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Progression pattern and adverse events with bevacizumab in glioblastoma

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ABSTRACT

Background The use of bevacizumab in the management of glioblastoma multiforme (GBM) remains controversial. In Canada, bevacizumab is approved for the treatment of recurrent GBM. We describe a pattern of progression across treatment lines in GBM.

Methods During 2008–2014, 64 patients diagnosed with GBM were treated with bevacizumab at McGill University hospitals. Of those patients, 30 (46.9%) received bevacizumab in the first line (B1L), and 34 (53.1%) received it in the second line and beyond (B2L+). The average length of treatment with bevacizumab was 24.4 weeks (range: 0–232.7 weeks). The patterns of progression were categorized as local, distant, diffuse, multifocal, or multi-pattern.

Results Local progression was seen in 46.7% of B1L patients and 26.5% of B2L+ patients, distant in 3.3% and 2.9%, diffuse in 20% and 47%, multifocal in 10% and 8.8%, and multi-pattern in 3.3% and 11.8%. No differences between the groups were observed for the distant ($p = 0.3$) or diffuse ($p = 0.4$) patterns. Grades 3 and 4 adverse events in the B1L and B2L+ groups were fatigue (33.3% vs. 17.6% respectively), hypertension (26.7% vs. 5.9%), thrombocytopenia (26.7% vs. 11.8%), neutropenia (26.7% vs. 11.8%), anemia (23.3% vs. 11.8%), leucopenia (20% vs. 8.8%), deep vein thrombosis (23.3% vs. 5.9%), seizure (16.7% vs. 8.8%), brain hemorrhage (6.7% vs. <1%), and delayed wound healing (6.7% vs. 2.9%). More total grades 3 and 4 adverse events occurred in the B1L group ($p = 0.000519$).

Conclusions In our cohort, patterns of progression were not different in B1L and B2L+ patients. Moreover, both groups experienced similar adverse events, although more grades 3 and 4 events occurred in the B1L group, implying that severe adverse events in B1L patients could negatively affect survival outcomes.

Key Words Glioblastoma multiforme, bevacizumab, patterns of progression, adverse events, survival

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INTRODUCTION

Despite extensive research into glioblastoma multiforme (GBM), outcomes remain poor, with 5-year survival being 3% and median overall survival (OS) being 14–16 months[1–5]. About 90% of patients will experience recurrence at the original location of the tumour[4,6]. Median OS after progression is short, in the range of 3–9 months[7,8]. Treatment options in the recurrent setting are limited and include surgery, re-irradiation, and systemic treatment[9,10].

The results of several studies demonstrated the clinical value of bevacizumab, an anti–vascular endothelial growth factor A molecule, in the treatment of recurrent GBM, either as monotherapy or in combination with a chemotherapeutic agent[11]—leading to approvals from the U.S. Food and Drug Administration and Health Canada.

Two large phase III studies evaluated the effect of bevacizumab addition to radiotherapy and temozolomide in the first-line setting, with conflicting results. The Radiation Therapy Oncology Group 0825 study[4] showed no survival advantage (15.7 months for the bevacizumab arm compared with 16.1 months for the placebo arm) and a trend of superior progression-free survival in the bevacizumab arm (10.7 months vs. 7.3 months)[4]. Contradicting the Radiation Therapy Oncology Group study, the AVAGlio (BO21990) phase III registration study showed numerically similar results for OS at 16.8 months and 16.7 months for bevacizumab and placebo respectively ($p = 0.049$)[12], with a significantly longer progression-free survival (10.6 months vs. 6.2 months) and improvement in quality of life and prolonged Karnofsky performance status[12,13].

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Given that the role and optimal use of bevacizumab in a GBM setting remains unclear in North America, use of bevacizumab is approved only for recurrent disease. Subsequent studies have explored the reasons for that lack of clarity. Two contributing hypotheses suggest that bevacizumab promotes a distant and diffuse pattern of progression as a resistance mechanism and that adverse events (AEs) are related to the use of bevacizumab. In the present study, we therefore set out to describe and compare the patterns of progression and the AEs associated with bevacizumab in both newly diagnosed and recurrent GBM.

METHODS

Patients diagnosed with GBM (primary or secondary) who started treatment with bevacizumab in combination with chemotherapy between 2008 and 2014 were identified from daily practice in participating McGill University Hospitals. The choice of the bevacizumab dose and the concomitant chemotherapeutic agent or agents was at the discretion of the treating oncologist. Bevacizumab was administered according to Canadian prescribing information after bevacizumab approval in Canada. 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, hypertension), GBM stage, details of chemotherapeutic regimens used concurrently with bevacizumab, duration of therapy, and line of therapy.

The endpoints of the analysis were patterns of progression and safety. Patterns of progression seen on magnetic resonance imaging or computed tomography were defined as follows: local progression (recurrence of tumour at the original site of surgery and radiation, originally seen on first imaging results), distant progression (a new area of enhancement or lesion distant from the original tumour site), diffuse recurrence (infiltrative pattern with increased areas of spread involving another area), and multifocal recurrence (multiple separate and unconnected foci). The grading of toxicities was based on safety guidelines per the *Common Terminology Criteria for Adverse Events*, version 4.0.

Statistical Analysis

Overall survival was defined as the date of diagnosis to the date of death. Survival on one line of treatment using bevacizumab was defined as extending from the date of diagnosis to the last date of bevacizumab administration for the given line of therapy.

Statistical analysis was performed using the Stata software application (version 10: StataCorp LP, College Station, TX, U.S.A.); survival analyses used the Kaplan–Meier method.

RESULTS

Patient Characteristics

During 2008–2014, 64 patients diagnosed with histologically confirmed GBM [40 men (62.5%), 24 women (37.5%)] were treated with bevacizumab at McGill University hospitals (Table I). Median age in the cohort was 54 years (range: 26–83 years). In 49 patients (76.6%), the diagnosis was primary GBM; in 15 patients (23.4%), it was secondary GBM. Karnofsky performance status was 70 in 56 patients (87.6%) and less than 70 in 7 patients (10.9%). The *O*-6-methylguanine-DNA methyltransferase promoter was found to be methylated in 10 patients (15.6%) and unmethylated in 14 patients (21.9%); methylation status was unknown for the remaining 40 patients (62.5%).

Bevacizumab was given to 30 patients (46.9%) in the first line and to 34 patients (53.1%) in the second line and beyond. The average duration of treatment with bevacizumab was 24.36 weeks overall (range: 0–232.7 weeks). In first-line treatment, average duration was 36.57 weeks; in the second line and greater, it was 14.21 weeks. The overall average number of chemotherapy lines per patient was 2 (range: 0–4; Table II). Bevacizumab was used mostly in combination with radiation and a temozolomide regimen ($n = 19$, 29.7%). After progression on bevacizumab, patients received chemotherapy agents including temozolomide only ($n = 4$), temozolomide plus procarbazine ($n = 6$), and lomustine ($n = 3$).

Patterns of Progression

Patterns of progression were determined by retrospective chart review and were categorized as local, distant, diffuse, multifocal, or multi-pattern. Patterns of progression in the B1L and B2L+ groups were, respectively, local in 14 (46.7%) and 9 (26.5%), distant in 1 (3.3%) and 1 (2.9%), diffuse in 6 (20%) and 16 (47%), multifocal in 3 (10%) and 3 (8.8%), and multi-pattern 1 (3.3%) and 4 (11.8%). No difference between the groups was observed for distant ($p = 0.3$) or diffuse progression ($p = 0.4$, Table III).

TABLE I Characteristics of the study population

Characteristic	Value
Patients (*n*)	64
Bevacizumab [*n* (%)]	
First line	30 (46.9)
Second or subsequent line	34 (53.1)
Sex [*n* (%)]	
Men	40 (62.5)
Women	24 (37.5)
Age at diagnosis (years)	
Median	54
Range	26–83
GBM histopathology [*n* (%)]	
Primary	49 (76.6)
Secondary	15 (23.4)
MGMT promoter status [*n* (%)]	
Methylated	10 (15.6)
Unmethylated	14 (21.9)
Unknown	40 (62.5)
Karnofsky PS [*n* (%)]	
Good (≥70 to 100)	56 (87.5)
Poor (<70)	7 (10.9)
Unknown	1 (1.6)

GBM = glioblastoma multiforme; MGMT = *O*-6-methylguanine-DNA methyltransferase; PS = performance status.

Safety

Grades 3 and 4 AEs in the B1L and B2L+ groups were, respectively, fatigue in 10 (33.3%) and 6 (17.6%), hypertension in 8 (26.7%) and 2 (5.9%), thrombocytopenia in 8 (26.7%) and 4 (11.8%), neutropenia in 8 (26.7%) and 4 (11.8%), anemia in 7 (23.3%) and 4 (11.8%), leucopenia in 6 (20%) and 3 (8.8%), deep vein thrombosis in 7 (23.3%) and 2 (5.9%), seizures in 5 (16.7%) and 3 (8.8%), brain hemorrhage in 2 (6.7%) and <1%, and delayed wound healing in 2 (6.7%) and 1 (2.9%). More total grades 3 and 4 AEs occurred in the B1L group ($p = 0.000519$, Table IV).

TABLE II Duration of bevacizumab treatment

Variable	Value
Treatment duration (weeks)	
Overall	
Average	24.36
Range	0 to 232.71
First-line	
Average	36.57
Range	<1 to 232.7
Second-line+	
Average	14.21
Range	<1 to 182.43
Lines of treatment per person (n)	
Average	2
Range	0 to 4

TABLE III Pattern of progression

Pattern of progression	Treatment group [*n* (%)]		*p* Value
	First line	Second line+	
Local	14 (46.7)	9 (26.5)	
Distant	1 (3.3)	1 (2.9)	0.3
Diffuse	6 (20)	16 (47)	0.4
Multifocal	3 (10)	3 (8.8)	
Local and distant	1 (3.3)	4 (11.8)	

TABLE IV Adverse events during bevacizumab treatment in new and recurrent glioblastoma multiforme

Grades 3 and 4 adverse events	Treatment group [*n* (%)]	
	First line	Second line+
Deep vein thrombosis	7 (23.3)	2 (5.9)
Hypertension	8 (26.7)	2 (5.9)
Anemia	7 (23.3)	4 (11.8)
Thrombocytopenia	8 (26.7)	4 (11.8)
Leucopenia	6 (20)	3 (8.8)
Neutropenia	8 (26.7)	4 (11.8)
Fatigue	10 (33.3)	6 (17.6)
Wound healing complications	2 (6.7)	1 (2.9)
Brain hemorrhage	2 (6.7)	(<1)
Seizures	5 (16.7)	3 (8.8)

Efficacy

Median OS for the entire group of patients was 22 months [95% confidence interval (CI): 15.0 to 27.0 months; Figure 1(A)]. Survival time for B1L patients was 13 months [95% CI: 10.0 to 26.0 months; Figure 1(B)]; for B2L+ patients, it was 7 months [95% CI: 5.0 to 9.0 months; Figure 1(C)].

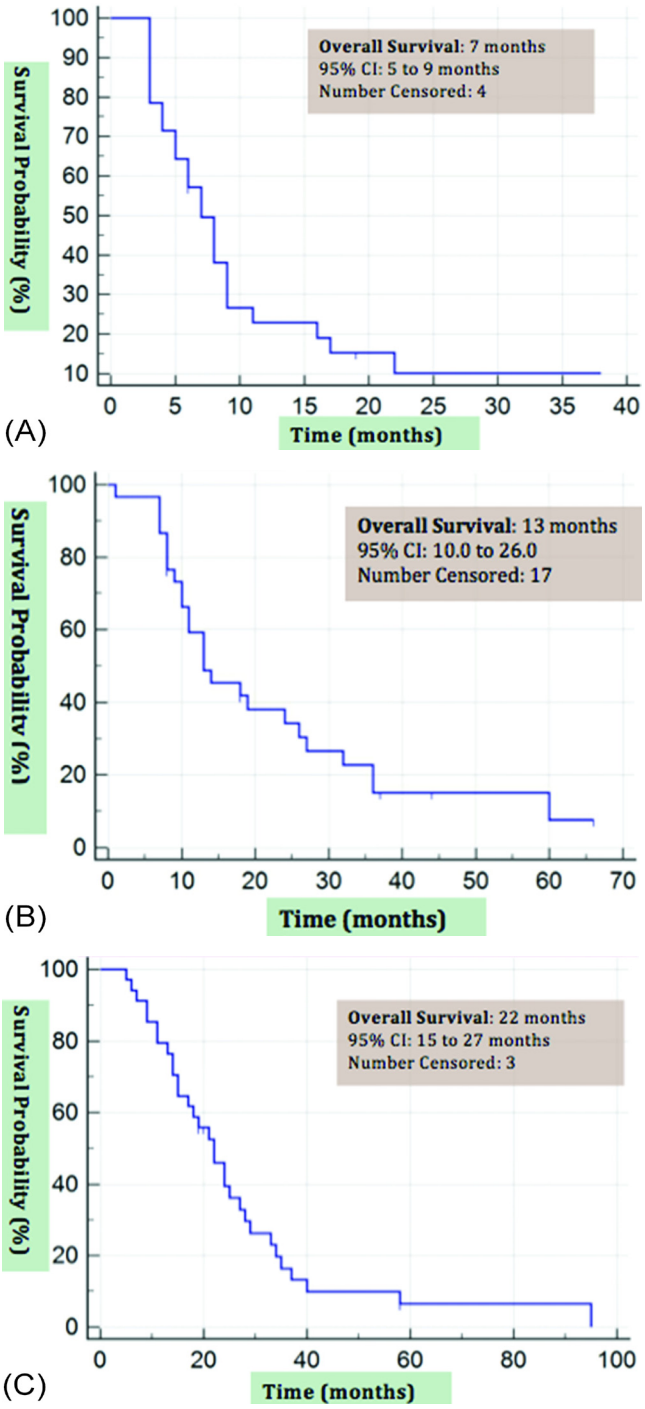

FIGURE 1 Kaplan–Meier curves for overall survival in patients treated with bevacizumab. (A) Total overall survival duration. (B) Survival duration with first-line bevacizumab. (C) Survival duration with second- and subsequent-line bevacizumab. CI = confidence interval.

DISCUSSION

The recent phase III studies Radiation Therapy Oncology Group 0825 and AVAGlio showed mixed survival results when bevacizumab was added to first-line GBM treatment. In North America, the use of bevacizumab is therefore approved only for recurrent disease. Subsequent studies explored the reasons for the failure to improve survival. In the present study, we set out to describe and compare patterns of progression and AEs associated with bevacizumab in both newly diagnosed and recurrent GBM. The analysis showed that severe AEs in the B1L group could be a factor in the failure of that treatment.

Our results showed that although patterns of progression were not different in the B1L and B2L+ groups, progression was more often diffuse than local. That result suggests that the benefit from early exposure to bevacizumab is uncertain.

Safety results obtained in the analysis showed similar AEs in the BL1 and BL2+ groups, with the AEs being manageable and reversible clinically and, in recurrent GBM settings, being comparable to events occurring in the registration trials. However, more grades 3 and 4 AEs occurred in the B1L group, supporting the use of bevacizumab in the B2L+ group. Some of the AEs occurring in the B1L group, such as deep-vein thrombosis, could potentially affect clinical outcomes.

We did not observe an OS advantage associated with the first-line use of bevacizumab in patients with GBM. In fact, median OS achieved in the B1L group was 13 months (95% CI: 10.0 to 26.0 months); in the B2L+ group, it was 7 months (95% CI: 3.2 to 8.0 months). Our results suggest that the use of bevacizumab in a second-line setting accords with the registration data for recurrent GBM[14–22] and should remain the current standard.

To confirm the reason for the failure of bevacizumab in the first line, our results have to be tested in a greater number of GBM patients.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

AUTHOR AFFILIATIONS

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