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ORIGINAL ARTICLE

First-line therapy for metastatic colorectal carcinoma: modified FOLFOX4 or FOLFIRI-bevacizumab

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Summary

Purpose: *The aim of this study was to compare the efficacy and toxicity of modified (m) FOLFOX4 (folinic acid, 5-fluorouracil [5-FU], and oxaliplatin) vs. FOLFIRI-B (folinic acid, 5-FU, irinotecan, and bevacizumab) as first-line treatment of metastatic colorectal carcinoma (MCRC).*

Methods: *The medical records of 89 MCRC patients treated with either mFOLFOX4 (group 1) or FOLFIRI-B (group 2) as first-line chemotherapy were evaluated retrospectively.*

Results: *Complete (CR) plus partial response (PR) were seen in 18 (36.7%) vs. 13 (32.5%) patients in the mFOLFOX4 vs. FOLFIRI-B, respectively (p=0.67). Median progression-free survival (PFS) was 9 months (95% CI 7.2-9.5) vs. 10 months (95% CI 7.6-12.3) in group 1 vs. group 2, respectively (p=0.30). Median overall survival (OS) was 22 months (95% CI 17.6-26.3) and 19 months (95% CI 13-24.9) in group 1 and 2, respectively (p=0.32). There was no statistically significant difference in grade 3-4 hematological toxicity between the groups, but grade 3-4 grade weakness, diarrhea, nausea and vomiting was observed more frequently in the FOLFIRI-B patients (p=0.03, p=0.01, p=0.05, respectively).*

Conclusion: *Our data suggest that mFOLFOX4 and FOLFIRI-B are equally effective as first-line chemotherapy in MCRC patients. This may partially be explained by the fact that almost 50% of those receiving FOLFOX in the first-line received FOLFIRI-B in the second-line, an observation suggesting that bevacizumab in the second line may be as effective as in the first line.*

Key words: bevacizumab, FOLFIRI, modified FOLFOX4, metastatic colorectal carcinoma

Introduction

Colorectal carcinoma (CRC) makes up 10-15% of all the malignancies in Europe and is the second most common cause of cancer deaths [1]. Fifteen percent of all cases are metastatic at the time of diagnosis and metastasis occurs in 40-50% of patients during the follow-up period after curative therapy [2].

The aim of treatment for MCRC may be palliation, or sometimes cure, primarily depending on the dissemination of the disease; however, age, performance status, and accompanying illnesses may also have an effect. When compared with best supportive care, palliative chemotherapy increases both survival and the quality of life [3]. With the addition of biologics including bevacizumab and cetuximab to the modern combination chemotherapy protocols containing irinotecan and/or oxaliplatin, OS of MCRC patients has increased from 6 months to as high as 30 months [4].

Irinotecan and oxaliplatin are the 2 new cytotoxic agents introduced into the treatment of MCRC. Irinotecan, a specific inhibitor of topoisomerase-1, in combination with bolus or infusional 5-FU/leucovorin (namely IFL or FOLFIRI) increased both response rates (RR) and PFS with somewhat increased but manageable toxicities [5,6].

Oxaliplatin is a member of the diaminocyclohexane platin family, and has a similar mechanism with the other platins. In experimental models it was shown that oxaliplatin and 5-FU have synergistic antitumor effects on colon carcinoma cell lines [7,8]. The combination of oxaliplatin with FULV (FOLFOX) was shown

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to increase both RR and PFS in advanced CRC, but the prolongation of OS was not statistically significant (p=0.12) [9].

After proving the effectiveness, the new question arising was which chemotherapy regimen is best. After several trials [10-14], it was understood that the effectiveness of newer drugs in combination with infusional 5-FU, namely FOLFOX and FOLFIRI were similar, but the toxicity profiles were different. Oxaliplatin is neurotoxic and irinotecan causes diarrhea. Since then, FOLFOX and FOLFIRI became the standard of care for MCRC [6,9,10,13,14].

Targeted therapies added much to the treatment strategies of MCRC. Bevacizumab as a recombinant, humanized monoclonal antibody, binds to vascular endothelial growth factor (VEGF) [15]. It was proved that the treatment effectiveness increases when bevacizumab was added to IFL in the first-line therapy of MCRC [16]. Also, the effectiveness of the combination of bevacizumab and infusional regimens like FOLFIRI (FOLFIRI-B) was investigated and it was found that the PFS was more than 11 months [4,17-19]. The combination of bevacizumab with FOLFOX (or XELOX, where infusional 5-FU was substituted for oral capecitabine) was also superior than the chemotherapy alone [20].

In Turkey, bevacizumab is licensed only with irinotecan- and 5-FU-containing regimens. Therefore, if a medical oncologist likes to prescribe first-line bevacizumab to a MCRC patient, it is required to be combined with irinotecan and/or 5-FU, and practically mostly with FOLFIRI. Before the era of bevacizumab, first-line therapy selection was most often with FOLFOX. Therefore, we compared retrospectively mFOLFOX4 and FOLFIRI-B as first-line treatment of MCRC.

Methods

We retrospectively analyzed the medical records of 89 MCRC patients who were treated from July 2005 to May 2009 with mFOLFOX4 (group 1) or FOLFIRI-B (group 2) as first-line chemotherapy. Forty-nine (55.1%) patients were treated with mFOLFOX4 (oxaliplatin 85 mg/m^2, D1; folinic acid 200 mg/m^2, d1; 5-FU 400 mg/m^2 i.v. bolus, d1; 5-FU 1600 mg/m^2 46 h infusion, every 2 weeks), and 40 (44.9%) were treated with FOLFIRI-B (irinotecan 180 mg/m^2, d1; folinic acid 200 mg/m^2, d1; 5-FU 400 mg/m^2 i.v. bolus, d1; 5-FU 2600 mg/m^2, 46 h infusion; bevacizumab 5 mg/kg, every 2 weeks). All of the patients received prophylactic antiemetic treatment with 5-HT3 receptor blockers and dexamethasone. Administration of chemotherapeutics every 14 days was accepted as one cycle. Patients received 12 cycles in the absence of intolerable toxicity or disease progression. Performance status (PS) was graded according to the Eastern Cooperative Oncology Group scale (ECOG PS). Response was evaluated according to the Response Evaluation Criteria In Solid Tumors (RECIST) [21]. Toxicity was evaluated with Common Terminology Criteria for Adverse Effects v3.0 criteria. Kaplan-Meier method was used to analyse OS and PFS.

Statistical analysis

PFS was defined as the time elapsed from the start of treatment to detection of new metastasis or death. OS was defined as the time from treatment onset till death or last day of follow up. Fischer's exact and chi square (x^2) test were used for nominal variables, Student's t-test was used for age, Mann-Whitney U-test was used for the other numeric variables. Kaplan-Meier method was used for censored data and log-rank test to compare survival. All p-values were 2-sided and a value ≤ 0.05 was considered as significant. Statistical Package for Social Sciences version 15.0 (SPSS 15.0) software was used for analysis.

Results

Patient characteristics

The characteristics of the patients in both groups are shown in Table 1. Fifteen patients (30.6%) in group 1 had received bolus FU/LV in the adjuvant setting. In group 2, 21 patients (75.0%) had been treated with adjuvant FOLFOX, and 7 (25.0%) with infusional or bolus FU/LV (p<0.01). After the first-line chemotherapy 20 (40.8%) and 14 (35%) patients in group 1 and 2, respectively, were treated with second-line, and 15 (30.6%) and 3 (7.5%) patients with third-or more lines of chemotherapy (Figure 1). The group 1 patients took more lines of chemotherapy and the difference was statistically significant (p=0.01). Twenty-nine (59.2%) patients in group 1 were treated with FOLFIRI-B in the subsequent lines and 8 (20.0%) patients in group 2 were treated with mFOLFOX4 in the subsequent lines. After the first-line chemotherapy metastasectomy was realized in 3 (6.1%) patients in group 1 and in 2 (5.0%) in group 2. Complete metastasectomy was performed in only one patient in each group (2.0 vs. 2.5%). The median follow-up period was 17 months (range 1-51).

Objective tumor responses

Response rates are shown in Table 2. CR was ob-

Table 1. Patient and disease characteristics in group 1 and 2

Parameter	*mFOLFOX4 N (%)*	*FOLFIRI-B N (%)*	*p-value*
Sex			0.53
Male	29 (59.2)	21 (47.5)	
Female	20 (40.8)	19 (52.5)	
Age, years			
Mean (SD)	58.8 (±9.9)	48.8 (±9.7)	<0.01
ECOG PS			0.72
0	2 (4.1)	1 (2.5)	
1	44 (89.8)	35 (87.5)	
2	3 (6.1)	4 (10)	
Primary site			0.33
Colon	33 (67.3)	23 (57.5)	
Rectum	16 (32.7)	17 (42.5)	
Metastatic sites			
Liver	27 (55.1)	24 (60)	
Lung	9 (18.4)	8 (20)	
Other	26 (53.1)	19 (47.5)	
No of metastatic sites			0.57
1	28 (59.2)	26 (65.0)	
≥2	20 (40.8)	14 (35.0)	
Metastasis at the time of diagnosis			0.02
Yes	30 (61.2)	12 (30.0)	
No	19 (38.8)	28 (70)	
Adjuvant treatment			0.01
Yes	15 (30.6)	28 (70)	
No	4 (8.1)	0 (0)	

mFOLFOX4: folinic acid, fluorouracil, and oxaliplatin, FOLFIRI-B: folinic acid, fluorouracil, irinotecan, and bevacizumab, SD: standard deviation, ECOG PS: Eastern Cooperative Oncology Group performance status

tained in 7 (14.3%) patients in group 1 and in 3 (7.5%) in group 2. Partial response (PR) was obtained in 11 patients (22.4%) in group 1 vs. 10 patients (25.0%) in group 2 (p=0.77). Disease control (CR+PR+SD) was achieved in 40 (81.6%) vs. 34 (85.0%) patients in group 1 and 2, respectively (p=0.67).

Progression-free survival

Progression was detected in 46 (93.9%) patients in group 1 and in 34 (85%) patients in group 2 (p=0.28). Median PFS was 9 months (95% CI, 7.2-9.5) in group 1 and 10 months (95% CI, 7.6-12.3) in group 2 (p=0.30) (Figure 2).

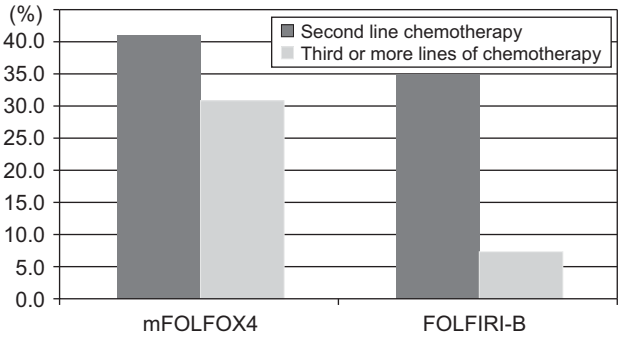

Figure 1. Percentage of patients treated after first-line chemotherapy (mFOLFOX4 vs. FOLFIRI-B).

Table 2. Response rates in group 1 and group 2

Response	*mFOLFOX4 N (%)*	*FOLFIRI-B N (%)*	*p-value*
Overall response	18 (36.7)	13 (32.5)	0.67
Complete response	7 (14.3)	3 (7.5)	0.31
Partial response	11 (22.4)	10 (25)	0.77
Stable disease	22 (44.9)	21 (52.5)	0.47
Disease control	40 (81.6)	34 (85.0)	0.67
Progressive disease	9 (18.4)	6 (15.0)	0.67

For abbreviations see footnote of Table 1

Overall survival

Thirty-four (69.4%) patients in group 1 and 24 patients (60%) in group 2 died (p=0.35) during the follow up period. Median OS was 22 months (95% CI, 17.6-26.3) in group 1, and 19 months (95% CI, 13-24.9) in group 2 (p=0.32) (Figure 3).

Toxicity

In both groups, the median number of cycles were 12 (group 1: range 2-18, group 2: range 1-16) (p=0.80). There was no difference in grades 3-4 hematologic toxicity between the groups, but grades 3-4 weakness, diarrhea, nausea and vomiting was observed more fre-

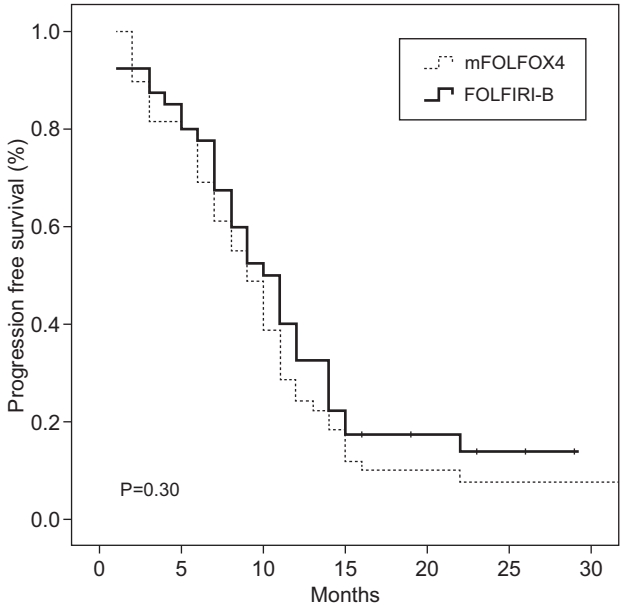

Figure 2. Progression-free survival of patients treated with first-line mFOLFOX4 vs. FOLFIRI-B.

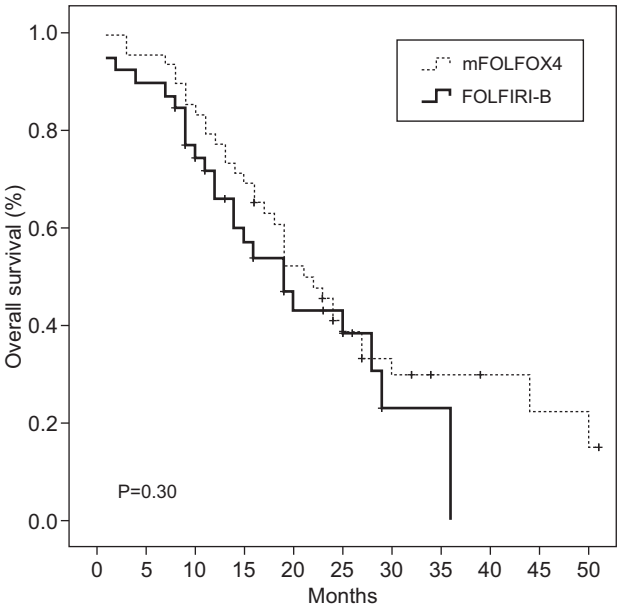

Figure 3. Overall survival of patients treated with first-line mFOLFOX4 vs. FOLFIRI-B.

quently in group 2 (p=0.03, p=0.01, p=0.05, respectively) (Table 4). Toxicity is summarized in Table 3 for both groups. Nineteen patients (38.7%) in group 1 and 16 (40.0%) in group 2 could not complete 12 cycles of chemotherapy (p=0.781). Underlying reasons of treatment cessation are summarized in Table 4. Dose reduction was done in 3 patients (6.1%) in group 1 due to neutropenia, diarrhea and allergic reaction and in 9 (22.5%) in group 2 due to neutropenia (n=3, 7.5%), diarrhea (n=5, 12.5%) and allergic reaction (n=1, 2.5%) (p=0.02). Fifteen (30.6%) patients in group 1 and 11 (27.5%) in group 2 received at least one cycle of chemotherapy with delay due to toxicity (p=0.74). The most frequent cause of delay in group 1 was neutropenia seen in 13 (26.5%) patients and diarrhea and neutropenia (n=5, 12.5%; and n=4, 10%, respectively) in group 2.

Discussion

There are numerous published trials containing oxaliplatin- and irinotecan-based chemotherapy showing increase of RR and survival in MCRC administered as first-line chemotherapy [10-14]. Irinotecan and oxaliplatin in combination with bevacizumab were also reported to be superior than chemotherapy alone in patients with MCRC [4,16-20].

Tournigand et al. and Colucci et al. compared FOLFIRI, then FOLFOX, after disease progression and the reverse sequence (FOLFOX then FOLFIRI) in a phase 3 trial and found that either sequence was equal in efficacy (Table 5) [13,14]. In our trial the RR in the mFOLFOX was similar to the trial of Colucci et al. (36.7 vs. 34%) [14]. Although Tournigand et al. reported a response rate of 54%, fewer patients had received

Table 3. Toxicities

Toxicity	*mFOLFOX4*		*FOLFIRI-B*		*p-value*
	Grade 1-2 %	*Grade 3-4* %	*Grade 1-2* %	*Grade 3-4* %	
Anemia	30.6	2	37.5	0	NS
Neutropenia	24.5	16.3	27.5	27.5	NS
Thrombocytopenia	30.6	0	32.5	0	NS
Nausea/vomiting	10.2	2	10	12.5	0.05
Weakness	6.1	0	0	10	0.03
Diarrhea	8.1	2	5	17.5	0.01
Neuropathy	16.3	0	0	0	NS
Venous thrombosis	0	0	0	2	NS

mFOLFOX4: folinic acid, fluorouracil, and oxaliplatin, FOLFIRI-B: folinic acid, fluorouracil, irinotecan, and bevacizumab, NS: not significant

Table 4. Cross-comparison of the trials including FOLFOX and/or FOLFIRI ± bevacizumab

	*FOLFOX6 [13], FOLFOX4 [14], mFOLFOX 4**			*FOLFIRI [13], FOLFIRI [14], FOLFIRI-B**		
No. of patients	111	172	49	109	164	40
PFS (months)	8.1	7	9	8.5	7	10
OS (months)	20.6	15	22	21.5	14	19
RR (%)	54	34	36.7	56	31	32.5
One metastatic site (%)	59	54	59.2	59	56	65
Adjuvant CT (%)	23	29	31.9	19	31	59.6

FOLFOX: folinic acid, fluorouracil, and oxaliplatin, FOLFIRI-B: folinic acid, fluorouracil, irinotecan, and bevacizumab, RR: response rate, PFS: progression-free survival, OS: overall survival, CT: chemotherapy
*Present study

Table 5. Reasons for chemotherapy discontinuation

	mFOLFOX4 N (%)	*FOLFIRI-B N (%)*	*p-value*
Disease progression*	12 (24.4)	2 (5.0)	NS
Chemotherapy toxicity	3 (6.1)**	3 (7.5) ***	NS
Patient refusal	2 (4.1)	8 (20.0)	NS
Death from			
Chemotherapy toxicity	0 (0)	1 (2.5)	NS
Disease progression	2 (4.1)	2 (5.0)	NS

mFOLFOX4: folinic acid, fluorouracil, and oxaliplatin, FOLFIRI-B: folinic acid, fluorouracil, irinotecan and bevacizumab, NS: not significant, *Except death, **Neutropenia (n=1), anorexia (n=1), allergic reaction (n=1), ***Neutropenia (n=1), intraabdominal abcess (n=1), anal abcess (n=1)

adjuvant treatment compared with our study (31.9 vs. 21%) [13]. The RR of FOLFIRI-B in our trial was also similar to the trial of Colucci et al. (32.5 vs. 31%) rather than Tournigand et al. (56%) [13,14]. In our trial 59.6% of the patients in the FOLFIRI-B group had received adjuvant chemotherapy and this ratio was greater than the one in the trials by Tournigand et al. and Colucci et al. (17 and 31%, respectively) [13,14]. On the other hand, of the patients who had adjuvant chemotherapy, 75% had received oxaliplatin. In our trial, although bevacizumab was added to FOLFIRI, there was no difference between groups in terms of objective tumor response, PFS and OS, similar to the trials by Tournigand et al. and Colucci et al. [13,14].

The median PFS reported in the trials of first-line FOLFOX in MCRC ranges between 7 to 9 months and in irinotecan-containing trials between 6.7 to 8.5 months [5,6,9,10,13,14]. The median PFS in the trial by Colucci et al. [14] was 7 months in both arms, but it was 8.1 months in the FOLFOX arm and 8.5 months in the FOLFIRI arm in the trial by Tournigand et al. [13]. In both trials, there was no statistically significant difference between the groups. On the other hand, in some other trials when FOLFIRI was combined with bevacizumab, PFS increased from 10.9 to 12.8 months [4,17,18,19,22]. Although our trial was a retrospective one, the median PFS was similar to literature data and there was no statistically significant difference between the mFOLFOX and FOLFIRI-B (9 vs. 10 months, p=0.30).

The reported median OS with FOLFOX was 15-20.6 months, and with irinotecan-containing regimens it was 14.8-20.6 months [5,6,9,10,13,14]. No statistically significant difference was reported in terms of OS between the arms in the trials by Colucci et al. and Tournigand et al. (p=0.28 and p=0.98, respectively). In bevacizumab-containing regimens including AVIRI and BICC-C trials, the median OS ranged between 22.2-28 months [17,23]. In our trial, patients in FOLFIRI-B reached a 3-month prolongation of OS but the difference was not statistically significant (19 vs. 22 months, p=0.32). On the other hand, 71.4% of the patients in mFOLFOX were able to receive 2 or more lines of chemotherapy, but this proportion was only 42.5% in group 2. In group 1, 49.0% of the patients were able to proceed with FOLFIRI-B, whereas only 17.5% of group 2 could receive mFOLFOX4 in the second-line.

There were no difference in hematological toxicities but grade 3-4 weakness, nausea, vomiting and diarrhea were more often in the FOLFIRI-B group. No neuropathy was observed in group 2 but the reported neuropathy in group 1 was grade 1-2. Bevacizumab-related hypertension, colon perforation and bleeding were not observed in any of the patients but venous thrombosis was diagnosed in 2 patients.

In our country, bevacizumab cannot be prescribed in combination with FOLFOX. Therefore, FOLFIRI-B is usually prescribed in the first-line setting of MCRC. Our data suggest that starting with FOLFOX alone in the first-line seems to be equally effective as FOLFIRI-B. This may partially be explained by the fact that almost 50% of those receiving FOLFOX alone in the first-line receive FOLFIRI-B in the second-line, an observation suggesting that bevacizumab in the second-line may be as effective as as in the first-line.

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