Short-Term Clinico-Radiographic Response to Super-Selective Intra-Arterial Cerebral Infusion of Bevacizumab for the Treatment of Vestibular Schwannomas in Neurofibromatosis Type 2

H.A. RIINA¹, J-K. BURKHARDT², A. SANTILLAN², L. BASSANI¹, A. PATSALIDES², J.A. BOOCKVAR²

¹ Department of Neurosurgery, New York University Langone Medical Center; New York, NY, USA

² Department of Neurosurgery, Weill Cornell Medical College, New York Presbyterian Hospital; New York, NY, USA

Key words: bevacizumab, superselective intra-arterial cerebral infusion, Neurofibromatosis type 2, vestibular schwannoma

Summary

Neurofibromatosis type 2 (NF2) is an autosomal dominant syndrome with a prevalence of approximately 1 in 30,000. NF 2 is characterized by bilateral vestibular schwannomas, as well as meningiomas, ependymomas and gliomas. Currently, surgical resection and radiotherapy represent the mainstay of treatment, although new studies suggest a role for certain chemotherapeutic agents. Intravenous administration of Bevacizumab (Avastin, Genetech Pharmaceuticals) has been shown to be active in the treatment of vestibular schwannomas. The IV route of administration, however, carries a risk of known systemic side-effects such as bowel perforation, wound dehiscence and pulmonary embolism. In addition, the percentage of drug that reaches the tumor site may be restricted by the blood tumor barrier. This report describes the super-selective intra-arterial infusion of Bevacizumab following blood brain barrier disruption for the treatment of vestibular schwannomas in three patients with Neurofibromatosis type 2. It represents the first time such a technique has been performed for this disease. Additionally, this method of drug delivery may have important implications in the treatment of patients

with vestibular schwannomas associated with Neurofibromatosis type 2.

Introduction

Neurofibromatosis type 2 (NF2) is an autosomal dominant syndrome with a prevalence of approximately 1 in 30,000¹. NF2 is characterized by bilateral vestibular schwannomas (VS), as well as meningiomas, ependymomas and gliomas. In NF2 a mutation in Chromosome 22q11-13 leads to a deficiency or defect of the Merlin protein, normally a tumor suppressor². The lack of or deficiency in Merlin leads to a lack of tumor suppression and, thus, the characteristic tumors of neurofibromatosis.

The most profound effect of NF 2 is the characteristic bilateral VS that lead to profound progressive hearing loss by an early age^{1,2}. Traditionally, treatment options for sporadic VS include surgical removal or radiation therapy³. While these have been shown to control tumor growth, they can lead to further significant hearing loss in the affected ear, as well as facial nerve weakness, trigeminal neuropathy, vestibular dysfunction and an increased risk for development of secondary malignancies later in

life. However, in patients with NF2 presenting with bilateral VS, the risks become even greater. These patients often have significant pre-operative hearing loss and surgical intervention may only worsen their deficits. In addition, both surgical and radiation therapy have been shown to have poor rates of tumor control in VS^{4,5}. Recently, the anti-vascular endothelial growth factor bevacizumab (BV) has been assessed for its ability to control tumor growth in NF2 patients with untreatable VS⁶⁻⁸.

Vascular endothelial growth factor (VEGF), a signal protein that stimulates angiogenesis and vessel permeability, has been shown to be associated with tumor growth of VS in NF2 patients⁹. Multiple groups have recently shown that administration of intravenous BV, a humanized monoclonal antibody against VEGF, with a concentration of 5 mg/kg biweekly can lead to tumor regression and improved hearing in patients with untreatable VS. The tumor volume reduction is also in accordance with a recently published human VS xenograft model in mice showing that the tumor growth rate decreased by an average of 50%, and the survival of the treated mice was prolonged by at least 50% after intravenous treatment with 10 mg/kg BV¹⁰. Our group hypothesized that intra-arterial BV would increase concentrations of the drug via local delivery of the anti-VEGF compound into the VS, thus leading to further reduction in tumor size and improvement in overall hearing, specifically word discrimination, in patients with NF2.

Recently, we published on the technical feasibility of super-selective intra-arterial cerebral infusion (SIACI) of mannitol followed by BV for treatment of recurrent malignant supraten-

torial disease¹¹⁻¹⁴. The protocol for selective infusion includes focal disruption of the blood tumor barrier (BTB) and high-dose first-pass infusion of the chemotherapy directly to the target. Given the preliminary data using IV BV in the treatment of VS, we wanted to test the hypothesis that SIACI of BV after BTB disruption would be effective in the treatment of VS in patients with NF2.

This report details the protocol and technique of using endovascular SIACI of BV following blood brain barrier disruption in three patients with VS with NF2 (Table 1). If proven both safe and effective in larger trials, this novel delivery method may offer a better way to treat VS in this patient population.

Case Reports

Case 1

Medical History and Post-Interventional Follow-up

A 56-year-old man with a history of neurofibromatosis type 2 presented with complete right-sided hearing loss for 1 year and a progressive intermittent hearing loss and ringing on the left side. The patient did not present with either dizziness or ataxia. An MRI revealed bilateral T1 hypointense, T2 hypointense, enhancing masses within the cerebello-pontine angles with extension into the internal auditory canals. The tumors, with typical radiographic findings for VS, measured $1.3 \times 1.9 \times 1.2$ cm on the right and $1.4 \times 2.0 \times 1.1$ cm on the left side, respectively (Figure 1A). The decision to treat the left VS was made to improve the

Table 1 Summary of patients with vestibular schwannoma associated with NF2 treated with super-selective intra-arterial infusion of Bevacizumab.

No	Age (years)/ Sex	Previous treatment	Baseline tumor Size (L/R) (cm ³)	Feeding arteries	Tumor blush	Early filling of draining veins
1	56/M	None	$1.4 \times 2.0 \times 1.1$ cm (L)	L-AICA, L-MMA	No	No
2	32/M	None	$2.8 \times 3.1 \times 3.1$ cm (L)	L-AICA, L-MMA	Yes	Yes (through the SPS)
3	31/F	RT + I.V. BEV	$4.2 \times 2.5 \times 2.9$ cm (R)	R-AICA, R-MMA, R-MHT	Yes	Yes (through the SPS)

AICA, anteroinferior cerebellar artery; BEV, bevacizumab; I.V., intravenous; L, left; MMA, middle meningeal artery; MHT, meningohypophyseal trunk; NF2: Neurofibromatosis type 2; R, right; RT, radiotherapy; SPS, superior petrosal sinus

Figure 1 MRI (A) and digital subtraction angiogram (B) of a 56-year-old man with bilateral VS. A) The VS measures $1.3 \times 1.9 \times 1.2$ cm on the right and $1.4 \times 2.0 \times 1.1$ cm on the left side on T1 post-contrast MRI. B) Lateral projections of the left AICA demonstrated normal anterograde flow after blood tumor barrier disruption with mannitol and BV infusion.

Figure 2 MRI (A) and digital subtraction angiogram (B, C) of a 32-year-old man with bilateral VS. (A) The VS measures $2.4 \times 2.1 \times 2.2$ cm on the right and $2.8 \times 3.1 \times 3.1$ cm on the left side on T1 post-contrast MRI. Lateral projections of the left ECA (B) and left AICA (C) demonstrated normal anterograde flow after blood tumor barrier disruption with mannitol and BV infusion.

patient's progressive intermittent hearing loss and after confirmed consent, the patient was treated by SIACI BV. Since the right-sided hearing loss was already present for over one year, no indication for treatment for this side was made at this time. After successful intra-arterial intervention, the patient presented with a progressive hearing improvement of his left ear starting one week post treatment. Post-contrast T1 MRI one month after treatment of the lesions measured $1.3 \times 1.9 \times 1.2$ cm on the right and $1.4 \times 2.0 \times 1.1$ cm on the left side with a

tumor volume reduction of 11% of the right and 19% of the left side, respectively. No adverse effects with regard to the IA BV administration were seen.

Super-Selective Intra-Arterial Cerebral Infusion Treatment

The patient was placed under general anesthesia and anticoagulated with heparin. A 5F guide catheter was placed into the left vertebral artery (VA), and then an Excelsior SL 10 microcatheter (Target Therapeutics/Boston Sci-

entific, Fremont, CA, USA) with a 45 degree angle was advanced over a Synchro 2 soft microwire into the left anterior inferior cerebellar artery (AICA). The microwire was then carefully removed. Then, 10 cc of 25% mannitol were infused through the microcatheter over a period of two minutes. Post mannitol infusion, posteroanterior (PA) and lateral projections of the left AICA demonstrated normal antero-grad flow. No tumor blush of the VS was detected. After blood brain barrier disruption, 17 cc of BV (15 mg/kg) were infused through the same microcatheter over 20 minutes. Post-infusion angiography was performed demonstrating normal antero-grad flow (Figure 1B). Using the same technique, a microcatheter was positioned in the left external carotid artery (ECA) and 10 cc of 25% mannitol was infused over a period of two minutes. Post-mannitol infusion, PA and lateral projections of the left middle meningeal artery (MMA) demonstrated normal antero-grad flow. Then, 17 cc of BV (15 mg/kg) was infused through the microcatheter over 20 minutes. Post infusion angiography confirmed the microcatheter tip still in the left MMA. The microcatheter was withdrawn to the left ECA. Then, 17 cc of BV (15 mg/kg) were infused through the microcatheter over 20 minutes. Post-infusion angiography of the left ECA demonstrates normal antero-grad flow.

Case 2

Medical History and Post-Interventional Follow-up

This 32-year-old man with a history of multiple cranial and spinal tumors associated with neurofibromatosis type 2 presented with progressive bilateral hearing loss (left > right) and tinnitus for one year. MRI revealed bilateral T1 hypointense and T2 hypointense enhancing masses in the cerebellopontine angles with extension into the internal auditory canals. The masses measured $2.4 \times 2.1 \times 2.2$ cm on the right and $2.8 \times 3.1 \times 3.1$ cm on the left side (Figure 2A). Indication for IA BV treatment of the left-sided lesion was made and the patient received 15 mg/kg BV through the supplying tumor vessels. The post-interventional course was uneventful and the left-sided hearing loss improved within a month. No adverse effects with regard to the IA BV administration were present in this patient. Follow-up MRI did not show

any increase or decrease in the contrast-enhanced tumor size after 1 month and was therefore stable compared to the pre-interventional measurements.

Super-Selective Intra-Arterial Cerebral Infusion Treatment

As described in *Case 1* endovascular technique was performed to explore the tumor supplying vessels. First the left MMA was displayed and PA and lateral projections demonstrated normal antero-grad flow with some tumor blush arising from the left MMA. Ten cc of 25% mannitol were infused through the microcatheter over a period of two minutes. Then, 30 cc of 45 cc BV (15 mg/kg) were infused through the microcatheter over 30 minutes. Post-infusion angiography of the left ECA after mannitol and BV infusion demonstrated normal antero-grad (Figure 2B).

In a second step, 10 cc of 25% mannitol were infused into the left AICA through an Excelsior SL 10 microcatheter over a period of two minutes. Post-mannitol infusion, PA and lateral projections of the left AICA demonstrated normal antero-grad flow with no evidence of vascular injury. Then, 15 cc of 45 cc BV (15 mg/kg) were infused through the microcatheter over 20 minutes (Figure 2C). Approximately two thirds of BV concentration was administered into the left MMA and one third into the left AICA.

Case 3

Medical History and Post-Interventional Follow-up

A 31-year-old woman presented with a long history of NF2 and bilateral VS including complete left hearing loss and left facial nerve palsy since surgical tumor removal three years ago in a different hospital. Hearing on the right side was stable at the time of clinical presentation and IV BV treatment was started two months ago. An MRI revealed multiple small enhancing masses involving the skull base foramina and a large heterogeneously enhancing extra-axial mass ($4.2 \times 2.5 \times 2.9$ cm) located in the right cerebellopontine angle extending into the internal auditory canal. The mass led to an enlargement of the porous acusticus and the adjacent right cerebellar hemisphere, brainstem and cerebellopontine angle was compressed

Figure 3 MRI (A) and digital subtraction angiogram (B, C) of a 31-year-old woman with NF2. A) T1 post-contrast MRI demonstrates a large right-sided VS measuring $4.2 \times 2.5 \times 2.9$ cm. Lateral projections of the right AICA (B) and right MMA (C) demonstrated normal anterograde flow after blood tumor barrier disruption with mannitol and BV infusion.

(Figure 3A). Surgical removal of the right VS lesion was declined by the patient and indication for IA BV was made to ensure the right hearing capacity. Follow-up MRI one month after treatment showed a stable tumor size of $4.2 \times 2.5 \times 2.9$ cm without any progression. No adverse effects with regard to the IA BV administration were present.

Super-Selective Intra-Arterial Cerebral Infusion Treatment

With selective endovascular technique via the basilar artery the right AICA was explored and selective angiogram showed a moderate degree of tumor opacification. Ten cc of 25% mannitol were infused through the microcatheter over a period of two minutes and post-infusion angiography demonstrated anterograde flow into the right AICA and its branches. The tumor opacification was increased after mannitol infusion (Figure 3B). Next, 20 cc of Bevacizumab (15 mg/kg) were infused through the microcatheter over 20 minutes. Using the same technique, an Excelsior SL 10 microcatheter with a 45 degree angle was advanced over a Synchro 2 soft microwire through the guide catheter into the right ECA and into the right MMA. A minimal degree of tumor opacification was visualized via petrosal branches arising from the right MMA (Figure 3C). Then, 10 cc of 25% mannitol were infused through the microcatheter over a period of two minutes. Post-infusion angiography demonstrated anterograde flow into the right MMA and its branches. Then, 14 cc of Bevacizumab (15 mg/kg) were infused through the microcatheter over 14 minutes for a total infusion time of 34

minutes. Approximately 60% of the Bevacizumab dose was infused into the right AICA and 40% of the dose into the right MMA.

Discussion

Bevacizumab (BV) is a monoclonal antibody that binds to vascular endothelial growth factor (VEGF) and blocks the formation of new blood vessels, but also affects existing vasculature⁹. Anti-angiogenic therapy may normalize the structure and function of blood vessels and decrease tumor-related edema. Recent studies demonstrating the effectiveness of BV has established it as a possible treatment of VS⁶⁻⁸. Systemic toxicity has been noted with its use, including infections, venous thromboembolic events, and wound-healing complications. Our group hypothesized that intra-arterial BV would increase concentrations of the drug via local delivery of the anti-VEGF compound into the VS, thus leading to further reduction in tumor size and improvement in overall hearing, specifically word discrimination, in patients with NF2. Especially in hypervascular VS, as shown in case 3, endovascular SIACI of BV seems to be a promising approach to locally increase BV concentration¹⁵. In our study, we found a decreased tumor volume after one month in one patient and a stable tumor volume in the other two patients. Mautner et al. argued that radiographic regression is dependent on sustained administration of IV Avastin over time⁷. Therefore, follow-up studies are needed to assess the effect of more than one IA administrations over time. However in this

study, we show for the first time that IA BV treatment was safe for all patients without any procedure related side-effects. We had no thromboembolic events, hemorrhage, congestive heart failure, gastrointestinal perforation, or delayed wound healing after IA BV treatment. The use of intra-arterial delivery of chemotherapy has been shown to be advantageous to IV dosing in cerebral disease in both animal models of glioma and human studies¹⁶. In addition, techniques for BTB disruption with osmotic agents have been developed and safely utilized with chemotherapy infusion for over 20 years.

This case describes the first report of SIACI of an osmotic agent and BV for VS. The efficacy of BTB disruption is demonstrated by increased vascular hyperemia in the tumor after mannitol injection. This brief hyperemia allows

for increased exposure of the monoclonal antibody BV to tumor vascular endothelial growth factor targets.

Conclusion

Recent studies suggest the efficacy profile of IV BV on VS in patients with NF2. We have combined this treatment protocol with endovascular techniques to accurately and selectively disrupt the BTB before chemotherapy infusion. This technical report describes the method of SIACI of BV after BTB disruption for VS in patients with neurofibromatosis type 2. If proven safe and effective in a larger cohort of patients this paradigm may significantly alter the way chemotherapies are delivered to patients with NF2 and VS.

References

- 1 Evans DG, Moran A, King A, et al. Incidence of vestibular schwannoma and neurofibromatosis 2 in the North West of England over a 10-year period: higher incidence than previously thought. *Otol Neurotol*. 2005; 26: 93-97.
- 2 Evans GR, Lloyd SK, Ramsden RT. Neurofibromatosis type 2. *Adv Otorhinolaryngol*. 2011; 70: 91-98.
- 3 Samii M, Matthies C, Tatagiba M. Management of vestibular schwannomas (acoustic neuromas): auditory and facial nerve function after resection of 120 vestibular schwannomas in patients with neurofibromatosis 2. *Neurosurgery*. 1997; 40: 696-705; discussion 705-696.
- 4 Murphy ES, Suh JH. Radiotherapy for vestibular schwannomas: a critical review. *Int J Radiat Oncol Biol Phys*. 2011; 79: 985-997.
- 5 Philip R, Prepageran N, Raman R, et al. Surgical management of large acoustic neuromas: a review. *Med J Malaysia*. 2009; 64: 294-297.
- 6 Plotkin SR, Stemmer-Rachamimov AO, Barker FG, 2nd, et al. Hearing improvement after bevacizumab in patients with neurofibromatosis type 2. *N Engl J Med*. 2009; 361: 358-367.
- 7 Mautner VF, Nguyen R, Kutta H, et al. Bevacizumab induces regression of vestibular schwannomas in patients with neurofibromatosis type 2. *Neuro Oncol*. 2010; 12: 14-18.
- 8 Mautner VF, Nguyen R, Knecht R, et al. Radiographic regression of vestibular schwannomas induced by bevacizumab treatment: sustain under continuous drug application and rebound after drug discontinuation. *Ann Oncol*. 2010; 21: 2294-2295.
- 9 Uesaka T, Shono T, Suzuki SO, et al. Expression of VEGF and its receptor genes in intracranial schwannomas. *J Neurooncol*. 2007; 83: 259-266.
- 10 Wong HK, Lahdenranta J, Kamoun WS, et al. Anti-vascular endothelial growth factor therapies as a novel therapeutic approach to treating neurofibromatosis-related tumors. *Cancer Res*. 2010; 70: 3483-3493.
- 11 Boockvar JA, Tsiouris AJ, Hofstetter CP, et al. Safety and maximum tolerated dose of superselective intraarterial cerebral infusion of bevacizumab after osmotic blood-brain barrier disruption for recurrent malignant glioma. *Clinical article. J Neurosurg*. 2011; 114: 624-632.
- 12 Burkhardt J-K, Riina HA, Shin BJ, et al. Intra-arterial delivery of bevacizumab after blood brain barrier disruption for the treatment of recurrent glioblastoma: progression free survival and overall survival. *World Neurosurg*, in press, 2011.
- 13 Riina HA, Fraser JF, Fralin S, et al. Superselective intraarterial cerebral infusion of bevacizumab: a revival of interventional neuro-oncology for malignant glioma. *J Exp Ther Oncol*. 2009; 8: 145-150.
- 14 Riina HA, Knopman J, Greenfield JP, et al. Balloon-assisted superselective intra-arterial cerebral infusion of bevacizumab for malignant brainstem glioma. A technical note. *Interv Neuroradiol*. 2010; 16: 71-76.
- 15 Yamakami I, Kobayashi E, Iwadata Y, et al. Hypervascular vestibular schwannomas. *Surg Neurol*. 2002; 57: 105-112.
- 16 Burkhardt J-K, Riina HA, Shin BJ, et al. Intra-arterial chemotherapy for malignant gliomas. A critical analysis. *Interv Neuroradiol*. 2011; 17: 286-295.

Howard Riina, MD
Department of Neurosurgery
New York University Langone Medical Center
550 First Avenue
New York, NY 10016, USA
Tel.: 212.263.5382
Fax: 212.263.8664
E-mail: Howard.Riina@nyumc.org