Letters to the Editor

Complete pain relief after bevacizumab in a patient with neurofibromatosis type 2

ATTILA KOLLÁR1, EKKEHARD HEWER2, FRAUKE KELLNER-WELDON3 & ADRIAN OCHSENBEIN4

1Department of Medical Oncology, University Hospital of Bern, Switzerland, 2Institute of Pathology, University of Bern, Switzerland and 3Department of Neuroradiology, University Hospital of Bern, Switzerland

To the Editor,

Neurofibromatosis type 2 is a hereditary tumor predisposition syndrome manifesting with bilateral vestibular schwannomas, schwannomas of other cranial nerves, meningiomas, spinal schwannomas, ependymomas and other gliomas. It is caused by mutations of a tumor suppressor gene called ‘Merlin’ [1]. Surgery and radiation therapy are the only established treatment options [2,3]. Recently, a hearing improvement and a reduction of tumor volume of vestibular schwannomas and intracerebral meningiomas after systemic treatment with bevacizumab have been documented [4–12]. We now report an impressive effect of bevacizumab treatment on symptomatic peripheral schwannomas with a fast and complete pain relief in a patient with neurofibromatosis type 2.

Case report

A 27-year-old woman with known neurofibromatosis type 2 was referred to our outpatient clinics because of symptomatic progression.

According to the Manchester criteria the diagnosis of neurofibromatosis type 2 was made eight years earlier, at which time the patient presented with bilateral hearing impairment. The radiological findings were consistent with the manifestation of bilateral vestibular schwannomas. In the following years both lesions were treated with stereotactic radiosurgery. Some years later, after a symptomatic progression, the right-sided tumor was treated with a partial resection. Histologically, a schwannoma (WHO grade I) was confirmed. Additionally, multiple symptomatic spinal and peripheral schwannomas were resected in the following years (Supplementary Figure 1 available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.956185).

At the time of admission the patient mainly suffered from progressive left-sided hearing loss and a severe lumbovertebral pain syndrome. The brain magnetic resonance imaging (MRI) showed a progressive lesion in the left cochlear apex. Figure 1 shows a T1-weighted sagittal gadolinium-enhanced MRI of the lumbar spine with numerous partially confluent schwannomas. Compared to a previous MRI there was a progression of an intraspinal schwannoma at T12/L1 and a newly described schwannoma at L4 with typical features of heterogeneous contrast enhancement and some cystic changes. Due to the high number of schwannomas, no single lesion could be identified as cause for the pain.

Due to the symptomatic multifocal disease progression and particularly the progressive hearing loss we decided to start an intravenous treatment with bevacizumab (5 mg/kg). Before treatment the lumbovertebral pain intensity was severely interfering with daily life even though the patient was on a combined analgetic treatment with opioids, metamizol and gabapentin. Interestingly, only a few days after the first infusion, the patient reported a dramatic reduction and finally disappearance of the lumbovertebral pain syndrome. Hence, all analgetic drugs could be stopped within two weeks. In contrast, the follow-up audiometry did not
Bevacizumab in a patient with neurofibromatosis type 2

Discussion

Neurofibromatosis type 2 is an inherited disease associated mainly with benign tumors such as schwannomas, meningiomas, ependymomas and other gliomas. A majority of these tumors can be treated with surgery or radiotherapy in the case of symptomatic disease [2,3]. Until recently, systemic therapy had no role in the treatment of neurofibromatosis type 2. Cytotoxic chemotherapy has no significant impact in these slowly proliferating neoplasms. Therefore, a number of potential therapeutic targets have been investigated taking into account the complex downstream signaling pathways involved in the pathogenesis of this disease [4–12].

Whereas vestibular schwannomas are causing hearing deficits, pain is more often the leading symptom in peripheral schwannomas. This neuropathic pain is often difficult to manage and resistant to document a hearing improvement. The treatment was continued for 18 months without pain recurrence. Figure 2 shows MRI follow-up four months after therapy stop with mixed response, but stable disease measured by RECIST 1.1 criteria. The tumor at level T12/L1 had diminished in size, while the tumor at level L4 had increased in size and multiple additional schwannomas were stable in size.

Five months after bevacizumab was stopped the patient became symptomatic again with pain in the lumbovertebral region irradiating into the right leg. The neurological exam excluded sensomotoric deficits. New pathologic bony lesions were excluded by x-ray. We concluded that again, the known spinal schwannomas caused the pain and reinstalled a treatment with bevacizumab. Before treatment start, the patient was on an analgetic medication with metamizol and gabapentin without any relevant success; 8/10 points were documented on the visual pain scale. After applying the first infusion of bevacizumab the pain decreased again very rapidly (Figure 3).

The patient was pain-free without analgetic drugs two weeks thereafter.
treatment with analgetic drugs. The patient in this case report experienced an impressive and very fast symptomatic response after only one infusion of bevacizumab.

The effect of bevacizumab on intracranial vestibular schwannomas and meningiomas has been reported before, whereas hardly any date is available on the effect on peripheral schwannomas [4–12]. Antiangiogenic therapy targeting VEGF or its receptors modifies the vascular network by decreasing the number of blood vessels and normalizing the remaining vessels with regard to morphology and functionality. However, the observed effect with a pain relief within a few days most likely is not due to a reduction or normalization of blood vessels with a consecutive effect on the tumor cells. Most likely, the effect of bevacizumab is a consequence of the reduced endothelial permeability and subsequent tumor edema [8]. This is supported by the fact that the mean apparent diffusion coefficient (ADC) value of the tumor at baseline is associated with radiographic response in vestibular schwannoma treated with bevacizumab [9].

In summary, we document a dramatic reduction of pain caused by peripheral schwannomas after treatment with bevacizumab in a patient with neurofibromatosis type 2. These findings may warrant further investigation of bevacizumab in this specific clinical situation.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Supplementary material available online

Supplementary Figure 1 available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.956185.