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ORIGINAL ARTICLE

Comparison of first-line bevacizumab in combination with mFOLFOX6 or XELOX in metastatic colorectal cancer

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Summary

Purpose: *Currently, there are several oxaliplatin combination regimens for first-line therapy of metastatic colorectal cancer (mCRC). In this study, we compared the survival outcomes of mCRC patients treated with bevacizumab in combination with either modified 5-FU/FA/oxaliplatin (mFOLFOX6) or capecitabine/oxaliplatin (XELOX).*

Methods: *We designed a two-arm retrospective study of mCRC patients with adenocarcinoma of the colon or rectum who were treated with bevacizumab and either mFOLFOX6 or XELOX and who had complete clinical and treatment data. We analysed their therapeutic responses, adverse events, progression-free survival (PFS), and overall survival (OS), and then determined whether there were any statistically significant differences.*

Results: *A total of 131 patients (85 male; 65% and 46 female; 35%) were evaluated. Fifty-seven patients (43.5%) were treated with bevacizumab and mFOLFOX6 and 74 (56.5%) with bevacizumab and XELOX. The median PFS was 9.1 months (95% CI, 4.9–13.1) and 10 months (95% CI, 4.2–15.9) in the mFOLFOX6 and XELOX arms, respectively (p=0.610). The median OS was 29 months (95% CI, 21.6–34.3) and 27.5 months (95% CI 20–38) in the mFOLFOX6 and XELOX arms (p=0.812), respectively. The most common reason for treatment withdrawal was disease progression (102 patients; 91%) and the most common grade 3-4 toxicity was neuropathy (≤14%).*

Conclusion: *Our results show that XELOX is a safe and effective alternative to mFOLFOX6 when combined with bevacizumab as first-line treatment for mCRC patients.*

Key words: *bevacizumab, colorectal cancer, FOLFOX, metastasis, XELOX*

Introduction

CRC is one of the leading causes of cancer mortality worldwide. Although surgery is potentially curative, palliative chemotherapy is more appropriate for approximately 20–25% of CRC patients who present with distant metastases at the time of initial diagnosis [1].

5-Fluorouracil/folinic acid (5-FU/FA) is the standard chemotherapeutic regimen for patients with mCRC. However, recent studies have shown that the combination of 5-FU/FA and oxaliplatin (FOLFOX) is superior to 5-FU/FA alone in advanced CRC [2]. Oxaliplatin also is used in several other combination chemotherapy regimens for mCRC, such as FOLFOX4, FOLFOX6, and XELOX. Both FOLFOX4, which is the most common regimen, and mFOLFOX6, which is a simplified version of FOLFOX4, have equivalent antitumor activity [3]. XELOX combines capecitabine, which is an oral prodrug of 5-FU, and oxaliplatin. Several randomised phase III clinical trials have demon-

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strated that XELOX is not inferior to FOLFOX4 with respect to PFS, OS, and overall response rate (ORR) as first-line therapy for mCRC patients [4-7]. Other studies also have shown that XELOX and mFOLFOX6 have similar efficacy and safety [8,9].

Bevacizumab is a monoclonal antibody against vascular endothelial growth factor (VEGF). Some studies have shown that bevacizumab can prolong PFS and OS when used with first- and second-line combination chemotherapy for CRC [10,11]. However, Saltz et al. reported that using bevacizumab with either FOLFOX4 or XELOX significantly improved PFS by 1.4 months, without any improvement in OS or ORR [12]. As a result, we compared the clinical outcome and safety profile of first-line bevacizumab ORR with either mFOLFOX6 or XELOX in mCRC patients.

Methods

Study design and inclusion/exclusion criteria

We conducted a non-randomised retrospective study of patients with histologically confirmed adenocarcinoma of the colon or rectum with measurable metastatic disease who were treated with first-line bevacizumab in combination with either mFOLFOX6 or XELOX between February 2010 and June 2013. Patients with a history of adjuvant chemotherapy were allowed into the study if their treatment was completed ≥6 months earlier. Other inclusion criteria included age 18 years or older; Eastern Cooperative Oncology Group (ECOG) [13] performance status (PS) 0–2; and adequate haematological, hepatic, and renal function. The exclusion criteria included withdrawal from first-line chemotherapy due to treatment intolerance; rejection of treatment; drug toxicity; history of metastasectomy or chemotherapy for metastatic disease; and uncontrolled concurrent illnesses such as hypertension, cardiovascular disease, and thromboembolic disorders.

Treatment

All patients were treated with bevacizumab and either mFOLFOX6 or XELOX. The mFOLFOX6 regimen was administered as follows: 2-h infusion of oxaliplatin (85 mg/m^2), leucovorin (400 mg/m^2), and an intravenous bolus injection of 5-FU (400 mg/m^2) followed by a 46-h infusion of 5-FU (2400 mg/m^2) on day 1, followed by a 12-day rest period (14-day cycle). The XELOX regimen was administered as follows: 2-h infusion of oxaliplatin (130 mg/m^2) on day 1 and oral capecitabine (1000 mg/m^2) twice daily on days 1–14, followed by a 7-day rest period (21-day cycle). In addition, patients who were treated with mFOLFOX6 received 5 mg/kg bevacizumab, while those who were treated with XELOX received 7.5 mg/kg.

Response evaluation

Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) [14] were used to evaluate and classify treatment responses as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD). Specific responses were assessed both during and after treatment with laboratory tests, including tests for haematological and biochemical parameters, and computed tomography (CT) or magnetic resonance imaging (MRI) of the abdomen and pelvis. Tumor size was measured after 4 cycles of XELOX and after 6 cycles of mFOLFOX6. In addition, carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 levels were measured every 4 weeks after treatment. Patients with increased levels of CEA or CA 19-9 underwent imaging for measurement of tumor size earlier. The primary endpoint of the study was PFS, which was defined as the time from the first day of treatment to the first day of documented progression or death. For patients who died without known disease progression, we censored the PFS data at the time of their last follow-up. Toxicity grading was performed using the National Cancer Institute Common Toxicity Criteria (NCI-CTC, version 2) [15].

Statistics

Quantitative data are presented as means, medians, and ranges, and qualitative data are presented as frequencies and percentages. The follow-up duration was calculated from the date of the first bevacizumab administration to the date of death or last follow-up visit. Differences between the mFOLFOX6 and XELOX treatment groups were compared by using the chi-square test or Fisher's exact test. In addition, differences between median measurements, such as those between serum levels of CEA and CA 19-9, were analysed by using the Mann-Whitney U test. All statistical tests were two-sided and the level of statistical significance was set at 5%. SPSS version 18.0 (SPSS Inc., Chicago, IL) was used for all statistical analyses.

Results

Patient characteristics

Of 374 metastatic colon or rectal cancer patients who were considered for this study, 131 met the inclusion/exclusion criteria and were evaluated for the outcomes of bevacizumab plus either mFOLFOX6 or XELOX. As shown in Table 1, 83 (63%) of these patients had colon cancer, 38 (29%) rectal cancer, and 10 (7%) colorectal cancer. Male patients were about 2-fold more than female. Fifty seven (43.5%) patients were treated with mFOLFOX6, while 74 (56.5%) were treated with XELOX. The median patient age was 60 years (range 27–76). Nearly all of the patients had an ECOG PS 0 or 1.

Table 1. Patient characteristics

Characteristics	*Group A XELOX*		*Group B mFOLFOX6*		*Total*		*p value*
	N	*%*	*N*	*%*	*N*	*%*	
Sex							
Male	43	58	42	73	85	65	0.06
Female	31	42	15	27	46	35	
Age (years)							
<60	35	47	35	61	70	53	0.10
≥60	39	53	22	39	61	47	
KRAS status							
Mutant	18	24	14	25	32	24	
Wild-type	31	42	20	35	51	39	0.68
Unknown	25	34	23	40	48	37	
ECOG PS							
0 or 1	64	86	52	91	116	89	0.39
2	10	14	5	9	15	11	
Number of metastatic sites							
1	50	67.5	34	59.6	84	64	0.35
>1	24	32.5	23	40.4	47	36	
Metastatic sites							
Liver	63	85	44	77	107	82	0.24
Lung	22	30	13	23	35	27	0.37
Peritoneum	9	12	10	17	19	15	0.38
Other	8	11	12	21	20	15	0.10
Primary tumor site							
Rectum	23	31	15	27	38	29	
Rectosigmoid colon	6	8	4	7	10	7	
Sigmoid colon	22	30	18	31	40	31	0.70
Left colon	4	5	7	12	11	9	
Right colon	16	22	11	19	27	21	
Transverse colon	3	4	2	4	5	3	
Tumor grade							
1	2	3	5	9	7	5	
2	52	70	25	44	77	59	0.05
3	11	15	8	14	19	15	
Unknown	9	12	19	33	28	21	
CEA ng/mL							
median (range)	19.7 (1.1–20.000)		21 (1. 0–2.932)		21 (1–20.000)		0.93
CA 19-9 U/mL							
median (range)	59.5 (3–15.120)		38 (2–11.650)		47.5 (1–15.120)		0.97

ECOG PS: Eastern Cooperative Oncology Group performance status, CEA: Carcinoembryonic antigen, CA 19-9: Carbohydrate antigen 19-9

Treatment

At the time of initial diagnosis, 74 (56%) patients had metastatic disease. In the remaining 57 (44%), the primary tumor was resected and the disease recurred later. Furthermore, 39 patients received adjuvant chemotherapy and 18 received adjuvant radiotherapy or chemoradiotherapy. Of those who received chemotherapy, 23 were treated with an oxaliplatin regimen and 16 were treated with 5-FU/FA in the adjuvant setting. The me-

Table 2. Treatment characteristics and efficacy of XELOX and mFOLFOX6 in 131 patients

Characteristics	*Group A XELOX*		*Group B mFOLFOX6*		*Total*		*p value*
	N	*%*	*N*	*%*	*N*	*%*	
Primary tumor resection							
Yes	31	42	26	46	57	44	0.5
No	43	58	31	54	74	56	
Number of treatment cycles							
Median	9		8		9		0.5
Range	3–22		2–34		2–34		
Response							
Objective response (CR+PR)	44	59	31	54	75	57	
CR	6	8	4	7	10	8	
PR	38	51	27	47	65	49	
SD	14	19	12	21	26	20	
Disease control rate	58	78	43	75	101	77	
CR+PR	44	59	31	54	75	57	0.6
SD+PD	30	41	26	46	56	43	
Median PFS, months (95% CI)	10 (4.2–15.9)		9.1(4.9–13.1)		10 (6,5–13.5)		0.610
Median OS, months (95% CI)	27.5 (20–38)		29 (21.6–34.3)		28 (21,6-34.5)		0.812

CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, PFS: progression free survival, OS:overall survival, CI: confidence interval

Table 3. Toxicity

Toxicity	*NCI worst toxicity*							
	XELOX (N:74)				*FOLFOX (N:57)*			
	Grade 1-2		*Grade 3-4*		*Grade 1-2*		*Grade 3-4*	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*
At least one adverse event	63 (85%)				47 (83%)			
Hematological								
Anemia	12	16	2	3	8	10	2	4
Neutropenia	11	15	1	7	18	31	6	14
Thrombocytopenia	8	10	1	6	11	19	5	9
Non-hematological								
Neuropathy	19	26	10	13	19	34	11	19
Mucositis	11	15	2	3	2	4	1	2
Vomiting	9	12	4	5	4	7	2	4
Hand-foot syndrome	11	15	5	6	2	4	-	-
Nausea	17	23	4	5	1	2	2	4
Diarrhea	11	15	6	8	5	8	3	5
Hypertension	11	15	2	3	11	19	3	5

dian number of treatment cycles for bevacizumab with XELOX and mFOLFOX was 9 and 8, respectively (range 2–34; Table 2). The median duration of treatment for mFOLFOX6 was 6 months (range 2–20) and for XELOX 8 months (range 2–24). However, at the time of analysis, treatment was still ongoing in 20 (15%) patients. The most common reason for treatment withdrawal during the study was disease progression (102 patients; 91%).

Outcome

The objective response (complete or partial response) rates in the mFOLFOX6 and XELOX arms were similar (54 and 59%, Table 2). Likewise, the disease control (complete, partial response or stable disease) rates in the mFOLFOX6 and XELOX arms were also similar (75 and 78%, Table 2). The median PFS and OS for all patients were 10 months (95% CI, 6.5–13.5) and 28 months

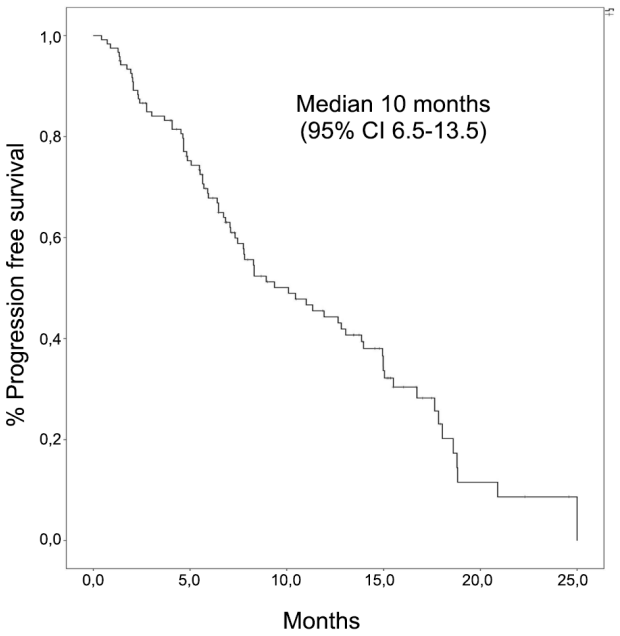

Figure 1. Progression free survival of all patients.

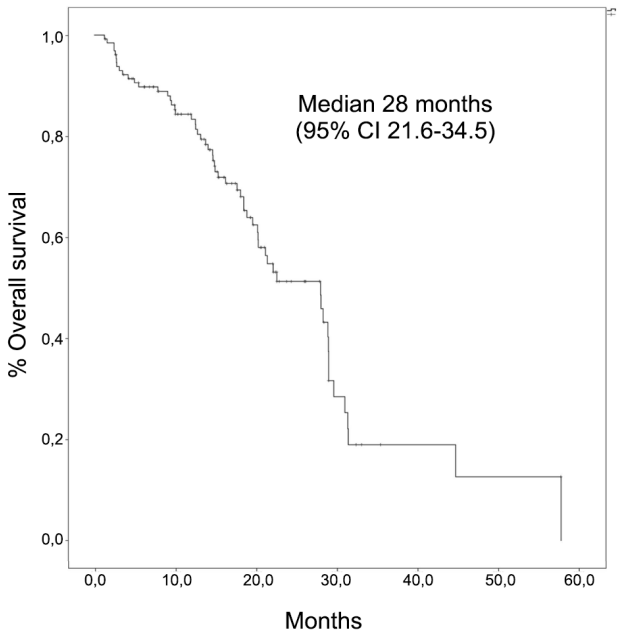

Figure 2. Overall survival of all patients.

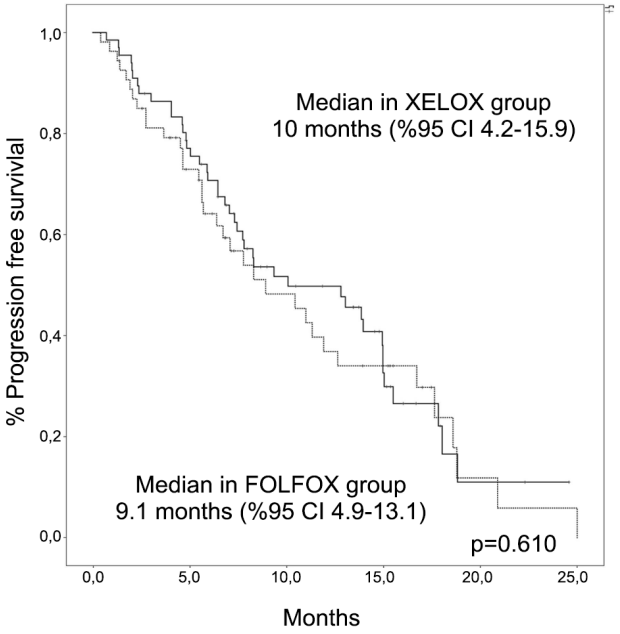

Figure 3. Progression free survival of mFOLFOX6 and XELOX treatment groups.

(95% CI, 21.6–34.5) respectively (Figures 1,2). In particular, the median PFS was 9.1 months (95% CI, 4.9–13.1) in the mFOLFOX6 group and 10 months (95% CI, 4.2–15.9) in the XELOX group (p=0.610) (Figure 3). Furthermore, the OS was 29 months (95% CI, 21.6–34.3 months) in the mFOLFOX6 arm and 27.5 months (95% CI, 20–38) in the XELOX group (p=0.812) (Table 2). PFS and OS were not associated with the demographic characteristics [initial stage (local vs metastatic), primary tumor resection (present vs not), organ involved like lung, liver or peritoneum (present vs not), sex (male vs female), age (>60 vs <60) years] of patients in either group by univariate analysis. Multivariate analysis was not performed because of the limited sample size and the low number of outcome events.

Toxicity

The most common treatment-related toxicities are shown in Table 3. In both the mFOLFOX6 and XELOX groups, the most common grade 3-4 haematological and non-haematological adverse events were neutropenia and neuropathy, respectively (Table 3). In addition, hand-foot syndrome and diarrhea were more common in patients who were treated with XELOX than in those who were treated with mFOLFOX6. Gastrointestinal perforation occurred in one patient due to bevacizumab treatment. The occurrence of bevacizumab-induced hypertension was similar in both treatment groups. All adverse events resulted in dose reductions in 23 (17.5%) patients. Proteinuria is the other toxic effect of bevacizumab, but it has not been evaluated in our study.

Discussion

This study was conducted to compare the efficacy and safety of using bevacizumab in com-

bination with either mFOLFOX6 or XELOX as a first-line combination chemotherapy regimen in mCRC. We found that survival outcome and response were similar in patients treated with bevacizumab and either mFOLFOX6 or XELOX (PFS 9.1 and 10.0 months, objective response rates 54 and 59 %, and disease control rates 75 and 78%, in the mFOLFOX6 and XELOX groups, respectively).

Since 5-FU/FA and oxaliplatin combinations were first demonstrated to be effective first- and second-line treatments for mCRC patients, many different dosing regimens have been used in clinical trials, such as FOLFOX4, FOLFOX6, and mFOLFOX6 [16-20]. Although studies have shown that the efficacy and toxicity of FOLFOX4 and FOLFOX6 are similar in mCRC patients, mFOLFOX6 is becoming the standard regimen because it uses a lower dose of oxaliplatin [3]. The XELOX regimen, which uses oral capecitabine instead of 5-FU/FA, is also popular because it requires less intravenous administration than FOLFOX regimens.

Previous studies have shown that bevacizumab in combination with FOLFOX4 or XELOX regimen is either equivalent or superior to these regimens alone [21,22]. Saltz et al. reported that addition of bevacizumab to either FOLFOX4 or XELOX significantly improved PFS (PFS: 9.4 vs 8.0 months), although OS did not reach statistical significance (OS: 21.3 vs 19.9 months) [12]. In the BEAT trial, similar to other randomised studies of first-line bevacizumab in mCRC treatment, median PFS was about 10 months and median OS was 25.9 and 23.0 months in FOLFOX and XELOX group, respectively. These results were also consistent with our results [23]. Meanwhile, although comparison of first-line treatment outcome with mFOLFOX6 plus bevacizumab vs XELOX plus bevacizumab was not basically investigated before, it is known from indirect comparisons that their efficacy seemed to be similar. In the HORIZON III study, median PFS was 10.3 months and likewise, in a Japanese study, median PFS and OS were 12.6 and 28.5 months by mFOLFOX6 plus bevacizumab. Furthermore, in another trial evaluating XELOX plus bevacizumab in Japanese population, median PFS and OS were 11.0 and 27.4 months [24-26].

In our study, the toxicities of the XELOX and mFOLFOX6 regimens were similar, but there were some differences in their side effects. Specifically, mFOLFOX6 was associated with higher rates of myelosuppression, whereas XELOX was associated with higher rates of hand-foot syndrome and gastrointestinal toxicity. Nevertheless, the incidence of both haematological and non-haematological adverse effects of these combination chemotherapy regimens were similar to previous reports [22]. For example, gastrointestinal perforation, a serious adverse event in bevacizumab therapy, occurred in only one patient (1.5%) in our study, which is comparable to its incidence reported in a meta-analysis of published randomised controlled trials [27]. In addition, the incidence of peripheral neuropathy, a common side effect of oxaliplatin, was 16% (grades 3-4) in our study, which is consistent with previous studies that used similar treatment regimens (17–18%).

Although our conclusions need to be tempered by the relatively small number of patients in the study, they are consistent with those from other clinical trials, which support the addition of bevacizumab to either mFOLFOX6 or XELOX to the oncological arsenal for mCRC patients. Having multiple treatment options is helpful because there are several other important issues besides efficacy and toxicity to consider when selecting a chemotherapy regimen, such as cost and patients' preference. For example, Pelusi and Tucker showed that patients preferred oral, rather than intravenous, antineoplastic drugs because they were easier to administer and required fewer medical office visits [28]. Twelves et al. also reported that oral capecitabine treatment results in a higher quality of life than intravenous 5-FU/FA [29]. Similarly, Conroy et al. showed that mCRC patients who were treated with XELOX or FOLFOX6 considered XELOX to be more convenient and less disruptive to their lifestyle than FOLFOX6 [30]. Several studies also have compared the cost-effectiveness of XELOX with other regimens [31,32]. For example, Aitini et al. found that the cost of XELOX for both mCRC patients and hospitals was significantly less than that for FOLFOX6 [33]. Thus, there are both clinical and economic advantages of using oral capecitabine instead of intravenous 5-FU/FA, in combination with oxaliplatin for first-line treatment of mCRC.

In conclusion, our results showed that XELOX plus bevacizumab is a safe and effective alternative to mFOLFOX6 plus bevacizumab as a first-line therapy of mCRC patients. Most likely, the choice between these two options will require a cost-benefit analysis for each patient and hospital.

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