

Bevacizumab induces regression of vestibular schwannomas in patients with neurofibromatosis type 2[†]

Victor-Felix Mautner, Rosa Nguyen, Hannes Kutta, Carsten Fuensterer, Carsten Bokemeyer, Christian Hagel, Reinhard E. Friedrich, and Jens Panse

Department of Maxillofacial Surgery (V.M., R.N., R.E.F.); Department of Otolaryngology (H.K.); Institute of Neuropathology (C.H.); Department of Oncology/Hematology, Cancer Center (J.P., C.B.); University Medical Center Hamburg-Eppendorf, Hamburg, Germany; MRI Institute, Hamburg Othmarschen, Germany (C.F.)

Bilateral vestibular schwannomas are the hallmark of neurofibromatosis type 2 (NF2), and these tumors impair hearing and frequently lead to deafness. Neurosurgical intervention, the only established treatment, often damages the vestibular nerve. We report 2 cases in which treatment with bevacizumab (for 3 months in one case and 6 months in the other) induced regression of progressive vestibular schwannomas by more than 40% and substantially improved hearing in the patient treated for 6 months. Bevacizumab therapy may thus provide an effective treatment for progressive vestibular schwannomas in patients with NF2.

Keywords: bevacizumab, neurofibromatosis type 2, vestibular schwannoma

Introduction

Neurofibromatosis type 2 (NF2) is an autosomal dominant syndrome characterized by tumors in the peripheral and cerebral nervous systems, including schwannomas, meningiomas, and gliomas. The hallmark of NF2 are bilateral schwannomas of the vestibular nerves, which are present in up to 90% of all patients.¹ Neurosurgical intervention is the only established treatment option for vestibular

schwannomas. However, surgical resection may further damage the vestibular nerves and worsen hearing, in some cases resulting in ultimate deafness.² Stereotactic irradiation of the tumors can be used to induce regression or slow progression, but the potential complications include facial nerve weakness, trigeminal neuropathy, vestibular dysfunction, and an increased risk for development of secondary malignancies later.^{3, 4} Very recently, erlotinib, an endothelial growth factor receptor (EGFR) tyrosine kinase inhibitor, has been reported to have induced substantial regression of a vestibular schwannoma and significantly improved hearing in a patient with NF2,⁵ suggesting that patients with slow-growing benign tumors may also benefit from so-called targeted therapies, such as tyrosine kinase inhibitors or monoclonal antibodies, originally developed for the treatment of malignant tumors. Bevacizumab, a humanized monoclonal antibody against vascular endothelial growth factor (VEGF), is a recently approved drug for treatment of various malignancies such as colon and breast cancers in combination with classic chemotherapeutic agents. Tumors with high levels of VEGF expression such as glioblastomas are considered as suitable for bevacizumab treatment.⁶ Because vestibular schwannomas express VEGF-1,⁷ NF2 patients with imminent total hearing loss because of tumor progression may benefit from bevacizumab treatment. At the 2008 NF conference in Bonita Spring, Florida, preliminary results from an ongoing treatment of NF2 patients using bevacizumab were presented by the group of Dr Scott Plotkin (Massachusetts General Hospital, Boston, Massachusetts), demonstrating potential efficacy of this drug for vestibular schwannomas.

In this current study, 2 NF2 patients for whom no other treatment options were available opted for treatment with bevacizumab after extensive consultation, discussions, and informed consent on an individual basis.

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[†]As we were submitting this manuscript, Dr Scott Plotkin informed us that their manuscript describing the outcome of bevacizumab treatment on NF2 patients was accepted for publication in the *New England Journal of Medicine*.

Corresponding Author: Victor-Felix Mautner, MD, Department of Maxillofacial Surgery, University Medical Center Hamburg-Eppendorf, Martinistrasse 52, 20246 Hamburg, Germany (kluwe@uke.uni-hamburg.de).

Patient Histories

Patient 1

A 17-year-old male patient was seen by an ear, nose, and throat physician in 2003 with progressive hoarseness because of paresis of the right vocal cord. Radiological work-up identified a causative vagus tumor. Additional cranial magnetic resonance imaging (MRI) revealed small vestibular schwannomas of 8×15 and 11×20 mm² on the left and right vestibular nerves, respectively. A tumor of the left trigeminal nerve and a right parietally located meningioma were also detected. Magnetic resonance imaging of the cervical spine revealed an intramedullary C3–C4 lesion suspected to be an ependymoma. These findings confirmed the diagnosis of NF2.

In 2004, at the age of 18 years, the patient suffered a sudden bilateral pantonal hearing loss with thresholds of 40–60 decibels hearing level (dBHL) on the right side and 20–30 dBHL on the left side. The right vestibular schwannoma had grown by 30%. The patient underwent surgery to resect the left vestibular schwannoma, which was smaller, with the hope of preserving the hearing on the left side. The resection did not further impair the hearing. Magnetic resonance imaging scan in 2005 detected a substantial progression of the right vestibular schwannoma, which led to a pantonal hearing loss of 70–90 dBHL in the pure-tone audiogram. Because of brain stem compression, this tumor was resected with an outcome of total right-side hearing loss.

The hearing in the left ear continued to decrease because of regrowth of the left vestibular schwannoma. In 2008, the patient became unable to differentiate voices and could no longer converse fluently over the phone even with a hearing aid. He was aware that further surgery would be required because of tumor progression and that deafness was imminent. Because of the risk of brain stem herniation, radiation therapy was not recommended. In addition to his progressive vestibular schwannoma, the intramedullary cervical spine tumor showed slow progression leading to an asymptomatic syrinx.

Patient 2

In 1992, a 22-year-old man presented with sudden right-sided hearing loss. The patient was treated with corticosteroids and rheologica, which transiently restored partial hearing function. In 1996, at the age of 26 years, he had a sudden decline in hearing of the left ear. Cranial MRI revealed bilateral vestibular schwannomas and a left ventricular meningioma and confirmed the diagnosis of NF2. In the same year, the patient underwent neurosurgery of the left vestibular schwannoma (then 2 cm in diameter), resulting in total hearing loss in the left ear. In 1997, the right vestibular schwannoma was 1.6 cm in diameter, and the patient had a 15% hearing impairment on the right side. In 2001, the patient suffered a sudden hearing loss with tinnitus, which was almost completely recovered after infusion of corticoids and

rheologica. The right vestibular schwannoma progressed to a diameter of 1.7 cm.

Two years later, the patient experienced another sudden hearing loss in 0.5–2 kHz of about 40 dBHL and was treated again with corticoids and rheologica. Annual cranial MRI revealed a continuous progression of the right vestibular schwannoma with an associated decline in hearing. In 2008, pure-tone audiometry demonstrated a pantonal hearing loss of 30–60 dBHL with the peak at 1–2 kHz. Speech audiogram revealed a hearing loss for numbers up to 60 dBHL and 85% recognition of single syllables at 100 dBHL. The risk of total hearing loss in the case of surgery was estimated to be very high. Radiation therapy was not recommended because of the risk of brainstem herniation during treatment.

Bevacizumab Treatment

Bevacizumab was given to each patient as an infusion every 2 weeks at a dose of 5.0 mg/kg body weight. The infusion time was 90 minutes at the beginning and then gradually reduced to 30 minutes. Before the treatment, the patients had a thorough medical evaluation including blood pressure, urine analysis, liver and kidney function tests, coagulation status, and history of thrombosis, hemoglobin, leukocyte count, and thrombocyte count. These tests were repeated before each treatment. Patients gave reports about their condition weekly via e-mail. The treatment was administered in the oncology outpatient clinic of University Medical Center Hamburg-Eppendorf by nurses experienced in administration of bevacizumab. Treatment with bevacizumab was scheduled for a total of 1 year.

Results

Patient 1

Six months after the start of therapy, the left vestibular schwannoma had regressed from a calculated volume of 10.4 mL (Fig. 1A) to 5.9 mL (Fig. 1B). Mitigation of brain stem compression was clearly visible on the cranial MRI scans. The intramedullary tumor showed slight regression, whereas the volume of the syrinx decreased more substantially (Fig. 1C and D).

Both pure-tone audiometry and Freiburger speech audiogram displayed slight improvement in hearing and word recognition (Fig. 2). Subjectively, the patient experienced a more significant hearing improvement, as he regained the ability to communicate via phone and to distinguish voices.

The patient had slight fatigue after each infusion therapy and mild epistaxis episodes at the beginning of treatment. No other side effects were reported or observed.

Patient 2

Three months after the start of therapy, the right vestibular schwannoma regressed from 7.3 mL (Fig. 3A) to

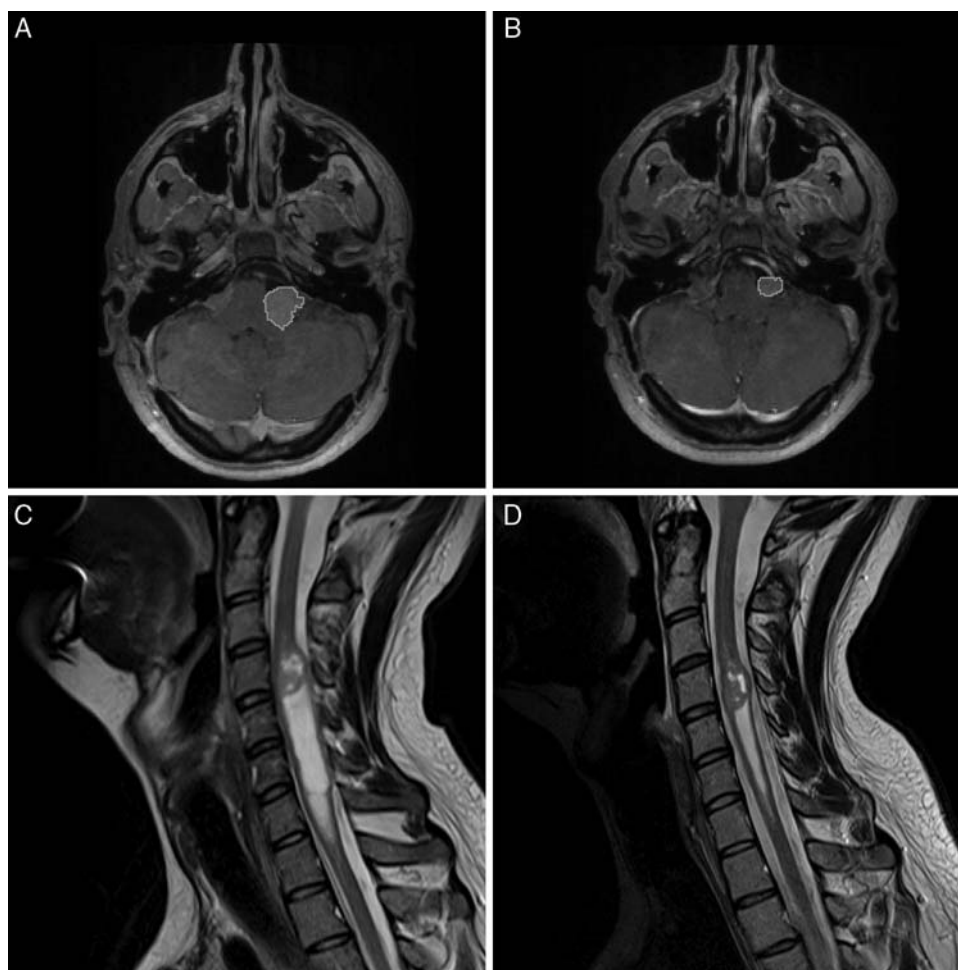


Fig. 1. Cranial (A and B) and spinal (C and D) MRIs of patient 1 before (A and C) and 6 months after (B and D) bevacizumab treatment. Homogeneous contrast enhancement revealed vestibular schwannoma in the cerebellar pontine angle compressing the brain stem and the 4th ventricle before treatment (A), which was substantially decreased after 6 months of treatment (B). Cervical spine MRI showed a syrinx associated with the intramedullary tumor (suspected ependymoma) before treatment (C), which was visibly decreased 6 months after the start of treatment (D).

4.3 mL (Fig. 3B). The cystic part regressed more than the solid part in the tumor. Brain stem compression was clearly relieved. Audio tests did not show improvement, nor did the patient himself report any hearing improvement.

After the 10th infusion, the patient developed high blood pressure. After consultation with his local general practitioner, he was given a calcium antagonist. Subsequently, he was switched to a sartan (angiotensin-1 antagonist), which resulted in better control of his blood pressure.

Discussion

In these case reports, bevacizumab had notable efficacy in the treatment of benign vestibular schwannomas in the 2 patients with NF2. In both patients, total hearing loss was imminent because of tumor progression, with no other treatment options left. Within short treatment

periods of 3 and 6 months, vestibular schwannomas regressed substantially in both patients. In the first patient, hearing improved significantly after 6 months of treatment, both objectively and subjectively. Although such improvement has not yet been seen in the second patient, he has been treated for only 3 months so far. Also for the first patient, hearing tests did not reveal improvement at 3 months of treatment, although the patient himself reported better hearing subjectively.

Both patients are still receiving medication, and follow-up examination will reveal if the tumors further regress during ongoing treatment. Treatment is scheduled for up to 1 year, and both patients will be closely monitored for subsequent side effects of bevacizumab and regrowth of tumors that might occur after cessation of treatment. Disease recurrence and more aggressive progression have been reported following bevacizumab treatment of malignant gliomas.^{8,9} This, however, may not necessarily occur in patients with benign vestibular

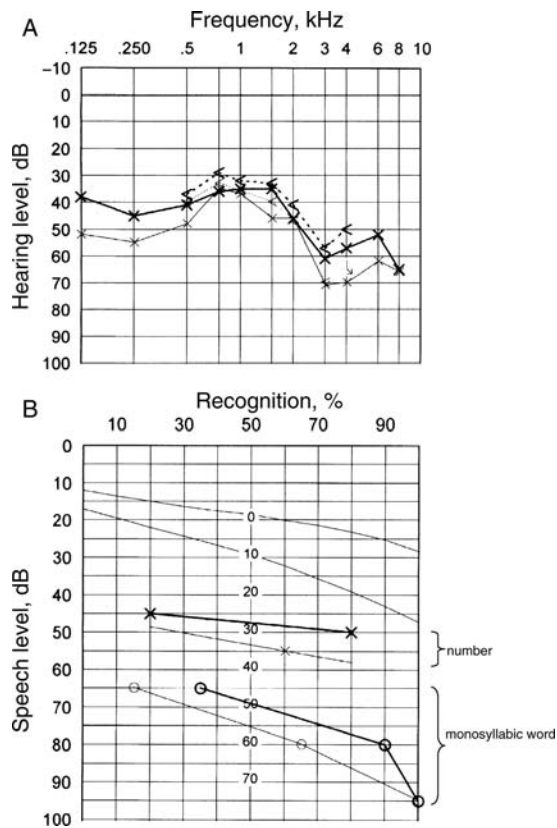


Fig. 2. Hearing of patient 1 before (thin lines) and after 6 months of treatment (thick lines). (A) Pure-tone audiometry. Solid and dotted lines are measures of the middle and inner ear, respectively, (B) Freiburg speech audiogram. The y-scale on the left refers to the speech level for the monosyllabic word test, whereas that in the middle refers to the speech level for numbers. The upper 2 thin lines are reference values for number and monosyllabic word recognition, respectively.

schwannomas, and although recurrence of glioblastomas is normally associated with rapid deterioration and ultimately patient death, resumption of bevacizumab treatment can be considered for NF2 patients with vestibular schwannomas. However, unknown side effects and the high risk for thrombosis and bleeding events argue against long-term use of the drug. Nonetheless, treatment with bevacizumab can postpone surgical procedures, which carry a high risk of total hearing loss. In addition, tumor regression after bevacizumab treatment increases the chance of hearing preservation in the case of surgical intervention. Combined treatment with bevacizumab and subsequent surgery thus provides a new treatment option for large and progressing vestibular schwannomas.

In both patients, intramedullary tumors were not affected by the medication. Interestingly, the syrinx and the bulging of the myelon caused by such a tumor in the first patient were visibly reduced. In contrast to the drastic regression of the vestibular schwannomas, no visible change was found for the cerebral meningiomas on MRI. One possible explanation is that only the progressive vestibular schwannomas responded to the drug, whereas meningiomas in the 2 patients were not in a progressive phase during the treatment period and thus did not respond.

This is another success in medical treatment for vestibular schwannoma after the impressive result by Plotkin et al.⁵ with erlotinib. These successes are the fruits of modern anticancer drugs and the recent NF2 research focused on directly inhibiting tumor Schwann cell proliferation (eg, using erlotinib) and suppression of vascularization (eg, with bevacizumab). The exact mechanism of the action of bevacizumab on vestibular schwannomas remains to be elucidated. The drug may also suppress growth of tumor Schwann cells directly, a possibility that can be tested in vitro in future studies.

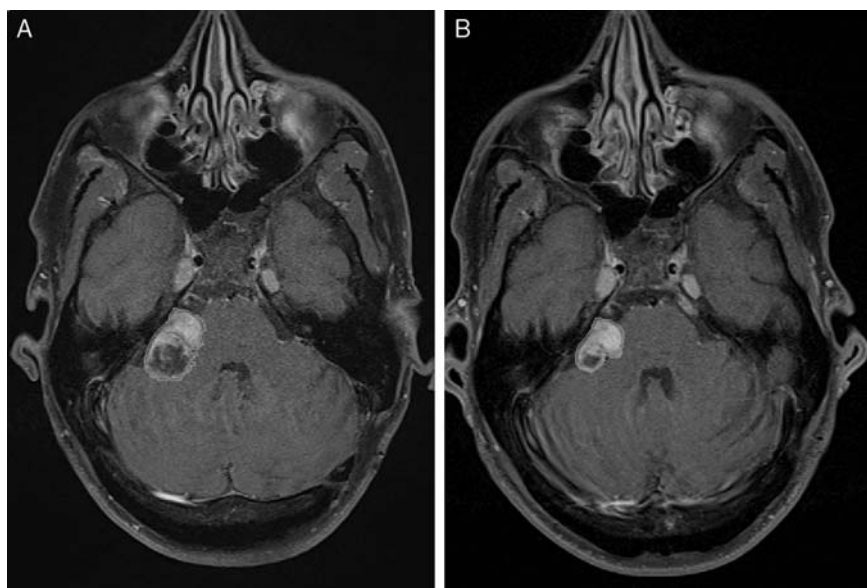


Fig. 3. Cranial MRI for patient 2 before (A) and 3 months after (B) treatment. The cystic component of the right vestibular schwannoma regressed substantially, whereas mitigation of the associated brain stem compression was clearly seen.

Erlotinib is given orally but daily, while bevacizumab has to be given i.v. yet only once every 2 weeks. As an EGFR inhibitor, erlotinib frequently causes skin alterations including dry skin, acne, and onychia, as well as other side effects known for tyrosine kinase inhibitors. Bevacizumab, on the other hand, targets VEGF and is associated with the risk of hypertension, bleeding, embolism, and kidney complications. In our limited experience, however, bevacizumab is well tolerated by patients. Further systematic studies are essential to evaluate the advantages and disadvantages of both drugs in treating vestibular schwannomas.

Our encouraging results with bevacizumab suggest consideration of a prospective clinical trial for

progressive NF2-related vestibular schwannomas, especially for patients with imminent total hearing loss. In addition, other modern anticancer drugs may also be effective against slow-growing benign tumors such as vestibular schwannomas and should be further evaluated.

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Conflict of interest statement. None declared.

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