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ORIGINAL ARTICLE

Bevacizumab-based therapy for colorectal cancer: experience from a large Canadian cohort at the Jewish General Hospital between 2004 and 2009

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ABSTRACT

Background

Before its regulatory approval in Canada, bevacizumab to treat patients with colorectal cancer (CRC) was accessed through the Bevacizumab Expanded Access Trial and a special-access program at the Jewish General Hospital. We retrospectively evaluated patient outcomes in that large cohort.

Methods

All patients (n = 196) had metastatic CRC, were bevacizumab-naïve, and received bevacizumab in combination with chemotherapy at the Jewish General Hospital between 2004 and 2009. We collected patient demographics and clinical characteristics; relevant medical history, disease stage and tumour pathology at diagnosis; type, duration, and line of therapy; grades 3 and 4 adverse events (AEs), time to disease progression (TTP), and overall survival (OS) from diagnosis.

Results

Median follow-up was 36.0 months. Median TTP was 8.0 months [95% confidence interval (CI): 7.0 to 9.0 months). Median OS was 41.0 months (95% CI: 36.0 to 47.0 months). Of the 40 grades 3 and 4 bevacizumab-related AEs experienced by 38 patients (19.4%), the most common were thrombocytopenia (n = 17), deep-vein thrombosis (n = 6), pulmonary embolism (n = 4), and hypertension (n = 3).

Conclusions

In an expanded access setting, our data reflect the efficacy and safety of bevacizumab-based therapy in the controlled post-registration clinical trial setting.

KEY WORDS

Bevacizumab, colorectal cancer, efficacy, safety

1. INTRODUCTION

Bevacizumab (Avastin: Genentech, San Francisco, CA, U.S.A.) is a recombinant humanized monoclonal antibody that binds to and inhibits the activity of vascular endothelial growth factor[1] and shows activity against various tumours such as colorectal cancer[2–5]. In first-line treatment, two randomized phase II trials comparing combined bevacizumab, bolus 5-fluorouacil (5FU), and leucovorin with 5FU and leucovorin alone suggested improvements in response rate, progression-free survival (PFS), and overall survival (OS) for combination therapy in untreated metastatic colorectal cancer (mCRC)[3,6]. Other studies in the same setting showed that the addition of bevacizumab to the FOLFIRI (irinotecan–5FU–leucovorin) or FOLFOX4 (5FU–leucovorin–oxaliplatin) regimens achieved results superior to those with the chemotherapy alone[7,8]. In second-line treatment, the phase III trial ECOG3200 showed that the addition of bevacizumab to FOLFOX4 improved response rate, PFS, and OS in patients already treated with fluoropyrimidines[9].

Based on the foregoing studies, bevacizumab is now considered a standard of care for patients in the relevant settings. However, data about the usefulness of bevacizumab in the third and subsequent lines of treatment in mCRC are limited. Kang *et al.* reported a retrospective analysis of pre-treated mCRC patients receiving salvage bevacizumab plus either FOLFIRI or FOLFOX. They reported a response rate of 9.5%, a PFS of 5.3 months, and an OS of 9.5 months[10]. Recently, Bennouna *et al.* showed that maintenance of vascular endothelial growth factor inhibition with bevacizumab, plus standard second-line chemotherapy, has clinical benefits beyond disease progression in patients with mCRC[11]. The

same conclusion is supported by the results of the randomized BEBYP study[12].

Based on clinical trial results, bevacizumab was, in February 2004, approved for use in the United States in combination with intravenous 5FU-based chemotherapy for first- or second-line treatment of MCRC; however, the drug was not approved in Canada until September 2005, potentially resulting in undertreatment of patients during the intervening period.

Before its regulatory approval in Canada, bevacizumab was accessed through the Bevacizumab Expanded Access Trial and a special-access program at the Segal Cancer Centre. We decided to retrospectively evaluate patient outcomes in response to bevacizumab therapy in a large cohort treated at the Segal Cancer Centre, reflecting the experience in patients previously unexposed to the drug across all lines of treatment in a real-life setting.

2. METHODS

2.1 Patient Population

Patients who had not previously received bevacizumab were treated at the Jewish General Hospital, Montreal, Quebec. Our goal was to assure the introduction of this drug across all lines of MCRC treatment by using a clinical trial and special-access program at our institution. All patients had MCRC amenable to treatment with bevacizumab. Patients started treatment with bevacizumab between July 2004 and October 2009, and received bevacizumab therapy in combination with chemotherapy. The choice of dose for the bevacizumab and concomitant chemotherapeutic agents was at the discretion of the attending physician directly responsible for the care of each patient. Bevacizumab was administered according to the U.S. prescribing information (for example, with respect to dose, contraindications, warnings) until September 2005; after bevacizumab was approved in Canada, it was administered according to the Canadian prescribing information.

Available patient data were collected from the time of initial diagnosis to the time of chart review, including relevant medical history (type 2 diabetes, coronary artery disease, and hypertension); disease stage and tumour pathology at initial diagnosis; and details of chemotherapeutic regimens used concurrently with bevacizumab, duration of therapy, and line of therapy. We also collected details concerning the primary surgery and any hepatectomy or metastasectomy.

2.2 Statistical Analysis

The primary endpoint of the present report was OS. Secondary endpoints were time to progression (TTP) and safety. Overall survival was defined as the time from diagnosis of metastatic disease to the time of death from any cause. Time to progression was defined as the time from initiation of chemotherapy for metastatic disease to the time of progression and death. Tumour progression was determined by the Response Evaluation Criteria in Solid Tumors (version 1.0) or clinical deterioration documented by the treating clinician. Patients underwent computed tomography imaging every 3 months per standard clinical guidelines for tumour assessments or for confirmation of suspected clinical deterioration (clinician's choice). Reported adverse events were graded by the treating physicians in patient charts during medical visits. The grading of toxicities was based on the safety guidelines given in the *Common Terminology Criteria for Adverse Events* (version 3.0).

The statistical analysis was performed using the Strata 10 software application (StataCorp LP, College Station, TX, USA), and the survival analysis used Kaplan–Meier estimation[13].

3. RESULTS

3.1 Patient Characteristics

Table 1 summarizes baseline demographics and clinical characteristics for the study population. Patients had stage IV disease, with typical metastatic locations at the time of diagnosis. Mean age at diagnosis was 56 years, with an approximately equal sex distribution. Pathology grade of the tumour was "moderately differentiated" in most patients (78.1%). Approximately half the patients (44.6%) had lymphatic or vascular infiltration. With respect to prior medical history, 21.4% of the patients had hypertension, 9.7% had type 2 diabetes, and 2.6% had coronary artery disease.

All patients were treated with bevacizumab in the metastatic setting. Bevacizumab was administered in the first, second, third, and even fourth lines of therapy for metastatic disease in 46.9%, 44.9%, 33.2%, and 18.4% of patients respectively (Table II). Some patients continued on maintenance bevacizumab (11.2% and2.6%, Table II), but received a needed break from chemotherapy. No patient received monoclonal antibody therapy against the epidermal growth factor receptor as third-line treatment. On relapse or in certain settings (for example, before or after surgery for the primary tumour and before or after hepatectomy or metastasectomy), patients could receive bevacizumab for more than one course of treatment. Bevacizumab was administered to approximately 25% of MCRC patients in association with primary tumour surgery or hepatectomy, or both.

Irinotecan- or oxaliplatin-based regimens were the chemotherapies most commonly used with bevacizumab (47.4% and 41.9% of courses respectively). A total of 308 courses of bevacizumab were administered. Median duration of treatment with bevacizumab was 7.0 months (range: 0.5–37.0 months).

TABLE I Baseline demographic and clinical characteristics of the study cohort

Characteristic	*Value*[a]
Patients	196
Age at diagnosis (years)	
Median	56
Range	18–79
Sex [*n* (%)]	
Men	108 (55.1)
Women	88 (44.9)
Disease stage at Dx [*n* (%)]	
I	2 (1.1)
II	16 (8.5)
III	39 (20.7)
IV	131 (69.7)
Missing	8
Tumour pathology grade	
Well differentiated	6 (4.0)
Moderately differentiated	118 (78.1)
Poorly differentiated	27 (17.9)
Missing	45
Lymphatic or vascular infiltration	
Yes	78 (44.6)
No	97 (55.4)
Missing	21
Metastatic sites	
Lung	39 (30.2)
Liver	98 (76.0)
Lymph nodes	27 (20.9)
Other	31 (24.0)
Missing	2
Prior medical history	
Type 2 diabetes	19 (9.7)
Coronary artery disease	5 (2.6)
Hypertension	42 (21.4)

[a] All percentages calculated using the number of patients with known data as the denominator.
Dx = diagnosis.

TABLE II Bevacizumab treatment setting in 196 patients with metastatic colorectal cancer

Treatment setting	*Patients [*n *(%)]*[a]
First line	92 (46.9)
Second line	86 (44.9)
Third line	65 (33.2)
Fourth line	36 (18.4)
Maintenance	29 (14.8)
Before or after surgery for	
Primary tumour	10 (5.1)
Hepatectomy, lung resection, or metastasectomy	43 (21.9)
Primary tumour and another procedure[b]	9 (4.6)
Use not associated with a procedure	134 (68.4)

[a] Percentages calculated using the denominator for patients with known data. Patients could have received bevacizumab across different lines of therapy or setting.
[b] Hepatectomy, lung resection, or metastasectomy.

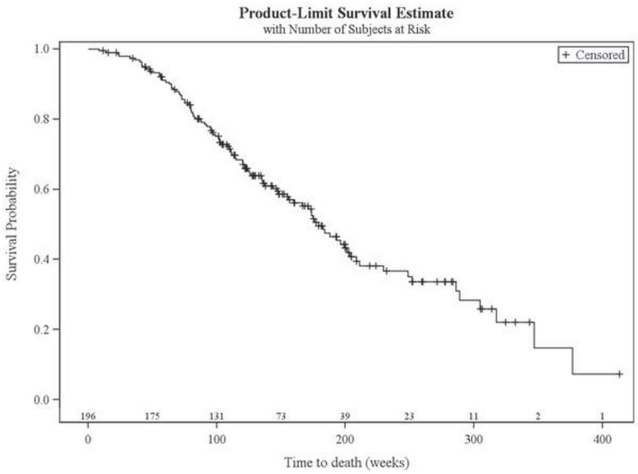

FIGURE 1 Overall survival for 196 patients receiving bevacizumab in addition to chemotherapy treatment.

3.2 Efficacy

3.2.1 Time to Progression

Median follow-up was 36.0 months. For the 196 patients analyzed, 174 progressions (89%) and 22 censored observations (11%) were recorded. Median TTP was 8.0 months [95% confidence interval (CI): 7.0 to 9.0 months].

3.2.2 Overall Survival

For the 196 patients analyzed, 100 deaths (51%) and 96 censored observations (49%) were recorded. Median OS from the time of diagnosis of metastatic disease was 41.0 months (95% CI: 36.0 to 47.0 months). Figure 1shows the associated Kaplan–Meier curve.

3.3 Safety

A total of 155 grade 3 or 4 chemotherapy-related adverse events (AEs) were experienced by 97 patients (49.5%). A total of 40 grade 3 or 4 bevacizumab-related AEs were experienced by 38 patients (19.4%, summarized in Table III). The most common AEs were thrombocytopenia (17 episodes), deep-vein thrombosis (6 episodes), pulmonary embolism (4 episodes), and hypertension (3 episodes). Two episodes each of rectal bleeding and gastrointestinal perforation occurred, and 1 episode each of allergic reaction to infusion, epistaxis, esophageal varices, impaired wound healing, nephrotic syndrome, and posterior reversible encephalopathy syndrome.

TABLE III Bevacizumab-related grades 3 and 4 adverse events in 196 patients with metastatic colorectal cancer

Event	*Episodes [*n *(%)]*
Thrombocytopenia	17 (8.7)
Deep-vein thrombosis	6 (3.1)
Pulmonary embolism	4 (2.0)
Hypertension	3 (1.5)
Rectal bleeding	2 (1.0)
Gastrointestinal perforation	2 (1.0)
Allergy	1 (0.5)
Epistaxis	1 (0.5)
Esophageal varices	1 (0.5)
Impaired wound healing	1 (0.5)
Nephrotic syndrome	1 (0.5)
Posteriorreversible encephalopathy syndrome	1 (0.5)

4. DISCUSSION

This retrospective analysis documents the efficacy and safety of bevacizumab administered across multiple lines of treatment to a large cohort of Canadian patients referred from various hospitals to be treated at the Jewish General Hospital (because bevacizumab was not available in Quebec at that time).

Median TTP was 8.0 months, and the narrow 95% CI of 7.0 to 9.0 months indicates a remarkably uniform response across lines of treatment and during repeated bevacizumab therapy. Median OS was 41.0 months, indicating promising efficacy with respect to long-term survival in a cohort that included a high proportion of patients with advanced disease who received multiple lines of therapy, thereby confirming a real clinical value for bevacizumab. Reports from various trials showed that the addition of bevacizumab to combinations with irinotecan or oxaliplatin in first-line treatment improved PFS (7–11 months vs. 4.7–6 months without bevacizumab treatment)[3,9,14,15]. Continuation of bevacizumab with second-line chemotherapy was associated with a significant improvement in PFS as shown in the observational BRiTE registry of 1953 patients who progressed after receiving the first-line bevacizumab-containing regimens[16] and in the European TML trial, which analyzed 820 patients with unresectable mCRC[17]. A survival advantage ranging between 23 and 28 months was also reported for all of those trials[3,9,14–17]. Our data demonstrate an even greater median OS of 41 months, indicating that, even for patients in whom either oxaliplatin or irinotecan needs to be held, it is reasonable to continue the fluoropyrimidine plus bevacizumab or even bevacizumab alone beyond second-line treatment (Table II).

Notably, no increase in toxicity was observed, as Table III shows. The AEs reported in our patients are those generally reported with bevacizumab treatment[18–20], but they appeared to occur slightly less frequently in our cohort.

5. CONCLUSIONS

The data from our large cohort of patients with mCRC confirm the clinical value of bevacizumab given with combination therapy or as a single agent and demonstrate a very acceptable toxicity profile across multiple lines of treatment. In this sense, our results argue in favour of maintaining bevacizumab treatment, instead of discontinuing it, in patients with a good Eastern Cooperative Oncology Group performance status of 0–1. Moreover, it is encouraging for us to report long-term OS and uniform TTP in a group of patients with such advanced disease, who lived longer than expected thanks to the bevacizumab access program in our institution.

6. ACKNOWLEDGMENTS

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7. CONFLICT OF INTEREST DISCLOSURES

All authors declare no financial conflicts of interest.

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