Radiographic regression of vestibular schwannomas induced by bevacizumab treatment: sustain under continuous drug application and rebound after drug discontinuation

Bilateral vestibular schwannomas (VS) are the hallmark of tumor suppressor gene syndrome, neurofibromatosis type 2 (NF2). As they continuously grow, these benign tumors impair hearing and lead frequently to deafness. Surgical resection, the only established treatment, often further damages the vestibular nerve. Recent studies showed that bevacizumab can induce substantial radiographic regression of progressive VS in NF2 patients and improve hearing significantly in a subset of them [1, 2].

In the first case of a 22-year-old male NF2 patient, treatment with bevacizumab at 5 mg/kg bi-weekly led to a 43% radiographic regression of VS (Figure 1, upper), shrinkage of the syrinx of a spinal ependymoma, reduced ataxia and improved hearing [1]. During the 1-year period of treatment, VS remained stable. Also 2 months after drug discontinuation, magnetic resonance imaging (MRI) revealed no significant change in the VS volume. However, 5 months later, increase of VS volume was detected (Figure 1, upper). Also the spinal syrinx associated with the ependymoma increased in size. Audio tests revealed slight worsening in hearing though the patient himself did not notice any change. Because of the enlarging tendency of the VS and because the patient tolerated the drug well during the previous treatment, bevacizumab therapy was resumed in March 2010.

In the second case of a 38-year-old male patient, bevacizumab infusion at 5 mg/kg bi-weekly led to rapid radiographic regression of the right VS and complete resolution of ataxia (Figure 1, lower). However, no hearing improvement was achieved in this case. Shortly after start of the therapy, the patient developed hypertension (grade 2 toxicity), a known side-effect of bevacizumab [3], which was however well controlled with an angiotensin-1 antagonist sartan. After 1-year treatment and considering that the half-life time of bevacizumab is 20 days [4], the infusion interval was extended from 2 to 3 weeks, corresponding to a 70% dose reduction. The patient’s VS remained stable on MRI 4 months after the dose reduction. The overall dose was then further reduced to 50% by means of extending infusion interval to 4 weeks while keeping the same single dose. The VS remained stable 1 month after the second dose reduction. The hypertension normalized gradually along with the dose reduction.

In both cases, no size change was detected for cerebral non-VS, cutaneous schwannomas and cerebral and spinal meningiomas.

Our finding demonstrates that radiographic regression of VS can be sustained under continuous bevacizumab application and that dose reduction is possible. However, the tumors will gradually return to their original size upon drug discontinuation. Bevacizumab does not seem to directly target the tumor cells but rather likely induces reversible shrinkage of VS via, for example, increasing vascular permeability of the tumor cells and reducing intratumoral edema.

By optimizing the dose, side-effects of the drug can be minimized and cost of the therapy reduced, opening the possibility of long-term application of bevacizumab for VS.
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