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Bevacizumab for pediatric radiation necrosis

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Abstract

Background. Radiation necrosis is a frequent complication occurring after the treatment of pediatric brain tumors; however, treatment options remain a challenge. Bevacizumab is an anti-VEGF monoclonal antibody that has been shown in small adult cohorts to confer a benefit, specifically a reduction in steroid usage, but its use in children has not been well described.

Methods. We describe our experience with bevacizumab use for symptomatic radiation necrosis at 5 institutions including patients treated after both initial irradiation and reirradiation.

Results. We identified 26 patients treated with bevacizumab for symptomatic radiation necrosis, with a wide range of underlying diagnoses. The average age at diagnosis of radiation necrosis was 10.7 years, with a median time between the last dose of radiation and the presentation of radiation necrosis of 3.8 months (range, 0.6-110 months). Overall, we observed that 13 of 26 patients (50%) had an objective clinical improvement, with only 1 patient suffering from significant hypertension. Radiological improvement, defined as reduced T2/fluid-attenuated inversion recovery signal and mass effect, was observed in 50% of patients; however, this did not completely overlap with clinical response. Both early and late radiation necrosis responded equally well to bevacizumab therapy. Overall, bevacizumab was very well tolerated, permitting a reduction of corticosteroid dose and/or duration in the majority of patients.

Conclusions. Bevacizumab appears to be effective and well-tolerated in children as treatment for symptomatic radiation necrosis and warrants more robust study in the context of controlled clinical trials.

Keywords

bevacizumab | dexamethasone | pediatric brain tumors | radiation | radiation necrosis

External beam irradiation is an integral component in the treatment of most pediatric brain tumors, but a major complication of high-dose radiotherapy is radiation-induced injury, termed *radiation necrosis*.[1] Radiation necrosis can present in the immediate period after completion of radiotherapy in the subacute phase, but can also present years later as late radiation necrosis.[2] The mechanism of radiation necrosis is not completely known but is thought to be related to direct injury to the vasculature, resulting in upregulation of hypoxia-inducible factor 1a with ensuing release of VEGF.[2] This release of VEGF results in increased vascular permeability, angiogenesis, and subsequently brain edema and inflammation. Dexamethasone is the mainstay of therapy but has significant side effects, precludes novel immunotherapies because of T-cell depletion, and is frequently ineffective. In adults, the VEGF monoclonal antibody bevacizumab has been reported to improve neurological symptoms, improve the T2/fluid-attenuated inversion recovery (FLAIR) abnormalities on MRI, and allow weaning of corticosteroids; however, the pediatric experience is very limited.[3–7] Moreover, the application of reirradiation as salvage therapy for patients has increased the risk of radiation necrosis, necessitating effective therapeutic approaches.[8] Although there have been a few case series, there remains a paucity of data to support its use in children beyond small series.[9] Herein, we describe our experience with the use of bevacizumab for the treatment of symptomatic radiation necrosis.

Methods

We recruited a cohort of 26 patients from 5 institutions (the Hospital for Sick Children, the Hospital JP Garrahan, the University Hospital Motol, the Hospital Virgen del Rocío, and Royal Children's Hospital) who were treated for symptomatic radionecrosis with bevacizumab. A retrospective analysis of imaging and clinical parameters was performed to determine bevacizumab dosing, tolerability, and outcome. The diagnosis of radionecrosis was established through evaluation of MRI including pregadolinium and postgadolinium administration sequences and was defined as a ring-enhancing mass with variable edema and mass effect, or new nodular-enhancing lesion exhibiting a soap bubble or Swiss cheese pattern. Imaging response was evaluated after at least 2 doses of bevacizumab, and a response to treatment was defined as a reduction in bidirectional measurements on T2/FLAIR images by at least 20% in the product of the 2 measures.

Results

Demographics

A total of 26 patients were identified at the Hospital for Sick Children, the Hospital JP Garrahan, the University Hospital Motol, the Hospital Virgen del Rocío, and Royal Children's Hospital with either acute or late symptomatic radiation necrosis treated with bevacizumab (Table 1). Seventeen patients presented with radiation necrosis after the first course of radiation, 8 patients after the second course, and 1 patient after the third course. In those patients presenting after reirradiation, the median time between the first course and second course of radiation was 15.9 months (range, 5.3-156 months). The median age at radiation necrosis was 10.7 years. The median time between last course of radiation and radiation necrosis diagnosis was 3.8 months (range, 0.6-110 months). Radiation necrosis occurred within 3 time periods: acute (during or immediately following therapy) in 3 patients, early-delayed (between 3 weeks and 6 months after the therapy) in 18 patients, and late-delayed (after 6 months from the completion of therapy) in 5 patients. Only 2 patients with late-delayed radiation necrosis presented 12 months after external beam irradiation was completed.

Dosing and Toxicity of Bevacizumab

The most common dose of bevacizumab was 10 mg/kg (18 patients), and the dosing varied between 5 and 10 mg/kg administered every 2 weeks with an average of 4 doses (range, 2-7 doses). Toxicities were identified through a retrospective chart review, and overall bevacizumab was very well tolerated with only 1 patient having severe hypertension (grade 3) after 4 doses of bevacizumab, with normalization of blood pressure on discontinuation. No other adverse events were identified; specifically no hemorrhagic events or gastric perforation were observed in any patient. No patients discontinued bevacizumab because of an adverse event clearly attributed to bevacizumab use.

Radiotherapy Dosing and Field

Twenty-two patients received external photon beam radiation using intensity-modulated radiotherapy therapy (IMRT) and 4 patients received proton therapy. The mean total radiation dose for these patients was 54 Gy (range, 50.4-59.4 Gy) for the first course in 30 fractions (range, 30-33 fractions) and 54 Gy for the second course (range, 20-54 Gy) in 30 fractions (range, 10-30 fractions). Only 1 patient received a third course of radiation with 36 Gy (craniospinal irradiation) and 54 Gy (IMRT). The most frequent location of necrosis was the brainstem in 22 patients, followed by temporal lobe in 2 patients, frontal lobe in 1 patient, and frontoparietal in 1 patient.

Response to Bevacizumab

Twenty-two patients received high doses of dexamethasone at the time of initial presentation. Bevacizumab was initiated in all patients within 1 to 2 weeks of the first dose of dexamethasone, and 18 patients were able to taper their dexamethasone dose on initiation of therapy. Thirteen of 26 patients had objective improvement in neurological symptoms after 2 cycles of bevacizumab, most commonly an improvement in new-onset weakness. Thirteen of 23 patients showed a radiological response, specifically as reduced signal intensity and midline shift on T2/FLAIR imaging (Fig. 1). Four of 23 patients showed disease progression during therapy with bevacizumab. No correlation

Table 1 Demographics and Response of Patients Treated for Symptomatic Radiation Necrosis

ID	Diagnosis	Total Radiation, Gy	Age at BVZ, y	Onset of RN, mo	Dose of BVZ mg/kg (× No. of Doses)	MRI Response: FLAIR/T2 Intensity	Clinical Response	Adverse Effects
1	DIPG	108	10.7	< 6	10 (× 4)	Stable	Improvement	HTN
2	DIPG	84.6	10.7	Acute	10 (× 5)	N/A	Improvement	None
3	Chordoma	50.4	1.4	Acute	10 (× 2)	Reduction	Improvement	None
4	LGG	54	13.2	< 6	10 (× 7)	Reduction	Improvement	None
5	ST-EPN-RELA	167.3	15.5	> 6 (6.1)	10 (× 6)	Stable	Stable	None
6	DIPG	54	7	< 6	10 (× 6)	Stable	Stable	None
7	DIPG	54	14.6	< 6	5 (× 5)	Reduction	Stable	None
8	PF-EPN-A	59.4	12.2	> 12 (110)	5 (× 4)	Reduction	Improvement	None
9	HGG	113.4	9.2	< 6	10 (× 4)	Reduction	Improvement	None
10	DIPG	54	8.3	< 6	10 (× 6)	Reduction	Progression	None
11	HGG	60	12.4	<6	10 (× 6)	Reduction	Stable	None
12	DIPG	54	8.8	Acute	10 (× 4)	Stable	Stable	None
13	HGG	113.4	11.8	< 6	10 (× 2)	Progression	Progression	None
14	DIPG	74	5.8	< 6	10 (× 4)	N/A	Improvement	None
15	HGG	54	13.4	< 6	5 (× 2)	Reduction	Improvement	None
16	LGG	59.4	13.8	< 6	7.5 (× 6)	Reduction	Improvement	None
17	LGG	54	14.4	> 12 (22)	7.5 (× 6)	Reduction	Stable	None
18	PF-EPN-A	59.4	5	< 6	7.5 (× 6)	Reduction	Stable	None
19	MB	99	16.6	< 6	10 (× 4)	Reduction	Improvement	None
20	MB	54	5.1	< 6	10 (× 4)	Reduction	Stable	None
21	MB	54	4.6	> 6 (7)	10 (× 7)	Progression	Progression	None
22	CP	54	7.4	< 6	10 (× 7)	Stable	Progression	None
23	DIPG	54	4.1	< 6	10 (× 4)	N/A	Stable	None
24	ATRT	54	4.1	< 6	10 (× 4)	Stable	Improvement	None
25	LGG	100	18.3	> 6 (7)	7.5 (× 6)	Stable	Improvement	None
26	PF-A EPN	110	12.7	< 6	7.5 (× 3)	N/A	Improvement	None

Abbreviations: ATRT, atypical teratoid rhabdoid tumor; BVZ, bevacizumab; CP, craniopharyngioma; DIPG, diffuse intrinsic pontine glioma; FLAIR, fluid-attenuated inversion recovery; Gy, gray; HGG, high-grade glioma; HTN, hypertension (severe); ID, identification; LGG, low-grade glioma; MB, medulloblastoma; PF-EPN-A, posterior fossa type A ependymoma; N/A, not available/not evaluated; RN, radiation necrosis; ST-EPN-RELA, RELA-fused ependymoma.

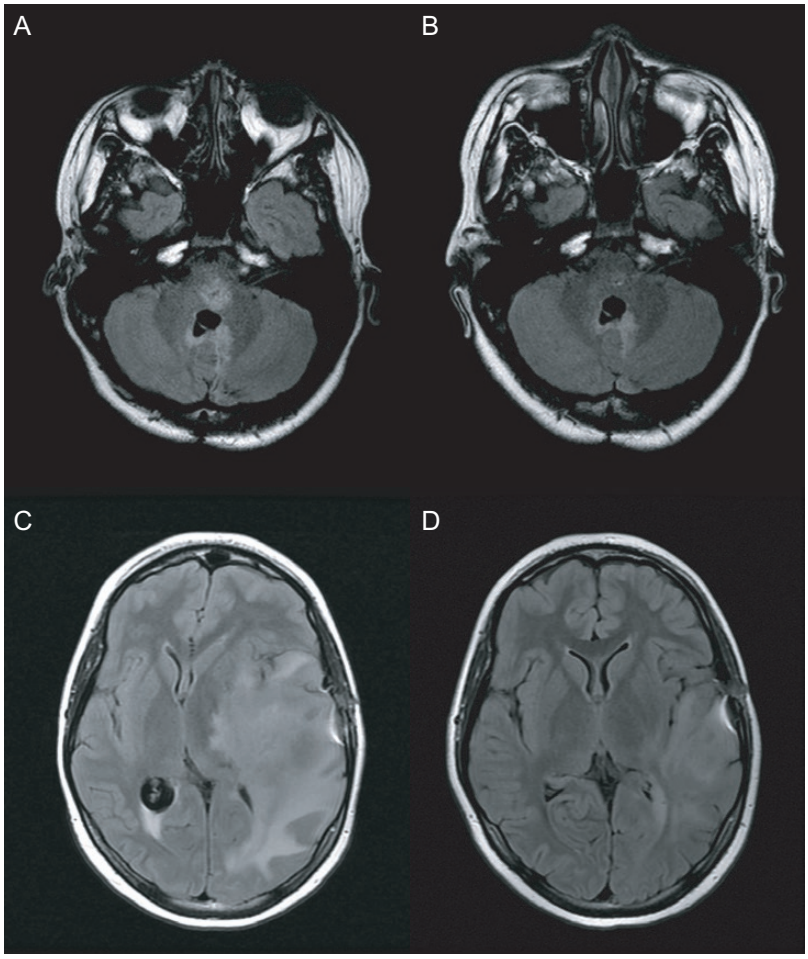

Fig. 1 Case 8: Axial fluid-attenuated inversion recovery (FLAIR) MRI of a posterior fossa type A ependymoma presenting with late radionecrosis 9 years after completion of radiation at A, diagnosis and B, after 4 doses of bevacizumab. Case 9: Axial FLAIR MRI of a high-grade glioma 2 months postradiotherapy presenting with radionecrosis at C, diagnosis and D, after 6 doses of bevacizumab.

between cumulative dose of radiation (> or < 59.4 Gy) and either clinical and/or radiological response to bevacizumab was observed ($P = .47$). We did not identify any significant correlation between bevacizumab dose and imaging/clinical response. The most frequent dose used in our cohort was 10 mg/kg per dose in 18 patients (75%). The use of a higher dose of bevacizumab (10 mg/kg) in comparison with the lower dose (5-7.5 mg/kg per dose) did not appear to be associated with any clinical or radiological benefit. No statistically significant predictor of either radiological or clinical response to bevacizumab was identified including tumor type (glioma vs nonglioma), radiation dose or location, bevacizumab dose and frequency, or age at bevacizumab use (Supplementary Table 1).

Discussion

To our knowledge, this study represents the largest cohort of pediatric brain tumors treated with bevacizumab for symptomatic radiation necrosis. Overall, bevacizumab is safe, well-tolerated, and effective in the majority of patients, with objective clinical and radiological improvement observed.

Current treatment options are limited, with most patients receiving high doses of dexamethasone. In adults, dexamethasone has been shown to improve symptoms in most patients; however, in small studies, bevacizumab appears to be effective in reducing the duration of symptoms and allows tapering of steroids.[10–17] Moreover, dexamethasone has significant disadvantages, specifically its cushingnoid side effects, and may interfere with the efficacy of novel immunotherapies. Our experience suggests that bevacizumab can be an effective treatment modality that allows for a steroid-sparing approach to radiation necrosis. However, because most patients were treated initially with corticosteroids before the initiation of bevacizumab, we cannot disregard a potential synergistic effect, which warrants further evaluation in prospective studies. Other therapies have been investigated such as hyperbaric oxygen therapy, anticoagulation, NSAIDs, and

oral vitamin E; however, none have undergone any rigorous clinical trials.[18–20]

A major limitation in interpreting our findings is its retrospective design with limited patient numbers, precluding any additional subanalysis identifying either clinical or radiological predictors of response to bevacizumab. Particularly with DIPG patients, we were not able to definitively distinguish tumor necrosis from radiation necrosis. Despite its widespread use in adult and pediatric radiation necrosis, with the exception of a single small, randomized controlled trial, the experience of using bevacizumab has been limited to anecdotal case series, with a paucity of properly controlled randomized and/or prospective trials.[21] Our study, coupled with other small pediatric series, suggests that a prospective study controlling for corticosteroid use and central review of imaging is urgently required to objectively assess the efficacy of bevacizumab in the treatment of radiation necrosis.[6,9] A major challenge remains the ascertainment of radiation necrosis. The MRI characteristics of tumor progression and radiation necrosis are highly overlapping in the acute phase, resulting in significant interobserver variability. Establishing a standard or uniform criteria for radiation necrosis is limited by the inability of current imaging modalities from reliably establishing an objective diagnosis. Advanced imaging, including fluorine-18 fluorodeoxyglucose (FDG)-PET and MR spectroscopy, have shown promise in establishing a diagnosis of radiation necrosis but are still limited, suggesting that new imaging paradigms are urgently needed to help differentiate tumor progression from radiation necrosis.[19,20,22] Biopsy of the lesion could be of benefit in some cases but carries the risks of invasive surgery, particularly the risk of hemorrhage, and has the potential of sampling error.[20] Prospective studies, including the incorporation of advanced imaging, are required to help distinguish these entities and help establish standard diagnostic criteria.

Another major consideration with bevacizumab use is the high cost, with each course of therapy costing approximately $1000 depending on the weight of the child. As such, the optimal dose and schedule both need to be established in future studies. Indeed, several adult studies suggest low-dose bevacizumab can be as effective including 6-week intervals between doses.[4,15,23,24] To establish the true cost to benefit ratio of bevacizumab use, dedicated analyses of cost-effectiveness associated with bevacizumab therapy are required, especially considering that the cost of bevacizumab is based on the number of vials used, which is proportional to weight. This will likely require a prospective multi-institutional study with uniform diagnostic criteria, and careful attention to corticosteroid use and standardized quality of life measures. Nevertheless, we believe our report suggests bevacizumab use will likely have a favorable cost to benefit ratio, which warrants future study. Specifically, we observe in several patients it either prevents or shortens hospital admissions for neurological decline and dexamethasone-related side effects.

Our results suggest bevacizumab is a safe, efficacious, and well-tolerated treatment of radiation necrosis incurred after treatment of pediatric brain tumors. Controlled prospective clinical trials with robust companion advanced neuroimaging correlative studies and quality of life metrics are urgently required to help inform the appropriate use of bevacizumab in the treatment of radiation necrosis in children.

Supplementary material

Supplementary material is available online at *Neuro-Oncology* (http://neuro-oncology.oxfordjournals.org/).

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Conflict of interest statement. None declared.

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