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Single low-dose targeted bevacizumab infusion in adult patients with steroid-refractory radiation necrosis of the brain: a phase II open-label prospective clinical trial

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OBJECTIVE There is an unmet need for safe and rapidly effective therapies for refractory brain radiation necrosis (RN). The aim of this prospective single-arm phase II trial was to evaluate the safety and efficacy of a single low-dose targeted bevacizumab infusion after blood-brain barrier disruption (BBBD) in adult patients with steroid-refractory brain RN.

METHODS Ten adults with steroid-refractory, imaging-confirmed brain RN were enrolled between November 2016 and January 2018 and followed for 12 months after treatment. Bevacizumab 2.5 mg/kg was administered as a one-time targeted intra-arterial infusion immediately after BBBD. Primary outcomes included safety and > 25% decrease in lesion volume. Images were analyzed by a board-certified neuroradiologist blinded to pretrial diagnosis and treatment status. Secondary outcomes included changes in headache, steroid use, and functional status and absence of neurocognitive sequelae. Comparisons were analyzed using the Fisher exact test, Mann-Whitney U-test, linear mixed models, Wilcoxon signed-rank test, and repeated-measures 1-way ANOVA.

RESULTS Ten adults (mean ± SD [range] age 35 ± 15 [22–62] years) participated in this study. No patients died or exhibited serious adverse effects of systemic bevacizumab. At 3 months, 80% (95% CI 44%–98%) and 90% (95% CI 56%–100%) of patients demonstrated > 25% decrease in RN and vasogenic edema volume, respectively. At 12 months, RN volume decreased by 74% (median [range] 76% [53%–96%], p = 0.012), edema volume decreased by 50% (median [range] 70% [−11% to 83%], p = 0.086), and headache decreased by 84% (median [range] 92% [58%–100%], p = 0.022) among the 8 patients without RN recurrence. Only 1 (10%) patient was steroid dependent at the end of the trial. Scores on 12 of 16 (75%) neurocognitive indices increased, thereby supporting a pattern of cerebral white matter recovery. Two (20%) patients exhibited RN recurrence that required further treatment at 10 and 11 months, respectively, after bevacizumab infusion.

CONCLUSIONS For the first time, to the authors' knowledge, the authors demonstrated that a single low-dose targeted bevacizumab infusion resulted in durable clinical and imaging improvements in 80% of patients at 12 months after treatment without adverse events attributed to bevacizumab alone. These findings highlight that targeted bevacizumab may

ABBREVIATIONS AE = adverse event; AVM = arteriovenous malformation; BBB = blood-brain barrier; BBBD = BBB disruption; FSIQ = full-scale intelligence quotient; HIT-6 = Headache Impact Test-6; IA = intra-arterial; IV = intravenous; KPS = Karnofsky Performance Status; MIDAS = Migraine Disability Assessment Test; RN = radiation necrosis; SAE = serious AE; SRS = stereotactic radiosurgery; SRT = stereotactic radiation therapy; VEGF = vascular endothelial growth factor.

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be an efficient one-time treatment for adults with brain RN. Further confirmation with a randomized controlled trial is needed to compare the intra-arterial approach with the conventional multicycle intravenous regimen.

Clinical trial registration no.: NCT02819479 (ClinicalTrials.gov)

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KEYWORDS bevacizumab; radiation necrosis; radiosurgery adverse effects; blood-brain barrier disruption; arteriovenous malformation; stereotactic radiosurgery; intra-arterial therapy; neurocognitive assessment; cerebral white matter; subcortical decline; adverse radiation effect; oncology

Radiation necrosis (RN) of the brain is a devastating demyelinating disease of the subcortical white matter that can cause debilitating headaches, recurrent seizures, focal neurological deficits, and subcortical neurocognitive slowing.[1,2] As many as 20% of patients will develop RN after cerebral stereotactic radiation therapy (SRT) or stereotactic radiosurgery (SRS).[3,4] In addition to malignant brain tumors, radiation therapy is increasingly used as a noninvasive treatment for benign diseases such as arteriovenous malformation (AVM), epilepsy, and meningioma.[5–9] As the number of SRT/SRS procedures performed each year increases,[10] the number of patients at risk for cerebral RN may potentially increase in parallel. The symptoms of most patients can be managed medically with steroids, but severe cases require combined therapies such as pentoxifylline, vitamin E, hyperbaric oxygen, resection, or laser interstitial thermal therapy. However, as many as 40% of patients experience severe symptoms that are refractory to prevailing treatments.[11,12]

Vascular endothelial growth factor (VEGF) is generally recognized as a root cause of cerebral RN. Excess VEGF production activates a family of receptors that amplifies the inflammatory cascade of leaky capillaries, localized edema, and focal ischemia, resulting in white matter necrosis and surrounding vasogenic edema with associated intracranial mass effect.[13] Intravenous (IV) bevacizumab (Avastin, Genentech BioOncology), a recombinant humanized murine monoclonal antibody to VEGF, is an emerging therapy for refractory brain RN that is typically administered as 5.0–10.0 mg/kg IV infusions every 2–3 weeks for 2–6 cycles.[14–18] Although previous studies focused on multicycle IV bevacizumab regimens, one fundamental challenge persists: how to transport a large 149-kD molecule out of the systemic circulation and through the blood-brain barrier (BBB), and then deliver it directly to the white matter encircling the RN focus.[19]

Targeted bevacizumab delivered intra-arterially into the affected brain territory after osmotic BBB disruption (BBBD) may be an attractive solution.[20] Intra-arterial (IA) bevacizumab promises rapid eradication of VEGF and swift resolution of both microvascular pathology and RN symptoms while minimizing known systemic toxicities, including intracranial hemorrhage, uncontrolled hypertension, gastrointestinal tract perforation, venous sinus thrombosis, wound dehiscence, and pulmonary embolus.[14,21–24]

We previously treated 2 pediatric patients with refractory brain RN by using a single 2.5 mg/kg targeted bevacizumab infusion immediately after osmotic BBBD.[20] Both patients demonstrated remarkable clinical and imaging improvement in less than 12 months, with complete resolution of inflammation-related symptoms and MRI findings at 3 years and no recurrence after 8 years (unpublished data).

These encouraging results led us to design this prospective clinical trial, which we piloted with 10 patients diagnosed with treatment-refractory brain RN. The primary aim of this study was to evaluate safety and MRI efficacy after a single targeted low-dose bevacizumab infusion. Our secondary end points included change in headache, steroid use, and functional status and absence of neurocognitive sequelae. We determined that if 3 or more patients (i.e., ≥ 30%) exhibited a positive imaging response, then the outcomes of this trial would inform a post hoc power analysis and sample size determination for increased patient enrollment at multiple sites.

Methods

Trial Design and Participants

We conducted a phase II, multicenter, single-arm, open-label, prospective clinical trial in patients with steroid-refractory brain RN. The trial consisted of baseline measurements, targeted IA bevacizumab infusion under general anesthesia immediately after BBBD, and 12 months of follow-up. Per protocol, we planned to enroll 10 patients in this pilot study. The protocol was approved by the Institutional Review Board at each participating center in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice guidelines, in addition to all applicable state and federal research-related laws and statutes. Trial design and study-related activities are described in greater detail in the Online Appendix. This study was registered with the ClinicalTrials.gov database (https://clinicaltrials.gov), and its registration number is NCT02819479.

Qualifying patients were adults aged 18 years and older with a Karnofsky Performance Status (KPS) score ≥ 70% and life expectancy ≥ 3 months who had previously undergone SRT or SRS of the brain. The included patients presented with the characteristic finding of increased postcontrast T1-weighted enhancement with central hypointensity in the irradiated area, which is indicative of necrosis, and confluent increased surrounding vasogenic edema on T2-weighted FLAIR MRI.[25,26] To be eligible, patients had to demonstrate at least 1 RN symptom (severe headache, recurrent seizures, or neurological deficit) that was refractory to steroid treatment, which was defined as a failed 3-week steroid regimen or inability to tolerate steroids due to adverse effects. Patients may have received other therapies such as vitamin E, pentoxifylline, laser interstitial thermal therapy, and hyperbaric oxygen. Patients were excluded if they had a biopsy-proven active malignant brain tumor, active bleeding, or a pathological

condition with a high risk of bleeding or were taking anticoagulation therapy other than aspirin. Additional exclusion criteria included abdominal fistula, abscess, gastrointestinal tract perforation, major surgery within 4 weeks of study enrollment, significant uncontrolled intercurrent illness, and pregnancy.

Procedures

All enrolled patients were lucid and able to provide written informed consent without a legally authorized representative. Within 4 weeks of baseline measurements, patients were brought to the interventional vascular neuroradiology suite where the ipsilateral internal carotid or vertebral artery was catheterized (see the Online Appendix for descriptions of the procedures). After confirmatory angiography, osmatic BBBD was performed with warmed (37°C) 25% mannitol infused at the optimal rate for 30 seconds. Immediately after BBBD, 2.5 mg/kg bevacizumab was administered intraarterially over 10 minutes while systolic arterial blood pressure was maintained either above 120 mm Hg or at preoperative baseline if greater than 120 mm Hg. Patients were closely monitored in the recovery unit for 2–4 hours and then observed overnight in the transitional care unit until discharge home the following day.

Outcomes

The primary outcomes included safety and MRI efficacy. Patients were evaluated for adverse events (AEs) on posttreatment days 0 and 1 and posttreatment months 1.5, 3, 6, 9, and 12. MRI was performed with a standard brain-imaging protocol, precontrast and postcontrast sequences, and 1.5-T and 3-T magnets (Siemens Medical Solutions USA) at baseline and 3 and 12 months posttreatment. Postgadolinium axial T1-weighted fat-saturated images were used to evaluate volume of RN, and axial T2-weighted FLAIR images were used to calculate volume of vasogenic edema. Lesion volumes were quantified[27] with postprocessing software (TeraRecon, Inc.) after trial completion by an independent board-certified neuroradiologist blinded to pretrial diagnosis and treatment status. Greater than 25% reduction in lesion volume compared with baseline volume constituted a positive imaging response.[14]

The secondary outcomes included changes in headache scores, steroid usage, and functional status and absence of neurocognitive sequelae (which are described in greater detail in the Online Appendix). Headache was measured with the Migraine Disability Assessment Test (MIDAS), which included the total MIDAS score, days with headache, and pain score, as well as the Headache Impact Test-6 (HIT-6). Total cumulative days of steroid intake during the 12 months prior to bevacizumab therapy were compared with the 12 months immediately after. Functional status was assessed with the KPS score. Lastly, neurocognitive status was assessed with 16 subtests from the Neuropsychological Assessment Battery (R.A. Stern and T. White, PAR Inc.). The Wechsler Test of Adult Reading (Pearson Inc.) was used to measure full-scale intelligence quotient (FSIQ) at baseline as an estimate of premorbid intelligence. Although our aim was to document the absence of neurocognitive sequelae, we performed exploratory analyses to determine whether patients demonstrated statistically significant neurocognitive changes.

Statistical Analysis

Statistical analyses were performed with PC-SAS version 9.4 (SAS Institute Inc.) and SPSS version 27.0 (IBM Corp.). Safety was gauged by documenting all treatment-emergent AEs and serious AEs (SAEs) according to Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 and the Agent Specific Adverse Event List.[28]

Primary efficacy was assessed on the basis of the proportion of patients with > 25% reductions in RN and vasogenic edema volumes compared with baseline. Absolute change was calculated as (measurement at posttreatment time point — measurement at baseline). Percent change was calculated as ([(measurement at posttreatment time point — measurement at baseline)/measurement at baseline] × 100%). Negative changes were described as reductions or decreases. The Clopper-Pearson method was used to calculate 95% CIs. The baseline categorial characteristics of the patients who were enrolled at the 2 study sites were compared with the Fisher exact test, and continuous variables were compared with the Mann-Whitney U-test.

Durability of radiographic and clinical responses were explored with linear mixed models, in which we addressed the heterogeneity of time points by fitting the most appropriate model among compound symmetry, Huynh-Felt structure, and unstructured covariance matrix (multivariate ANOVA). Cumulative days of steroid use during the 12 months before and after bevacizumab infusion were compared by using the Wilcoxon signed-rank test. Exploratory analyses of neurocognitive variables were performed by using 1-way repeated-measures ANOVA with FSIQ placed in the model as a covariate. All p values were 2-tailed. The null hypothesis was rejected for $p < 0.05$.

Results

Between November 2016 and January 2018, we enrolled 10 adult patients (mean ± SD [range] age 35.1 ± 14.8 [22–62] years; median 31 years); 5 patients were enrolled from each study site.

Pretrial diagnoses included 8 (80%) cases of AVM, 1 (10%) meningioma, and 1 (10%) metastatic non–small cell lung carcinoma with biopsy-proven absence of active neoplastic disease. Regarding previous radiotherapies, 5 (50%) patients underwent Gamma Knife radiosurgery, 3 (30%) underwent CyberKnife, and 1 (10%) each underwent proton radiotherapy, Novalis Tx linear accelerator radiotherapy, and whole-brain external beam radiotherapy (Table 1). One patient underwent whole-brain external beam radiotherapy followed by Gamma Knife radiosurgery. The patients enrolled from both study sites were statistically similar in terms of age, weight, sex, race, ethnicity, pretrial diagnoses, prior treatments, and baseline lesion volumes. Although not a criterion for exclusion, none of the 10 patients had received IV bevacizumab prior to study enrollment.

After informed consent was obtained and all inclusion criteria were met, none of the 10 patients refused to par-

TABLE 1. Baseline demographic and clinical characteristics

Patient No.	Age (yrs)	Sex	Weight (kg)	Pathology	SRT/SRS	Total Dose (Gy)	Nonsteroid Therapy	RN Vol (cm^3)	Edema Vol (cm^3)	RN Recurrence
1	22	F	62.1	AVM	Proton	18.0	PTX, Vit-E	2.4	7.2	No
2	22	M	115.2	AVM	Novalis Tx linear accelerator	54.0	None	22.1	67.9	No
3	25	F	64.0	AVM	Gamma Knife	54.0	PTX, Vit-E	36.6	297.0	No
4	36	F	94.3	AVM	Gamma Knife	20.0	PTX, Vit-E	1.9	5.5	No
5	60	M	81.0	Met lung CA	WBEB followed by Gamma Knife	54.5	PTX, Vit-E, LITT	10.3	55.6	No
6	25	F	59.7	AVM	CyberKnife	33.0	None	23.4	54.3	No
7	37	F	53.3	AVM	Gamma Knife	15.0	None	19.3	108.0	No
8	62	F	73.9	Menin-gioma	CyberKnife	30.0	PTX, Vit-E, HBO, LITT	3.6	16.9	Yes
9	36	F	59.0	AVM	Gamma Knife	44.0	PTX, Vit-E	23.3	213.0	Yes
10	26	F	62.8	AVM	CyberKnife	18.0	None	2.0	42.8	No
Median (range)*	31.0 (22–62)		63.4 (53.3–115.2)			31.5 (15.0–54.5)		14.8 (1.9–36.6)	55.0 (5.5–297.0)	

HBO = hyperbaric oxygen; LITT = laser interstitial thermal therapy; Met lung CA = metastatic lung cancer; PTX = pentoxifylline; Vit-E = vitamin E; WBEB = whole-brain external beam radiotherapy.
* Shown for continuous variables with nonnormal distributions.

ticipate or withdrew their consent during the trial. Data from all 10 patients were available from baseline through the 9-month follow-up (Fig. 1). Two patients (20%) experienced recurrence of RN and opted for medical or surgical intervention at 10 and 11 months after infusion, respectively. The first patient to relapse was lost to follow-up prior to the 12-month visit, but her steroid data later became available for analysis. The second patient underwent study-related procedures through study completion, but her 12-month measurements—except those related to steroid use—were treated as outliers and excluded from the analysis owing to craniotomy and wedge resection at 11 months after infusion (Fig. 1).

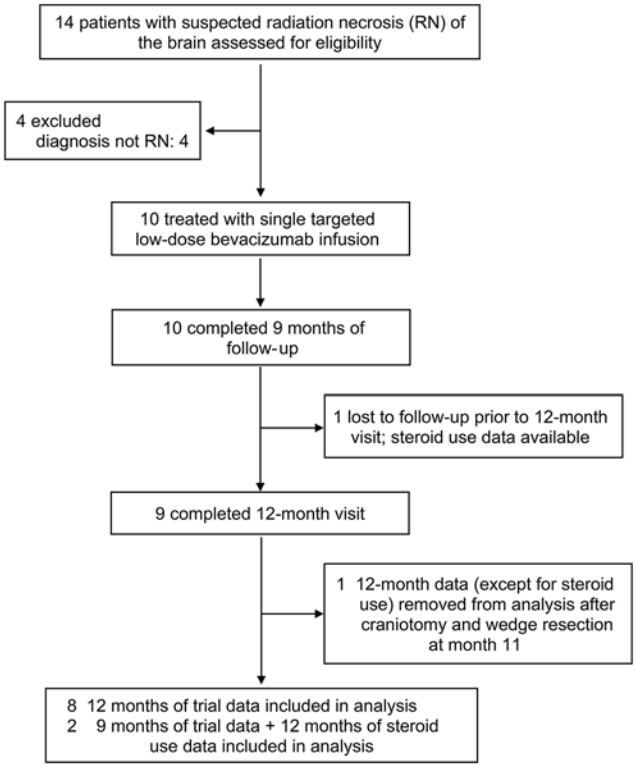

FIG. 1. Flow diagram of study progress.

Safety

All documented AEs were treatment emergent (Table 2). No patients died or experienced known SAEs associated with systemic bevacizumab such as intracranial hemorrhage, uncontrolled hypertension, gastrointestinal perforation, venous sinus thrombosis, or pulmonary embolus. Six (60%) patients experienced 11 SAEs, all of which were determined to be unrelated to bevacizumab, though 2 SAEs were deemed possibly related to BBBD (a single episode of double vision and dizziness in 1 patient lasting approximately 2 hours). Nine (90%) patients experienced 99 AEs, with 51 (52%) classified as grade 1, 47 (47%) grade 2, and 1 (1%) grade 3. Four AEs of moderate severity were experienced by 2 (20%) patients and determined to be probably related to BBBD (patient 1 had tonic/clonic seizures with altered mental status 2 hours after the procedure) or the combination of BBBD followed by IA bevacizumab (patient 4 had transient monocular blurred vision with diplopia on day 1 after infusion). Another episode of transient monocular blurred vision 1 day after infusion was characterized as possibly related to BBBD (Table 2).

Primary Efficacy Outcomes

At the 3-month follow-up, 8 (80%) (95% CI 44%–98%) patients exhibited > 25% reduction in RN volume and 9 (90%) (95% CI 56%–100%) exhibited > 25% reduction in vasogenic edema (Fig. 2). At 12 months, the median (range) decrease in RN volume was 76% (53%–96%) (me-

TABLE 2. Summary of SAEs and AEs in the study population (n = 10)

Characteristic	No. (%) of Patients	No. of Events
All-cause mortality	0/10 (0)	0
Any treatment-emergent SAE	6/10 (60)	11
Possibly or probably related to bevacizumab	0/10 (0)	0
Possibly related to BBBD	2/10 (20)	2
Double vision (1 day after treatment)*	1/10 (10)	1
Dizziness (1 day after treatment)*	1/10 (10)	1
Any treatment-emergent AE	9/10 (90)	99
Possibly or probably related to bevacizumab	0/10 (0)	0
Probably related to BBBD	2/10 (20)	2
Tonic/clonic seizures (2 hrs after treatment)†	1/10 (10)	1
Altered mental status (2 hrs after treatment)†	1/10 (10)	1
Probably related to combination of BBBD & bevacizumab	2/10 (20)	2
Transient monocular blurred vision (1 day after treatment)‡	1/10 (10)	1
Transient diplopia (1 day after treatment)‡	1/10 (10)	1
>10% frequency		
Headache	5/10 (50)	7
Blurred vision	4/10 (40)	6
Leg cramps	2/10 (20)	3
Fall	2/10 (20)	2
Neck pain	2/10 (20)	2
Numbness	2/10 (20)	2
Seizures	2/10 (20)	2
Traumatic fall	2/10 (20)	2
Vomiting	2/10 (20)	2

* Patient 8.
† Patient 1.
‡ Patient 4.

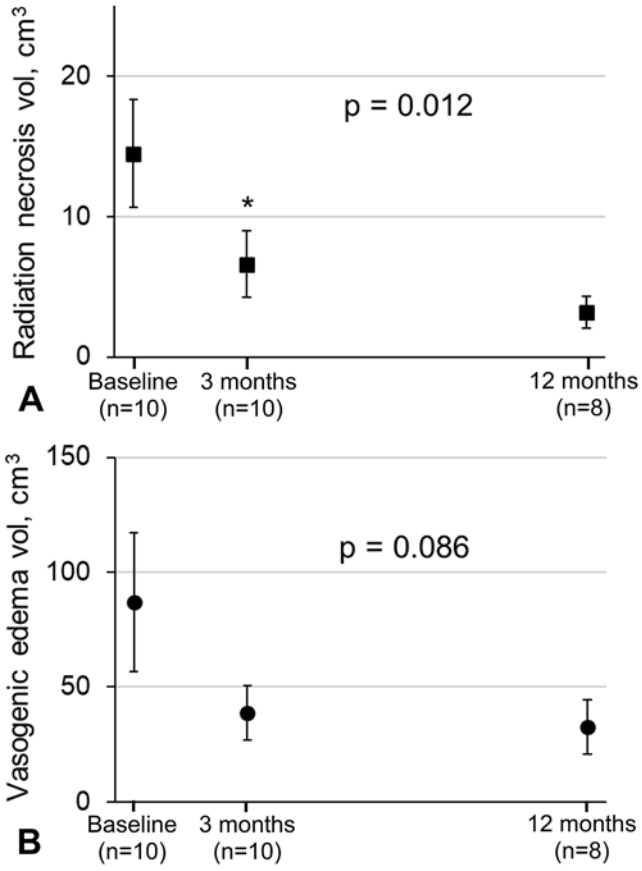

FIG. 2. Graphs of RN (**A**) and vasogenic edema (**B**) volumes. Mean ± standard error values are shown. Images were analyzed after trial closure by a board-certified neuroradiologist blinded to pretrial diagnosis and treatment status. Postcontrast T1-weighted axial images were used to calculate RN volume. T2-weighted FLAIR axial images were used to calculate vasogenic edema volume. Two patients experienced recurrence of RN and required further treatment at 10 and 11 months, respectively, after infusion; their data (months 0–9) are included graphically but were omitted from the analysis. *Significant difference ($p < 0.05$) from baseline on post hoc analysis.

dian [range] difference –12.1 [–1.0 to 27.3] cm^3, $p = 0.012$), and the median (range) decrease in vasogenic edema was 70% (range –11% to –83%) (median [range] difference –27.6 [0.6 to –216.1] cm^3, $p = 0.086$) (Fig. 2). MRI typically demonstrated progressively decreasing enhancement on postcontrast T1-weighted images, as well as decreased hyperintensity on T2-weighted FLAIR images (Fig. 3). Figure 3 shows continued improvements on MRI in 2 patients 1 year beyond the end of the study (24 months after single low-dose IA bevacizumab infusion), a common observation in our experience.[20]

Secondary Outcomes

Significant decreases in all 4 headache indices were most pronounced at 3 months after bevacizumab infusion (Fig. 4) and were sustained throughout the 12-month follow-up period. Among the 8 patients without RN recurrence, total MIDAS score decreased by 84% (median [range] 92% [58%–100%], $p = 0.022$), days of headache reported on MIDAS decreased by 61% (median [range] 77% [–11% to 95%], $p = 0.019$), MIDAS pain score decreased by 36% (median [range] 33% [–43% to 100%], $p < 0.001$), and HIT-6 score decreased by 18.3% (median [range] 24.8% [–14.1% to 39.0%], $p = 0.020$) (Fig. 4). There were fewer days of steroid use during the 12 months after bevacizumab infusion (median [range] 13 [0–355] days) compared with the 12 months prior (median [range] 61.5 [0–365] days), but the difference did not reach statistical significance ($p = 0.374$). Only 1 (10%) patient was steroid dependent 12 months after IA bevacizumab therapy for reasons unrelated to necrosis. KPS scores increased by median (range) 10.0 (–10 to 10) points ($p = 0.232$). No patient's KPS score decreased to less than 70 points throughout the trial.

Baseline neuropsychological testing revealed FSIQ scores within the normal range (mean [range] 95.8 [76–114]) (Table 3). Baseline performance on 14 of 16 (88%) subtests were within the normalized population mean, and 2 of 16 (12%) subtests were below the normalized mean. At 12 months after bevacizumab infusion, 12 (75%) subtests demonstrated increased scores, including statistically

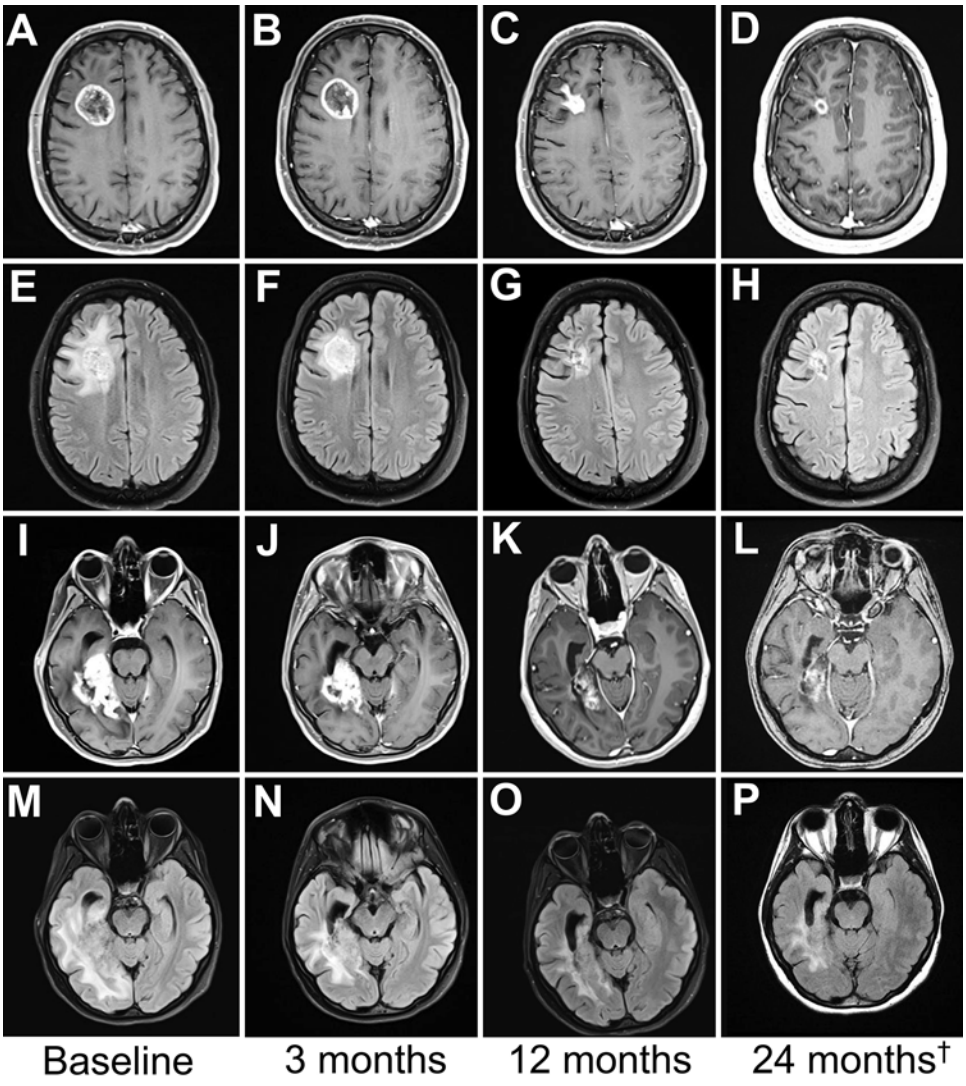

FIG. 3. Representative serial axial MR images demonstrating progressively decreased RN volume and surrounding vasogenic edema, starting from baseline (**A, E, I, and M**) to 24 months (**D, H, L, and P**) after single low-dose targeted bevacizumab infusion. Postcontrast T1-weighted images depict right-sided frontal RN (**A–D**) and T2-weighted FLAIR images depict the surrounding vasogenic edema (**E–H**) in patient 2. Right-sided temporal RN (**I–L**) and vasogenic edema (**M–P**) are depicted in patient 6. †These images (D, H, L, and P) were acquired 1 year after trial completion (24 months after bevacizumab infusion) and are reproduced with signed patient informed consent.

significant increases on scores for subtests measuring error detection (numbers & letters errors) and memory recall (list learning, list long delayed recall). Four (25%) subtests revealed decreased scores, but no subtest demonstrated significantly decreased scores during the 12-month follow-up (Table 3).

Two (20%) (95% CI 3%–56%) patients experienced recurrence of RN during the trial. Patient 8 was a 62-year-old woman who developed RN after CyberKnife radiosurgery (30.0-Gy total dose) for occipital meningioma. She previously underwent multiple rounds of steroids, pentoxifylline, vitamin E, hyperbaric oxygen therapy, and laser interstitial thermal therapy, all of which failed. Three months after IA bevacizumab therapy, she demonstrated 100% decrease in total MIDAS score and notable radiographic decreases in volumes of RN (58% decrease) and vasogenic edema (82% decrease) from baseline. However, at 8.2 months, she presented with symptoms consistent with cerebral edema that did not improve after 2 multiweek courses of oral dexamethasone. MRI demonstrated isolated recurrence of RN at 9.1 months after infusion, for which the patient received 4 cycles of IV bevacizumab therapy (5.0 mg/kg) starting at 10 months; this additional treatment was not part of the current trial and was performed at another facility. Patient 9 was a 36-year-old woman (59.0 kg) who previously underwent 2-stage (44.0-Gy total dose) Gamma Knife radiosurgery for a sizable right-sided frontal AVM. She had 33% and 45% decreases in volumes of RN and vasogenic edema, respectively, at 3 months and a 75% decrease in total MIDAS score. This patient presented 7.0 months after treatment with worsening headache, which was initially treated with dexameth-

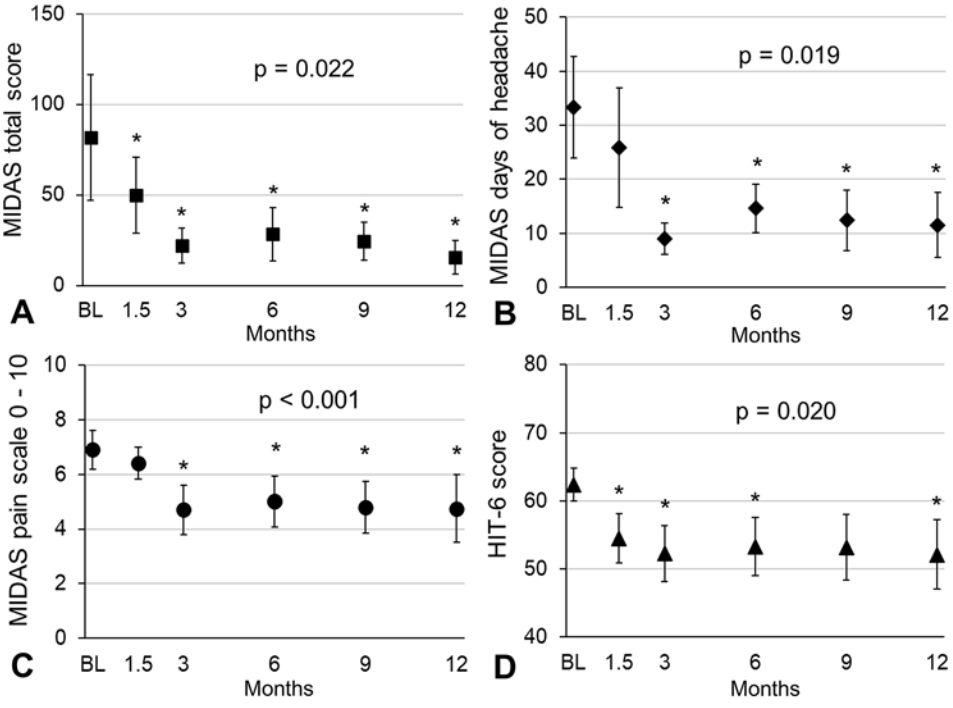

FIG. 4. Graphs of headache outcomes. Mean ± standard error values are shown. **A:** Total MIDAS score. **B:** Days of headache reported on MIDAS. **C:** MIDAS pain score. **D:** HIT-6 score. Ten patients were included at all time points, except at 12 months (n = 8). Two patients experienced recurrence of RN and required further treatment at 10 and 11 months, respectively, after infusion; their data (months 0–9) are included graphically but were omitted from the analysis. BL = baseline. *Significant difference ($p < 0.05$) from baseline on post hoc analysis.

asone, but her headache symptoms later intensified. At 11.0 months after treatment, MRI demonstrated recurrent RN for which the patient opted for open craniotomy and wedge resection.

Discussion

To our knowledge, the current study is the first prospective clinical trial of single-dose targeted bevacizumab for the treatment of cerebral RN. These results demonstrated that a one-time IA infusion may be an efficient option to achieve durable clinical and imaging improvements, without the need for multiple IV infusions over several weeks to months. Benefits appeared early, with most patients displaying improved headache scores at 6 weeks and positive imaging responses at 3 months. Improvements persisted through trial completion in 80% of patients. Trends in steroid usage and functional status both suggested improvement, but neither reached statistical significance in our small cohort. On exploratory analyses, patients demonstrated enhanced information-processing speed, planning, and visual spatial construction, with reliable improvements in error detection and memory recall compared with baseline, thereby supporting reversal of subcortical dysfunction[29] and a pattern of cerebral white mater recovery. Although 2 (20%) patients briefly experienced 4 moderate AEs during the first 24 hours after treatment, there were no instances of significant cognitive decline, and none of our patients died or demonstrated known SAEs of systemic bevacizumab.[14,21–24]

We hypothesized that a single targeted bevacizumab infusion after BBBD would provide massive blockade of VEGF activity and maximally disrupt the positive feedback loop of cellular damage and vasogenic edema while avoiding systemic toxicity. Anti-VEGF therapies are now the primary focus of cerebral RN treatment because upregulation of VEGF is widely accepted as a key event in the pathophysiology. Two pediatric patients from our prior experience[20] showed progressive clinical and MRI improvement for as long as 8 years after a single IA bevacizumab infusion (unpublished data). Since 2013, we have treated approximately 25 adult patients with steroid-refractory RN with an identical protocol and found consistently prolonged MRI and symptomatic improvement in the majority of patients (unpublished data).

Bevacizumab for RN of the Brain

Reports of the effectiveness of multidose IV bevacizumab are growing, including a recent meta-analysis[18] demonstrating successful outcomes in most patients after multiple systemic administrations. However, serious toxicity due to repeated IV bevacizumab dosing is well documented.[14,21–24] Furthermore, although not yet studied, patient and caregiver preferences may favor the convenience of a single IA infusion compared with a multidose cyclic IV regimen, assuming both are equally efficacious for the treatment of brain RN. Additionally, cost might be another factor that significantly impacts patient and caregiver preference.[30] A 4-cycle IV regimen of 7.5 mg/kg bevacizumab

TABLE 3. Neurocognitive indices

Variable	All Patients (n = 10)		Patients w/o RN Recurrence at 12 mos (n = 8)	Difference Btwn Baseline & 12 mos	
	Baseline	3 mos		Mean (SE) (95% CI)	p Value
Attention					
Digits forward	41.1 (3.7)	44.1 (3.9)	42.3 (4.1)	1.0 (2.2) (−6.5 to 8.5)	0.660
Digits backward	44.9 (2.6)	44.9 (3.8)	40.3 (4.6)	−5.0 (3.5) (−16.7 to 6.7)	0.100
Numbers & letters speed	38.2 (3.4)	36.7 (3.4)	36.8 (3.8)	−4.1 (2.7) (−10.4 to 2.1)	0.149
Numbers & letters errors	44.6 (3.8)	47.4 (4.0)	52.9 (3.6)	6.0 (1.7) (0.6 to 11.4)	**0.041**
Numbers & letters efficiency	41.0 (4.6)	36.6 (3.7)	36.6 (3.9)	−3.6 (2.7) (−10.3 to 3.0)	0.124
Language					
Naming	47.6 (3.4)	49.9 (2.3)	49.1 (3.9)	1.9 (2.4) (−6.5 to 10.3)	0.898
Learning & memory					
List learning					
List immediate recall	44.6 (2.4)	44.2 (4.1)	46.4 (2.8)	2.9 (2.3) (−5.3 to 11.0)	0.754
List long delayed recall	44.6 (3.5)	42.6 (3.5)	51.3 (4.3)	9.0 (2.0) (3.1 to 14.9)	**0.031**
Shape learning					
Immediate recognition	42.9 (3.0)	48.6 (3.4)	50.0 (4.0)	6.8 (3.6) (−4.5 to 18.0)	0.426
Delayed recognition	41.3 (3.6)	46.0 (3.9)	47.3 (3.2)	4.9 (3.0) (−3.9 to 13.7)	0.326
Story learning, phrase unit					
Immediate recall	43.2 (2.9)	47.1 (4.0)	49.6 (4.5)	6.4 (4.0) (−7.7 to 20.4)	0.790
Delayed recall	43.7 (2.3)	48.5 (2.9)	48.5 (2.9)	2.6 (3.5) (−9.8 to 7.9)	0.505
Visuospatial					
Design construction	41.4 (3.5)	41.6 (4.5)	45.8 (3.4)	3.5 (1.5) (−0.2 to 7.2)	0.080
Executive function					
Mazes	39.8 (2.9)	43.3 (3.9)	43.0 (4.2)	1.6 (2.2) (−3.0 to 6.2)	0.052
Categories	41.8 (2.2)	44.5 (3.3)	39.9 (2.9)	−2.0 (3.0) (−12.5 to 8.5)	0.968
Word generation	45.0 (3.7)	45.6 (3.1)	49.0 (4.0)	4.0 (2.9) (−5.2 to 13.2)	0.469
FSIQ	95.8 (4.1)				

Values are shown as mean (SE) unless indicated otherwise. Boldface type indicates statistical significance ($p < 0.05$).

per cycle represents a 12-fold greater drug quantity than the single 2.5 mg/kg dose administered in the present trial. A recent cost analysis that compared IA with IV bevacizumab in patients with glioblastoma multiforme confirmed 58% cost savings in favor of the IA route.[31] The potential cost advantages of the single-dose approach deserve future investigation.[32]

The state of current research has yet to prove which is superior: the long-term efficacy, risks, and costs of a one-time IA invasive procedure versus those of a multicycle IV regimen lasting several months. A cooperative 2-arm multicenter randomized trial with 3 years of follow-up that compares single-dose IA with multidose IV bevacizumab in patients with cerebral RN is needed to evaluate the long-term efficacy, risks, and cost effectiveness of these therapies. By setting $\alpha = 0.05$ and assuming an effect size of 0.5 for cost, we used post hoc power analysis to determine that 64 patients would be needed in each arm to obtain statistical power at the desired level of 0.80. Assuming an effect size of 0.25 for long-term efficacy, we estimated that 264 patients per arm, or 528 total, would be required.

Bevacizumab is a monoclonal antibody with a high molecular weight (149 kD). There is general agreement that IA infusion significantly increases drug delivery to cerebral tissue,[33] decreases volume dilution in peripheral circulation, and reduces first-pass degradation by systemic metabolism.[34] In clinical studies of cerebral chemotherapy and technetium-based contrast media, the IA route increased delivery 5-fold for hydrosoluble substances[35] and by as much as 50-fold for liposoluble agents[36] compared with IV administration. BBBD immediately prior to IA infusion further enhances drug delivery.[37] The selective permeability of the BBB blocks the entry of many drugs into the brain, especially large molecules. Increasing evidence from both animal models and humans indicates that the concentrations of high-molecular-weight molecules, including those of monoclonal antibodies, are significantly increased in brain tissue after osmotic BBBD.[19,38–40]

The safety of BBBD followed by IA infusion may be a concern to patients and caregivers. After 30 years of study, osmotic BBBD followed by IA chemotherapy is now generally accepted as feasible and safe with a low incidence rate of complications across multiple centers.[37] Seizures may occur in approximately 6% of cancer patients within the first 24 hours after BBBD,[33,41] but the effects are brief and complete recovery is the norm. Targeted IA bevacizumab itself is well tolerated in doses as great as 15 mg/kg in patients with malignant brain tumors, without causing direct neurotoxicity even when administered repeatedly in multistage IA cycles.[19,31,42] We anticipate that future studies

will demonstrate similar safety profiles for the administration of IA bevacizumab to patients with RN of the brain.

RN Recurrence

There are multiple reports of patients whose RN improved with multidose IV bevacizumab, only to relapse weeks to months later.[14,16,43] In a recent randomized controlled trial, 3 of 11 (27%) patients required repeat IV bevacizumab treatment due to RN recurrence weeks after drug cessation.[14] Similarly, in the current study, 2 (20%) patients experienced RN recurrence after exhibiting initial improvement. The first to relapse was the oldest patient (62 years) in our cohort and the only patient to undergo 4 nonsteroid RN treatments prior to enrollment (pentoxifylline, vitamin E, hyperbaric oxygen, and laser interstitial thermal therapy). Advanced age is a known risk factor of cerebral RN[1,2] and may be revealed as a risk factor of RN recurrence in future studies.

The second patient previously underwent staged Gamma Knife radiosurgery (44.0-Gy total dose) for a sizeable right-sided frontal AVM, which resulted in a substantial necrosis volume (23.3 cm^3) and the second largest vasogenic edema volume (213.0 cm^3) in our cohort. Furthermore, this patient had the second lowest body weight (59.0 kg) and therefore received a relatively small dose of bevacizumab. Due to the unique size and arterial blood flow in the brain, weight-based dosing may not be advantageous for targeted bevacizumab treatments. Studies of cerebral chemotherapy have revealed that hemispheric dose predicts toxicity, not dose calculated on the basis of body weight.[34] Furthermore, cerebral blood flow decreases with age, previous resection, and increased radiation dose.[34] We expect that increased dosing may be necessary to ensure adequate tissue delivery in patients with high-risk features, such as advanced age, greater radiation dose, previous surgery, or whose necrotic lesion and surrounding vasogenic edema span a sizeable cerebral territory. Another consideration is the BBB itself and the inherent challenges in achieving uniform chemically induced disruption. Evidence from both human and animal studies suggests that the extent and duration of artificially induced BBBD may be inconsistent due to the innate physiological variability among individuals.[44,45] It is conceivable that the RN recurrences observed in this trial were at least in part secondary to insufficient BBBD.

Advantages and Limitations

This trial had advantages and limitations. The predominant advantage was that AVM was the underlying pathology in 80% of patients enrolled. Selecting patients without active neoplastic disease afforded investigational superiority because recurrent tumor closely resembles RN, both symptomatically and radiographically,[15] and could potentially be a confounding issue. Our principal limitation was the small number of patients (n = 10) who received only 12 months of trial-related follow-up. This trial was likely underpowered, which is not unusual for an early phase trial. Because our results are underpowered, it is impossible to make definitive treatment recommendations. However, these results are promising and highlight the possibility that a single targeted bevacizumab infusion may provide efficient long-term symptomatic relief and radiographic improvement with minimal systemic toxicity.

Conclusions

Single low-dose targeted IA bevacizumab infusion appears to be a safe and effective treatment option for patients with refractory brain RN. In this prospective trial, 80% of patients experienced early benefits that continued through trial completion, with no AEs or SAEs directly attributed to bevacizumab. A controlled prospective randomized clinical trial is needed to determine whether the one-time low-dose IA approach is a safer, cheaper, and equally efficacious alternative for cerebral RN compared with the conventional multicycle systemic IV bevacizumab regimen.

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Author Contributions

Conception and design: Dashti, Kadner, Folley, Sheehan, La Rocca. Acquisition of data: Dashti, Folley, Han, Yao, Fraser. Analysis and interpretation of data: Dashti, Kadner, Folley, Kryscio, Carter. Drafting the article: Dashti, Kadner, Folley, Kryscio, Carter. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Dashti. Statistical analysis: Kryscio, Carter. Administrative/technical/material support: Dashti, Folley, Carter, Fraser. Study supervision: Dashti, Fraser.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

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Previous Presentations

Portions of this work were presented as a podium presentation at the American Association of Neurological Surgeons Annual Scientific Meeting, Orlando, Florida, August 21–25, 2021; as a poster highlight at the 2021 European Society for Radiotherapy and Oncology Conference, Madrid, Spain, August 27–31, 2021; as an e-poster at the 2021 European Society of Minimally Invasive Neurological Therapy Congress, Nice, France, September 8–10, 2021; and as a virtual poster at the 2021 National Academy of Neuropsychology Conference, Virtual Edition, Washington, DC, December 9–10, 2021.

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