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Intraarterial delivery of bevacizumab and cetuximab utilizing blood-brain barrier disruption in children with high-grade glioma and diffuse intrinsic pontine glioma: results of a phase I trial

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OBJECTIVE Delivery of drugs intraarterially to brain tumors has been demonstrated in adults. In this study, the authors initiated a phase I trial of superselective intraarterial cerebral infusion (SIACI) of bevacizumab and cetuximab in pediatric patients with refractory high-grade glioma (diffuse intrinsic pontine glioma [DIPG] and glioblastoma) to determine the safety and efficacy in this population.

METHODS SIACI was used to deliver mannitol (12.5 ml of 20% mannitol) to disrupt the blood-brain barrier (BBB), followed by bevacizumab (15 mg/kg) and cetuximab (200 mg/m^2) to target VEGF and EGFR, respectively. Patients with brainstem tumors had a balloon inflated in the distal basilar artery during mannitol infusion.

RESULTS Thirteen patients were treated (10 with DIPG and 3 with high-grade glioma). Toxicities included grade I epistaxis (2 patients) and grade I rash (2 patients). There were no dose-limiting toxicities. Of the 10 symptomatic patients, 6 exhibited subjective improvement; 92% showed decreased enhancement on day 1 posttreatment MRI. Of 10 patients who underwent MRI at 1 month, 5 had progressive disease and 5 had stable disease on FLAIR, whereas contrast-enhanced scans demonstrated progressive disease in 4 patients, stable disease in 2, partial response in 2, and complete response in 1. The mean overall survival for the 10 DIPG patients was 519 days (17.3 months), with a mean posttreatment survival of 214.8 days (7.2 months).

CONCLUSIONS SIACI of bevacizumab and cetuximab was well tolerated in all 13 children. The authors' results demonstrate safety of this method and warrant further study to determine efficacy. As molecular targets are clarified, novel means of bypassing the BBB, such as intraarterial therapy and convection-enhanced delivery, become more critical.

Clinical trial registration no.: NCT01884740 (clinicaltrials.gov)

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KEYWORDS DIPG; diffuse intrinsic pontine glioma; glioblastoma; pediatrics; blood-brain barrier; BBB; mannitol; intraarterial chemotherapy; oncology

In 2014, brain cancer overtook leukemia as the leading cancer cause of death (29.9% of cancer deaths) in US children between 1 and 19 years of age.[1] Gliomas account for 47% of pediatric CNS tumors, with WHO grade IV and malignant glioma accounting for 14.6% combined. The prognosis of high-grade glioma (HGG) is uniformly dismal. In children 0–19 years old from 1995 to 2012, the 1- and 5-year relative survival rates were 65.5% and 32.1%, respectively, for anaplastic astrocytoma (WHO grade III) and 57.1% and 17.7% for glioblastoma (GBM; WHO grade IV).[2]

In children, 10%–20% of CNS tumors have a brainstem location,[2–6] with 80% being diffuse intrinsic pontine glioma (DIPG), which carries an extremely poor prognosis.[3]

ABBREVIATIONS BBB = blood-brain barrier; BBBD = BBB disruption; CTCAE = Common Toxicity Criteria for Adverse Events; DIPG = diffuse intrinsic pontine glioma; GBM = glioblastoma; HGG = high-grade glioma; ICA = internal carotid artery; SIACI = superselective intraarterial cerebral infusion.

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The survival rate for children with DIPG is typically less than 10% at 2 years, with a median survival of 1 year or less.[3,7–10] The vast majority of DIPG falls under the new WHO entity of diffuse midline glioma, H3 K27M-mutant.[11] Non-brainstem HGGs are treated surgically, with gross-total resection, histological grade, and sex affecting survival.[9,12–15] In contrast, DIPG is unresectable and typically treated with fractionated radiation therapy. In the developing brain, radiation therapy and high-dose chemotherapy contribute to developmental, endocrinological, behavioral, and cognitive problems in children who survive their initial tumor; however, chemotherapy is typically utilized after radiation therapy in cases of unresectable HGG and DIPG. Many intravenously administered medications have limited ability to penetrate the blood-brain barrier (BBB), making achieving therapeutic concentrations at the tumor, without systemic toxicity, challenging. The difficulty of administering chemotherapy is amplified in brainstem gliomas, which may have a less permeable BBB than supratentorial gliomas.[16]

Superselective intraarterial cerebral infusion (SIACI) is one mechanism of increasing drug concentration within tumors through selective BBB opening followed by drug delivery to target tissue during a permissive therapeutic window. New data unequivocally show that delivering bevacizumab through an intraarterial approach with mannitol to open the BBB increases drug delivery.[17] In addition, on a hypoxia-enhanced chip model of the BBB, adding mannitol prior to infusion of cetuximab (Erbitux) improved penetration of the drug through the BBB.[18]

Cetuximab is currently used to treat recurrent adult GBM after failure of radiation therapy and temozolomide. A phase I clinical trial demonstrated that SIACI of cetuximab is safe in adult patients at 200 mg/kg with recurrent malignant glioma.[19] Bevacizumab (Avastin) was shown to be active in a range of tumors, including GBM and anaplastic astrocytoma.[20–24] An additional phase I clinical trial demonstrating the safety of SIACI of bevacizumab at 15 mg/kg in adults was completed at our institution.[25] To address safety concerns of delivering drugs via SIACI within pediatric neurovasculature, we utilized well-vetted drugs with known efficacy against glioma. Therefore, we designed this phase I clinical trial to test the hypothesis that bevacizumab and cetuximab can be safely delivered via SIACI with BBB disruption (BBBD) in patients < 22 years of age with relapsed/refractory intracranial glioma, and we report our phase I results. Although we presumed that efficacy would require multiple doses, as a first step to focus on safety, this trial was designed with a one-time dose.

Adult and pediatric HGGs were historically treated as similar tumors, given the similar histology; however, genetic and molecular evidence reveals significant differences between adult and pediatric HGGs, and the pediatric brain likely has a different tolerance to treatment modalities given its developmental state.[26–31] EGFR/ERBB1 and VEGF are overexpressed in DIPG, and thus are attractive therapeutic targets. A recent molecular profiling study reported EGFR protein overexpression in 14 of 16 high-grade pediatric brainstem gliomas (compared with up to 50% of adult HGG).[32] While EGFR protein overexpression is common in DIPG, EGFR gene amplification is a rarity, suggesting that this molecular target may be useful in only a subset of patients.[33,34] Similarly, a search of an mRNA expression database suggested that VEGF is overexpressed in DIPG compared with normal brain, low-grade brainstem gliomas, and nonpontine adult and pediatric HGGs.[35] Thus, bevacizumab, a VEGF inhibitor, is another rational drug for these tumors, although it has been primarily studied in adults. In a pediatric prospective study, bevacizumab plus irinotecan was well tolerated but not effective in children with brainstem or recurrent malignant gliomas.[36] Although these studies question the success of VEGF and EGFR inhibitors in improving survival for patients with DIPG, none deliver the drugs after BBBD, which has been shown in preclinical studies to improve drug delivery. Therefore, we sought to treat pediatric patients with HGG and DIPG with SIACI of cetuximab and bevacizumab in conjunction with BBBD to determine its safety and potential efficacy.

Methods

Patient Eligibility

Patients < 22 years of age with a histological diagnosis of relapsed or refractory HGG or radiological diagnosis of DIPG were recruited from November 2013 to August 2018. Eligibility included a Karnofsky or Lansky performance score ≥ 60. Patients received standard-of-care therapy prior to enrollment and were permitted to enroll in other clinical trials either before or after this trial. EGFR and VEGF status were recorded if known, but determination of status was not required. Prior treatment with intravenous bevacizumab and/or cetuximab was not an exclusion criterion.

Study Design and Safety Oversight

The Weill Cornell institutional review board approved this study, parents/guardians gave informed consent, and children > 7 years of age gave assent prior to enrollment. Imaging and clinical status were reviewed prior to entry. Patients received a one-time intraarterial dose of 15 mg/kg bevacizumab and 200 mg/m^2 cetuximab after BBBD with mannitol. After the procedure, patients were hospitalized overnight in the pediatric ICU for hourly neurological assessments. Patients were discharged home on postprocedure day 1 after neurological examination by the neurosurgery team and completion of MRI. Dose-limiting toxicity was evaluated using the National Cancer Institute's Common Toxicity Criteria for Adverse Events (CTCAE) software, version 4.0. This study is registered with the ClinicalTrials.gov database (registration no. NCT01884740; http://www.clinicaltrials.gov).

Imaging Protocol

Preprocedure MRI was typically performed within 3 days prior to the intraarterial procedure and in all cases within 9 days prior. Postprocedure MRI was performed on postprocedure day 1 and at 1 and 3 months posttreatment. A standardized brain MRI protocol was used to maximize comparison for MR images when performed at our institution. Patients underwent brain MRI on a 1.5-T

scanner (Skyra, Siemens Healthcare). Sequences included axial T1-weighted (3- to 5-mm slice thickness) or 3D T1-weighted SPACE (1-mm slice thickness) sequences, axial T2-weighted sequences, and axial T2-weighted FLAIR or 3D T2-weighted FLAIR (1-mm slice thickness), and axial diffusion-weighted sequences with apparent diffusion coefficient maps. Additionally, T1-weighted dynamic contrast-enhanced perfusion MRI was performed. There was some heterogeneity in MRI acquisition protocol, as some patients underwent baseline or follow-up MRI at referring institutions to minimize travel; however, the MRI protocol at each time point included T1-weighted pre- and postcontrast sequences and T2-weighted FLAIR sequences in all but one case.

MRI Analysis

MRI-based analysis of tumor volumes was performed using volumetric segmentation of T1-weighted postcontrast and T2-weighted FLAIR volume sequences using Advantage Workstation 2 software (General Electric Healthcare). The extent of enhancing tumor and T2-weighted FLAIR hyperintense tumor, respectively, were manually measured on each axial slice by a board-certified neuroradiologist, and software subsequently generated tumor volumes for each evaluated sequence. Volumetric response assessment was evaluated based on previously published criteria: complete response, 100% decrease in tumor volume; partial response, greater than 50% decrease; stable disease, 50% decrease to 25% increase; and progressive disease, greater than 25% increase in tumor volume.[37]

Intraarterial Procedure

Under general anesthesia, the common femoral artery was accessed with a micropuncture needle, which was exchanged for a 4-Fr sheath. Using standard technique, a distal access catheter was exchanged into the distal dominant vertebral or basilar artery when possible for the majority of posterior fossa and brainstem lesions and the internal carotid artery (ICA) for 1 supratentorial HGG. After intravenous weight-based heparin was administered, a HyperGlide 4 × 7 balloon (ev3 Neurovascular) was advanced over the microwire into the basilar artery distal to the site of planned intraarterial mannitol infusion. Next, 12.5 ml of 20% mannitol was infused through the catheter over 2 minutes with the balloon inflated in the distal basilar artery to occlude flow of the medication to nontargeted areas in the distal posterior circulation (Fig. 1).

Following BBB disruption, the balloon was deflated and removed, and weight-based dosages of cetuximab and bevacizumab were selectively infused through the distal access catheter at either 1 ml/min or 60 minutes (whichever time period was shorter). The balloon was used in 6 of 13 patients with mannitol delivery. The other 7 had mannitol delivered without any distal obstruction, as the tumor was more diffusely located and a larger territory of BBBD was desired.

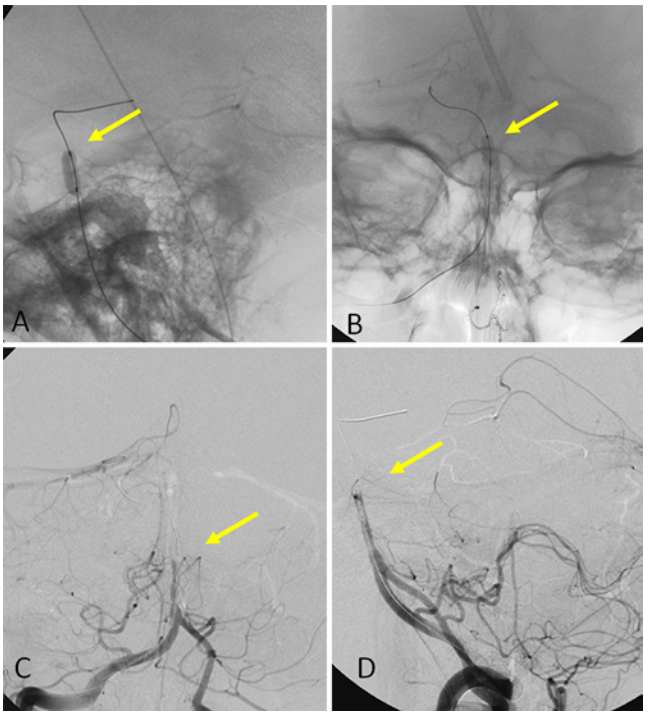

FIG. 1. Lateral (**A**) and AP (**B**) projections demonstrating an inflated balloon in the distal basilar artery. *Yellow arrows* point to the location of the inflated balloon. AP (**C**) and lateral (**D**) angiogram injections of contrast dye demonstrating distribution of mannitol delivery while the balloon is inflated. *Yellow arrows* show the location of the balloon/the point at which contrast cannot pass distally. Figure is available in color online only.

Results

Patient Characteristics

Thirteen patients ranging in age from 4 to 14 years were enrolled between November 2013 and August 2018. Ten patients had DIPG, 1 had thalamic HGG, 1 had supratentorial nonmidline GBM, and 1 had GBM of the cerebellum and brainstem. Seven patients were female, and 6 were male. Table 1 details patient demographic and clinical characteristics. All DIPG patients underwent radiation therapy prior to enrollment. Some patients were enrolled in other clinical trials prior or subsequent to our trial.

Safety of Treatment

No complications were noted during the intraarterial portion of the procedure. In 6 of 13 treatments, a balloon was used during delivery of mannitol to selectively target BBBD to the brainstem. This was well tolerated in all patients. Neurological examinations were stable postprocedure in all 13 patients. No patients had MRI changes suggestive of hemorrhage or stroke. Safety was evaluated for 28 days after the procedure. There were no grade III or IV adverse events, and there were 4 grade I events. Two patients developed a mild rash, which resolved on its own with no therapy. Two patients had epistaxis, which in one was a mild one-time event. The other patient had 3 minor episodes a week after treatment; however, this patient also had a history of 2 nosebleeds prior to enrollment in the trial. Laboratory values were within normal limits, and the nosebleeds in both cases were minor and self-resolving.

TABLE 1. Demographics and treatment effects

Pt No.	Age at Time of Tx (yrs), Sex	Dx	Tumor Grade/Path*	EGFR Positive	VEGF Positive	Tumor Location	Vessel Injected	Prior Bevaciz	Prior Cetuximab	AE (CTCAE)	Attributable to Trial	Sx Improvement	Balloon
1	12, F	DIPG	Grade IV	Yes	Yes	Pons	BA (mannitol), lt VA (chemo)	Yes	No	None	NA	Yes	Yes
2	6, M	DIPG	No biopsy	Unk	Unk	Pons	Lt VA	No	No	None	NA	No change	No
3	14, M	DIPG	No biopsy	Unk	Unk	Pons	Rt VA	No	No	Rash (grade I)	Possible	No change	No
4	13, M	GBM	Grade IV	Unk	Unk	Supratentorial	Distal BA/ lt ICA	Yes	No	Epistaxis (grade I)	Possible	No? (improvement but Ommaya tapped concurrently)	No
5	5, F	DIPG	No biopsy	Unk	Unk	Pons	Rt VA	No	No	None	NA	No Sx	No
6	5, F	DIPG	No biopsy	Unk	Unk	Pons	Lt & rt VA	No	No	None	NA	Yes	No
7	7, F	DIPG	No biopsy	Unk	Unk	Pons	Rt VA	No	No	None	NA	Yes	No
8	5, M	DIPG	Unk grade	Unk	Unk	Brainstem	Rt VA	No	No	Rash (grade I)	Possible	Yes	Yes
9	6, M	DIPG	Unk grade	Unk	Unk	Brainstem	Rt VA	No	No	None	NA	No Sx	Yes
10	12, F	GBM	Grade IV	Unk	Unk	Brainstem & cerebellum	Rt VA	No	No	None	NA	Yes	Yes
11	4, M	DIPG (also frontal lesion)	Grade III	Unk	Unk	Pons	Lt VA, BA, AICA	No	No	None	NA	No change	Yes
12	4, F	DIPG	No biopsy	Unk	Unk	Pons	Distal lt VA	No	No	Epistaxis (grade I)	Possible	Yes	Yes
13	5, F	Thalamic glioma	HGG w/ H3.1K27M	Yes (autopsy)	Unk	Thalamus	Mid-BA	No	No	None	NA	No change	No

AE = adverse events; AICA = anterior inferior cerebellar artery; BA = basilar artery; bevaciz = bevacizumab; chemo = chemotherapy; Dx = diagnosis; NA = not applicable; path = pathology; pt = patient; Sx = symptoms; Tx = treatment; unk = unknown; VA = vertebral artery.

* Grades according to the WHO grading system.

TABLE 2. Changes in MRI volume

	Day 1		Assessment Day 1		Mo 1		Assessment Mo 1	
Pt No.	Change in Contrast %	Change in T2-Weighted FLAIR %	EV T1-Weighted w/ Gd	FV T2-Weighted FLAIR	Change in Contrast %	Change in T2-Weighted FLAIR %	EV T1-Weighted w/ Gd	FV T2-Weighted FLAIR
1	173%	–40%	PD	SD	34%	–52%	PD	SD
2	–39%	–7%	SD	SD	721%	37%	PD	PD
3	–40%	–23%	SD	SD				
5	–15%	6%	SD	SD	–100%	–47%	CR	SD
6	–50%	27%	SD	PD	–26%	30%	SD	PD
7	–64%	–4%	PR	SD				
8	–14%	16%	SD	SD	–52%	5%	PR	SD
9	–80%	–6%	PR	SD	18%	42%	SD	PD
10	–89%	–9%	PR	SD		–20%		SD
11	–88%	41%	PR	PD	–87%	73%	PR	PD
12	–51%	–21%	PR	SD	42%	104%	PD	PD
13	–36%	–14%	SD	SD	30%	25%	PD	SD

CR = complete response; EV = enhanced volume; FV = FLAIR volume; PD = progressive disease; PR = partial response; SD = stable disease.

Symptom Improvement

Ten patients had symptoms at the time of treatment. Of these, 6 experienced subjective symptom relief after treatment. One patient with DIPG with prior biopsy (EGFR and VEGF positive, WHO grade IV) who had previously received intravenous bevacizumab treatment received two injections—both with symptom relief. Prior to treatment, she had nausea, vomiting, and fatigue and had stopped both school and extracurricular activities due to these symptoms. Her first injection produced significant symptom relief, allowing her to return to school and extracurricular activities. This improvement lasted approximately 1 month, at which point she received intravenous bevacizumab at the direction of her oncologist with no symptom relief. She subsequently received repeat intraarterial delivery of cetuximab and bevacizumab at 3 months after initial injection with some symptom improvement in speech, swallowing, and urinary retention, although the improvement was less than with the initial intraarterial dose. She succumbed to tumor progression and died approximately 2 months after the second injection. A second patient experienced resolution of nausea and vomiting after treatment. A third patient experienced decreased fatigue and improved gait. This patient was able to attend school regularly and decrease steroid dosing during this time. A fourth patient was noted to have improved alertness and interaction as well as reduced drooling and improved balance. A fifth patient had mild subjective improvement in balance. A sixth patient was weaned from steroids and experienced decreased headache and improved vision. The duration of symptom improvement was approximately 1 month for all patients. One additional patient had improvement in fatigue; however, this patient had an Ommaya reservoir tapped at the same time. We considered this as no improvement, as the improvement may have been secondary to lowering of intracranial pressure secondary to CSF removal rather than the intraarterial procedure.

Imaging

All patients underwent MRI on postprocedure day 1 to rule out stroke or hemorrhage. No patients demonstrated these complications. DIPGs do not typically exhibit significant enhancement; however, some small areas of contrast uptake can be seen and were seen in all 10 patients with DIPG. One patient with a supratentorial tumor had a limited preoperative MRI study that was performed at an outside institution, which did not enable accurate comparison. Volumetric change in T2-weighted FLAIR and T1-weighted postcontrast volumes was evaluated for the remaining 12 patients. Of these patients, 92% (11/12) had a reduction in T1-weighted postcontrast volume on postprocedure day 1, with 42% (5/12) demonstrating greater than 50% reduction (Table 2). Visualization of a change on imaging suggests that the treatment reached the area of tumor. Changes in T2-weighted FLAIR volumes, which are generally considered more representative of tumor size in DIPG, demonstrated greater heterogeneity. Ten patients had stable disease on postprocedure day 1, while 2 patients exhibited progressive disease. The increase on FLAIR so early may simply be a reflection of swelling with treatment; however, none of the patients were symptomatic from this change. Ten MRI studies were available for review at 1 month, of which one MRI study was only a noncontrast MRI. On the 1-month postprocedure T1-weighted postcontrast sequence, 4 patients had progressive disease, 2 had stable disease, 2 had partial response, and 1 had complete response. On volumetric analysis of T2-weighted FLAIR imaging at 1 month, 5 patients had progressive disease and 5 had stable disease.

Survival

The mean overall survival for the 10 DIPG patients treated was 519 days (approximately 17.3 months; range 221–761 days). The mean survival after treatment was 214.8 days (approximately 7.2 months; range 41–448

TABLE 3. Survival data

Pt No.	Age at Time of Tx (yrs), Sex	Dx	Tumor Grade/Path	EGFR Positive	VEGF Positive	Overall Survival Dx to Death (days)	Survival Tx to Death (days)
1	12, F	DIPG	Grade IV	Yes	Yes	582	142
2	6, M	DIPG	No biopsy	Unk	Unk	517	123
3	14, M	DIPG	No biopsy	Unk	Unk	361	41
4	13, M	GBM	Grade IV	Unk	Unk	914	42
5	5, F	DIPG	No biopsy	Unk	Unk	685	448
6	5, F	DIPG	No biopsy	Unk	Unk	516	371
7	7, F	DIPG	No biopsy	Unk	Unk	221	84
8	5, M	DIPG	Unk grade	Unk	Yes	484	241
9	6, M	DIPG	Unk grade	Unk	Unk	676	165
10	12, F	GBM	Grade IV	Unk	Unk	311	166
11	4, M	DIPG	Grade III	Unk	Unk	387	145
12	4, F	DIPG	No biopsy	Unk	Unk	761	388
13	5, F	Thalamic glioma	HGG w/ H3.1K27M	Yes (autopsy)	Unk	318	54

days). Survival data are listed in Table 3. While imaging studies for these patients were classic for DIPG in 9 of the 10 patients (Figs. 2 and 3), this population was a heavily treated population, who may not be fully representative of the average DIPG patient since they made it to a clinical trial. In addition, 6 patients participated in other clinical trials, including immunotherapy, convection-enhanced delivery, MK-1775/Wee1 inhibitor, and oral panobinostat. One patient also traveled to Mexico for therapy. The ranges for overall survival and survival posttreatment for the 3 non-DIPG patients were 311–914 days and 42–166 days, respectively.

Discussion

This prospective phase I trial assessed the safety of a single administration of SIACI of cetuximab and bevacizumab after BBBD in patients < 22 years of age. Doses utilized were adjusted based on those previously used in adult clinical trials with acceptable safety profiles,[19,25] but they had not been tested in pediatric and adolescent patients. Additionally, the location and types of gliomas seen in children are substantially different from those in adults, with the majority of cases treated in the < 22-year-old age group being DIPG. There is only one report of an adult patient who had received treatment for a tumor in this location.[38] We found SIACI of cetuximab and bevacizumab after mannitol was well tolerated in this age group and with this tumor location. There were no dose-limiting toxicities, and there were no serious adverse events. There were 4 minor adverse events that were possibly attributable to the treatment—2 rashes and 2 cases of epistaxis—all of which were self-limiting. Thus, we conclude that superselective intraarterial delivery of cetuximab and bevacizumab was well tolerated in this patient population.

Deploying a balloon during delivery of mannitol was also well tolerated. This technique was utilized in 6 of 13 patients treated with the goal of preventing distal flow of mannitol, resulting in greater retention of mannitol in the basilar artery and pontine perforators and allowing a more targeted delivery of mannitol within the pons to maximize the potential for mannitol-induced intratumoral BBB breakdown in patients with DIPG. Four of the 6 patients with symptom relief had the balloon inflated during mannitol delivery. Although the numbers of patients are too small for statistical analysis, this trend may suggest that patients had an increased likelihood of symptom relief with use of the balloon during mannitol infusion. One could hypothesize that use of the balloon led to greater opening of the BBB in a more restricted location since mannitol was retained in the basilar artery and perforators rather than flowing more distally. This may in turn have led to higher levels of cetuximab and bevacizumab in the tumor area given a potentially increased or more localized BBB disruption. Further studies with direct agent labeling that could be tracked noninvasively would allow testing of this hypothesis.

While EGFR and VEGF status was unknown for most patients, 2 patients with symptom relief had VEGF-positive tumors and one of the tumors was also EGFR positive. Biopsy was not a requirement of treatment. Pathology tissue of those who had undergone biopsy was requested for all patients but could not be obtained for most. It would be beneficial to know the status of a patient's tumor prior to enrollment, as one would hypothesize a higher likelihood of benefit if drug targets were present in the tumor. An additional patient had a tumor positive for EGFR, but this patient had no symptoms at the time of treatment.

This phase I trial suggests that intraarterial delivery of mannitol followed by bevacizumab and cetuximab is safe in the pediatric population. Although efficacy cannot be determined given the limited number of patients, the highly pretreated patient population, and utilization of only a single dose, the overall survival we report is longer than that for historic controls. Additionally, some patients did experience subjective symptom improvement. Future trial plans include initiation of a multicenter trial with repeat dosing to increase patient numbers and determine efficacy.

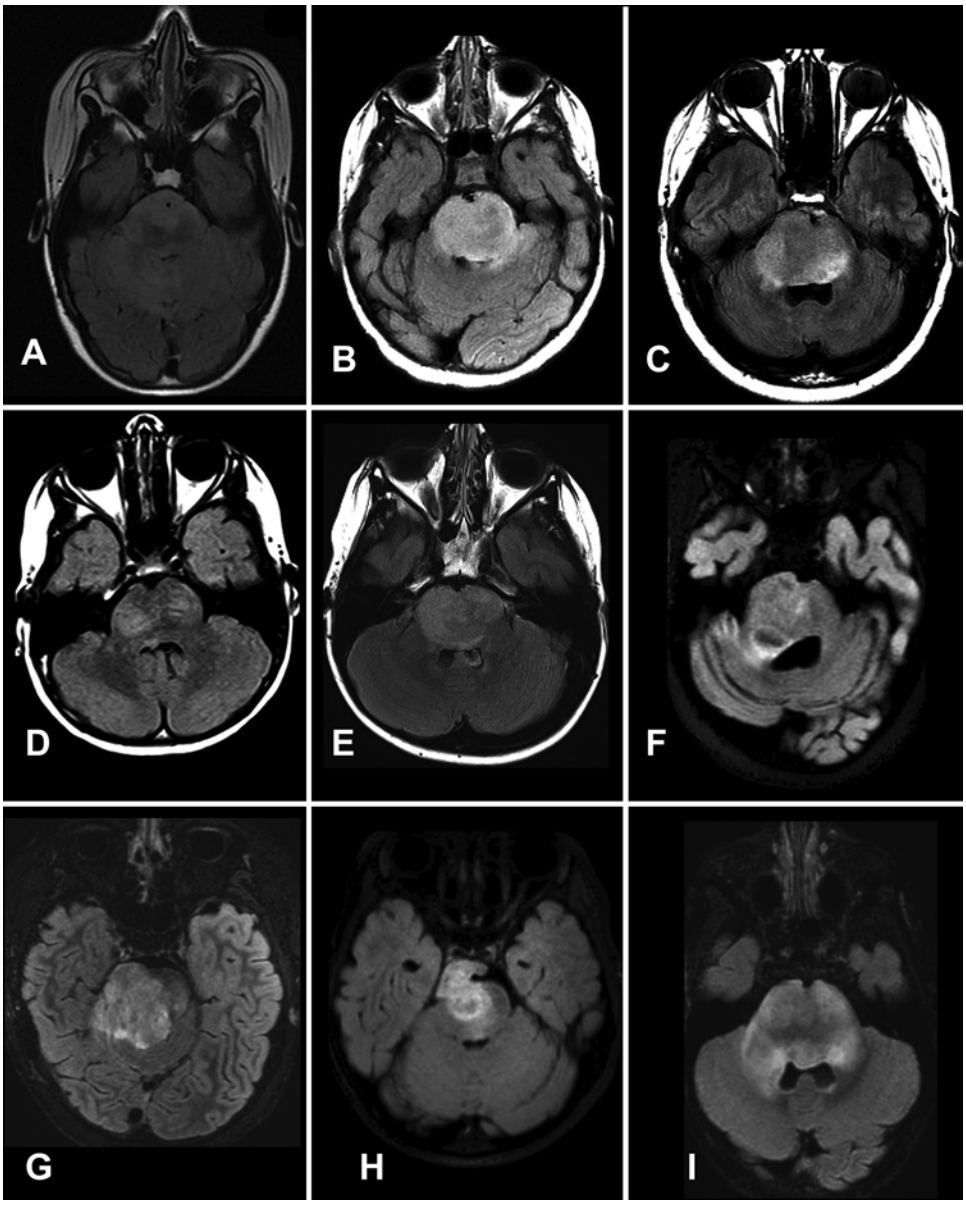

FIG. 2. Axial T2-weighted FLAIR images obtained in 9 of the 10 DIPG patients demonstrating images representative of typical DIPG imaging.

The safety of this delivery method will also allow for investigation of additional agents through this method in the future. Using a labeled agent as one of the drugs delivered would allow for assessment of drug delivery distribution, which could not be assessed in the current study.

There has been a significant push in neurooncology to move toward precision medicine. The DIPG field has also begun to move toward consideration of biopsy. This is done for atypical cases of DIPG, as part of clinical trials, or with family request, but the number of biopsies is increasing. Performing biopsy of a DIPG with a choice of intraarterial agent after determination of molecular targets may be a valid strategy for future investigation. Additionally, future trial designs will likely increasingly include biopsy to assess drug delivery. As our understanding of the biology of these tumors improves, we will have additional drugs that more effectively target tumor cells. Having delivery methods that allow these drugs to bypass the BBB and achieve effective concentrations within these tumors will become even more critical. Our trial is an important first step in demonstrating the safety of one such method.

Conclusions

Our prospective phase I trial demonstrated that SIACI of bevacizumab and cetuximab was well tolerated in all 13 children. Our results demonstrate the safety of this method and warrant further study to determine efficacy.

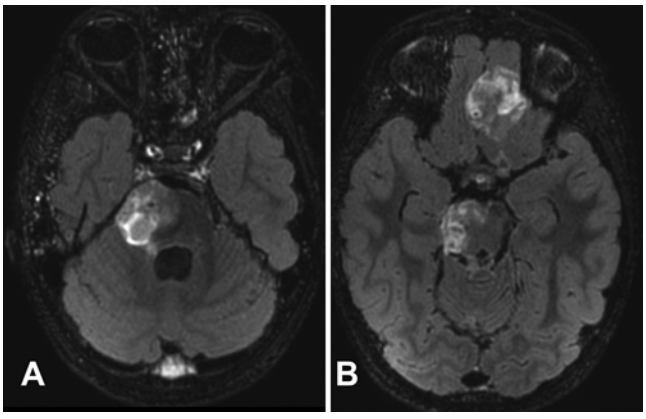

FIG. 3. Axial T2-weighted FLAIR images obtained in an additional DIPG patient, demonstrating both a pontine lesion (**A**) and additional spread to the frontal lobe (**B**) present at the time of intraarterial treatment. The patient had typical imaging of DIPG on initial diagnosis but had progressed since his initial diagnosis.

As molecular targets are clarified, novel means of bypassing the BBB, such as intraarterial therapy and convection enhanced delivery, become more critical.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: McCrea, Boockvar, Greenfield. Acquisition of data: McCrea, O'Connor, Gobin, Knopman, Greenfield. Analysis and interpretation of data: McCrea, Ivanidze. Drafting the article: McCrea, Hersh. Critically revising the article: McCrea, Ivanidze, Hersh, Knopman, Greenfield. Reviewed submitted version of manuscript: McCrea, Ivanidze, O'Connor, Boockvar, Gobin, Knopman, Greenfield. Approved the final version of the manuscript on behalf of all authors: McCrea. Statistical analysis: McCrea, Ivanidze. Administrative/technical/material support: O'Connor, Greenfield. Study supervision: Greenfield.

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