı Training and Research Hospital, Istanbul, Turkey between April 2014 and September 2016 were enrolled in this retrospective study. Upon examining their files, patients with a histologically confirmed colon cancer diagnosis, radiologically confirmed metastasis, genetically established KRAS and NRAS status, and a performance status was 0-2 on the ECOG scale were included in the study. KRAS and NRAS analyses were conducted by a real-time polymerase chain reaction (PCR) on DNA extracted from fixed tumor sections. We performed a two-round nested PCR for the amplification of Exons 1, 2, and 3 of KRAS and NRAS genes harboring codons 12, 13, 59, 61, 117, and 146. This was followed by a multiplex minisequencing reaction for the detection of potential mutations. As a first-line treatment, panitumumab (6 mg/kg), FOLFIRI irinotecan (180 mg/m^2), and leucovorin (400 mg/m^2), followed by a 5fluorouracil 400 mg/m^2 bolus and a 2,400-3,000 mg/m^2 continuous infusion] regimen, was administered every 14 days for 6 cycles. Doxycycline 100 mg 2x1 and creams with corticosteroids were used during the chemotherapy along with it to reduce the dermatological side effects of panitumumab. Patients were evaluated with radiological imaging methods every eight weeks according to RECIST1.1 criteria. Objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) durations were calculated. Safety was evaluated in terms of the incidence and severity of adverse events (AEs), using the National Cancer Institute Common Toxicity Criteria version 3.0. SPSS 15.0 for Windows was used for statistical analysis. Descriptive statistics were expressed as mean, standard deviation, minimum, maximum, and median for numerical variables, and they were expressed as numbers and percentages for categorical variables. Since the numerical variables of two independent groups were not normally distributed, they were analyzed with a Mann-Whitney U test. A chi-square test was used for comparisons of ratios in groups. Monte Carlo simulation was applied when the conditions were not met. The survival analyses were made with a Kaplan-Meier analysis. The statistical significance level of alpha was accepted as $p<0.05$.

RESULTS

A total of 47 patients were enrolled in the study. The median age was 60 years (range of 35-78 years). Twenty-seven patients were male, and 20 were fema-

Table 1. Patient characteristics.

		mean±SD	Range (Median)
Age		60.0±9.8	35-78 (60)
		n	**%**
Sex	Female	20	42.6
	Male	27	57.4
Pathology	Adenocarcinoma	45	95.7
	Mucinous	2	4.3
Grade	I	1	2.1
	II	43	91.5
	III	3	6.4
KRAS	Wild	47	100.0
NRAS	Wild	34	72.3
NRAS	unknown	13	27.6
Biopsy location	Primary tumor	44	93.6
	Metastasis	3	6.4
Tumor location	Rectum	17	36.2
	Sigmoid colon	25	53.2
	Transverse colon	1	2.1
	Ascending colon	4	8.5
	Right colon	5	10.6
	Left colon	42	89.4
Metastasis location	Liver	33	70.2
	Peritoneum	4	8.5
	Lung	6	12.8
	bone	2	4.3
	Local mass	1	2.1
	Other	1	2.1

le. From the localization point of view, 42 patients had a tumor in the left colon (89.4%) while five patients had one in the right colon (10.6%). During the follow-up period, 33 patients (70.2%) had liver metastases, six patients (12%) had lung metastases, and four patients (8.5%) had peritoneal metastases (Table 1). The median follow-up duration was 16.4 months. Progression was seen in 36 patients (76.6%) while 11 patients (23.4%) had no progression. Sixteen patients (34%) died during follow-up. After eight weeks of therapy, the evaluation of the response rates indicated that a complete response (CR) was achieved in two patients (4.7%). Thirty-four patients (79.1%) showed a partial response (PR). Four patients had stable disease (SD) (9.3%), and three patients (7%) had progressive disease (PD) (Table 2). The median progression-free survival of wild-type KRAS mCRC patients was 11.6 months (95% confidence interval [CI], 6.3-17.7 months) (Figure 1). The median OS was 26 months (95% CI, 21.7-30.3 months) (Figure 2) with 89.0% six-month, 81.2% one-year, 59.7% two-year, and 37.3% three-year survival (Table 2). PFS was calculated as 14 months both in wild-type KRAS and NRAS mCRC patients (Figure 3). The median OS had not yet been reached (Figure 4). The rate was found to be 90.7% for six-month OS, 82.6% for one-year OS,

Table 2. Respond, PFS, OS, Toxicite rate.

Response to treatement	**%**		
CR	4.7		
PD	79.1		
SD	9.3		
PD	7.0		
KRAS Wild, PFS, OS	months	%95 CI min-max	
Median PFS	11.6	6.3-17.7	
Median OS	26.0	21.7-30.3	
6 months OS	89.0 %		
1 year OS	81.2 %		
2 years OS	59.7 %		
3 years OS	37.3 %		
KRAS and NRAS Wild PFS, OS	months	%95 CI min-max	
Median PFS	14	8.1-19.9	
Median OS	NR		
6 months OS	90.7 %		
1 year OS	82.6 %		
2 years OS	82.6 %		
3 years OS	66.1 %		
Tumor Location	PFS (months)	%95 CI min-max	P value
Right colon	4	0-8.3	0.50
Left colon	13	9.5-16.5	
Tumor Location	OS (months)	%95 CI min-max	P value
Right colon	18	0-48.1	0.066
Left colon	27	23-31	
Toxicity	Grade 1-2	Grade 3-4	
Diarrhea	34.1 %	7.3 %	
Acne like rash	46.7 %	6.7 %	
neutropenia	35.1 %	11.1 %	

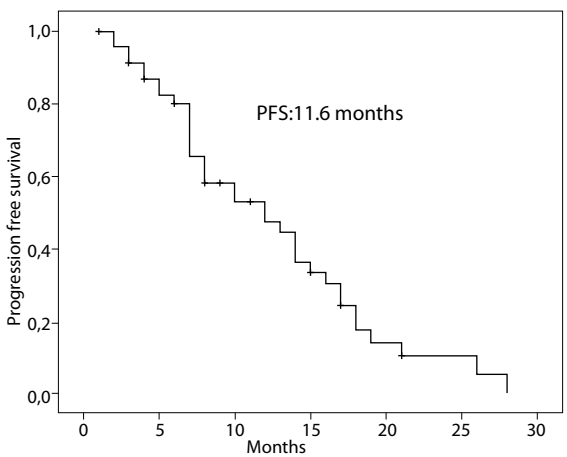

Figure 1. Patients with KRAS wild type mCRC is PFS

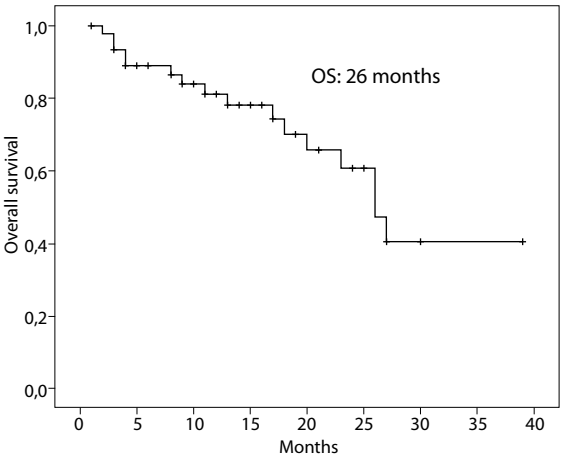

Figure 2. Patients with KRAS wild type mCRC is OS

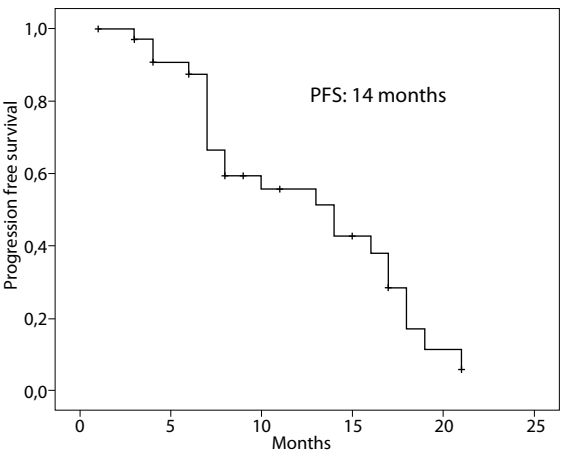

Figure 3. Patients with KRAS and NRAS wild type mCRC is PFS

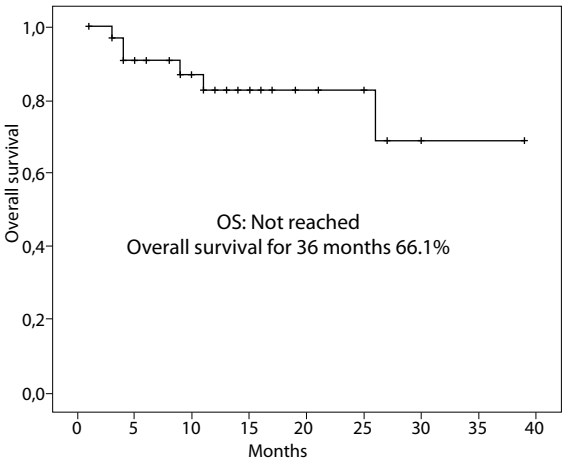

Figure 4. Patients with KRAS and NRAS wild type mCRC is OS

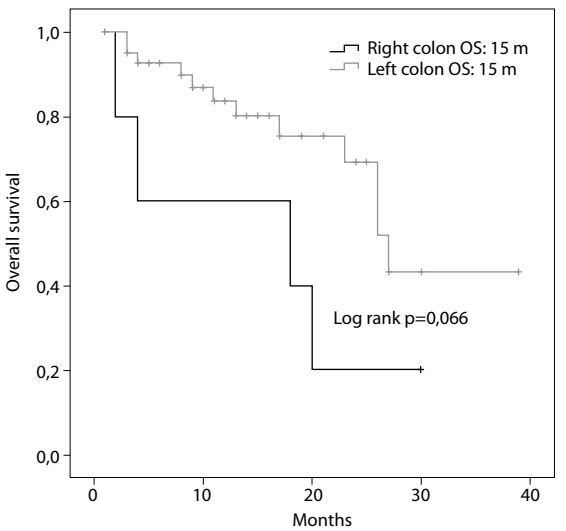

Figure 5. Patients with KRAS wild type mCRC is OS Tumor location

82.6% for two-year OS, and 66.1% for three-year OS (Table 2). The median PFS was four months (95% CI, 0-8.3 months) for patients with a tumor in the right colon. In contrast, it was 13 months for patients with a tumor in the left colon (95% CI, 9.5-16.5 months). The difference was not statistically significant. The median OS was found to be 18 months (95% CI, 0-48.1 months) in patients with a tumor in the right colon and 27 months in patients with a tumor in the left colon (95% CI, 23-31 months) (Table 2) (Figure 5). This difference was also not statistically significant. The assessment of toxicity showed that the most frequent grade 1/2 toxicities were diarrhea (34.1%), acne-like rash (46.7%), and neutropenia (35.1%). Similarly, the most frequent grade 3/4 toxicities were diarrhea (7.3%), acne-like rash (6.7%), and neutropenia (11.1%).

DISCUSSION

While treating patients with mCRC, finding predictive and prognostic markers as well as tailoring the treatment according to these markers has prolonged the survival of the patients [14]. The best known predictive marker for mCRC patients has been KRAS. Recently, searching for NRAS and BRAF mutations in addition to KRAS, arranging the treatment according to mutation status, has increased survival [8]. Panitumumab and cetuximab, which are anti-EGFR drugs, are used in combination with the FOLFIRI and FOLFOX chemotherapy regimens in wild-type KRAS and NRAS mCRC patients. In our study, we evaluated the effect of the combination of panitumumab, an anti EGFR drug, with FOLFIRI chemotherapy on survival. In the PRIME trial, after using panitumumab plus FOLFOX as the first-line treatment, PFS was 9.6 months and OS was 23.9 months in wild-type KRAS patients. In contrast, PFS was 10.1 months and OS was 26 months in wild-type RAS patients (both wild-type KRAS and NRAS) [15]. In the PEAK trial, evaluation of the response rates according to the results of the FOLFOX plus panitumumab administration ended up with 2% CR, 56% PR, 32% SD, 3% PD, and, consequently, 57.8% ORR [8]. In the PEAK trial, after using panitumumab plus FOLFOX as the first-line treatment in mCRC patients, PFS was 10.9 months and OS was 34.2 months in wild-type KRAS patients; PFS was 13.0 months and OS was 41.3 months in wild-type RAS patients (both wild-type KRAS and NRAS) [8]. In the CYRSTAL study that was conducted with cetuximab (another anti-EFGR drug), PFS was found to be 9.9 months and OS was 23.5 months in wild type KRAS patients who received FOLFIRI plus cetuximab; PFS was found to be 11.4 months and OS was 28.4 months in wildtype RAS patients (both wild-type KRAS and NRAS) [15]. In the FIRE 3 trial, PFS of the patients who used FOLFIRI plus cetuximab was 10 months and OS was 28.7 months; PFS in mCRC patients with wildtype RAS was 10.4 months, and OS was 33.1 months [16]. The CAPRIGOIM trail, which is another study, used a FOLFIRI plus cetuximab combination; the median PFS was found to be 11.1 months in wild-type KRAS and NRAS mCRC patients [17].

Our PFS was 11.6 months, and OS was 26 months in wild-type KRAS mCRC patients who received FOLFIRI plus panitumumab. For wild-type KRAS mCRC patients in our study, six-month OS was 89.0%, one-year OS was 81.2%, two-year OS was 59.7%, and three-year OS was 37.3%. OS could not be reached during follow-up duration while PFS was 14 months in wild-type KRAS and NRAS mCRC patients. Our rates of OS were found to be 90.7% for six months, 82.6% for one year, 82.6% for two years, and 66.1% for three years. Our single center results were similar to the studies mentioned above. Moreover, although we used a combination of panitumumab and FOLFOX, our study demonstrated very similar results to the PEAK study. PFS was found to be 13 months in the PEAK study for wild-type NRAS patients, and it was 14 months in our study. OS was found to be 41.3 months in the PEAK study for wild-type NRAS patients; in our study, the mean OS was not reached, and the 36-month overall survival rate was 66.1%. In the first prospective phase 2 trial using a FOLFIRI-panitumumab combination in wildtype KRAS patients, TTP time was found to be 11.2 months by Köhne [10]. In a study by Karthaus, PFS was found to be 11.2 months in wild-type KRAS patients [18]. Furthermore, PFS was found to be 11.6 months for wild-type KRAS patients in our study. Our results were similar to those of Karthaus and Köhne. In our retrospective study, the rate of diarrhea was detected to be 41.4% and that of acne-like rash was 53.3% in all grades. In the study of Köhne, the rate of diarrhea was detected to be 23% and that of dermatological toxicity was 29% [11]. Although our rates seem to be higher than the rates of Köhne's study, other studies observed higher rates of diarrhea and dermatological toxicity [19]. In the PEAK study, serious adverse events were observed in 7% of wild-type KRAS mCRC patients using FOLFOX-panitumumab [8]. In our study, 7.3% diarrhea and 6.7% acne-like rash occurred as grade 3/4 toxicity. Our rate of serious adverse effects was found to be very similar to the results of the PEAK study. In our study, we observed that diarrhea and skin toxicity, which are the most common side effects of the FOLFIRI-panitumumab regimen, could be managed easily with prophylactic precautions (doxycycline 100 mg BID/day as well as creams with antibiotic and corticosteroid) taken at the beginning of chemotherapy. In this study, even though our number of patients was low, we also analyzed the rates of tumor localization, which has recently been a highly discussed topic. In retrospective analyses indicating the tumor localization of the CYRSTAL and FIRESS 3 studies [20,21], PFS was 8.1 months in the right colon patients and 12 months in the left colon patients for those using the FOLFIRI-cetuximab regimen in the CYRSTAL study. Furthermore, in the CYRSTAL study, OS was found to be 18.5 months in the right colon and 28.7 months in the left colon. In the FIRE3 study, for patients receiving FOLFIRI-cetuximab regimen, PFS was found to be 7.6 months in the right colon patients and 10.7 months in the left colon patients; OS was found to be 18.3 months in the right colon patients and 38.3 months in the left colon patients [20,21]. Out of the 47 patients in our study, only five had a tumor in the right colon. PFS was four months for the patients with a tumor in the right colon and 13 months for those with a tumor in the left colon. We found that OS was 18 months in patients with a tumor in the right colon and 27 months for those with a tumor in the left colon. There was no statistically significant difference regarding the tumor localization. We believe that the reason for this was having fewer patients with a tumor in the right colon. For as much as the CYRSTAL and FIRE3 studies that used the combination of cetuximab (which is another anti-EGFR drug) with FOLFIRI, OS was also found to be 18 months in the right colon patients in our study. In the PRIME study that was conducted with the combination of FOLFOX and panitumumab, PFS was 7.5 months and OS was 11.1 months in the right colon patients; PFS was 12.9 months and OS was 30.3 months in the left colon patients [18]. In the PEAK study that used the combination of FOLFOX and panitumumab, PFS was 8.7 months and OS was 17.5 months in the right colon patients whereas PFS was 14.6 months and OS was 43.4 months in the left colon patients [18]. The overall survival rate of our right colon patients, which was 18 months, was found to be consistent with the OS of the right colon patients in the PEAK study, which was 17.5 months.

Conflict of interest

The authors declares that there is no conflict of interest regarding the publication of this paper.

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