# Bevacizumab in combination with FOLFIRI chemotherapy in patients with metastatic colorectal cancer: an assessment of safety and efficacy in the province of Newfoundland and Labrador

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## ABSTRACT

### Background

In 2005, bevacizumab was approved by Health Canada for patients with metastatic colorectal cancer (mCRC). Newfoundland and Labrador was one of the first Canadian provinces to fund this agent in combination with FOLFIRI (irinotecan, 5-fluorouracil, leucovorin) chemotherapy. In this analysis, the entire provincial bevacizumab sample for the first 2 years was assessed for overall safety and efficacy.

### Methods

The medical records of 43 patients with mCRC who had received FOLFIRI with bevacizumab were identified and reviewed. The longitudinal data collection format that was adopted assessed occurrences of adverse events after each cycle of treatment. Toxicity outcomes such as gastrointestinal (GI) perforations, bleeding, diarrhea, myelosuppression, proteinuria, and venous thromboembolic events (VTEs) were collected and graded using the U.S. National Cancer Institute's *Common Terminology Criteria for Adverse Events,* version 3.0. Time to treatment failure (TTF) and overall survival (OS) were determined using the Kaplan–Meier method.

### Results

Overall, the 43 study patients received 398 cycles of anticancer therapy (median: 6 cycles; range: 1–24 cycles). No GI perforations were identified. However, 4 bleeding events occurred (9.3%), 3 requiring permanent discontinuation of bevacizumab. Also, 6 grade 3 or 4 VTEs occurred (14.0%), 3 of which required a hospital admission. In addition, grades 3 and 4 diarrhea, febrile neutropenia, and proteinuria showed cumulative incidences of 11.6%, 2.3%, and 2.3% respectively. Median TTF was 6.3 months; median OS was 24.4 months.

### Conclusions

Bevacizumab in combination with FOLFIRI appears to be well tolerated, and efficacy is consistent with trial reports. However, patients should be closely monitored to avoid potentially serious events such as bleeding and VTEs.

## KEY WORDS

Bevacizumab, colorectal cancer, metastatic, safety, FOLFIRI

## 1. INTRODUCTION

Bevacizumab represents an important advance in the treatment of metastatic colorectal cancer (mCRC): survival with bevacizumab in combination with first-line fluorouracil-based chemotherapy has now exceeded 20 months [1,2]. The drug is also active in the second-line setting when combined with FOLFOX4 [oxaliplatin, 5-fluorouracil (5FU), leucovorin], providing an overall survival benefit of approximately 2 months [hazard ratio (HR): 0.75; $p = 0.0011$] [3]. After presentation of the initial findings, Newfoundland and Labrador (NL) became one of the first Canadian provinces to approve bevacizumab for funding.

Despite bevacizumab's status as a relatively safe agent when added to existing chemotherapy, some grades 3 and 4 events have been reported to occur at higher frequencies in patients randomized to bevacizumab. The main adverse events associated with bevacizumab include gastrointestinal (GI) perforation, bleeding, diarrhea, proteinuria, and venous thromboembolic events (VTEs). The frequency of GI perforation was 1.5% during the pivotal randomized trial [1]. The frequency of grades 3 and 4 diarrhea increased by 8%, and VTEs, by 3% [1]. Overall, the need for hospitalization secondary to adverse events also increased by 5% in patients randomized to the bevacizumab group [1]. The incremental risk for VTE was confirmed in a recent meta-analysis of randomized trials of

bevacizumab, which reported a doubled risk of arteriole VTEs (HR: 2.0; $p = 0.031$) [4]. Furthermore, higher rates of diarrhea and VTE were also reported in other patient populations treated with bevacizumab [5–7].

Complications such as bleeding, diarrhea, and VTE can reduce quality of life for patients, increase the use of health care resources, and even become life-threatening in certain situations [8–10]. These events can also cause treatment delays, dose reductions, and even premature discontinuation of chemotherapy. This latter effect is particularly relevant in the setting of advanced CRC, in which the objective is effective disease palliation. The risk of severe diarrhea and VTEs can be substantially reduced with preventive agents such as octreotide and low molecular weight heparins [11,12].

It has been suggested that results from randomized trials are not fully generalizable to the community setting because trials tend to recruit patients with better performance status, many of whom receive treatment in large academic centres with a highly experienced staff [13]. Randomized oncology trials are also likely to recruit more white men and younger patients than ethnic minorities, women, and elderly people [14]. To illustrate, a review by Hutchins *et al.* [15] of 164 Southwest Oncology Group treatment trials determined that patients 65 years of age and older were underrepresented relative to the U.S. population (25% vs. 63%, $p < 0.001$) in trials involving 15 major tumour types. It would therefore be of interest to measure the efficacy of bevacizumab and the prevalence of serious side effects such as GI perforation, bleeding, diarrhea, and VTEs with its use in a naturalistic non-trial setting. We conducted a retrospective cohort analysis evaluating the efficacy and safety of bevacizumab in combination with FOLFIRI (irinotecan, 5-fluorouracil, leucovorin) in mCRC patients treated in NL in the first 2 years after the institution of provincial funding.

## 2. PATIENTS AND METHODS

Our retrospective cohort study considered all patients with advanced-stage CRC who received FOLFIRI chemotherapy in combination with bevacizumab from January 1, 2006, until October 1, 2008. To be entered into the study, patients also had to have received their chemotherapy–bevacizumab treatment as part of routine clinical practice and according to institutional administration guidelines. Patients were excluded if they received bevacizumab as part of a clinical trial or in combination with oxaliplatin-based chemotherapy.

### 2.1 Data Collection

The baseline data collected consisted of patient demographics, disease characteristics, body surface area, Eastern Cooperative Group performance status, and existing comorbidities (for example, cardiovascular disease, diabetes), measured using the Charlson index [16]. From the first cycle until completion of bevacizumab, data were collected on hemoglobin, white blood cells (WBCs), absolute neutrophil count (ANC), and platelets; on the use of growth factors, octreotide, and other antidiarrheal medication; and on the total number of red blood cell units and platelets administered. Data abstraction also included the doses of individual anticancer drugs, total number of cycles delivered, number of dose reductions, delays, premature discontinuations of treatment, hospitalizations, visits to an emergency department or unscheduled clinic visits, and resource utilization for patient supportive care (for example, blood products, duration of hospital stay) secondary to treatment-related toxicity. The U.S. National Cancer Institute's *Common Terminology Criteria for Adverse Events,* version 3.0, was used to grade each toxicity event [17]. The probable or possible cause of every clinically relevant event (for example, bleeding, VTE) was also recorded. All of this information was collected on a standardized data collection form.

The primary efficacy parameter was time to treatment failure (TTF), defined as the duration from the first dose of anticancer therapy until disease progression (using a switch in treatment as a surrogate marker), patient death, or discontinuation of first-line treatment because of side effects. Overall survival (OS) was measured from the first day of chemotherapy until death (if it occurred before the censoring date, which was March 30, 2009). The TTF and OS endpoints were measured only in patients who received bevacizumab in the first-line setting.

### 2.2 Statistical Analysis

All outcomes data are presented descriptively as means, medians, or proportions. Estimates for the TTF and OS endpoints were generated using the Kaplan–Meier method. In an exploratory analysis, the relationships between TTF and various baseline patient or treatment factors were assessed using Cox proportional hazard regression. All of the statistical analyses were performed using the Stata software application (release 9.0: Stata Corporation, College Station, TX, U.S.A.).

## 3. RESULTS

Overall, 43 patients received bevacizumab in combination with FOLFIRI. The median age of these patients was 62 years, and their baseline biochemical parameters were within normal limits before the start of chemotherapy (Table I). Of the 43 patients, 40 (93%) had metastatic disease before the start of treatment, and in 41 cases, FOLFIRI plus bevacizumab was used in the first-line setting. The most common site of metastasis was liver (53.5%), followed by lung (23.3%).

The Charlson comorbidity index is scored in a range from 0 to 35 points [16]. The weighted comorbidity classes are "low" (0), "median" (1–2), "high" (3–4), and "very" high (≥5). In our patient sample, the median Charlson score was 8, indicating a very high level of existing comorbidity before the start of chemotherapy. Bevacizumab was administered at a dose of 5 mg/kg, and 43 of 43 patients received the drug on the every-2-weeks protocol (Table I).

Approximately 398 cycles of FOLFIRI plus bevacizumab were administered to the 43 patents (overall median: 6 cycles; range: 1–24 cycles). No growth factor support, octreotide, and low molecular weight heparins were being used by any patient before the start of chemotherapy; however, before the first dose of bevacizumab, 1 patient was receiving warfarin for another indication. Over the course of therapy, support with granulocyte colony–stimulating factor was required in 47 cycles of treatment (11.8%) and with recombinant erythropoietin, in 18 cycles (4.5%, Table II).

Occurrences of toxicity were then assessed. No GI perforations occurred in our sample of 43 patients. However, 4 bleeding events occurred, 3 severe enough to require permanent discontinuation of bevacizumab (Table II). There were also 6 VTEs (14.0%), 5 of which required treatment with low molecular weight heparin, and 3 of which ultimately led to a hospital admission. Grade 2 and grade 3 diarrhea occurred in 8 and 5 patients respectively, with 2 patients requiring rehydration and 1 requiring hospitalization (Table II). Grade 3 or 4 neutropenia occurred in 13 patients, but only 1 case was febrile. There were 7 cases of grade 3 or 4 anemia. Only 1 patient developed grade 3 hypertension. No cases of grade 3 or 4 thrombocytopenia or proteinuria were observed.

Clinical outcomes in the patients were then assessed. Of the 41 patients who received FOLFIRI plus bevacizumab in the first-line setting, 16 experienced treatment failure as of December 31, 2008. By our censoring date (March 30, 2009), 15 patients had died. Median TTF was 6.3 months and median OS was 24.4 months in patients receiving first-line FOLFIRI plus bevacizumab. An exploratory Cox regression analysis using a forward step-wise approach was applied to TTF in this group of 41 patients. The baseline variables evaluated were patient age, sex, Charlson score, hemoglobin, WBCS, ANC, platelets, previous pelvic radiation, previous red blood cell transfusions, and prior adjuvant chemotherapy. The two variables that were significantly associated with TTF were prior adjuvant chemotherapy and baseline ANC (Table III). Patients who received adjuvant chemotherapy were approximately 4 times more likely to fail first-line therapy (HR: 4.01; $p = 0.043$). In addition, patients with a higher baseline ANC had an increased likelihood of failure (HR: 1.32; $p = 0.013$). Notwithstanding, it is important to remember that this analysis was exploratory; it should be viewed as hypothesis-generating.

TABLE I Baseline patient and treatment characteristics

| *Variable* | *Value*[a] |
|---|---|
| Patients (*n*) | 43 |
| Age (years) | |
| Median | 62 |
| Range | 44–78 |
| Mean body surface area | 1.92±0.03 |
| Male sex (%) | 62.3 |
| ECOG PS 0 or 1 (%)[b] | 100 |
| Charlson comorbidity index[c] | |
| Median score | 8 |
| Range | 6–13 |
| Mean baseline biochemistry | |
| Hemoglobin (g/L) | 129.3±2.1 |
| While blood cells ($\times 10^9$/L) | 7.1±0.48 |
| Absolute neutrophil count ($\times 10^9$/L) | 6.4±1.50 |
| Platelets ($\times 10^9$/L) | 312±16.6 |
| Urea (mmol/L) | 4.5±0.25 |
| Disease stage and characteristics (%) | |
| Resected stage IV | 7.0 |
| Metastatic | 93.0 |
| Colostomy present | 25.6 |
| Previous pelvic radiation | 42.9 |
| Central venous access present | 83.3 |
| Prior red blood cell transfusions | 62.2 |
| Prior VTE | 2.4 |
| Prior adjuvant chemotherapy | 53.5 |
| Current line of chemotherapy | |
| First | 95.4 |
| Second | 4.6 |
| Stool habit at baseline (%) | |
| Grade 1 or 2 diarrhea | 7.0 |
| Constipation | 7.0 |
| Mean absolute dose at cycle 1 (mg) | |
| 5FU bolus | 711±14.0 |
| 5FU continuous infusion | 4223±128 |
| Irinotecan | 321±6.2 |
| Bevacizumab | 390±15.8 |
| Bevacizumab cycle length (%) | |
| Every 2 weeks | 100 |
| Every 3 weeks | 0 |

[a] Mean ± standard error, or other value as stated.
[b] Eastern Cooperative Oncology Group performance status performance status (ECOG PS) could be accurately assessed in only 22 patients.
[c] The weighted comorbidity classes were low (0 points), median (1–2 points), high (3–4 points), and very high (≥5 points).

5FU = 5-fluorouracil; VTE = venous thromboembolic event.

## 4. DISCUSSION

In the present study, FOLFIRI plus bevacizumab was evaluated for safety and efficacy in all patients treated with that regimen in the province of NL during the first 2 years of provincial funding. Our findings suggested that this regimen is reasonably tolerated, the most serious adverse events being bleeding, diarrhea, and VTE. In the original trial report, which evaluated bevacizumab with the more toxic IFL (irinotecan, fluorouracil, leucovorin) chemotherapy regimen, grades 3 and 4 bleeding, diarrhea, and VTEs were reported in 3.1%, 32.4%, and 19.4% of patients respectively [1]. Even with the better tolerated FOLFIRI protocol, these complications still occurred in a substantial proportion of our patients.

Such adverse events are clinically relevant because, as the current study confirmed, they can lead to unplanned clinic or emergency room visits, hospital admissions, initiation of supportive therapy, and even premature discontinuation of bevacizumab. To avoid these events, clinicians need to be able to identify high-risk patients before bevacizumab is started. However, quantifying risk for an individual patient is difficult without the aid of validated prediction models that simultaneously consider multiple risk factors. In other words, in the presence of mathematical models that are easy to use and able to accurately identify patients at high risk for bevacizumab complications such as VTE, it should be possible and cost-effective to intervene preventively. Predictive tools of this kind could then be made available as an "add-on" to existing computer-based chemotherapy ordering systems. A model has already been developed for identifying patients at high risk for grades 3 and 4 diarrhea after FOLFIRI or FOLFOX (leucovorin, fluorouracil, oxaliplatin) chemotherapy [18]. In principle, such models could be developed for grades 3 and 4 bleeding, diarrhea, and VTE associated with FOLFIRI plus bevacizumab.

In our cohort of patients receiving bevacizumab plus FOLFIRI in the first-line setting, the median TTF and OS were estimated to be 6.3 months and 24.4 months respectively. In the original trial reported by Hurwitz *et al.,* median progression-free survival (PFS) and OS in the IFL plus bevacizumab group were 10.6 months and 20.3 months, both being statistically superior to PFS and OS with IFL alone [1]. In another randomized trial in which patients received either capecitabine plus oxaliplatin, or fluorouracil and leucovorin plus oxaliplatin (FOLFOX4) with or without bevacizumab, the median PFS and OS were 9.4 months and 21.3 months [2]. Although the caveats associated with a comparison of trial data with data for non-trial patients must be kept in mind, the experience in NL suggests that TTF may be lower than the trial-reported estimates. This finding

TABLE II Treatment-related safety outcomes in 43 patients

| *Outcome* | *Value* |
|---|---|
| Cycles administered (*n*) | |
| Total | 398 |
| Median | 6 |
| Range | 1–24 |
| Cycles (%) supported with | |
| G-CSF | 11.8 |
| Recombinant erythropoietin | 4.5 |
| Gastrointestinal perforations (*n*) | 0 |
| Bleeding events (*n*) | |
| Overall | 4 |
| Requiring permanent discontinuation of bevacizumab | 3 |
| VTEs (*n*)[a] | |
| Grade 3 | 3 |
| Grade 4 | 3 |
| VTE-related consequences (*n*) | |
| Unplanned clinic or ER visit | 5 |
| Hospital admission | 3 |
| Treatment with low molecular weight heparin | 5 |
| Diarrhea (*n*) | |
| Grade 2 | 8 |
| Grade 3 | 5 |
| Diarrhea-related events (*n*) | |
| Unplanned clinic or ER visit | 7 |
| Hospital admission | 1 |
| Rehydration required | 2 |
| Antibiotics | 2 |
| Neutropenia (*n*) | |
| Grade 3 or 4 | 13 |
| Febrile | 1 |
| Anemia [*n* (grade 3 or 4)] | 7 |
| Thrombocytopenia [*n* (grade 3 or 4)] | 0 |
| Hypertension [*n* (grade 3 or 4)] | 1 |
| Proteinuria [*n* (grade 3 or 4)] | 0 |

[a] According to the U.S. National Cancer Institute *Common Terminology Criteria for Adverse Events* (version 3.0), venous thromboembolic events (VTEs) requiring active therapy are grade 3. Life-threatening VTEs are grade 4.

G-CSF = granulocyte colony–stimulating factor; ER = emergency room.

TABLE III Exploratory Cox proportional hazard analysis of time to treatment failure (TTF)

| *Variable* | *Hazard ratio* | *95% CI* | p *Value* | *Effect on TTF* |
|---|---|---|---|---|
| Prior adjuvant chemotherapy | 4.01 | 1.11 to 16.0 | 0.043 | 4 Times more likely to fail first-line treatment |
| Absolute neutrophil count at baseline | 1.32 | 1.06 to 1.65 | 0.013 | Increased likelihood of failure at higher levels |

could be because better-risk patients were recruited to the pivotal clinical trials (that is, the "Olympic athlete" phenomenon). However, it is also important to keep in mind that TTF incorporates treatment discontinuations because of toxicity into its estimation. Median TTF is therefore typically lower than PFS because the latter calculation considers only death and disease progression. Notwithstanding, the median OS in our cohort is comparable with that reported in the main first-line bevacizumab trials [1,2].

A number of important limitations in the present study need to be addressed. Because this analysis was retrospective, we need to acknowledge the challenges associated with accurate collection of retrospective chart data, especially when those data deal with treatment-related toxicity. In addition, the small sample size makes it difficult to accurately measure median TTF and OS. Furthermore, secondary therapies after first-line FOLFIRI plus bevacizumab may not have been identical to those used in the pivotal randomized trials [1,2]. As a result, a comparison of OS between our cohort and the trial populations should be interpreted with caution.

## 5. CONCLUSIONS

Despite the limitations associated with a retrospective analysis of a small patient sample, our study represents the first formal Canadian evaluation of bevacizumab in the first-line treatment of patients with advanced colorectal cancer. Bevacizumab in combination with FOLFIRI appears to be well tolerated for the most part; the side effects identified were consistent with those previously reported. In addition, we found no GI perforations or grades 3 and 4 proteinuria. However, patients should be closely monitored to avoid potentially serious events such as bleeding, diarrhea, and VTE.

## 6. CONFLICT OF INTEREST DISCLOSURES

This study was supported by an unrestricted educational grant from Roche Canada. There are no other financial conflicts of interest to declare.

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