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Single-agent bevacizumab in the treatment of recurrent or refractory pediatric low-grade glioma: A single institutional experience

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Abstract

Introduction: Bevacizumab-based therapy has been demonstrated to be effective in the treatment of refractory or recurrent pediatric low-grade glioma (LGG); however its efficacy as a single agent is less understood.

Methods: We report our experience with single-agent bevacizumab for the treatment of recurrent or refractory LGG treated with either standard 2 week dosing (10 mg/kg/dose every 2 weeks) or with a standard 2 week dosing followed by an increased interval dosing (10 mg/kg/dose every 4 weeks).

Results: From 2012 to 2017, 15 patients (five males and 10 females) with recurrent/refractory LGG (nine suprasellar, three thalamic, two brainstem, and one intramedullary spinal cord) were treated with a total of 156 doses of bevacizumab (115 every 2 week dosing, 41 every 4 week dosing, median 10 doses). Patients were refractory to a median of one nonsurgical therapy (range 0–3) prior to treatment with bevacizumab. Twelve of 15 demonstrated radiographic response (three complete, nine partial, and three stable disease). Significant clinical responses including improved visual fields (four), cranial neuropathy (three3), strength (seven), and gait (two) were observed. Bevacizumab was discontinued in 12 patients (resolution, one; disease stability, seven; progression, two; toxicity, one; and other, one) and three patients continue to receive monthly bevacizumab. Eleven patients eventually had radiographic progression (median 5 months, range 0.5–31) without clinical progression, and four of five receiving bevacizumab rechallenge had lpartial response.

Conclusion: Single-agent bevacizumab is efficacious in the management of recurrent or refractory pediatric LGG with radiographic and clinical responses similar to those reported for bevacizumab-based therapies.

KEYWORDS

bevacizumab, central nervous system tumors, immunotherapy, low-grade glioma

1 | INTRODUCTION

Low-grade glioma (LGG) is the most common pediatric brain tumor, accounting for approximately 30% of the primary central nervous system tumors in children less than 19 years of age.[1] Although pediatric LGG has a very good 5-year overall survival rate (95%),[2] it can be associated with significant morbidity and rare mortality.

Various chemotherapeutic regimens have been used for the treatment of LGG in children, including carboplatin and vincristine; 6-thioguanine, procarbazine, lomustine, and vincristine[3]; vinblastine[4]; temozolomide[5]; and bevacizumab plus irinotecan,[6–8] with varying degrees of success. Event-free survival at 5 years for LGG with less than gross total resection treated with chemotherapy and/or

Abbreviations: FLAIR, fluid attenuation inversion recovery; LGG, low-grade glioma; MRI, magnetic resonance imaging

TABLE 1 Demographic and treatment characteristics of patients treated with single-agent bevacizumab for recurrent/refractory LGG

Demographic or treatment variable	All patients
Age at initial diagnosis, median (range)	1 year (1–12)
Age at time of bevacizumab, median (range)	7 years (1–20)
Sex	
Male	5
Female	10
Prior chemotherapy	
Yes	12
No	3
Prior surgery	
Gross total resection	1
Near total resection	2
Subtotal resection	4
Biopsy	7
No surgery	1
Prior radiation	
Yes	4
No	11
Number of doses, median (range)	10 (4–20)
Total number of doses	156
Doses given at 2 weeks interval	115
Doses given at 4 weeks interval	41
Doses according to courses of bevacizumab	
Initial course	126
Rechallenge	30
Best response	
Complete response	3
Partial response	9
Stable disease	3
Progressive disease	0
Time to initial response, median (range)	7 weeks (1–18)
Time to best response, median (range)	10 weeks (1–30)
Reason for discontinuation	
Resolution of disease	1
Stable disease	7
Progression of disease	2
Toxicity	1
Others	1
Ongoing treatment	3
Interval to progression, median (range)	5 months (0.5–31)
Bevacizumab rechallenge given	
Yes	5
No	10
Interval between initial course and rechallenge, median (range)	6 months (4–15)
Response to bevacizumab rechallenge	
Complete response	0
Partial response	4
Stable disease	0
Progressive disease	1
Interval to progression after rechallenge, median (range)	6 months (0.5–45)
Reason for discontinuation of rechallenge	
Sustained stable disease	2
Toxicity	2
Progression of disease	2

radiotherapy remains suboptimal, and recurrences may result in the use of multiple salvage regimens.[9]

Bevacizumab-based therapies (including bevacizumab plus irinotecan) have been used in pediatric LGG with reported disease control.[7,8] However, irinotecan is often associated with significant gastrointestinal adverse events requiring dose adjustments, discontinuation of the treatments, and change in treatment intervals. Previously, Hwang et al.[7] and Kalra et al.[8] have reported favorable results of bevacizumab-based therapies including bevacizumab as a single agent in a small number of patients who did not tolerate the combination of bevacizumab and irinotecan, suggesting single-agent responsiveness. We describe the largest single institutional experience of single-agent bevacizumab using every 2 week and every 4 week dosing in previously treated children with recurrent or refractory LGG.

2 | METHODS

We reviewed 15 consecutive patients with recurrent/refractory LGG treated with bevacizumab at Rady Children's Hospital, San Diego, from May 2012 to April 2017. Of 15 patients, 12 had received prior cytotoxic chemotherapy and four had received prior radiation therapy. An informed consent for treatment was obtained before initiation of the bevacizumab. Bevacizumab (10 mg/kg/dose) was given intravenously either at a standard dosing interval of every 2 weeks or an initial standard dosing of bevacizumab every 2 weeks followed by an increased dosing interval of every 4 weeks. The duration of each phase was individualized for each patient, based on the clinical response, radiological response, and tolerance to bevacizumab. If a patient initially responded to bevacizumab and had subsequent progression following discontinuation, they were offered rechallenge with bevacizumab.

The most commonly used dosing schedule for bevacizumab was 10 mg/kg/dose every 2 weeks. Notably, bevacizumab has been used previously with a longer interval between doses, but only for the patients who were not able to tolerate every 2 weeks dosing, with good disease control and better adverse event profiles.[7] Clinical response and adverse events were evaluated by the treating pediatric neuro-oncologist at the time of clinic visit. Laboratory monitoring including complete blood count, comprehensive metabolic panel, liver function panel, urinalysis, and urine pregnancy in females of

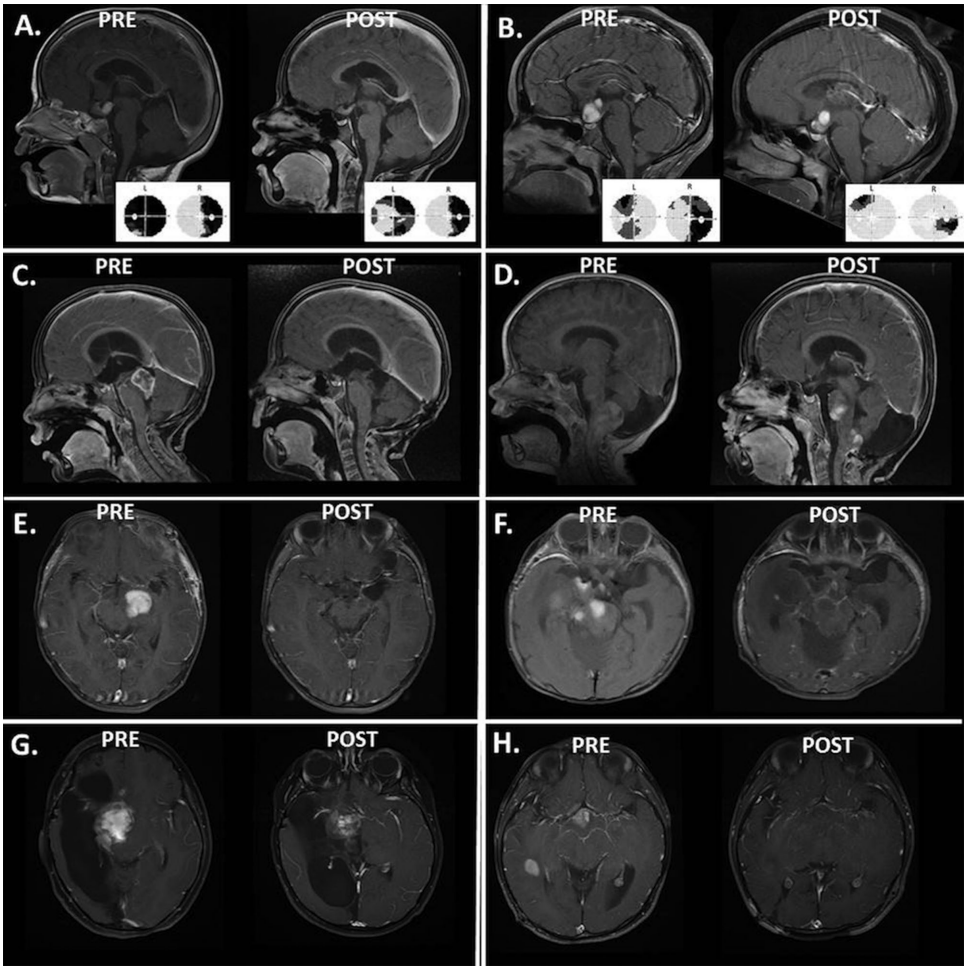

FIGURE 1 Radiographic response of recurrent/refractory LGG to single-agent bevacizumab. Post gadolinium T1 sequences reveal radiographic responses post bevacizumab therapy for Patient 7 (A), Patient 11 (B), Patient 14 (C), Patient 9 (D), Patient 12 (E), Patient 3 (F), Patient 2 (G), and Patient 5 (H). Improvements in formal visual field testing were seen in Patients 7 (A) and 11 (B)

childbearing potential was assessed prior to the initiation of therapy. Adverse events were categorized according to Common Terminology Criteria for Adverse Events Version 4.0. Formal visual fields were evaluated by a pediatric neuro-ophthalmologist pre- and post-therapy in patients with suprasellar chiasmatic LGG. Routine magnetic resonance imaging (MRI) neuroimaging was performed every 8 weeks from the initiation of treatment or earlier in some cases to assess for velocity of bevacizumab response. MRI responses were characterized by diameter-based measurement on a single-axial section containing the largest diameter of the tumor on T1 postgadolinium sequences by a pediatric neuroradiologist, and in some cases correlated with T2 fluid attenuation inversion recovery (FLAIR) sequences. The study was approved by the University of California San Diego Institutional Review Board.

3 | RESULTS

The demographic and treatment characteristics of 15 patients (five males and 10 females) with a diagnosis of recurrent/refractory LGG treated with single-agent bevacizumab (median age 7 years, range 1–20 years) are shown in Table 1. Histologic diagnosis was made in 14 patients, while one patient was diagnosed with optic pathway glioma based on MRI findings alone. Nine patients had molecular sequencing information, the most common being the BRAF KIAA1549 fusion in four children. One patient had a diagnosis of neurofibromatosis type 1. Twelve patients had received prior chemotherapies (median 1, range 0–3) while four had received radiation therapy. There were, in total, 156 doses of bevacizumab given (median 10, range 4–20); 115 doses of bevacizumab were given at every 2 weeks interval and 41 at 4 weeks interval. There were 126 initial course doses and 30 rechallenge doses of bevacizumab. Objective response was seen in 12 patients (three complete responses and nine partial responses) while three patients had stable disease after the initial course of bevacizumab (Figure 1). Early radiographic responses were seen at a median of 7 weeks (range 1–18 weeks) while best responses were seen at a median of 10 weeks (range 1–30 weeks). The earliest responses were seen in five patients after 4 weeks or less of bevacizumab therapy. In addition to the radiologic response, clinical responses were seen in 12 patients (Table 2), including improvements in strength (7), cranial neuropathy (three with improved eye movements and two with improved speech and swallowing), gait (2), and visual fields (4). Examples of improvement in formal visual fields assessed pre- and post bevacizumab therapy are shown in Figures 1A and 1B. One patient with LGG of the brainstem (Patient 9) had near obstruction of the foramen magnum prior to

TABLE 2 Treatment characteristics of patients treated with single-agent bevacizumab for recurrent/refractory LGG

No.	Demographics and tumor characteristics	Prior nonsurgical therapies	Experience with bevacizumab	Earliest radiographic response (weeks)	Best radiographic response (weeks)	Best clinical response	Best radiographic response	Outcome
1	9-year-old male with NF1 and optic pathway glioma WHO Grade 1	1. VCN,CARB 2. Erlotinib	Single dose of bevacizumab was given for recurrence with radiographic response. Repeat course given 6 months after progression with partial response	4	4	None	Complete response	Radiographic progression at 6 months post therapy. Treated with second course of bevacizumab with partial response. Died of disease at 13 years old
2	12-year-old male with suprasellar chiasmatic JPA (Gli 1, p53 mutant) WHO Grade 1	1. VCN,CARB 2. PROCARB 3. TEMO 4. Radiation	Eleven doses of bevacizumab were given at every 2 weeks interval with progression 5 months post therapy and repeat course given with no response	10	10	Improved vision	Partial response	Radiographic progression at 5 months post therapy, received a second course of bevacizumab with no response. Alive at 16 years old
3	1-year-old female with disseminated suprasellar pilomyxoid astrocytoma (MUTYH mutant) WHO Grade 2	1. CARB	Four doses were given at every 2 weeks interval followed by one dose at 4 weeks interval for progression of disease. Patient responded to bevacizumab initially, but it was discontinued due to parental preference	10	10	None	Complete response	Radiographic progression at 3 months post therapy. Died of disease at 20 months
4	7-year-old female with suprasellar chiasmatic JPA (BRAF KIAA-1549 fusion) WHO Grade 1	1. VCN,CARB 2. TEMO 3. PCVT	Two doses were given at every 2 weeks interval. Patient initially responded to bevacizumab and was discontinued because of prolonged stable disease. Following progression 4 months post therapy, repeat course was given with partial response	3	3	Improved strength	Partial response	Radiographic progression at 4 months post therapy and received a second course with partial response. Alive at 12 years old
5	1.5-year-old male with suprasellar JPA (BRAFKIAA-1549 fusion) WHO Grade 1	1. VCN,CARB	Eleven doses were given at every 2 weeks interval for refractory disease. Patient responded to bevacizumab and it was discontinued with prolonged disease stabilization. Patient had progression 13 months post therapy with a partial response to repeat course	8	20	Improved strength; language and drooling	Partial response	Radiographic progression at 13 months post therapy and received a second course with partial response. Alive at 5 years old
6	3-year-old male with intramedullary spinal cord JPA (BRAFKIAA-1549 fusion) WHO Grade 1	None	Eight doses were given at every 2 week intervals followed by two doses at 4 weeks interval for recurrence. Patient responded to bevacizumab and it was discontinued because of prolonged stable disease	6	16	Improved strength	Complete response	Radiographic progression at 5 months post therapy. Alive at 8 years old

(Continues)

TABLE 2 (Continued)

No.	Demographics and tumor characteristics	Prior nonsurgical therapies	Experience with bevacizumab	Earliest radiographic response (weeks)	Best radiographic response (weeks)	Best clinical response	Best radiographic response	Outcome
7	7-year-old female with suprasellar pilomyxoid astrocytoma WHO Grade 2	1. VCN,CARB	Five doses were given at every 2 weeks interval followed by five doses at every 4 weeks interval for refractory disease. Patient responded to bevacizumab but it was discontinued because of toxicity (headache)	18	18	Improved visual fields	Stable disease	Radiographic progression 6 months post therapy. Alive at 11 years old
8	13-year-old female with thalamic JPA WHO Grade 1	1. Radiation	A single dose was given for local recurrence. Patient responded to bevacizumab and it was discontinued because of prolonged stability. Received second course 5 months post therapy for progression, with a partial response	1	1	Improved strength	Partial response	Radiographic progression 5 months post therapy and received a second course with partial response. Alive at 21 years old
9	3-year-old female with brainstem low-grade glioma (BRAF V600E mutation) WHO Grade 1	1. VCN,CARB	Seven doses were given at every 2 weeks interval followed by seven doses at every 4 weeks interval for refractory disease. Patient responded to bevacizumab and was discontinued because of prolonged disease stability	4	24	Improved strength; cranial neuropathy, speech, and swallowing	Partial response	Radiographic progression 6 months post therapy. Alive at 5 years old
10	20-year-old female with thalamic low-grade glioma (FGFR1 mutation) WHO Grade 1	1. VCN,CARB 2. PCVT 3. Radiation	Eight doses were given at every 2 weeks interval for progression of disease. Patient initially responded to bevacizumab	4	4	None	Partial response	Radiographic progression 3 months post therapy. Alive at 21 years old
11	12-year-old female with suprasellar low-grade glioma WHO Grade 1	1. VCN,CARB 2. PCVT	Eight doses were given at every 2 weeks interval followed by 12 doses at every 4 weeks interval for progression of disease. Patient responded to bevacizumab and was discontinued because of prolonged stabilization	11	25	Improved visual fields	Partial response	Radiographic progression 21 months post therapy. Alive at 17 years old
12	3-year-old female with thalamic pilomyxoid astrocytoma (BRAFKIAA-1549 fusion) WHO Grade 2	1. VCN,CARB	Four doses at 2 weeks interval followed by seven doses at 4 weeks interval, and patient responded to bevacizumab	4	30	Improved strength and gait	Partial response	Remains on treatment. Alive at 5 years old

(Continues)

TABLE 2 (Continued)

No.	Demographics and tumor characteristics	Prior nonsurgical therapies	Experience with bevacizumab	Earliest radiographic response (weeks)	Best radiographic response (weeks)	Best clinical response	Best radiographic response	Outcome
13	12-year-old male with R optic glioma, non-NF1 WHO Grade 1	1. VCN,CARB 2. Radiation	Nine doses were given at every 2 weeks interval for four doses, and patient clinically responded to bevacizumab	8	8	Improved visual fields	Stable disease	Remains on treatment. Alive at 13 years old
14	5-year-old female with disseminated tectal low-grade glioma (EGFR mutant) WHO Grade 1	1. VCN,CARB	Nine doses were given at every 2 weeks interval and patient responded to bevacizumab	7	7	Improved eye movements and strength	Partial response	Remains on treatment. Alive at 6 years old
15	13-year-old female with hypothalamic low-grade glioma WHO Grade 1	None	Four doses were given every 2 weeks for progression of endocrinopathies. Patient clinically responded to bevacizumab	8	8	Improved obesity	Stable disease	Stable response, alive at 15 years old

CARB, carboplatin; JPA, juvenile pilocytic astrocytoma; NF1, neurofibromatosis type 1; PCVT, procarbazine, lomustine 6-thioguanine, and vincristine; PROCARB, procarbazine; TEMO, temozolomide; VCN, vincristine; WHO, World Health Organization.

TABLE 3 Adverse events associated with single-agent bevacizumab for the treatment of recurrent/refractory LGG

Number	Systems	Adverse events	Incidence (%)
1	Central nervous system	Hypersomnolence	1 (6.7)[a]
		Fatigue	3 (20)[a]
		Encephalopathy	2 (13)[a]
		Headache	3 (20)[a]
	Urinary	Proteinuria	5 (33)[a]
2	Bleeding	Hematochezia	1 (6.7)[a]
		Epistaxis	2 (13)[a]
3	Gastrointestinal and metabolic	Emesis	1 (6.7)[a]
		Constipation	3 (20)[a]
		Hyperglycemia	1 (6.7)[b]
		Hyperkalemia	1 (6.7)[b]
		Hypokalemia	1 (6.7)[a]
		Hypernatremia	1 (6.7)[a]
		Hyperbilirubinemia	2 (13)[a]
		Transaminitis	1 (6.7)[a]
4	Musculoskeletal	Bone pain	5 (33)[a]
			1 (6.7)[b]
5	Respiratory	Coughing	1 (6.7)[a]
6	Cardiovascular	Hypertension	2 (13)[a]

[a]Common Terminology Criteria for Adverse Events (CTCAE) v4.0 grade 2.
[b]CTCAE v4.0 grade 3.

therapy resulting in multiple cranial neuropathies and weakness. Following treatment with bevacizumab, she regained bulbar function and avoided tracheostomy with jejunostomy (Figure 1D).

Treatment was discontinued in 12 patients (complete response, one; stable disease, seven; progression, two; toxicity, one; and others, one), while three patients continue treatment at the time of data collection. Two patients had a progression of disease during treatment after initially responding to bevacizumab.

Overall, 11 patients demonstrated radiographic progression at 0.5–31 months after the discontinuation of bevacizumab (median 5 months). Out of these 11 patients, five were rechallenged with bevacizumab (Patient 1, 2, 4, 5, and 8) and all except Patient 2 responded to the rechallenge (Table 2). After the discontinuation of bevacizumab rechallenge, these patients had progression in 0.5–45 months (median 6 months). The reason for discontinuation after bevacizumab rechallenge was prolonged stable disease (2), progressive disease (2), and toxicity (2). Two patients (Patients 1 and 3) died from complications of progressive disease unrelated to bevacizumab.

Single-agent bevacizumab was well tolerated with limited toxicity. Grade 2 or higher adverse events associated with single-agent bevacizumab in our series are reported in Table 3. The most common adverse event noted was bone pain (33% grade 2, 6.7% grade 3). The most common site of bone pain reported was the leg, followed by the hip. Patients with bone pain (Patients 2, 5, 7, 12, and 13) had imaging studies including either X-ray or MRI, which were negative for avascular necrosis or any other pathology. Patient 7 was later diagnosed with flexor tendinitis by orthopedics. There was no dose reduction and no dose was withheld because of the adverse events. Bevacizumab was discontinued because of toxicity in only one patient (Patient 7) during the initial course and in two patients (Patient 1 and Patient 2) during rechallenge. All adverse events resolved within 4 weeks of discontinuation of treatment, and there were no long term sequelae noted with bevacizumab treatment.

4 | DISCUSSION

Bevacizumab-based therapies, including bevacizumab plus irinotecan, have been used successfully in children with LGG. There are reports of efficacy of single-agent bevacizumab in a small number of children who could not tolerate combination therapy.[7,8] We provide the largest single-agent bevacizumab series to date, and demonstrate both radiographic and clinical response in pediatric LGG with a better toxicity profile compared to bevacizumab-based therapies. Overall, bevacizumab was well tolerated without dose modifications and all adverse events resolved within 4 weeks of discontinuation of therapy. To the best of our knowledge, this is the largest study demonstrating clinical improvements with single-agent bevacizumab in recurrent or refractory LGG. The objective response rate (80%) in our series is similar to the response rates reported previously for bevacizumab-based therapies (11–85%).[7,8] Three of 15 patients showed sustained stable disease that would be considered a response in the context of a clinical trial setting. The time to best radiologic response to single-agent bevacizumab was 10 weeks, which is very similar to the time to best response reported previously for bevacizumab-based therapies in children (7–9 weeks).[7,8] Our reported progression rate of 91% after the discontinuation of bevacizumab is similar to that of previous studies, which reported progression rates of 29–93% after discontinuation of

bevacizumab-based therapy.[7,8] Even though almost all patients experienced radiological progression of the disease after the discontinuation of bevacizumab, clinical responses including improved visual fields, cranial nerve deficits, and strength and gait were meaningful and sustained in most of cases. The reason for sustained clinical response in the absence of sustained radiographic responses is not entirely clear. It is possible that bevacizumab has effects in reduction of tumor-associated edema that may not be apparent on postgadolinium or T2-weighted imaging, and is worthy of further study.

Our series demonstrates that after an initial radiographic response to every 2 weeks dosing of bevacizumab, it is feasible to transition to every 4 weeks dosing in an attempt to limit toxicity without compromising clinical efficacy. There was no disease progression noted after immediately switching to the every 4 weeks bevacizumab dosing. This is consistent with previous reports in the literature where dosing interval for bevacizumab was safely increased because of toxicity.[7] Four of five patients rechallenged with bevacizumab showed radiographic response, albeit transient, indicating that there may be a "ceiling effect" to therapy.

Two patients in our series progressed while on bevacizumab after showing initial partial response, and both of those patients had received radiation therapy prior to bevacizumab. Further studies are needed to determine whether there may be a specific subset of patients with LGG who may not be bevacizumab responders.

There are several limitations to this study aside from the retrospective design and small number of patients. The dosing interval for the patients in this study was not standardized. It was individualized for each patient based on the symptoms, radiographic features, tolerance to bevacizumab, and parental/patient preferences. Some patients received only biweekly doses, while others started with biweekly doses and were switched to every 4 week dosing later on, thus limiting our ability to make firm conclusions regarding optimal dosing frequency. Another limitation was that neuroimaging timing was not standardized. Future studies with more consistent dosing and neuroimaging regimens may help better understand the long term effects of alterations of dosing frequency on bevacizumab efficacy. The use of postgadolinium T1 MRI sequences as the radiographic endpoint may not be truly representative of disease response. Being a vascular endothelial growth factor inhibitor, bevacizumab is known to decrease edema/vascular permeability and we cannot be certain to what extent this enhancement decrease is reflective of decreased edema/vascular permeability versus disease response, or a combination of the two in the absence of a post-treatment biopsy. In cases of stable disease or treatment response, T2/FLAIR sequences did not show appreciable changes, possibly reflective of treatment-related changes and parenchymal gliosis, which may have static imaging characteristics over time. Because of the small sample size, any correlations between bevacizumab responsiveness and histologic diagnosis, grade, tumor location, or molecular features cannot be made and would require a larger multi-institutional study.

Overall, this study shows a favorable response of LGG to single-agent bevacizumab, and radiographic response time was faster than anticipated. Future studies are needed to see if a sustained response with bevacizumab can be achieved with combination therapies and whether there may be molecular determinants of responsiveness.

5 | CONCLUSION

Single-agent bevacizumab is efficacious in the management of recurrent or refractory pediatric LGG with radiographic and clinical responses similar to those reported for bevacizumab-based therapies.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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