Bevacizumab in First-line Therapy of Metastatic Colorectal Cancer: A Retrospective Comparison of FOLFIRI and XELIRI

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Abstract. *Background: The antivascular endothelial growth factor monoclonal antibody bevacizumab with infusional 5-fluorouracil, leucovorin and irinotecan (FOLFIRI) is a standard first-line treatment option for metastatic colorectal cancer. However, clinical data for capecitabine and irinotecan (XELIRI) with bevacizumab are limited. Patients and Methods: A retrospective study was conducted on 139 patients with metastatic colorectal cancer to assess the efficacy and safety of first-line bevacizumab in combination with XELIRI or FOLFIRI. Primary endpoints were overall response rate (ORR), disease control rate and radical resection rate. Secondary endpoints included overall survival (OS), progression-free survival (PFS) and safety. Results: No significant differences in efficacy were observed between patients administered XELIRI or FOLFIRI with bevacizumab. The ORR, median OS and PFS and recorded adverse events (AEs) were comparable to those previously reported, with no new or unexpected AEs observed. Conclusion: Bevacizumab is similarly efficacious and well tolerated when administered with XELIRI or FOLFIRI.*

Chemotherapy doublets including irinotecan or oxaliplatin in combination with intravenous (*i.v.*) 5-fluorouracil (5-FU) and leucovorin (LV) are well established first-line therapies for metastatic colorectal cancer (mCRC). Capecitabine (Xeloda®) is an oral prodrug that is converted into 5-FU *via* three enzymatic steps, and provides an alternative to *i.v.* 5-FU/LV (1). Accordingly, capecitabine is widely used to treat mCRC as a single agent and in combination with oxaliplatin (XELOX) (2).

There are conflicting reports regarding the efficacy and safety of capecitabine in combination with irinotecan (XELIRI) compared with the 5-FU/LV plus irinotecan regimen (FOLFIRI), with one report suggesting no difference between the regimens, and another suggesting shorter progression-free survival (PFS) and increased toxicity with XELIRI (3, 4). Therefore, the XELIRI chemotherapy regimen is currently less commonly used, and is not recognized as a standard chemotherapy regimen, unlike FOLFIRI (2).

The antivascular endothelial growth factor monoclonal antibody bevacizumab (Avastin®) improves outcomes when combined with all standard chemotherapy regimens (5-11). The use of bevacizumab in combination with standard chemotherapy is generally well tolerated by patients with mCRC and does not appear to significantly increase the incidence of chemotherapy-related toxicities compared with chemotherapy alone (5, 12). Bevacizumab is associated with an increased incidence of some adverse events (AEs) such as hypertension, bleeding and thromboembolic events, but these are generally mild-to-moderate in severity and easily managed using standard therapies (5, 12). In addition, the real-world tolerability of bevacizumab-containing regimens is broadly comparable to that observed in randomized clinical trials (8, 10).

The efficacy of bevacizumab in combination with 5-FU/LV and irinotecan has been demonstrated in several clinical trials. The phase III trial of bevacizumab plus bolus 5-FU/LV (IFL) reported a significant improvement in median PFS (10.6 *vs.* 6.2 months; hazard ratio [HR]=0.54; $p<0.001$) and median overall survival (OS) (20.3 *vs.* 15.6 months, HR=0.66; $p<0.001$) compared with IFL alone (5). A randomized phase III trial and a large, single-arm phase IV study of bevacizumab in combination with FOLFIRI reported median PFS of 11.2 and 11.1 months, respectively, and median OS of 28.0 and 22.2 months, respectively (3, 9, 13). In addition, subgroup analysis of the BEAT study by chemotherapy regimen found that patients treated with bevacizumab plus FOLFIRI (median PFS 11.6 months; median OS 23.7 months) obtained similar clinical benefit when compared with the total population (median PFS 10.8 months; median OS 22.7 months) (7).

In contrast to the data for bevacizumab plus FOLFIRI, the reported data on the use of bevacizumab plus XELIRI in the treatment of mCRC are limited to smaller studies. Various

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studies have reported response rates of 43-55%, median PFS of 8-13 months and median OS of 14-25 months in the first-line treatment of mCRC (14-17).

Preliminary data from other studies undertaking head-to-head comparisons of XELIRI or FOLFIRI in combination with bevacizumab have suggested that these two treatment regimens offer comparable efficacy, but potentially different safety profiles (18, 19). The present retrospective study further investigates the relative efficacy and safety of first-line bevacizumab in combination with XELIRI or FOLFIRI in patients with mCRC.

Patients and Methods

Study design. A retrospective analysis was performed on patients with mCRC treated with bevacizumab-based therapy at the Institute of Oncology, Ljubljana, Slovenia. This study was proposed in November 2007 and subsequently approved by local scientific and national Ethics Committees (Komisija Republike Slovenije za medicinsko etiko, reference number 71/12/07. Trial registration; Current Controlled Trials ISRCTN59241668 [http:// www.controlled-trials.com/ISRCTN59241668]).

Patients. Patients were eligible for inclusion if they were aged ≥18 years, had histologically or cytologically confirmed carcinoma of the colon or rectum with evidence of metastasis and were scheduled to commence first-line fluoropyrimidine-based chemotherapy. In addition, patients were required to have an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1, with adequate hematological and organ function.

Patients were excluded if they had received prior chemotherapy for mCRC (adjuvant chemotherapy was permitted), surgery within 28 days of starting treatment, clinical evidence of brain metastasis, a thrombotic or bleeding event within 6 months, clinically significant cardiovascular disease, therapeutic anticoagulation, hemorrhagic diathesis or coagulopathy, a serious non-healing wound, an ulcer or bone fracture, or treatment with aspirin (>325 mg/day) or any other medications predisposing to gastrointestinal ulceration.

Treatment. Patients were eligible if they had received one of two regimens, based on the multidisciplinary team's decision and patient's preference. One group received 7.5 mg/kg bevacizumab *i.v.* every 3 weeks in combination with 250 mg/m^2 irinotecan *i.v.* and 1,000 mg/m^2 oral capecitabine twice daily (days 1–14) (XELIRI) until disease progression. The other group received 5 mg/kg bevacizumab *i.v.* every 2 weeks in combination with 180 mg/m^2 irinotecan *i.v.*, 400 mg/m^2 LV *i.v.*, and a 400 mg/m^2 *i.v.* bolus dose of 5-FU, followed by 2,400 mg/m^2 5-FU as a 46-hour *i.v.* infusion (FOLFIRI) until disease progression.

Bevacizumab treatment was to be continued beyond disease progression in combination with other chemotherapy regimens, provided that the patient responded to first-line treatment and no serious AEs had been experienced.

Endpoints and analysis. All relevant data from medical files were entered into a database and baseline data collected and analyzed for age, PS at the time of inclusion, sex, primary tumor site (colon or rectum), number and location of metastases. Efficacy was evaluated using the Response Evaluation Criteria In Solid Tumours (RECIST) using computed tomography (CT) scans, magnetic resonance imaging scans, ultrasound, X-ray, bone scans, and clinical examination. Safety was monitored by physical examination, laboratory tests and by observing vital signs. Toxicity was assessed according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI–CTCAE) version 3.0 (20).

The primary endpoints were overall response rate (ORR) (based on RECIST criteria), disease control rate (DCR), and the rate of radical resection (R0). The secondary endpoints included PFS, OS and safety of bevacizumab in combination with FOLFIRI or XELIRI.

The χ^2–test was used to compare ORR and DCR between groups, with 95% confidence intervals (CI) calculated for the medians. PFS and OS were estimated using Kaplan-Meier estimates and compared using the log-rank test. Safety parameters were analyzed descriptively using frequency tables.

Results

In total, 139 patients with mCRC who received first-line treatment with bevacizumab plus FOLFIRI or XELIRI between February 2005 and December 2007 were included in the study. The cut-off date for the present analysis was April 2010.

The two treatment groups were generally well balanced with respect to baseline and disease characteristics (Table I). Treatment was initiated within 3 months of diagnosis of unresectable mCRC in 99.3% of patients, and a large proportion of patients (47%) had metastatic disease at initial diagnosis. Ninety-four patients (68%) received first-line treatment with bevacizumab plus XELIRI and the remainder (45 patients; 32%) received bevacizumab plus FOLFIRI. There was no significant difference in the median duration of chemotherapy between the groups of patients who received XELIRI (23.0 [range: 21.4-24.1] weeks) and those who received FOLFIRI (23.7 [range: 23.0-26.4] weeks; p=0.155). The median duration of bevacizumab treatment was also similar in patients treated with XELIRI (25.1 [range: 23.0-28.0] weeks) and those treated with FOLFIRI (25.0 [range: 23.3-31.4] weeks). Furthermore, bevacizumab monotherapy was administered as maintenance first-line treatment to 28 (30%) patients in the XELIRI group and 9 (20%) patients in the FOLFIRI group.

Efficacy. The ORR was similar in the XELIRI and FOLFIRI groups (49% *vs*. 40%, p=0.263; Table II). However, the DCR was significantly higher in the XELIRI group compared with the FOLFIRI group (86% *vs*. 76%, p=0.033).

Overall, disease progression was reported in 119 patients (86%). Median PFS was similar (p=0.414) in both treatment groups: 11.7 months (95% CI: 10.5-13.1) and 11.6 months (95% CI: 9.1-14.2) in the bevacizumab plus XELIRI and bevacizumab plus FOLFIRI groups, respectively (Figure 1). However, a trend towards a longer median OS was observed in the XELIRI group compared with the FOLFIRI group (27.8 months [95% CI: 24.0–not reached] *vs*. 24.8 months [95% CI: 22.3-32.5], p=0.072; Figure 2A).

Table I. *Baseline and disease characteristics of patients receiving bevacizumab (BEV) in combination with FOLFIRI or XELIRI.*

	BEV + FOLFIRI (n=45)	BEV + XELIRI (n=94)	Overall (n=139)
Male/female, (%)	58/42	64/36	62/38
Age, years			
Median (range)	57 (31-74)	60 (37-77)	58 (31-77)
WHO PS, n (%)			
0	35 (78)	85 (90)	120 (86)
1	10 (22)	9 (10)	19 (14)
Primary tumor location, n (%)			
Colon	35 (78)	64 (68)	99 (71)
Rectum	10 (22)	30 (32)	40 (29)
Metastatic site, n (%)			
Liver	26 (58)	60 (64)	86 (62)
Lung	1 (2)	9 (10)	10 (7)
Liver and lung	6 (13)	7 (7)	13 (9)
Other	12 (27)	18 (19)	30 (22)

WHO PS, World Health Organization performance status.

Table II. *Response rates in patients receiving bevacizumab (BEV) in combination with FOLFIRI or XELIRI.*

Response, n (%)	BEV + FOLFIRI (n=45)	BEV + XELIRI (n=94)	Overall (n=139)
Overall response rate (CR+PR)	18 (40)	46 (49)*	64 (46)
Disease control rate (CR+PR+SD)	34 (76)	81 (86)‡	115 (83)
CR	8 (18)	14 (15)	22 (16)
PR	10 (22)	32 (34)	42 (30)
SD	16 (36)	35 (37)	51 (37)
PD	9 (20)	7 (7)	16 (12)
Missing data	2 (4)	6 (6)	8 (6)

*p=0.263 *vs*. bevacizumab + FOLFIRI; ‡p=0.033 *vs*. bevacizumab + FOLFIRI. CR, Complete response; PR, partial response; SD, stable disease.

Surgical resection of liver metastases was performed in 24% (n=34/139) of patients from the overall population, representing 34% of patients who presented with liver metastases. R0 resection was achieved in 23 patients (17% of the overall population or 68% of those who underwent surgery), which included 4 (9%) patients who received first-line bevacizumab plus FOLFIRI and 19 (20%) patients who received first-line bevacizumab plus XELIRI (Table III). Furthermore, median OS was significantly longer in patients with R0 or R1 resection compared with patients who did not undergo resection (42.9 months [95% CI: 38.5–not reached] *vs*. 24.4 months [95% CI: 21.4-27.1], p<0.001; Figure 2B).

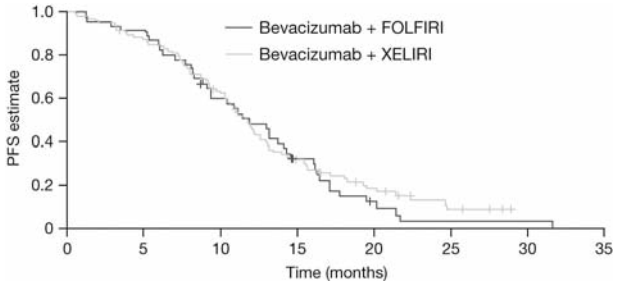

Figure 1. *Progression-free survival (PFS) in patients receiving bevacizumab in combination with FOLFIRI or XELIRI.*

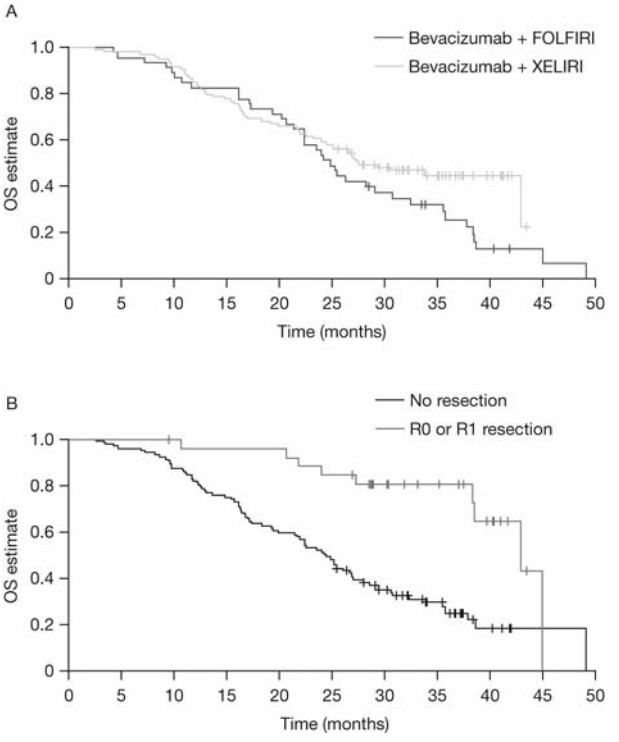

Figure 2. *Overall survival (OS) in A: all patients receiving bevacizumab in combination with FOLFIRI or XELIRI and B: patients who did or did not undergo R0 or R1 resection (p<0.001).*

Table III. *Resection rates of patients treated with bevacizumab (BEV) in combination with FOLFIRI or XELIRI.*

Surgical resection, n (%)	BEV + FOLFIRI (n=45)	BEV + XELIRI (n=94)	Overall* (n=139)
R0	4 (9)	19 (20)	23 (17)
R1	4 (9)	2 (2)	6 (4)
R2	2 (4)	3 (3)	5 (4)
No resection	35 (78)	70 (75)	105 (76)

*Total percentage not 100 due to rounding up of data.

Table IV. *AEs experienced by patients treated with bevacizumab (BEV) and FOLFIRI or XELIRI.*

AE (%)	BEV + FOLFIRI (n=45)		BEV + XELIRI (n=94)		Overall (n=139)	
	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4	Grade 1/2	Grade 3/4
Anemia	26	0	20	1	22	<1
Leucopenia	40	5	27	0	31	1
Neutropenia	26	23	26	5	26	11
Hand-foot syndrome	9	0	21	3	17	2
Mucositis	21	0	8	0	12	0
Nausea	23	0	26	0	25	0
Vomiting	9	0	17	0	15	0
Diarrhea	23	0	32	7	29	5
Infection	23	0	19	0	20	0
Febrile neutropenia	2		2		2	
Hypertension*	5	5	14	5	11	5
Proteinuria*	28	2	25	4	26	4
Bleeding*	33	0	12	2	19	1
Deep vein thrombosis*	0		7		5	
Pulmonary embolism*	0		2		1	
Fistula/abscess*	0		2		1	
Gastrointestinal perforation*	0		1		<1	

*AEs considered possibly or probably related to bevacizumab treatment. Incidence of AEs.

Safety and tolerability. The incidence of grade 1/2 and grade 3/4 AEs is reported in Table IV, including AEs of special interest to bevacizumab. The most common grade 3 and 4 AEs were neutropenia (23% FOLFIRI group) and diarrhea (7% XELIRI group). The most common grade 3 and 4 AEs related to bevacizumab were hypertension (5%) in the FOLFIRI group, and hypertension (5%), proteinuria (4%) and thrombosis (7%) in the XELIRI group.

AEs leading to discontinuation of any component of the treatment regimen occurred in 24% of patients. A total of 5 patients in the FOLFIRI group and 11 patients in the XELIRI group withdrew from chemotherapy due to an AE. The most frequent AEs leading to chemotherapy withdrawal were neutropenia, cardiac ischemia and thrombophlebitis in the FOLFIRI group, and diarrhea in the XELIRI group. A total of 23 patients (17%) withdrew from bevacizumab treatment due to bevacizumab-related AEs, which were more common in the XELIRI group (n=18, 19%) compared with the FOLFIRI group (n=5, 11%). The most common reasons for bevacizumab discontinuation were hypertension, deep vein thrombosis and bleeding (n=4 each) in the XELIRI group and proteinuria (n=3) in the FOLFIRI group. No grade 3 or 4 wound-healing complications or deaths due to AEs were reported.

Discussion

Bevacizumab plus XELIRI is proposed to be an effective and well-tolerated regimen for the first-line treatment of mCRC. This retrospective study found that bevacizumab plus XELIRI provided comparable efficacy and safety to bevacizumab plus FOLFIRI, a standard first-line treatment for patients with mCRC.

The results described here are in alignment with the preliminary data reported from two similar studies. Ducreux and colleagues (18) found that combining bevacizumab with XELIRI or FOLFIRI resulted in a median PFS of 9 months, and median OS of 23 months, in both groups. Another study by the Hellenic Cooperative Oncology Group (HeCOG) recorded a median PFS of 14.6 months following treatment with bevacizumab plus XELIRI, and 15.8 months with bevacizumab plus FOLFIRI (19). Median OS of 20.0 months and 26.2 months, respectively, were also reported in this study (19). Notably, there was no significant difference in PFS or OS between arms in both studies, as is the case here (18, 19). These two studies also reported that the ORR was similar in the bevacizumab plus FOLFIRI and bevacizumab plus XELIRI arms (18, 19). Thus, the three head-to-head studies indicate that the efficacy of bevacizumab plus XELIRI is

comparable to bevacizumab plus FOLFIRI. However, there are some small differences between the trials, such as the present study is based on retrospective analysis of a single institution, whereas the HeCOG and Ducreux studies were both prospective, randomized studies (18, 19). In addition, while each of these studies refers to the use of XELIRI and FOLFIRI chemotherapy regimens, there are slight variations in dosing, particularly in terms of the irinotecan dose.

The efficacy of bevacizumab plus FOLFIRI observed in this study is consistent with that reported in large observational and phase IV studies that also assessed bevacizumab plus FOLFIRI in the first-line treatment of mCRC (7, 9, 21). In addition, the efficacy of bevacizumab plus XELIRI reported here is consistent with earlier studies of bevacizumab plus XELIRI in the first-line treatment of mCRC (14–17). Overall, these data indicate that bevacizumab plus XELIRI is an effective first-line treatment regimen which appears to provide comparable efficacy to bevacizumab in combination with other standard chemotherapy regimens.

In this study, 32% of patients who presented with liver metastases (including 14 patients with metastases in multiple organs) underwent resection, with 23% achieving R0 resection. Notably higher rates of resection were reported in the bevacizumab plus XELIRI treatment group. Earlier studies reported that 19-22% of patients with previously unresectable liver-only metastases underwent resection following treatment with bevacizumab and irinotecan-based chemotherapy (22, 23). Approximately 12% achieved R0 resection (22). Accordingly, the resection rates reported in this study suggest that patients treated with bevacizumab plus XELIRI have a similar likelihood of undergoing resection when compared with patients receiving bevacizumab plus FOLFIRI therapy. However, it should be remembered that assessing resectability, particularly when making a cross-trial comparison, can be highly subjective, and influenced by small sample sizes, differences in patient selection/baseline characteristics and definition of resectability.

The treatment regimens used here were well tolerated, with the reported incidence of bevacizumab-related AEs being comparable to those observed in previous studies of bevacizumab-based therapy in the first-line treatment of mCRC (5, 7, 12, 21). However, a slightly higher incidence of some AEs was observed in the bevacizumab plus XELIRI group compared with bevacizumab plus FOLFIRI group. These findings are consistent with the HeCOG study, which reported higher levels of neutropenia, metabolic disorders and vomiting in the XELIRI treatment arm compared with the FOLFIRI arm (19). Earlier studies of chemotherapy alone have reported increased rates of grade ≥3 gastrointestinal toxicity in patients receiving XELIRI alone (3, 24). However, a later study reported improved tolerability with XELIRI in combination with bevacizumab by using lower doses of irinotecan (200 mg/m^2) and capecitabine (800 mg/m^2 twice daily), a 20% dose reduction from the current study, which reduced the incidence of chemotherapy-related events without compromising efficacy (15).

Conclusion

Overall, the XELIRI and FOLFIRI chemotherapy regimens were found to have comparable efficacy when used in combination with bevacizumab. Bevacizumab was also well tolerated with no new or unexpected AEs being reported. This study adds to a growing body of evidence in support of using XELIRI and bevacizumab in the first-line treatment of mCRC.

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Declaration of Competing Interests

Janja Ocvrik and Martina Rebersek have received symbolic investigator fees for participation in studies funded by F. Hoffmann-La Roche Ltd. These Authors have no other competing interests to declare. Marko Boc has no competing interests.

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