RESEARCH ARTICLE

XELOX Plus Bevacizumab *vs.* FOLFIRI Plus Bevacizumab Treatment for First-line Chemotherapy in Metastatic Colon Cancer: a Retrospective Study of the Anatolian Society of Medical Oncology

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Abstract

Background: XELOX plus bevacizumab (XELOX-Bev) and FOLFIRI plus Bevacizumab (FOLFIRI - Bev) treatments are an effective strategies patients with metastatic colorectal cancer (mCRC).The aim of this study was to compare efficacy of first-line XELOX-Bev treatment *vs* FOLFIRI-Bev treatment for mCRC. Materials and Methods: A total of 409 patients with mCRC who received chemotherapy were included and divided into 2 groups. Group 1 (n=298) received XELOX-Bev and Group 2 (n=111) FOLFIRI-Bev. Comparisons were made in terms of overall (OS) and progression-free (PFS) survival, response rate (RR), and grade 3-4 toxicity. Results: Median follow-up was 11 months in Group 1 and 15 months for Group 2. Complete remission was observed in 29 (9.7%) and 2 (1.8%) patients, partial remission in 139 (46.6%) and 27 (24.5%) , stable disease in 88 (29.5%) and 49 (44.1%) and progressive disease in 42 (14.1%) and 33 (30.0%) patients in Group 1 and 2, respectively. Median OS was 25 months (range 2-57 months, 95% CI; 22.2-27.7) for Group 1 and 20 months (range 1-67 months, 95% CI; 16.8-23.1) for Group 2 (p=0.036). Median PFS was 9.6 months (range 2-36 months, 95% CI; 8.8-10.4) for Group 1 and 9 months (range 1-44 months, 95% CI; 7.4-10.5) for Group 2 (p=0.019). Objective RR was 56.4% in Group 1 and 26.1% in Group 2 (p<0.001). Conclusions: First-line XELOX-Bev is more effective with a better response rate, prolongation of median PFS/OS, and a superior safety profile compared with FOLFIRI-Bev.

Keywords: Metastatic colorectal cancer - XELOX plus bevacizumab - FOLFIRI plus bevacizumab - comparison

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Introduction

Colorectal cancer is one of the most common type of cancer. Although appropriate screening strategies, significant number of patients are still diagnosed at late stages of the disease. Despite all the advances, the treatment of metastatic colorectal cancer (mCRC) remains an important clinical problem in the worldwide. mCRC patients live much longer with new combination of treatment agents. Cytotoxic regimens, include doublet combinations (FOLFOX/XELOX or FOLFIRI), constitute the main treatment in patients with mCRC. Addition of biologic agents, such as bevacizumab, to these regimens has improved clinical outcomes and combination chemotherapy with biologic agents is recommended for patients with metastatic disease (Temraz et al., 2014; Zhang et al., 2014). Although patients with mCRC have many treatment options, the optimal use and sequence of targeted agents remain to be unclear.

Bevacizumab is a monoclonal antibody that inhibits the vascular endothelial growth factor (VEGF) (Ferrara et al., 2003; Zhu et al., 2014). Bevacizumab improved rates of response, overall survival (OS) and progression-free survival (PFS) when combined with the standard chemotherapy treatments in patients with mCRC (Fuchs et al., 2007; Saltz et al., 2008, Sun et al., 2014). According to the use of bevacizumab alone, the combined use of bevacizumab and capecitabine plus oxaliplatin

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(XELOX) is an effective teatment strategy and resulted in significantly improved PFS by 20% in the first line treatment of mCRC (Hochster et al., 2008; Saltz et al., 2008). Additionaly, irinotecan, infusional 5-fluorouracil (FU), leucovorin (LV) (FOLFIRI) and bevacizumab combination offered well outcomes (Fuchs et al., 2007).

In this study, we aimed to evaluate and compare the efficacy and toxicity of XELOX plus Bevacizumab (XELOX-Bev) *vs*. FOLFIRI plus Bevacizumab (FOLFIRI-Bev) treatment for first-line chemotherapy in mCRC.

Materials and Methods

Study Population: This study enrolled 409 patients who had received first line chemotherapy combination with bevacizumab between December 2006 and March 2014, from 14 member center of Anatolian Society of Medical Oncology (ASMO) association in Turkey. Data were obtained from chart reviews of mCRC patients. 298 patients were administered XELOX-Bev (Group 1) and 111 patients were administered FOLFIRI-Bev (Group 2) as a first-line treatment. Eastern Cooperative Oncology Group Performance Status (ECOG-PS) of patients were two or less and patients had adequate hematological, liver and renal functions. Exclusion criteria were: 1) history of prior chemotherapy for mCRC, 2) history of malignancy other than mCRC, 3) patients with significant cardiovascular, hepatic and renal diseases, hypertension, haemorrhagic diathesis or coagulopathy.

Treatment

XELOX-Bev treatment consisted of 90-min I.V. infusion of bevacizumab (7.5mg/kg) on day 1, followed by oxaliplatin 130mg/m^2-i.v. infusion over 2h on day 1 in combination with capecitabine orally at a dose of 2,000mg/m^2/day with first dose on the morning of day 1 and last dose on the evening of day 14 every 3 weeks. FOLFIRI-Bev treatment consisted of a 90-min I.V. infusion of bevacizumab (5mg/kg) on day 1, followed by a 90-min I.V. infusion of irinotecan (180mg/m^2) on day 1, leucovorin (200mg/m^2) 2h infusion on day 1 and 2, bolus fluorouracil (400mg/m^2) on day 1 and 2, 24h infusion of fluorouracil (600mg/m^2)] on day 1 and 2. Treatment was continued until significant toxicity was observed and progressive disease (PD) was detected. Response evaluation was based on RECIST criteria every 2-3 cycles for XELOX-Bev regimen and 4-6 cycles for FOLFIRI-Bev regimen. We assessed the tumor progression with clinical evalution, imaging methods and tumour markers. Toxicity was evaluated according to the National Cancer Institute (NCI) common toxicity criteria.

Statistical analysis

Statistical analysis was performed using SPSS version 16.0 for Windows, statistical software (SPSS, Chicago, IL). p values of <0.05 were considered statistically significant. Independent two-sided t test, nonparametric Mann-Whitney U test, or chi-square test was applied to compare variables between groups, where appropriate. For correlation of metric and ordinal variables, Spearman rank correlation coefficient was computed. Survival analysis was performed by means of Kaplan-meier survival curves and log-rank test. Univariate and multivariate Cox proportional hazard models were used to identify predictors of progression-free and overall survival. Hazard ratios of >1.0 indicate an increased likelihood of death or recurrence.

Results

Patient characteristics

Patient and tumor characteristics data at baseline were compared across the two treatment groups (Table 1). A similar number of male and female patients were enrolled into each group (110 female in Group 1 and 52 female in Group 2, p=0.068) and the mean age was 61±11 years in Group 1 and 55±10 years in Group 2. All patients had baseline ECOG-PS scores of 0, 1 or 2.

Efficacy

Median follow-up was 11 months for Group 1 (range 1-57 months) and 15 months for Group 2 (range: 1-67 months). Responses were evaluated in both groups and in Group 1; 29 (9.7%) patients achieving a complete remision, 139 (46.6%) patients achieving a partial remision, 88 (29.5%) patients with stable disease and 42 (14.1%) patients with progressive disease. In Group 2, 2 (1.8%) patients achieving a complete remision, 27 (24.5%) patients achieving a partial remision, 49 (44.1%) patients with stable disease and 33 (30.0%) patients with progressive disease. Median OS was 25 months (range 2-57 months, 95%CI; 22.2-27.7) for Group 1 and 20 months (range 1-67 months, 95%CI; 16.8-23.1)

Table 1. Characteristics of Patient at Baseline and Efficacy and Safety of Treatment Groups

	Group 1	Group 2	p
Age (years)	61±11	55±10	<0.001
Female (n. %)	110 (36.9%)	52 (46.8%)	0.068
ECOG-PS			
0 (n.%)	148 (49.7%)	47 (42.3%)	0.001
1 (n. %)	126 (42.3%)	62 (55.9%)	
2 (n.%)	24 (8.1%)	2 (1.8%)	
Metastases			
Liver	167 (57.2%)	59 (53.6%)	
Lung	34 (11.6%)	22 (20%)	
Bone	13 (4.5%)	2 (1.8%)	
Lymph nodes	8 (2.7%)	6 (5.5%)	
Cranial	2 (0.7%)	0	
Periton	19 (6.5%)	3 (2.7%)	
Liver + lung	33 (11.3%)	16 (14.5%)	
Liver + periton	13 (4.5%)	1 (0.9%)	
Liver + bone	3 (1%)	1 (0.9%)	
Progression-free survival (months)	9.6	9	0.019
Overall survival (months)	25	20	0.036
Response Rate (n. %)	168 (56.4%)	29 (26.1%)	<0.001
Exitus (n. %)	124 (41.6%)	88 (79.3%)	<0.001
Grade 3/4 events (n.%)			
Neutropenia (n. %)	15 (5.0%)	34 (30.6%)	<0.001
Febril neutropenia	11 (3.7%)	2 (1.8%)	0.333
Thrombocytopenia	6 (2.0%)	0	0.132
Anemia	1 (0.3%)	1(0.9%)	0.466
Nausea and vomiting	4 (1.3%)	4 (3.6)	0.142
Diarrhea	15 (5.0%)	5 (4.5%)	0.825
Mucositis	0	4 (3.6%)	0.001
Asthenia	7 (2.3)	3 (2.7)	0.837

Group 1: XELOX – Bev. n:298. Group 2: FOLFIRI - Bev. n=111

Table 2. Incidence of Significant Bevacizumab-related Adverse Events

	Total	Group 1	Group 2	p
Hypertension	12 (2.9%)	10 (3.4%)	2(1.8%)	0.408
Bleeding	10 (2.4%)	6 (2%)	4(3.6%)	0.354
Arterial thromboembolic events	6 (1.5%)	6 (2%)	0 (0%)	0.132
Venous thromboembolic events	12 (2.9)	8 (2.7%)	4 (3.6%)	0.624
Fistula and ileus	4 (1.0%)	4 (1.3%)	0 (0%)	0.220
Gastrointestinal perforations	0 (0%)	0 (0%)	0 (0%)	

Group 1: XELOX - Bev, n:298, Group 2: FOLFIRI - Bev, n=111

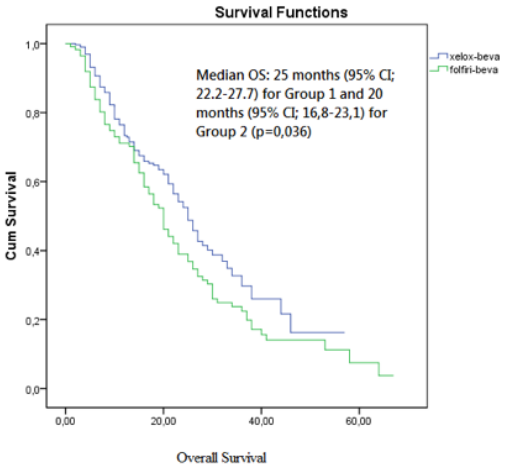

Figure 1. Overall Survival for Colorectal Cancer Patients Treated with XELOX-Bev *vs* FOLFIRI-Bev in First-line Treatment

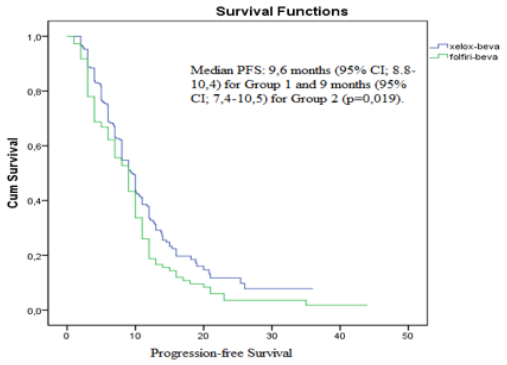

Figure 2. Progression-free Survival for Colorectal Cancer Patients Treated with XELOX-Bev *vs* FOLFIRI-Bev in First-line Freatment

for Group 2 (p=0.036). Median PFS was 9.6 months (range 2-36 months, 95%CI; 8.8-10,4) for Group 1 and 9 months (range 1-44 months, 95%CI; 7.4-10.5) for Group 2 (p=0.019). Objective response rate (RR) was 56.4% and 26.1% in Group 1 and 2 respectively (p<0.001). The corresponding Kaplan-Meier curves for OS and PFS are shown in Figure 1, 2.

In Group 1, patients were received median 6 (minimum 2-maximum 24) cycles chemotherapy and in Group 2, patients were received median 6 (minimum 2-maximum 10) cycles chemotherapy (p<0.001).

Safety

The safety profile of the XELOX-Bev and FOLFIRI-Bev arms were compared in Table 1 (all grade 3/4 adverse events). Grade 3/4 toxicities were as follows: neutropenia (5.0% in Group 1 and 30.6% in Group 2, p<0.001), febril neutropenia (3.7% in Group 1 and 2% in Group 2, p>0.05), thrombocytopenia (2% in Group 1 and 0 in Group 2, p>0.05), nausea and vomiting (1.3% in Group 1 and 3.6% in Group 2, p>0.05), diarrhea (5% in Group 1 and 4.5% in Group 2, p>0.05), mucositis (0 in Group 1 and 3.6% in Group 2, p=0.001), asthenia (2.3% in Group 1 and 2.7% in Group 2, p>0.05).

Table 3. Results of First Line Some XELOX-Bev and FOLFIRI-Bev Chemotherapy Studies in mCRC

Authors	N	Drug	RR (%)	PFS*	OS*
Buchler et al. (2014)	973	A	44.4%	11.5	30.6
Diaz-Rubio et al. (2012)	239	A	47.0%	10.4	23.2
Rosati et al. (2013)	44	A	52.0%	11.5	19.3
Uchima et al. (2014)	40	A	67.5%	9.6	27.2
Pecatasides et al. (2012)	142	B	40.1%	10.8	25.3
Fuchs et al. (2007)	57	B	47.2%	11.2	28
Bécouarn et al. (2014)	62	B	47.5%	10.3	25.7
Falcone et al. (2013)	256	B	53.0%	9.7	25.8

*: months; A: patients received XELOX - Bev. B: patients received FOLFIRI - Bev. RR: response rate. PFS: progression-free survival. OS: overall survival

Incidence of significant bevacizumab-related adverse events were: Hypertension (3.4 in Group 1 and 1,8 in Group 2, p=0.408), bleeding (2% in Group 1 and 3.6% in Group 2, p=0.354), arterial thromboembolic events (2% in Group 1 and 0% in Group 2, p=0.132), venous thromboembolic events (2.7% in Group 1 and 3.6% in Group 2, p=0.624), fistula and ileus (1.3% in Group 1 and 0% in Group 2, p=0.220) (Table 2).

Discussion

Double-agent chemotherapy with either XELOX and FOLFIRI were the most widely used cytotoxic agents in patients with mCRC (Colucci et al., 2005; Hochster et al., 2008; Cetin et al., 2012; Uygun et al., 2013). The combination of doublet chemotherapy regimens with biological agents, such as bevacizumab (a humanized monoclonal antibody that inhibits vascular endothelial growth factor (Ferrara et al., 2003) has been shown to prolong PFS, OS and RR although toxicity was also increased (Kabbinavar et al., 2005; Grothey et al., 2008; Hochster et al., 2008; Saltz et al., 2008; Welch et al., 2010; Macedo et al., 2012). Although all of this findings, the optimal combination of first-line treatment is still unclear (Cunningham et al., 2013). Results of first line some XELOX-Bev and FOLFIRI-Bev chemotherapy studies in mCRC were showed in Table 3. Up to now, each treatment regimens was studied by investigators but the comparison of XELOX-Bev *vs* FOLFIRI-Bev treatment was made by us for the first time. The primary result of our study was XELOX-Bev is superior to FOLFIRI-Bev in terms of PFS, OS and RR in the first-line treatment of patients with mCRC.

Addition of bevacizumab to XELOX resulted in PFS ranging between 9.3-11.4 mo, OS ranging between 20.3-27.4 mo and a RR ranging between 46%-67.5% (Hochster et al., 2008; Tol et al., 2009; Doi et al., 2010; Cassidy et al., 2011; Uchima et al., 2014). Previous studies reported that the median PFS was between 9-12 months and the median OS was between 22-31.3 months and RR was 57.9% with FOLFIRI-Bev (Fuchs et al., 2007; Hecht et al., 2009; Sobrero et al., 2009; Stathopoulos et al., 2010; Ducreux et al., 2013; Becouarn et al., 2014). In our study, the median PFS was 9.6 months in Group 1 and 9 months in Group 2 (p=0.019). The median OS was 25 months in Group 1 and 20 months in Group 2 (p=0.036). Although our study supports the findings of other studies with the median PFS, OS and RR, when the results of XELOX-Bev and FOLFIRI-Bev are compared, XELOX-Bev is better than FOLFIRI-Bev in terms of PFS, OS and RR.

Investigators reported that all response rate was 44.4-67.5%, complete response rate was 2-2.5%, partial response rate was 13-65%, stable disease was 22.5-25% and progressive disease rate was 2.5-8% in patients who received XELOX-Bev (Van Cutsem et al., 2009; Diaz-Rubio et al., 2012; Uchima et al., 2014; Buchler et al., 2014). In different studies, investigators reported various partial response rates such as 47.5 (Becouarn et al., 2014), 40.1% (Pectasides et al., 2012) and 36.8% (Stathopoulos et al., 2010) with FOLFIRI-Bev. Lopez et al, reported a 8.4% complete response, 42.1% partial response, 16.8% stable disease and 32.6% progressive disease with FOLFIRI-Bev (Lopez et al., 2010). In our study, response rates were evaluated in both groups and in Group 1; 29 (9.7%) patients achieving a complete remision, 139 (46.6%) patients achieving a partial remision, 88 (29.5%) patients with stable disease and 42 (14.1%) patients with progressive disease. In Group 2, 2 (1.8%) patients achieving a complete remision, 27 (24.5%) patients achieving a partial remision, 49 (44.1%) patients with stable disease and 33 (30.0%) patients with progressive disease. Objective RR was 56.4% and 26.1% in Group 1 and 2 respectively (p<0.001). According to our results, complate response and progressive disease rates were higher than, parsial response and stable disease rates were similar with other studies in patients who received XELOX-Bev. Complate remision and parsial response rate was lower, stable disese rate was higher and progressive disease rate was similar with other studies in patients who received FOLFIRI-Bev.

Using long term chemotherapy is limited even in patients who benefited from the treatment because of the cumulative toxicity of cytotoxic chemotherapy. However, if less toxic chemotherapy drugs can be used in this group of patients, it might be feasible to improve clinical results. The rate of grade ≥3 toxicities was low and strong toxic effects were primarily hematologic and gastrointestinal. The rate of severe toxic effects in patients treated with XELOX-Bev were: sensory neuropathy 15-26%, diarrhea 0-21%, fatigue 10-15%, hypertension 0-4%, gastrointestinal perforation <0.01, bleeding <0.01 (Hochster et al., 2008; Tol et al., 2009; Diaz-Rubio et al., 2012; Uchima et al., 2014). In the literature, investigators reported the rate of severe (grade 3-4) toxic effects in patients treatment with FOLFIRI-Bev were as follows: neutropenia 16.1% to 53.6, diarrhea (2-11.3%), mucositis (5.3%), astenia (2.1%), gastrointestinal perforation 0% to 2%, bleeding 0%-11.6%, proteinuria 1%; hypertension 5% to 12.5%; and venous thromboembolism 1% and 19% (Fuchs et al., 2007; Van Cutsem et al., 2009; Becouarn et al., 2014; Hasegawa et al., 2014). In the present study, grade 3 or 4 neutropenia (5% *vs* 30.6) and mucositis (0 *vs* 3.6%) were statistically significantly less common in patients who received XELOX-Bev than in those who received FOLFIRI-Bev (Table 1). Other severe toxic effects of the treatment arms were similar (febril neutropenia, thrombocytopenia, anemia, nausea and vomiting, diarrhea and astenia). According to the our study, incidence of significant bevacizumab-related adverse events were similar in both groups in accordance with other studies (Table 2).

Although the efficiency combination of XELOX-Bev and FOLFIRI-Bev, alone or in different combinations, were executed previously, the first comparison of the two treatment regimens were made in our study. We found that XELOX-Bev is superior to FOLFIRI-Bev in terms of PFS, OS and RR in the first-line treatment of patients with mCRC. We can explain the prolangation of PFS, OS and increasing in RR in Group 1 as follows: 1. Toxic effects (neutropenia and mucositis) were less common in Group 1 than in Group2. Although in previous studies reported that high frequency (Diaz-Rubio et al., 2012) of diarrhea in XELOX-Bev treatment, in our study, the incidence of diarrhea and nausea/vomiting was low and similar in both groups. Incidence of diarrhea and nausea/vomiting in our study was less than in a study reported from Western patients (Diaz-Rubio et al., 2012) and higher than in a study reported from Japanese patients (Uchima et al., 2014). 2. Due to the low toxicity profile and high therapeutic efficacy in Group 1, patients in Group 1 received much more chemotherapy cycle than Group 2 and it is likely to affect the results of the prolangation of PFS. 3. Prolongation of OS may be due to either the prolongation of PFS or chemotherapies that received after first line chemotherapy.

In conclusion, according to our results, the combination of XELOX-Bev induced a significant rate of disease control with safety profile and an acceptable toxicity rate in mCRC when compared with FOLFIRI-Bev.

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