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LETTER TO THE EDITOR

Reduced dosage of bevacizumab in treatment of vestibular schwannomas in patients with neurofibromatosis type 2

Said Farschtschi[1] · Philipp Kollmann[1] · Carsten Dalchow[2] · Alexander Stein[3] · Victor-Felix Mautner[1]

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Abstract Neurofibromatosis type 2 (NF2) is a tumor suppressor syndrome associated with vestibular schwannomas and other benign tumors of the central nervous system. Bevacizumab is used for treatment of progressive vestibular schwannomas, with the intent to reduce tumor size or preserve/improve hearing. Prolonged treatment can cause side effects such as hypertension and proteinuria, which can be cause for discontinuation of therapy. We report on 3 patients who were treated with bevacizumab for 66–76 months, with dose reductions that minimized side effects while sustaining the clinical effect of the antiangiogenic therapy. After dose reduction from 5 mg/kg bi- or tri-weekly to 2.5 mg bi- or tri-weekly, all patients appeared clinically stable and radiographic and audiologic follow-up showed sustained response. In conclusion, in some NF2 patients, dose reduction of bevacizumab seems to be an effective option for managing side effects.

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✉ Said Farschtschi
s.farschtschi@uke.de

[1] Department of Neurology, University Medical Center Hamburg-Eppendorf, Martinistr. 52, 20246 Hamburg, Germany

[2] Department of Otorhinolaryngology and Head and Neck Surgery, University Medical Center Hamburg-Eppendorf, Martinistr. 52, 20246 Hamburg, Germany

[3] Department of Internal Medicine II and Clinic (Oncology Center), University Medical Center Hamburg-Eppendorf, Martinistr. 52, 20246 Hamburg, Germany

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Introduction

Neurofibromatosis type 2 (NF2) is a neurogenetic tumor predisposition disorder with an birth incidence of about 1:27,000 defined by the occurence of bilateral vestibular schwannomas and other nervous system tumors as meningiomas, ependymomas and peripheral schwannomas [1]. Multiple groups have reported a beneficial effect of bevacizumab on vestibular schwannoma tumor size and hearing in patients with NF2 [2–8]. A recent article by Alanin et al. [9] similarly demonstrates this benefit, lending more support for this treatment strategy, which is the only medical treatment option for progressive vestibular schwannoma in NF2. However, the optimal dosing of bevacizumab remains a hotly debated issue in the NF2 clinical community. Given the potential need for long-term treatment, and the attendant risk of increasing toxicity [10], identification of dosage threshold values for optimal long-term treatment are needed.

Alanin et al. administered bevacizumab 10 mg/kg intravenously every second week for 6 months; afterwards, bevacizumab 15 mg/kg was given every third week. The dosage was chosen because of prior usage in patients with malignant brain tumors. As expected, in their study, side effects—although generally manageable—were frequent; one fatal event with death due to intracerebral hemorrhage occurred with questionable association to the given medication. Other studies of bevacizumab in NF2 (such as Plotkin et al. [2]) have used bevacizumab at doses of 5 mg/kg every second week. In the literature on bevacizumab,

even lower doses were suggested to be possibly effective in anticancer regimes and at least reach stable blood levels [11]. Here, we report that lower doses, i.e., bevacizumab 2.5 mg/kg every 2 or 3 weeks, can be sufficient to control the tumor growth and preserve hearing in some patients with NF2.

Methods

We report about 3 patients (2 male, 1 female, 44, 28 and 30 years of age, respectively) with the diagnosis of NF2 according to the National Neurofibromatosis Foundation (NNFF) diagnostic criteria [12]. All patients had bilateral vestibular schwannoma with progressive growth and hearing decline, and were treated with bevacizumab on a compassionate use basis. All patients underwent surgery of their contralateral vestibular schwannoma with subsequent hearing loss before bevacizumab treatment for the remaining tumor began. Initial dosage of bevacizumab was 5 mg/kg every 2 or 3 weeks and was reduced to 2.5 mg/kg every 2 or 3 weeks. Tumor volume was calculated on axial MRI scans (1 mm slices, post-contrast transversal T1 3D-MPR) with the software OsiriX for MacOS (V. 6.0.2) by manual segmentation. A volume change of 20 % was considered as a significant change in accordance with consensus criteria [13]. Hearing was measured by pure tone audiometry (Thresholds in dB are measured at octaves and half-octaves from 250 to 8000 Hz). An average of thresholds at 500, 1000, 2000, and 4000 Hz [=pure tone average (PTA)] is a recommended standard outcome measure for reporting in cases of VS and word recognition score (hearing response in percentage of correctly identified monosyllables based on a 50-item monosyllable word recognition test) according to suggested NF2-response criteria [13]. The patient's characteristics are listed in Table 1. There were no other patients treated in our center, who underwent dose reduction during their course of treatment with bevacizumab. All procedures performed were in accordance with the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

Results

Initially all patients responded to bevacizumab with tumor shrinkage >20 % observed in volumetric analysis of serial MRI imaging and with hearing preservation for at least 6 years. As expected, mild to moderate side effects occurred in all patients as listed in Table 1, which led to treatment discontinuation in all patients. After treatment discontinuation, all patients experienced a relapse of tumor growth and hearing decline. For this reason, bevacizumab was restarted at a lower dosage. In this manner, side effects could be controlled and tumor size and hearing remained stable for 12–13 months, respectively (Fig. 1).

Table 1 Clinical characteristics of patients treated with reduced doses of bevacizumab

Patient	1	2	3
Date of treatment start	24.09.2008	01.10.2008	01.07.2009
Age at treatment initiation	22	38	25
Age at NF2 diagnosis	17	22	19
Sex	M	M	W
Reason for Bevacizumab	Progr. VS right	Progr. VS right	Progr. VS right
Treatment duration (months)	76	75	66
Treatment discontinuation (months)	13	7	6
Initial dose	5 mg/kg 2-weekly	5 mg/kg 2-weekly	5 mg/kg 2-weekly
Radiographic response VS	Y*	Y*	Y*
Clinical response	Y	Y	Y
Dose reduction to	2.5 mg/kg 2-weekly	2.5 mg/kg 3-weekly	2.5 mg/kg 2-weekly
Stable disease	Yes	Yes	Yes
Proteinuria before dose reduction	1+	0	1+
Hypertension before dose reduction	H I	H II	H I
Proteinuria after dose reduction	0	0	0
Hypertension after dose reduction	Normal	Normal	Normal

Proteinuria-dipstick test: 0 = negative; 1+ = 30–100 mg/dL; 2+ = 100–500 mg/dL; 3+ = >500 mg/dL. Blood pressure levels: normal = <120/80 mmHg; pre-hypertension = 120–139/80–89 mmHg; hypertension I (H I) = 140–159/90–99 mmHg; hypertension II (H II) = ≥160/100 mmHg

* Volumetric data available

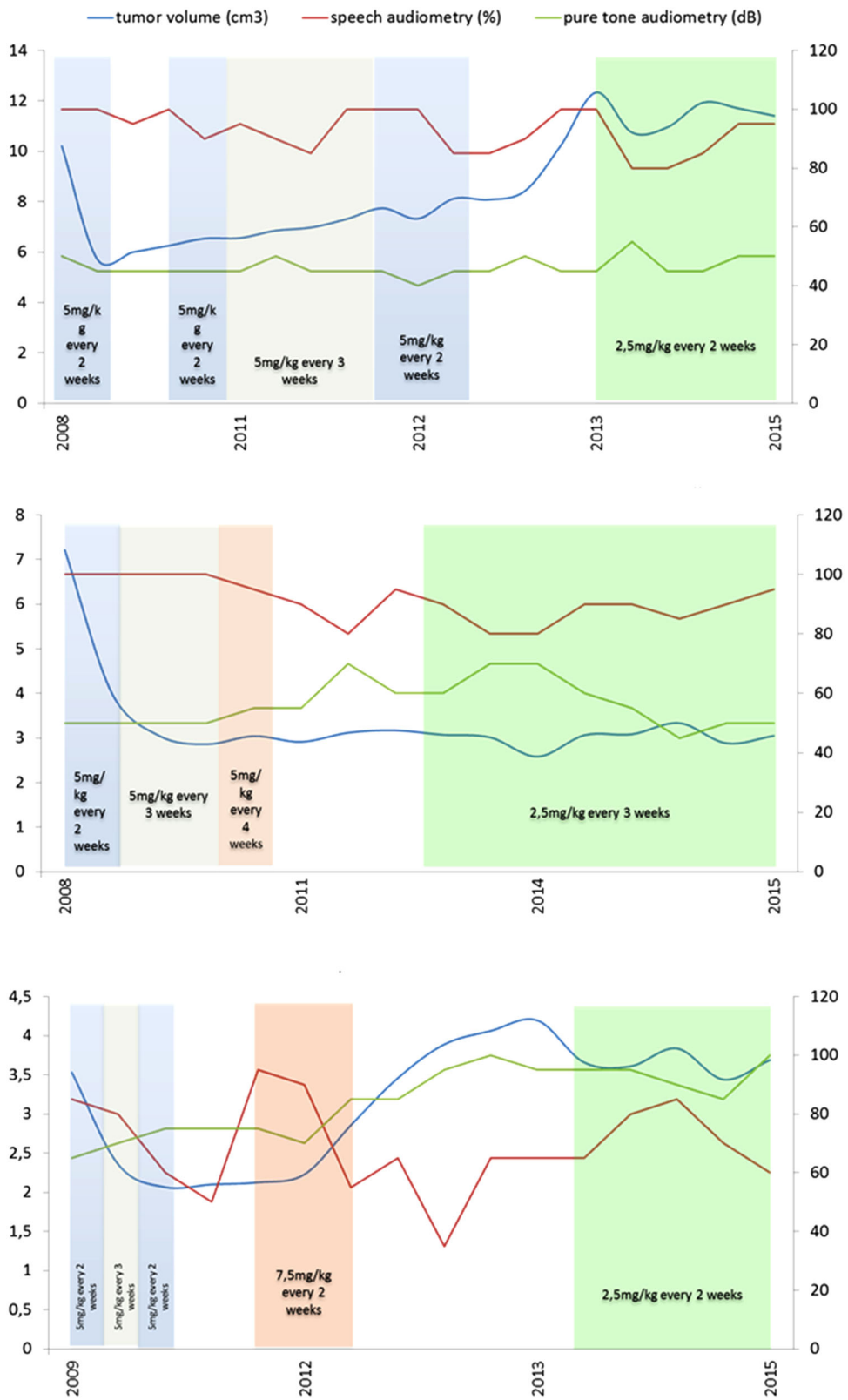

Fig. 1 Tumor volume, hearing response and bevacizumab dosage. *Top* patient 1, *center* patient 2, *bottom* patient 3. *Left y* axis tumor volume, *right y* axis hearing response in % for word recognition score or dB for pure tone audiometry (pure tone average; PTA), respectively

Discussion

Here, we report for the first time the use of bevacizumab at a reduced dosage for progressive vestibular schwannoma in patients with NF2. As bevacizumab is the only currently available drug to stabilize tumor volume and hearing in patients with NF2, long-term treatment is desired when alternative therapies are lacking. Treatment with lowered dosage may lead to lower toxicity, better tolerability and higher patient compliance. Dose reduction may temper side effects and possibly prevent adverse events while sustaining the impact on tumor size and hearing. We only have limited data about the use of bevacizumab in reduced dosages and studies on larger cohorts are needed to find the therapeutic window for bevacizumab. In conclusion, bevacizumab in low doses may be helpful in selected NF2 patients.

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical standard All procedures performed were in accordance with the Declaration of Helsinki.

Informed consent Informed consent was obtained from all individual participants included in the study.

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