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Retrospective comparison of efficacy and safety of CAPOX and FOLFOX regimens as adjuvant treatment in patients with stage III colon cancer

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Abstract

Objective: This study aimed to evaluate the efficacy and safety profile of capecitabine and oxaliplatin (CAPOX) and 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX) regimens as adjuvant treatment in patients with stage III colon cancer.

Methods: A total of 243 patients who received CAPOX and FOLFOX chemotherapy between 2014 and 2018 for stage III colon cancer in two centers were retrospectively studied. Among the patients, 106 (43.6%) and 137 (56.4%) were treated using CAPOX and FOLFOX regimens, respectively. Efficacy, treatment-related side effects, and overall survival rates with these two regimens were compared.

Results: The rate of disease progression was significantly higher in the presence of moderately/poorly differentiated histology, and *KRAS* and *NRAS* mutations. An increased number of metastatic lymph nodes and prolonged time from surgery to chemotherapy significantly increased disease progression. Patients who received CAPOX were significantly older than those who received FOLFOX. Disease progression, metastasis, and mortality rates were significantly higher in the FOLFOX arm than in the CAPOX arm. There was no significant difference in the overall survival rate between the two regimens.

Conclusion: The CAPOX regimen is preferred in older patients. Disease progression, metastasis, and mortality rates are higher with FOLFOX than with CAPOX.

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Introduction

Colorectal cancer is among the most common cancer worldwide and the third most frequent cause of cancer-related mortality. Currently, cancer statistics of Turkey are almost compatible with global data.[1] A study from Turkey on colorectal cancer epidemiology with the largest group of patients (n = 968) was published by the Turkish Oncology Group in 2015.[2] However, treatment and survival outcomes of these patients were not evaluated in this previous study.

Surgery is the mainstay of treatment of colorectal cancer. However, 5-year disease-free survival (DFS) is unfortunately approximately 49% in stage III cancer, despite recent advances in modern surgical techniques and treatment modalities. The 5-fluorouracil-based chemotherapy regimen has been used for treating high-risk stage II, stage III, and stage IV cases for almost 2 decades.[3] Ten years previously, the addition of oxaliplatin to fluorouracil-folinic acid in patients with stage III colon cancer was named the FOLFOX (5-fluorouracil, leucovorin, and oxaliplatin) regimen. This regimen was shown to be advantageous for progression-free survival and overall survival (OS) compared with the regimen without oxaliplatin.[4] Subsequently, a combination of capecitabine, which is a fluoropyrimidine analog, and oxaliplatin was used in stage III cancer and was found to be non-inferior to the FOLFOX combination.[5,6] Currently, capecitabine and oxaliplatin (CAPOX) and FOLFOX protocols are considered to be equivalent in adjuvant treatment of stage III cases.[5–7] There has been particular interest in the CAPOX protocol because of the absence of requirement of a vascular port or hospitalization and findings suggesting that CAPOX is more cost-effective compared with the FOLFOX regimen.[7] However, no prospective, randomized studies have compared these two protocols in a head-to-head fashion in terms of efficacy, safety, and survival rates.

Therefore, in the present study, we aimed to compare the efficacy, treatment-related side effects, and survival rates of the FOLFOX and CAPOX regimens in patients with stage III colon cancer.

Material and methods

Data of patients who were followed at the Medical Oncology Units of the hospitals of Mugla Sitki Kocman University and Pamukkale University, and received adjuvant CAPOX and FOLFOX chemotherapy between January 2014 and January 2018 for stage III colon cancer were retrospectively analyzed. Written informed consent was obtained from each patient. The study protocol was approved by the Non-Interventional Research Ethics Board of Pamukkale University (approval date: 04/04/2018; no. 23479). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Inclusion criteria were the presence of stage III colon cancer and receiving the first-line treatment of CAPOX or FOLFOX. Exclusion criteria included metastatic disease at the time of diagnosis,

coexisting rectal cancer, and administration of adjuvant chemotherapy in an external center.

Age at the time of diagnosis, Eastern Cooperative Oncology Group performance status, smoking status and alcohol use, comorbidities (including diabetes mellitus, hypertension, and coronary artery disease), prior elective or emergency surgery, localization of the tumor in the colon, T stage according to the American Joint Committee on Cancer classification,[8] the number of excised lymph nodes, the number of involved lymph nodes (N stage), chemotherapy protocols selected, the number of previous chemotherapy cycles, time from surgery to chemotherapy, the number of adjuvant chemotherapies, disease progression, OS and progression-free survival rates, and chemotherapy-related side effects as assessed by the Common Terminology Criteria for Adverse Events version 4[9] were recorded.

The modified FOLFOX-6 regimen was used in this study. This protocol was composed of intravenous oxaliplatin at a dose of 85 mg/m^2, intravenous leucovorin infusion at a dose of 400 mg/m^2, and intravenous bolus 5-fluorouracil and continuous infusion of 5-fluorouracil for 46 hours at a dose of 2400 mg/m^2 for 12 cycles once every 2 weeks. The CAPOX regimen was composed of intravenous oxaliplatin at a dose of 130 mg/m^2 on the first day and oral capecitabine at a dose of 1000 mg/m^2 every 12 hours on Days 1 and 14. This protocol was applied every 21 days for six to eight cycles.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) version 22.0 software (IBM Corp., Armonk, NY, USA). Descriptive data are expressed as mean, median, and percentages. The Student's t-test for continuous variables and Fisher's exact test for categorical variables were used. The Kaplan–Meier method was carried out to evaluate survival of the patients and the log-rank test was used for survival curves. OS and DFS were evaluated using the multivariate Cox proportional hazard model. A p value of $\leq$ 0.05 was considered statistically significant.

Results

Of the 243 patients included in the study, 146 (60.1%) were men and 97 (39.9%) were women. The mean age at the time of diagnosis was 61.7 years (range, 32–78 years). Demographic and clinical characteristics of the patients are shown in Table 1.

Histopathological properties of the patients and mutations are presented in Table 2. Only a limited amount of mutation

Table 1. Demographic and clinical characteristics of the patients.

	Number	%
Age (years)		
≤64	146	60.1
≥65	97	39.9
Sex		
Male	146	60.1
Female	97	39.9
Smoking		
No	147	60.5
Ex-smoker	89	36.6
Smoker	7	2.9
Alcohol		
No	231	95.1
Yes	12	4.9
Diabetes mellitus		
No	206	84.8
Yes	37	15.2
Hypertension		
No	129	53.1
Yes	114	46.9
Coronary artery disease		
No	231	95.1
yes	12	4.9

Table 2. Histopathological properties and mutations of patients.

	Number	%
Type of operation		
Elective	209	86.0
Urgent	34	14.0
Tumor side		
Right	93	38.3
Left	150	61.7
Differentiation		
Good	16	6.6
Moderate	85	35.0
Poor	142	58.4
Lymphovascular invasion		
No	76	31.3
Yes	167	68.7
Perineural invasion		
No	155	63.8
Yes	88	36.2
KRAS mutation		
No	49	40.8
Yes	71	59.2
NRAS mutation		
No	47	63.5
Yes	27	36.5
BRAF mutation		
No	53	60.9
Yes	34	39.1

data from patients who had stage III disease at the time of the diagnosis were able to be obtained. This is because mutation analyses of *KRAS*, *NRAS*, and *BRAF* were often evaluated following the development of progression.

Among the patients, 106 (43.6%) and 137 (56.4%) were treated with the CAPOX and FOLFOX regimens, respectively. Anthropometric data before chemotherapy according to the regimens are shown in Table 3. Patients who received CAPOX were significantly older than those who received FOLFOX ($p = 0.036$).

The effects of genetic mutations, type of surgery, location of involvement of the colon, and the degree of histological differentiation are shown in Table 4. Disease progression was significantly higher in patients with a *KRAS* mutation, an *NRAS* mutation, and moderately/poorly differentiated cases ($p = 0.05$, $p = 0.023$, and $p = 0.002$, respectively). Additionally, an increased number of metastatic lymph nodes and prolonged time from surgery to chemotherapy were significantly associated with disease progression ($p = 0.0001$ and $p = 0.02$, respectively).

Adverse events were evaluated using the Common Terminology Criteria for Adverse Events version 4 v4.03.[9] No Grade 4 adverse events were observed in any of the patients. Patients who experienced no adverse events were grouped in one arm and those with Grades 1 to 3 adverse events were grouped in another arm. Adverse events secondary to CAPOX and FOLFOX regimens are shown in Table 5. The frequency of dose reduction of chemotherapy and the rate of treatment discontinuation were higher in the CAPOX arm than in the FOLFOX arm ($p = 0.02$ and $p = 0.007$, respectively). Hand-foot syndrome was significantly more common in the CAPOX arm than in the FOLFOX arm ($p = 0.008$).

The effects of the applied chemotherapy protocols on disease progression, development of metastasis, and the final health condition of patients with stage III colon cancer are shown in Table 6. Disease progression, development of metastasis, and the mortality rate of patients were significantly higher in the FOLFOX arm than in the CAPOX arm ($p = 0.016$, $p = 0.001$, $p = 0.007$, respectively).

OS in high-risk patients for disease progression (TNM T4-N2-N3) was significantly shorter compared with that in low-risk patients (TNM T1-T2-T3-N1) ($p = 0.006$, Table 7). There was no significant difference in OS between the CAPOX and FOLFOX arms (Figure 1). Therefore, none of the chemotherapy regimens was superior to another in terms of OS in subgroup analyses.

Table 3. Anthropometric data before chemotherapy according to the regimens.

	Mean ± standard deviation	Median (minimum – maximum)	P
Height (cm)			
CAPOX (n = 106)	163.73 ± 8.91	164 (136 – 178)	0.142
FOLFOX (n = 137)	166.85 ± 9.34	168 (139 – 196)	
Weight (kg)			
CAPOX (n = 106)	72.5 ± 12.8	70.5 (45 – 99)	0.645
FOLFOX (n = 137)	73.25 ± 12.36	71.5 (38 – 120)	
BMI (kg/m^2)			
CAPOX (n=106)	27.06 ± 4.47	26.75 (17.78 – 43.16)	0.196
FOLFOX (n = 137)	26.34 ± 4.14	26.1 (12.87 – 42.02)	
BSA (m^2)			
CAPOX (n = 106)	1.77 ± 0.18	1.79 (1.32 – 2.1)	0.335
FOLFOX (n = 137)	1.79 ± 0.16	1.8 (1.21 – 2.1)	
Age (years)			
CAPOX (n = 106)	63.37 ± 10.15	64 (39 – 83)	0.036
FOLFOX (n = 137)	60.39 ± 9.72	62 (34 – 81)	
Operation to chemotherapy (days)			
CAPOX (n = 106)	45.6 ± 24.4	43 (13 – 229)	0.602
FOLFOX (n = 137)	46.46 ± 21.69	44 (15 – 188)	

CAPOX: capecitabine and oxaliplatin; FOLFOX: 5-fluorouracil, leucovorin, and oxaliplatin; BMI: body mass index; BSA: body surface area.

Discussion

Currently, the prognosis of colon cancer is best defined by the American Joint Committee on Cancer classification.[8] Consistent with previous findings,[8] disease progression was significantly higher in patients with a higher number of metastatic lymph nodes and high-risk patients (T4-N2-N3) in our study. Additionally, we found a negative effect of poor histological differentiation and the presence of *KRAS*/*NRAS* mutations on disease progression. In the Multicenter International Study of Oxaliplatin/5-Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial, addition of oxaliplatin to fluorouracil and leucovorin increased 5-year progression-free survival from 67.4% to 73.3% and 6-year OS from 76% to 78.5%.[4] Increased survival and a decreased mortality rate were achieved with adjuvant chemotherapy in patients with locally advanced (stage III) colon cancer.

An adjuvant treatment alternative in stage III patients is the CAPOX regimen. This regimen consists of intravenous oxaliplatin and capecitabine, which is an oral prodrug. Capecitabine is metabolized in the liver and reduced to 5-fluorouracil. Hospitalization of patients for 48 hours or placement of a subcutaneous vascular port is unnecessary because the CAPOX regimen contains no continuous infusion treatment. In a study by Aitini et al.[7], the CAPOX regimen was more cost-effective compared with the FOLFOX regimen, as the adjuvant treatment of colon cancer. Therefore, the CAPOX regimen is primarily preferred in clinical practice. The use of capecitabine was also found to be non-inferior to 5-fluorouracil and folinic acid combination in the X-ACT study.[5] Additionally, similar results were obtained with the CAPOX and FOLFOX treatment regimens in the

Table 4. Effects of genetic mutations, type of surgery, location of involvement, and the degree of histological differentiation.

	Progression		
	No	Yes	P
KRAS			
Wild	23 (52.27%)	26 (34.21%)	0.05
Mutant	21 (47.73%)	50 (65.79%)	
NRAS			
Wild	21 (80.77%)	26 (54.17%)	0.023
Mutant	5 (19.23%)	22 (45.83%)	
BRAF			
Wild	21 (70%)	32 (56.1%)	0.208
Mutant	9 (30%)	25 (43.9%)	
Operation			
Elective	136 (87.18%)	73 (83.91%)	0.481
Urgent	20 (12.82%)	14 (16.09%)	
Tumor side			
Right	59 (37.82%)	34 (39.08%)	0.846
Left	97 (62.18%)	53 (60.92%)	
Differentiation			
Good	10 (6.41%)	6 (6.9%)	0.002
Moderate	67 (42.95%)	18 (20.69%)	
Poor	79 (50.64%)	63 (72.41%)	
Operation to chemotherapy (days)	44.57 ± 23.51	48.8 ± 21.53	0.022
Total lymph nodes (n)	14.8 ± 5.9	15.9 ± 5.7	0.143
Metastatic lymph nodes (n)	2.5 ± 3	3.3 ± 2.88	0.0001

NO169968 study.[6] Although both combined chemotherapy regimens appear to have a similar efficacy profile, there has been no head-to-head prospective, randomized study that compared the two protocols in terms of efficacy, safety, and survival rates in the literature.

In a meta-analysis, Des Guetz et al.[10] showed that a delayed time from surgery to the initiation of chemotherapy (longer than 8 weeks) decreased the OS rate in patients with stage III colorectal cancer. In the present study, we found no significant difference in the time from surgery to initiation of either chemotherapy regimen, which is inconsistent with previous findings.[11] However, when the total patient group was considered, a delay in treatment caused a significant increase in the rate of disease progression.

The CAPOX regimen is preferred in patients with comorbid coronary artery disease. Additionally, the CAPOX regimen is mostly used in young patients,[12] although this regimen was used more often in older patients in our study. In our study, the CAPOX regimen was predominantly used in older patients because of existing comorbidities, which may develop secondary to vascular port intervention in this patient population and there is a risk of development of nosocomial infections secondary to hospitalization for fluorouracil infusion treatment. Sara et al.[13] also reported an increased incidence of coronary vasospasm, chest pain, angina, and myocardial

Table 5. Adverse events secondary to CAPOX and FOLFOX regimens.

	Chemotherapy		
	CAPOX, n (%)	FOLFOX, n (%)	P
Neutropenia			
No	54 (50.94)	74 (54.01)	0.634
Yes	52 (49.06)	63 (45.99)	
Thrombocytopenia			
No	75 (70.75)	104 (75.91)	0.365
Yes	31 (29.25)	33 (24.09)	
Anemia			
No	70 (66.04)	100 (72.99)	0.241
Yes	36 (33.96)	37 (27.01)	
Neuropathy			
No	72 (67.92)	103 (75.18)	0.211
Yes	34 (32.08)	34 (24.82)	
Hepatotoxicity			
No	103 (97.17)	130 (94.89)	0.52
Yes	3 (2.83)	7 (5.11)	
Hand-foot syndrome			
No	90 (84.91)	130 (94.89)	0.008
Yes	16 (15.09)	7 (5.11)	
Diarrhea			
No	58 (54.72)	80 (58.39)	0.566
Yes	48 (45.28)	57 (41.61)	
Dose reduction of chemotherapy			
No	87 (82.08)	126 (91.97)	0.02
Yes	19 (17.92)	11 (8.03)	
Discontinuation of chemotherapy			
No	95 (89.62)	134 (97.81)	0.007
Yes	11 (10.38)	3 (2.19)	

CAPOX: capecitabine and oxaliplatin; FOLFOX: 5-fluorouracil, leucovorin, and oxaliplatin.

infarction during fluorouracil bolus and continuous infusion compared with oral capecitabine use. We administered CAPOX in patients who were diagnosed with coronary artery disease to avoid the risk of cardiotoxicity.

The adverse event profile of the CAPOX and FOLFOX regimens is different among previous studies. Mamo et al.[14] reported that nausea, diarrhea, neutropenia, and peripheral sensorial neuropathy were more frequent in the FOLFOX arm than in the CAPOX arm. However, Loree et al.[15] found that mucositis and neutropenia in the FOLFOX arm and diarrhea and hand-foot syndrome in the CAPOX arm were more frequent. In our study, hand-foot syndrome was significantly more common in the CAPOX arm than in the FOLFOX arm. However, the rate of myelotoxic side effects, such as neutropenia, and other side effects (nausea, diarrhea, mucositis, neuropathy) were similar in both arms.

Table 6. Effects of chemotherapy protocols on disease progression, development of metastasis, and mortality rate.

	Chemotherapy		
	CAPOX, n (%)	FOLFOX, n (%)	P
Progression			
No	77 (72.64)	79 (57.66)	0.016
Yes	29 (27.36)	58 (42.34)	
Final status			
Alive	89 (83.96)	88 (64.23)	0.001
Dead	17 (16.04)	49 (35.77)	
Metastasis			
No	78 (73.58)	78 (56.93)	0.007
Yes	28 (26.42)	59 (43.07)	

CAPOX: capecitabine and oxaliplatin; FOLFOX: 5-fluorouracil, leucovorin, and oxaliplatin.

Loree et al.[11] found that DFS was significantly higher in the CAPOX arm than in the FOLFOX arm in their first retrospective study that included 176 patients. These authors also reported a significantly higher DFS with CAPOX in their subsequent study that included 394 patients.[15] However, there was no significant difference in the OS rate between the two studies. In our study, development of disease progression, development of metastasis, and the rate of mortality were higher in the FOLFOX arm than in the CAPOX arm. However, we found no significant difference in the OS rate between the CAPOX and FOLFOX arms.

Limitations of the present study include its retrospective nature, short duration

Table 7. Overall survival according to risk groups.

	Alive, n (%)	Dead, n (%)	Mean	Standard deviation	95% CI	P
T4-N2-N3	31 (62)	19 (38)	68.930	6.900	55.410–82.460	0.006
T1-T2-T3-N1	146 (76)	47 (24)	105.780	4.800	96.360–115.190	

CI: confidence interval.

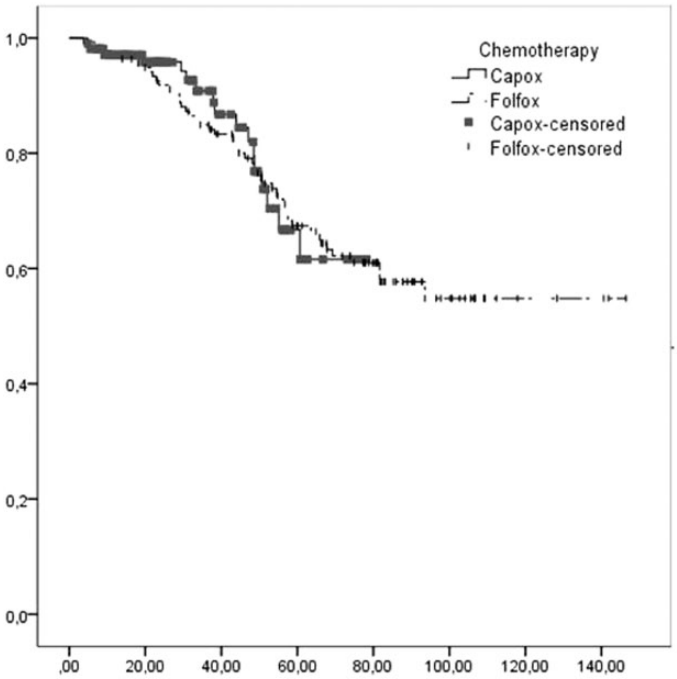

Figure 1. Kaplan–Meier overall survival curve according to chemotherapy.

of follow-up, and the low rate of expected events.

Conclusion

In this study, we used a real-life experience to describe baseline characteristics, the operation to chemotherapy interval, toxicity, and effect of FOLFOX and CAPOX on clinical outcomes in patients treated with either FOLFOX or CAPOX in the adjuvant setting in two different institutional practices in the western Anatolia region. The CAPOX regimen was preferred in older patients. Disease progression, metastasis, and the mortality rate were higher in the FOLFOX arm than in the CAPOX arm.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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