Bevacizumab in Combination with FOLFIRI in the First-Line Treatment of Patients with Advanced Colorectal Cancer: A Single-Institution Experience

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Abstract: *Introduction*: Bevacizumab combined with IFL (irinotecan, bolus 5-fluorouracil, and leucovorin) has been shown to improve outcomes for patients with metastatic colorectal cancer (mCRC). However, infusional 5-fluorouracil-based combinations are now considered optimal in this setting. We analyzed the efficacy and toxicity of FOLFIRI (irinotecan, infusional 5-fluorouracil, and leucovorin)–bevacizumab in an unselected cohort of consecutive patients with mCRC.

Materials and Methods: Patients with unresectable mCRC received bevacizumab 5 mg/kg and irinotecan 180 mg/m² on day 1, leucovorin 200 mg/m² on days 1 and 2, 5-fluorouracil 400 mg/m² bolus, and 600 mg/m² continuous infusion on days 1 and 2, every 14 days. Overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and safety were assessed.

Results: Overall, 127 patients were included (69% male, median age 64 years); 15 patients had diabetes, 40 had hypertension, and 23 were undergoing anticoagulant/antiplatelet therapy. Median PFS was 11.0 months (95% CI 10.0–12.0); median OS was 26.0 months (95% CI 21.9–30.1). The ORR was 55.1% (95% CI 46.3–63.6%), with 12 complete responses, 58 partial responses, and 44 patients with stable disease. Salvage surgery was performed in 31 patients (24%), including 23 with liver metastases and one with lung metastases. Grade 3/4 toxicities included neutropenia (17%), vomiting (6%), and diarrhea (17%); grade 3/4 bevacizumab-related toxicities included hypertension (2%), hemorrhage (2%), and venous (7%) and arterial thromboembolic events (5%).

Conclusion: FOLFIRI–bevacizumab was active and tolerable in this cohort of unselected patients with mCRC, resulting in a high surgical rescue rate and prolonged survival.

Keywords: Bevacizumab, colorectal cancer, FOLFIRI, anticoagulant therapy, surgical rescue.

INTRODUCTION

It has been estimated that more than 1.2 million new cases of colorectal cancer were diagnosed worldwide in 2008 [1]. In Europe, colorectal cancer accounts for approximately 200,000 deaths annually [2]. Most patients are diagnosed with early stage disease, but an estimated 20% of patients have metastatic disease at presentation [3] and 40–50% will go on to develop metastases during the course of their disease.

The standard treatment for patients with metastatic colorectal cancer (mCRC) is fluoropyrimidine-based chemotherapy, the aim of which is to improve survival and quality of life. Outcomes have improved for patients with mCRC since the addition of irinotecan and oxaliplatin to 5-fluorouracil (5-FU), and the more recent introduction of bevacizumab and cetuximab. For some patients in whom metastases are confined to one organ, such as the liver or lung, downsizing metastases may be an outcome of initial chemotherapy that can significantly extend survival.

The addition of bevacizumab, a humanized monoclonal antibody that inhibits tumor angiogenesis, to bolus irinotecan and 5-FU resulted in improved overall survival (OS), progression-free survival (PFS), and response rates compared with placebo plus chemotherapy in patients with previously untreated mCRC [4]. More recently, the BICC-C study demonstrated that an infusional irinotecan regimen (irinotecan, infusional 5-fluorouracil, and leucovorin [FOLFIRI]) plus bevacizumab was as well tolerated as and more effective than bolus IFL (irinotecan, bolus 5-fluorouracil, and leucovorin) plus bevacizumab [5]. Further evidence for the efficacy and tolerability of bevacizumab and FOLFIRI was provided by the Phase IV AVIRI study [6].

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Here we report a single-institution experience with bevacizumab in combination with FOLFIRI in an unselected cohort of patients with mCRC, including those with significant comorbidities and concomitant anticoagulation.

PATIENTS AND METHODS

Patients

Consecutive patients presenting at our institution (Hospital de Cruces, Barakaldo, Spain) were included in the study if they had histologically proven, colorectal adenocarcinoma with metastases, no prior chemotherapy for metastatic disease, were aged ≥18 years, and had an Eastern Cooperative Oncology Group (ECOG) performance status of ≤2. Patients were required to have adequate hematologic function (hemoglobin >9 g/dL, neutrophil count >1,500/μL, and platelet count >100,000/μL), renal function (creatinine clearance >50 mL/min/1.73 m^2), liver function (bilirubin) <1.5 × upper limit of normal), and proteinuria <2+. All major surgery should have been completed at least 28 days before the first infusion of bevacizumab. Patients were excluded if they had poorly controlled hypertension, severe cardiovascular disease, active bleeding or coagulopathy, or open wounds. Pregnant women were not included in the study, nor were patients with severe infection or a history of abdominal fistula or intestinal perforation.

Treatment Plan

Patients received bevacizumab 5 mg/kg and irinotecan 180 mg/m² on day 1, plus leucovorin 200 mg/m², and 5-FU 400 mg/m² bolus and 600 mg/m² by 22-hour continuous infusion on days 1 and 2, every 14 days. The initial irinotecan dose could be reduced to 150 mg/m^2 in patients older than 70 years. Subsequent dose reductions were dependent on toxicity assessed according to National Cancer Institute Common Terminology Criteria for Adverse Events (version 2.0): doses were reduced by 20–25% in cases of grade 4 hematologic toxicity or grade 3 non-hematologic toxicity. Before each cycle, complete blood counts, liver and kidney function tests, tumor markers (carcinoembryonic antigen [CEA] and cancer antigen [CA19.9]), urine sediment and proteinuria, and blood pressure were measured. To continue with the next cycle, patients had to have a platelet count >100,000/μL, neutrophil count >1,500/μL, and proteinuria ≤2 on routine urine dipstick. If proteinuria was 2+, urine collection had to demonstrate ≤1 g of protein over 24 hours.

Treatment was discontinued when a maximum response was achieved. Patients were withdrawn from the study if they had disease progression or unacceptable toxicity, if withdrawal was their expressed wish, or if discontinuation was considered by the investigator to be in their best interest.

The study was approved by the local ethics committee. It was conducted in accordance with the principles of the Declaration of Helsinki and adhered to Good Clinical Practice Guidelines. Patients provided written informed consent for the study.

Assessments

All patients were required to have a baseline computed tomography (CT) scan of the thorax, abdomen, and pelvis <28 days before other diagnostic tests were performed. Patients underwent a baseline medical examination to collect demographic data and information about concomitant diseases and ongoing treatments. Blood tests were performed in the 14 days before study entry to measure liver and kidney function, and CEA and CA19.9 levels; urinalysis was performed to measure proteinuria. KRAS status was also assessed in patients recruited after 2005, before which KRAS determination was not standard clinical practice.

Response was assessed every 8–12 weeks by CT scan and classified according to Response Evaluation Criteria in Solid Tumors (RECIST). PFS was calculated from the start of treatment cycle 1 until tumor progression or death from any cause. OS was calculated from the start of study treatment until death from any cause. Survival data for patients receiving second-line chemotherapy (with or without bevacizumab) were calculated from the date of commencement of the second-line regimen and from the start of the study until death from any cause.

Statistical Methodology

All statistical analyzes were performed using SPSS version 17 for Windows (SPSS, Chicago, IL, USA). *P*-values <0.05 were considered statistically significant. Chi-square (and Fisher's exact test where necessary) and Mann-Whitney tests were used for comparison of variables as appropriate. Survival analysis was performed using the Kaplan–Meier and log-rank tests.

RESULTS

Patient Population

A total of 127 patients were entered into the study between August 2005 and August 2008. Patient characteristics at baseline are summarized in Table **1**. White blood cell counts of >10,000/μL were observed in 22 patients (17%) and alkaline phosphatase levels >300 U/l in 12 patients (9%), indicating poor-prognosis patients.

Table 1: Patient Characteristics at Baseline (*n*=127)

Characteristic	Value
Median age, years (range)	64 (29–83)
Age >70 years, *n* (%)	38 (29.9)
Sex	
Male	87 (68.5)
Female	40 (31.5)
ECOG performance status, *n* (%)	
0	60 (47.2)
1	64 (50.4)
2	3 (2.4)
Metastases, *n* (%)	
Synchronous	73 (57.5)
Metachronous	54 (42.5)
Primary tumor type, *n* (%)	
Colon	73 (57.5)
Rectum	52 (40.9)
Both	2 (1.6)
Prior adjuvant therapy, *n* (%)	
Chemotherapy	44 (34.6)
Radiotherapy	24 (18.9)
Location of metastases, *n* (%)	
Liver	77 (60.6)
Liver only	42 (33.1)
Pulmonary	37 (29.1)
Peritoneal	23 (18.1)
Nodes	28 (22.0)
Other	7 (5.5)
Comorbidities	
Diabetes mellitus	15 (11.8)
Hypertension	40 (31.5)
Peptic ulcer	11 (8.7)
Prior vascular disease[1]	17 (13.4)
Concomitant anticoagulation and/or platelet-inhibitor therapy	23 (18.1)
Aspirin	12 (9.4)
Platelet-aggregation inhibitor[2]	5 (3.9)
Aspirin and platelet-aggregation inhibitor	1 (0.8)
Aspirin and low molecular weight heparin	1 (0.8)
Acenocoumarol	4 (3.1)

[1]Stroke or transient ischemic attacks, *n*=4; ischemia, *n*=9; deep vein thrombosis, *n*=2; lower limb claudication, *n*=2.
[2]Clopidogrel *n*=4, triflusal *n*=1, and ticlopidine *n*=1.
Abbreviation: ECOG = Eastern Cooperative Oncology Group.

In total, 122 patients (96%) had measurable disease according to RECIST; 29% had an unresected primary tumor or locally recurrent disease. The median number of metastatic sites was 1 (range 1–4). Liver metastases were bilobar in 27 patients (21%). The median size of liver metastases was 29 mm (range 8–140 mm).

Treatment

The median number of treatment cycles administered was 12 (range 1–29; total 1,424). A reduced initial dose of irinotecan (150 mg/m^2) was given to 28% of patients, most of whom were older than 70 years. Five patients had their initial dose of 5-FU reduced by 20–25% at the physician's discretion.

Following progression, 92 patients (72%) received second-line therapy. Of these, 62 patients (67%) were re-treated with bevacizumab (FOLFIRI–bevacizumab, *n*=49; 5-FU, leucovorin, and oxaliplatin [FOLFOX]–bevacizumab, *n*=11; irinotecan–bevacizumab, *n*=1; IFL–bevacizumab, *n*=1); these were primarily those patients who had achieved maximum benefit from treatment. A further 30 patients (33%) received other regimens, including FOLFOX (*n*=13), FOLFIRI (*n*=5), and cetuximab-based therapy (*n*=3).

A total of 55 patients (43%) received a third-line regimen, including 18 (33%) who received FOLFIRI–bevacizumab, 11 (20%) who received FOLFOX–bevacizumab, and 9 (16%) who received cetuximab-based therapies; 25 patients (20%) had a fourth-line regimen.

Efficacy

Response to treatment is summarized in Table **2**. The response rate was 55% and disease control was achieved in 90% of patients. The median OS was 26.0 months (95% confidence interval [CI] 21.9–30.1

Table 2: Response to Treatment (*n*=127)

Outcome	Value
Response, *n* (%)	
Complete response	12 (9.4)
Partial response	58 (45.7)
Stable disease	44 (34.6)
Progressive disease	7 (5.5)
Not evaluable, *n* (%)	2 (1.6)
Early withdrawal, *n* (%)	4 (3.1)
Overall response rate, %	55.1
Disease-control rate, %	89.8

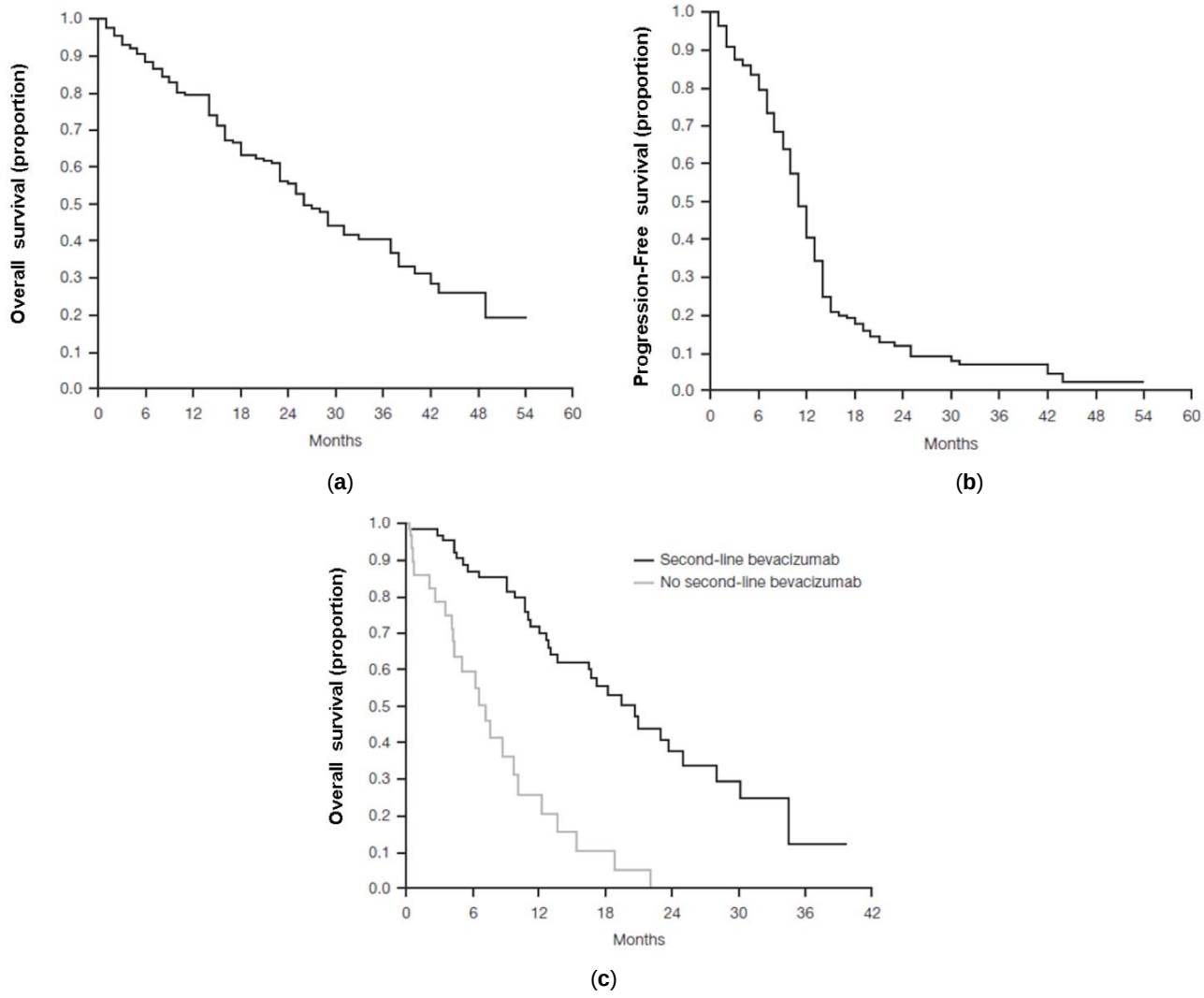

Figure 1: (**a**) Overall survival in the intent-to-treat population, (**b**) progression-free survival in the intent-to-treat population, and (**c**) overall survival from the start of second-line therapy according to second-line bevacizumab.

months) (Figure **1a**) and median PFS was 11.0 months (95% CI 10.0–12.0 months) (Figure **1b**).

Salvage surgery was undertaken in 31 patients (24%): liver metastases (*n*=23); primary tumor (*n*=2), distant lymph node metastases (*n*=2), peritoneal metastases (*n*=2), and pulmonary and ovarian metastases (*n*=1 each). Only one patient required reoperation as a result of complications from surgery. The pathologic complete response rate was 13%, with two responses in the liver, one in the lung, and one at node level.

OS was also analyzed according to whether patients had received second-line bevacizumab. In those with bevacizumab retreatment, median OS from the start of second-line therapy was 20.8 months (95% CI 17.3–24.3 months), compared with 7.9 months (95% CI 5.5–10.4 months) in those who received chemotherapy alone (p<0.001; log-rank test) (Figure **1c**).

Among patients re-treated with FOLFIRI–bevacizumab, response rates were 37% after the first re-treatment (median 12 cycles; range 1–29 cycles), 5% after the second re-treatment (median 11 cycles; range 1–22 cycles), and 0% after the third re-treatment (median 3.5 cycles; range 2–13 cycles).

Safety

The most common reason for treatment discontinuation was that maximum benefit had been achieved (*n*=88; 69%); other reasons were: disease progression (*n*=20; 16%); toxicity (*n*=16; 13%) and patient refusal (n=2; 1.6%). One patient was still on therapy at the time of this analysis. At the data cut-off, 60% of patients had died, 30% were alive with disease,

8% were alive without disease, and one patient was lost to follow-up. Two toxic deaths were reported as a result of septic shock without neutropenia. Grade 3/4 adverse events are summarized in Table **3**.

Table 3: Grade 3/4 Adverse Events Occurring in >2% of Patients Treated with FOLFIRI–Bevacizumab (*n*=127)

Adverse event	No. of patients (%)
Anemia	4 (3.1)
Neutropenia	21 (16.5)
Febrile neutropenia	5 (3.9)
Nausea	8 (6.3)
Vomiting	7 (5.5)
Diarrhea	21 (16.5)
Mucositis	5 (3.9)
Infection[a]	10 (7.9)
Subocclusion	4 (3.1)
Anorexia	4 (3.1)
Hepatic toxicity	5 (3.9)
Asthenia	13 (10.2)
Hemorrhage	3 (2.4)
Venous thromboembolism	9 (7.1)
Arterial thromboembolism	6 (4.7)
Intestinal fistula	3 (2.4)

[a]Includes two grade 5 events.
Abbreviation: FOLFIRI = infusional 5-fluorouracil, leucovorin, and irinotecan.

Among the 23 patients with anticoagulation and/or platelet-inhibitor therapy, there was no significant difference in the incidence of bleeding compared with those who were not treated with these agents (grade 2/3 bleeds in 4 versus 5 of 104 patients, respectively; p=0.056). Similarly there was no apparent increase in venous thromboembolic events (grade 2–4 events in 0 versus 10 patients; p=0.206) or arterial thromboembolic events (grade 3/4 events in 3 patients each; p=0.072). However, there appeared to be a slightly increased risk of arterial thromboembolism in the 19 patients undergoing treatment with antiplatelet therapy (grade 3/4 events in 3 patients) compared with patients who had no antiplatelet therapy (3 of 108 patients; p=0.043).

DISCUSSION

The present study adds to the available body of evidence showing that the combination of bevacizumab and FOLFIRI is an effective and well-tolerated regimen in patients with mCRC. Patients in this study had a median OS of 26 months, PFS of 11 months, and disease-control rate of 90%, with surgical resection of metastases in 24% of patients – results that compare favorably with results from studies such as BEAT [7], BRiTE [8], BICC-C [5], and AVIRI [6]. These promising results were obtained despite the fact that patients were only treated until a maximal response was reported and not until progressive disease, although the re-induction rate was high. In addition, patients were unselected, presented with a variety of comorbidities, and some were taking concomitant anticlotting agents.

Analysis of OS according to second-line treatment indicated that patients who received bevacizumab in the first and second lines had better OS than those who only had first-line bevacizumab. This is in agreement with the results of the ML18147 study, in which patients who progressed following first-line bevacizumab plus chemotherapy were randomized to either chemotherapy alone (crossed over from the first-line regimen) or bevacizumab plus chemotherapy [9]. Patients in that study who received bevacizumab plus chemotherapy had a median OS of 11.2 months compared with 9.8 months for chemotherapy alone (hazard ratio [HR] 0.81; 95% CI 0.69–0.94; unstratified log-rank test p=0.006) and a median PFS of 5.7 months versus 4.1 months (HR 0.68; 95% CI 0.59–0.78; unstratified log-rank test p<0.001).

The resection and pathologic complete response rates were 24% and 13%, respectively, in this group of patients, which included patients with either stage IV disease with synchronous metastases or stage I–III disease with metachronous metastases; resection of liver metastases occurred in 18% of patients. This compares well with the proportion of patients in the BEAT study, all of whom had stage IV disease at baseline, who underwent curative-intent surgery (12%); 77% of those patients achieved an R0 resection [10]. Cross-study comparisons must be made with caution, however, particularly where the patient profiles differ between the studies.

Adverse events were generally manageable in the present study and no new safety signals were identified. The incidence of neutropenia was lower than observed in other studies using this combination: 16% of our patients had grade 3/4 neutropenia, compared with 54% of patients treated with bevacizumab plus FOLFIRI in the BICC-C study [5] and 29% of patients in the Phase IV AVIRI study [6]. Allowing older patients to

begin treatment at a lower dose of irinotecan may have helped to reduce the incidence of neutropenia in the present study.

Randomized clinical trials frequently exclude patients with comorbidities, such as heart conditions requiring anticoagulation/antiplatelet therapy. The question of whether such patients can be treated in the real-world setting may be answered by observational studies such as that described in the present report. Treatment with bevacizumab did not appear to be associated with an increase in hemorrhage or venous thromboembolism in patients undergoing antithrombotic therapy in this study, although there appeared to be a slight increase in arterial thromboembolism in these patients. This may be due to a difference in medical history of patients requiring antiplatelet therapy for underlying disease. However, the numbers of patients in these subgroups were small, so these results should be interpreted with caution. In a subgroup analysis of the observational BEAT study, Van Cutsem and colleagues did not observe an increase in arterial thromboembolism in patients with concurrent bevacizumab and anticoagulants, although an increase in venous thromboembolism was apparent in that analysis [11]. Similar results have been described in other studies [12–14] and suggest that concurrent administration of bevacizumab and anticoagulant medication does not appear to adversely affect the safety profile of bevacizumab-based therapy.

Although representative of the real-life clinical setting, this was an observational study and therefore subject to the limitations of such studies including a greater likelihood of patient selection and attrition bias. Nonetheless, observational studies such as this provide an important insight into the application of treatment in a less rigorously controlled environment than a formal clinical study. Such studies also provide an opportunity to investigate the effect of a treatment on uncommon adverse events, such as the analysis of bleeding events in patients undergoing anticoagulant or antiplatelet therapy in the present study. That analysis was, however, limited by the small numbers of patients involved in the present study and our results require confirmation in larger studies.

This study provides evidence that the combination of bevacizumab and FOLFIRI is an effective and well-tolerated first-line treatment regimen for patients with mCRC in the real-world setting. The efficacy of this combination was comparable with results of other studies and no new safety signals were identified.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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