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Results of Adjuvant FOLFOX Regimens in Stage III Colorectal Cancer Patients: Retrospective Analysis of 667 Patients

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Key Words
Colorectal adenocarcinoma · Adjuvant · Oxaliplatin

Abstract
Objective: The aim of this study was to assess the use of 5-fluorouracil (5-FU), leucovorin and oxaliplatin (FOLFOX) regimens in clinical practice according to their efficacy and toxicity. ***Methods:*** Patients who received oxaliplatin-containing regimens after curative resection for colorectal carcinoma from 10 different oncology centers between May 2004 and December 2009 were included in the study. All patients were treated with FOLFOX regimens. Patients with rectal carcinoma were also treated with chemoradiotherapy with 5-FU after 2 cycles of a FOLFOX regimen. ***Results:*** The median age of the patients was 56 years (range 17–78). Of the total 667 patients, 326 were given FOLFOX-4, 232 were given modified FOLFOX-4 and 109 were given FOLFOX-6. The distribution according to disease stage was 33 patients with stage IIIA colorectal cancer, 382 patients with stage IIIB and 252 patients with stage IIIC. The most common adverse events were neutropenia (54%), nausea (36.9%), neuropathy (38.2%) and anemia (33.1%) for all grades. The median follow-up time was 23 months (range 1–79). Three-year disease-free survival and overall survival were 65 and 85.7%, respectively. ***Conclusion:*** The different oxaliplatin-containing 5-FU-based adjuvant chemotherapy regimens in patients with stage III colorectal cancer seemed to be at least equal in terms of efficacy regardless of the method of 5-FU administration or oxaliplatin dose.

Introduction

Colorectal cancer is the fifth leading cause of cancer death worldwide [1]. Worldwide, colorectal cancer accounted for approximately 1.2 million new cancer cases

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in 2008 [2, 3]. Surgical resection is the only curative treatment for locoregional disease, but 40–50% of patients have recurrences and or metastasis and die of metastatic disease [4].

The benefits of 5-fluorouracil (5-FU)-based adjuvant chemotherapy in reducing recurrence and prolonging survival are well established, especially for stage III disease, and this has become the standard of care worldwide [5–10]. The Intergroup Trial INT-0035 was the first important study and demonstrated that postoperative adjuvant treatment with 5-FU and levamisole reduced the mortality rate by 33% among stage III colon cancer cases [5]. Subsequently, a 5-FU and leucovorin (LV) combination became the standard of care in this group of patients [6, 7, 11].

The Multicenter International Study of Oxaliplatin/5-FU/LV in the Adjuvant Treatment of Colon Cancer (MOSAIC) trial revealed that adding oxaliplatin to infusional 5-FU and LV (FOLFOX-4) produced significant improvement in 3-year disease-free survival (DFS) compared with the same regimen of 5-FU and LV administered alone [10]. Based on the results of this trial, the US Food and Drug Administration approved the FOLFOX-4 regimen for postoperative adjuvant therapy in patients with stage III colon cancer.

The aim of this study is to assess the efficacy and toxicity of various FOLFOX regimens in stage III colorectal cancer in clinical practice.

Patients and Methods

Patients who received oxaliplatin-containing regimens after curative resection of colon and rectal cancer from 10 different oncology centers in Turkey between May 2004 and December 2009 formed the patient population. Patients with stage II disease and those who had received neoadjuvant chemotherapy were excluded. All of the patients had stage III colorectal cancer. Data were collected from medical records and daily observation notes of nurses. Local ethical committee approval was obtained.

A jugular venous titanium port catheter was inserted in each patient. Patients were treated with three different oxaliplatin-containing regimens. The FOLFOX-4 regimen consisted of 85 mg/m^2 oxaliplatin on day 1 and 200 mg/m^2 LV, followed by a bolus of 400 mg/m^2 5-FU and then a 22-hour infusion of 600 mg/m^2 5-FU given on 2 consecutive days every 14 days. The modified FOLFOX-4 (mFOLFOX-4) regimen consisted of 85 mg/m^2 oxaliplatin on day 1 and 200 mg/m^2 LV, followed by a bolus of 400 mg/m^2 5-FU on day 1 and then a 46-hour infusion of 1,600 mg/m^2 5-FU given every 14 days. The FOLFOX-6 regimen consisted of 100 mg/m^2 oxaliplatin on day 1 and 400 mg/m^2 LV, followed by a bolus of 400 mg/m^2 5-FU on day 1 and then a 46-hour infusion of 2,400 mg/m^2 5-FU given every 14 days. In rectal cancer patients, after 2 cycles of chemotherapy, 50.4 Gy (28 fractions of 1.8 Gy) of chemoradiotherapy was given as parallel anteroposterior/posteroanterior administration on the tumor bed and regional lymphatics as well as a concurrent continuous infusion of 225 mg/m^2/day 5-FU. After completion of chemoradiotherapy 6, more chemotherapy cycles were given.

Disease stage was assessed according to the American Joint Committee on Cancer tumor-node-metastasis system 2010 classification, and toxicity was determined according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.0.

DFS was considered to be the time from the first cycle of chemotherapy to the last visit, relapse or death, and overall survival (OS) was determined by the time from the first cycle of chemotherapy to the last visit or death, and both were expressed in months. Survival data of patients were updated in June 2010 and were assessed retrospectively. SPSS 13.0 for Windows was used for statistical analysis. Survival rates were calculated according to the Kaplan-Meier method.

Results

Patient Characteristics

A total of 667 patients were included in the study. Three hundred and eighty-seven of the patients (58%) were male. The median age of the patients was 56 years (range 17–78). Some characteristics of the patients are presented in table 1. All of the patients had stage III disease. Most of the patients (82.9%) were stage IIIB or IIIC. Forty percent of the patients had rectal carcinoma. Abdominoperineal resection was performed in 9% of the patients (n = 60) and low anterior resection in the rest of the rectal cancer patients. One hundred and sixteen (15.9%) and 16 patients (2.4%) had obstruction and perforation findings at diagnosis, respectively.

Twenty-two patients (3.3%) had pathological positive margins. Thirteen of them (1.9%) had rectal tumors. Lymphatic invasion was present in 197 patients (29.5%) and vascular invasion in 191 (28.6%).

A total of 6,667 cycles of chemotherapy were given. The median number of chemotherapy cycles was 12 (range 1–12). Median numbers of FOLFOX-4, mFOLFOX-4 and FOLFOX-6 cycles were 12, 8 and 12, respectively. Cumulative median doses of oxaliplatin were 1,020 mg/m^2 in FOLFOX-4-treated patients, 680 mg/m^2 in mFOLFOX-4-treated patients and 1,200 mg/m^2 in FOLFOX-6-treated patients. Two hundred and fifty-three patients received chemoradiotherapy. One hundred and sixty-five patients received chemoradiotherapy as a continuous 5-FU infusion, while 97 patients received bolus 5-FU after 2 cycles of chemotherapy.

Table 1. Some characteristics of the patients

Characteristic	
Total patients	667
Median age (range), years	56 (17–78)
Sex	
Male	387 (58)
Female	280 (42)
ECOG performance status	
0	289 (43.3)
1	346 (51.9)
2	32 (4.8)
Tumor localization	
Rectum	270 (40.5)
Colon	397 (59.5)
Histologic appearance	
Well differentiated	177 (26.5)
Moderately differentiated	343 (51.4)
Poorly differentiated	102 (15.4)
Unknown/data missing	45 (6.7)
Lymphovascular invasion	197 (29.5)
Positive surgical margin	22 (3.3)
Bowel obstruction	106 (15.9)
Perforation	16 (2.4)
Primary tumor	
T1	0
T2	38 (5.7)
T3	540 (81)
T4	89 (13.3)
Median number of harvested lymph nodes (range)	14 (0–86)
Regional lymph nodes	
N1	415 (62.2)
N2	252 (37.8)
Disease stage	
IIIA	33 (4.9)
IIIB	382 (57.3)
IIIC	252 (37.8)
Chemotherapy	
FOLFOX-4	326 (48.9)
mFOLFOX-4	232 (34.8)
FOLFOX-6	109 (16.3)
Radiotherapy	
Yes	253 (37.9)
No	414 (62.1)

Figures represent number of patients (percentage), except where indicated otherwise.
ECOG = Eastern Cooperative Oncology Group.

Toxicity

Generally, treatment was well tolerated, and there were no treatment-related deaths. Most of the adverse events were mild (table 2). Dose reduction was necessary in 131 patients (19.6%) and cycle delay in 239 (35.8%). The most common adverse events were neutropenia (54%), nausea (36.9%), neuropathy (38.2%) and anemia (33.1%).

Table 2. Adverse events due to treatment

Toxicity	Grade I/II	Grade III/IV	All grades
Neutropenia	164 (24.6)	196 (29.4)	360 (54.0)
Anemia	214 (32.1)	7 (1.0)	221 (33.1)
Thrombocytopenia	126 (18.9)	13 (1.9)	139 (20.8)
Nausea	229 (34.3)	17 (2.5)	246 (36.9)
Vomiting	183 (27.4)	11 (1.6)	194 (29.1)
Neuropathy	239 (35.8)	16 (2.4)	255 (38.2)
Diarrhea	168 (25.2)	41 (6.1)	209 (31.3)
Febrile neutropenia	–	18 (2.7)	18 (2.7)
Nephrotoxicity	4 (0.6)	2 (0.3)	6 (0.9)
Hepatotoxicity	14 (2.1)	–	14 (2.1)
Cardiac toxicity	–	5 (0.7)	5 (0.7)
Venous thrombosis	–	2 (0.3)	2 (0.3)

Figures represent number of events (percentage). Adverse events were determined according to the Common Terminology Criteria for Adverse Events, version 3.0.

The most common grade 3 or 4 toxicities were neutropenia (29.4%) and diarrhea (6.1%).

Efficacy

The median follow-up time was 23 months (range 1–79). Median DFS and OS was not reached. One hundred and sixty-nine patients relapsed (25.3%) and 70 patients (10.5%) died. Three-year DFS and OS were 65 and 85.7%, respectively. While sex, age, grade, tumor localization, nodal involvement, presence of obstruction and perforation had no statistical effect on DFS, Eastern Cooperative Oncology Group performance status, depth of invasion, stage, chemotherapy regimen, lymphovascular invasion and histopathological subtype did statistically affect DFS (table 3).

OS was statistically affected by stage, lymph node status, grade and tumor localization.

In multivariate Cox regression analyses, the only prognostic factor that affected DFS was disease stage [hazard ratio (HR) 1.8, 95% confidence interval (CI) 1.03–3.34; p = 0.038]. Factors that affected OS in our patients were disease stage (HR 2.7, 95% CI 1.13–6.66; p = 0.026) and tumor grade (HR 2.6, 95% CI 1.3–5.2; p = 0.005; table 4).

Discussion

The standard adjuvant treatment for lymph node-positive colon carcinoma is an oxaliplatin-based regimen [10]. FOLFOX regimens are efficiently used in clinical

Table 3. Parameters that statistically affected DFS and OS

	n	3-year DFS	p	3-year OS	p
Total patients	667 (100)	65%	–	85.7%	–
ECOG performance status					
0	289 (43.3)	70.3%	0.042	87.0%	0.20
1	346 (51.9)	63.1%		86.0%	
2	32 (4.8)	42.0%		68.0%	
Depth of invasion					
T2	38 (5.7)	84.4%	0.005	90.2%	0.41
T3	540 (81)	65.7%		86.5%	
T4	89 (13.3)	56.4%		82.9%	
Stage					
IIIA	33 (4.9)	68.2%	0.03	91.5%	0.001
IIIB	382 (57.3)	67.8%		90.0%	
IIIC	252 (37.8)	61.6%		78.1%	
Chemotherapy					
FOLFOX-4	326 (48.9)	59.3%	0.005	85.6%	0.42
mFOLFOX-4	232 (34.8)	65.6%		84.3%	
FOLFOX-6	109 (16.3)	80.4%		93.5%	
Lymphovascular invasion					
Yes	197 (29.5)	56.8%	0.030	82.6%	0.31
No	470 (70.5)	71.4%		87.2%	
Surgical margin					
Positive	22 (3.2)	49.1%	0.22	75.0%	0.13
Negative	645 (96.8)	68.6%		86.2%	
Perforation					
Yes	16 (2.4)	68.8%	0.97	85.0%	0.62
No	651 (97.6)	65.0%		85.7%	
Obstruction					
Yes	106 (15.9)	59.3	0.10	83.4%	0.87
No	561 (84.1)	66.8		85.9%	
Grade					
I	177 (26.5)	68.8%	0.29	89.7%	0.003
II	343 (51.4)	64.8%		88.6%	
III	102 (15.4)	64.2%		72.4%	
UN/M	45 (6.7)	–		–	
Histopathology					
Adenocarcinoma	571 (85.6)	66.1%	0.047	87.7%	0.12
Mucinous	71 (10.6)	56.9%		77.6%	
Signet ring cell	25 (3.8)	63.7%		74.7%	
Lymph nodes					
N1	415 (62.2)	66.8%	0.090	88.3%	0.042
N2	252 (37.8)	63.6%		81.3%	
Tumor localization					
Rectum	270 (40.5)	60.8%	0.15	80.7%	0.013
Colon	397 (59.5)	68.0%		89.4%	

Figures in parentheses represent percentages. ECOG = Eastern Cooperative Oncology Group; UN/M = unknown/missing.

Table 4. Multivariate analysis of factors that affected DFS and OS

		HR	p
Factors affecting DFS[1]			
Stage	I	1	–
	II	0.9 (0.50–1.67)	0.78
	III	1.8 (1.03–3.34)	0.038
Factors affecting OS[2]			
Stage	I	1	–
	II	1.2 (0.41–3.99)	0.66
	III	2.7 (1.13–6.66)	0.026
Grade	I	1	–
	II	1.0 (0.44–2.33)	0.97
	III	2.6 (1.32–5.21)	0.005

Figures in parentheses represent 95% CIs.
[1] Eastern Cooperative Oncology Group performance status, depth of invasion, stage, chemotherapy regimen, lymphovascular invasion and histopathology were included in the Cox regression analysis for DFS.
[2] Stage, lymph node stage, tumor grade and tumor localization were included in the Cox regression analysis for OS.

practice. In our study groups, FOLFOX regimens were found to be effective and safe.

Most of the clinical trials had better outcomes than those in clinical practice. Our findings were similar to the results of the MOSAIC and National Surgical Adjuvant Breast and Bowel Project (NSABP) C-07 trials, but the treatment was well tolerated in our clinical setting [10, 12].

In the MOSAIC trial, at a median follow-up of 82 months, 5-year DFS (the primary endpoint) was significantly higher with FOLFOX (73 vs. 67%). In addition, 6-year OS rates were also significantly higher, both in the entire group (79 vs. 76%; HR 0.84; p = 0.046) and in those patients with stage III disease (73 vs. 69%; HR 0.80; p = 0.023), but not in those with stage II disease [10, 13]. In the NSABP C-07 study, 3-year DFS was 76.1% for both stage II and III patients [12]. In our study group, 3-year DFS and OS were 65 and 86.2%, respectively. Our study group had worse prognostic parameters than the patients in previous studies. While 15% of the patients in the MOSAIC study were N2, this rate was 37.8% in our population. Our patients also had more poorly differentiated disease (12.6 vs. 15.4%). While we had 40.5% of patients with rectal cancer, this rate was 33% in the NSABP C-07 trial and there were no rectal cancer patients in the MOSAIC study.

In the MOSAIC trial, grade 3 or 4 neutropenia (41.1%) and grade 3 or 4 diarrhea (10.8%) were reported in the FOLFOX-treated arm [10]. Although some form of peripheral neuropathy developed in 92% of patients receiving FOLFOX, it was severe (grade 3) in only 13% and gen-

erally reversible. The toxicity profile in our population was better than in the published studies of oxaliplatin-containing regimens. The most common grade 3 or 4 toxicities in our study were neutropenia (29.4%) and diarrhea (6.1%). The incidences of grade 3 or 4 nausea and neurotoxicity were 2.5 and 2.4%, respectively. These findings might be related to our retrospective study design.

Orally active fluoropyrimidines such as capecitabine have also been tested in an adjuvant setting. Capecitabine plus oxaliplatin (XELOX) was directly compared to standard intravenous bolus 5-FU/LV in a phase III trial involving 1,886 patients with stage III colon cancer [14]. After a median follow-up of 57 months, DFS was significantly superior with XELOX compared to bolus 5-FU/LV (HR for DFS 0.80, 95% CI 0.69–0.93; 3-year DFS 71 vs. 67%). In contrast, there was only a trend toward improved OS with XELOX (HR for death 0.87, 95% CI 0.72–1.05; 5-year OS 78 vs. 74%) [14].

XELOX was associated with less grade 3 or 4 neutropenia (9 vs. 16%), febrile neutropenia (<1 vs. 4%), stomatitis (<1 vs. 9%) and alopecia (4 vs. 20%) but more neurotoxicity [78% (11% grade 3 or 4) vs. 8% (<1% grade 3 or 4)] [14]. Compared to the Mayo regimen, XELOX was associated with fewer grade 3 or 4 hematologic adverse events but more grade 3 or 4 gastrointestinal adverse events.

Adding bevacizumab to regimens containing 5-FU, LV and irinotecan or oxaliplatin improves outcomes among patients with metastatic colorectal cancer. The benefit of adding bevacizumab to oxaliplatin-based chemotherapy was tested in NSABP C-08, which enrolled 2,672 patients with stage II or III colon cancer [15]. The bevacizumab group had significantly higher rates of hypertension, wound complications, pain, proteinuria and hand-foot syndrome, but not gastrointestinal perforation, hemorrhage, arterial or venous thrombotic events or death. Unfortunately, there was no significant benefit with the addition of bevacizumab (3-year DFS 77 vs. 76%; HR for progression 0.89, 95% CI 0.76–1.04) [15].

In our study, three different FOLFOX regimens were used. The prognostic factors among the three groups were different, and the cumulative oxaliplatin dose was higher in FOLFOX-6-treated patients. There were fewer rectal cancer patients in the FOLFOX-6 group, and the cumulative oxaliplatin dose was lower in the mFOLFOX-4 group because there were more rectal cancer patients, who underwent chemoradiotherapy.

Microsatellite instability (MSI) occurs in 10–20% of colorectal cancers and has been attributed to both *MLH1* promoter hypermethylation and germline mutation in the mismatch repair genes. Mutations in these genes account for less than 5% of all colorectal cancers [16, 17]. MSI has been used as a classification variable for analyses of putative risk factors and prognosis [18, 19]. MSI is not routinely studied in our country.

In conclusion, the different oxaliplatin-containing 5-FU-based adjuvant chemotherapy regimens in patients with stage III colorectal cancer seemed to be at least equal in terms of efficacy, regardless of the method of 5-FU administration or oxaliplatin dose intensity, and can be used safely in clinical practice.

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