Clinical Commentary

Bevacizumab treatment for symptomatic spinal ependymomas in neurofibromatosis type 2


Background – Neurofibromatosis type 2 (NF2) is a tumor suppressor syndrome associated with vestibular schwannomas, meningiomas, and spinal ependymomas. There have been anecdotal reports of radiographic response of spinal ependymomas in NF2 patients being treated for progressive vestibular schwannomas with bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF).

Aims – The aim of this study was to review the clinical effects of bevacizumab treatment for symptomatic, NF2-associated ependymomas

Methods – We conducted a retrospective review of all patients with NF2 treated with bevacizumab for symptomatic ependymoma at three NF2 specialty centers. Tumor size was evaluated by linear measurements; radiographic response was defined as >20% reduction in tumor size. We also performed immunohistochemical evaluation of NF2-associated symptomatic ependymomas from five patients, including two from this clinical series. Results – Eight patients with NF2 and symptomatic ependymoma were treated with bevacizumab. All patients had subjective clinical improvement with bevacizumab, although only five of eight patients evaluated had radiographic response. All tumors expressed VEGF-R2. Four of five evaluated ependymomas expressed VEGF-R1; one without VEGF-R1 expression was from a patient who showed clinical but not radiographic response. Conclusions – Treatment using bevacizumab improved symptoms related to NF2-associated ependymomas, often without concurrent radiographic response. This treatment effect may be related to VEGF-R1 expression in NF2-associated ependymoma.

Introduction

Neurofibromatosis type 2 (NF2) is a neurogenetic tumor predisposition disorder with an incidence of ~1:27,000 (1). Hallmark lesions of NF2 include bilateral vestibular schwannomas, non-vestibular schwannomas, and meningiomas (2). In addition, an estimated 33% of patients with NF2 have spinal ependymomas (3,4). Histopathology of these lesions includes tanycytic and myxopapillary (WHO grade 1) and classic (WHO grade 2) ependymoma; signs of anaplasia are uncommon (4,5). In contrast to their sporadic counterparts, ependymomas in NF2 appear almost exclusively in the spinal cord and are characterized by multisegment tumor formation with large cystic compartments.

In most NF2 patients, spinal ependymomas are asymptomatic and therapy is not required; however, in about one-fourth of patients with
ependymomas, tumors can cause significant neurological symptoms. Currently, the most common treatment for NF2-related symptomatic ependymomas is surgical resection. However, surgery has a high risk of spinal cord injury and perioperative complications, especially in patients exhibiting severe neurological symptoms such as paraparesis or sensory loss prior to surgery (4,6,7). For this reason, chemotherapeutic options for treatment are highly desirable.

Recent investigations have revealed potentially promising effects of bevacizumab on NF2-related vestibular schwannomas (8,9). Bevacizumab is a recombinant humanized monoclonal antibody against vascular endothelial growth factor (VEGF-A). Neutralization of VEGF may lead to inhibition of tumor growth, decreases in interstitial fluid pressure, and increased tumor oxygenation (10).

The effect of bevacizumab on ependymomas has not been established. In a small case series, 87.5% of adults with sporadic, recurrent ependymoma achieved either a partial response or stable disease after treatment with bevacizumab (alone or in combination with cytotoxic chemotherapy) (11). However, in sporadic recurrent ependymoma in children, bevacizumab and irinotecan failed to show any sustained response (12). A report on the effect of bevacizumab in NF2 patients being treated for progressive vestibular schwannoma suggested an effect on spinal ependymomas (13), but to date, no studies have systematically addressed the response of symptomatic spinal ependymomas to bevacizumab in NF2. Here, we report the clinical effect of bevacizumab on ependymomas in eight patients with NF2, and VEGF receptor expression in five resected, NF2-related ependymomas.

Methods

All patients were diagnosed with NF2 by experienced clinicians based on consensus criteria. Patients received bevacizumab as treatment for symptomatic ependymoma after consulting neurosurgeons deemed them poor candidates for surgery or they refused surgical treatment. Using MRIs of the head and spine performed with intravenous gadolinium contrast, we measured ependymoma size (in mm) using T2-weighted images, with radiographic response defined as ≥20% reduction in linear measures. Volumetric assessment of ependymomas was not feasible due to the inhomogeneous appearance and cystic tumor formation. We measured vestibular schwannoma volume (in cm³) using T1 post-contrast images, with radiographic response defined as ≥20% reduction in volume. Clinical follow-up and radiological follow-up were performed routinely every 6–12 months.

Immunohistochemistry

Three NF2-associated ependymomas from a case series previously reported by Hagel et al. (5) were available for immunohistochemical evaluation of VEGF-R1 and VEGF-R2. In addition, pretreatment surgical specimens from patients 3 and 5 of this case series were also analyzed for VEGF-R1 and VEGF-R2. Immunohistochemical studies used four-micrometer-thick sections. Tissue sections were heat-pretreated following incubation with VEGFR-1 or VEGFR-2 antibodies (Santa Cruz sc-316, 1:100; Santa Cruz sc-504, 1:50, Santa Cruz Biotechnology, Inc., Heidelberg, Germany) in an automated stainer (Ventana Medical Systems, Tuscon, AZ, USA) according to standard protocols. Bound antibodies were detected by the peroxidase method using diaminobenzidine as chromogen (760-500, Ultraview DAB, Ventana). All antibody reactions were validated prior to the study using isotype negative controls and glioblastoma samples harboring pathological endothelial proliferations as positive controls (data not shown).

Results

Patient characteristics

Eight patients (seven male and one female) from three institutions were treated with bevacizumab for symptomatic spinal ependymomas (Table 1). Median age at time of treatment was 22 years (range 15–34 years). Symptoms prompting treatment included dysphagia, ataxic gait, spastic paraparesis, and intractable pain. Two patients underwent surgery prior to bevacizumab treatment (patients 3 and 5), with pathological confirmation of the diagnosis of ependymoma; for all other patients, diagnosis of ependymoma was made based on characteristic radiographic appearance. Seven patients had radiographically documented ependymoma growth prior to treatment.

Bevacizumab treatment

The initial dose of bevacizumab was either 5 or 7.5 mg per kg every 2 weeks. In some patients, the dose was decreased during the course of treatment to minimize long-term toxicity; four patients received 3.75 mg/kg every 2 weeks, and
Table 1: Patient characteristics. m: male, f: female, q3: every 3 weeks, q2: every 2 weeks

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age at diagnosis (years)</th>
<th>Age at treatment start (years)</th>
<th>Treatment indication</th>
<th>Ependymoma location</th>
<th>Pretreatment ependymoma growth</th>
<th>Treatment duration (months)</th>
<th>Average dose (mg/kg)</th>
<th>Radiographic response ependymoma</th>
<th>Clinical response</th>
<th>Treatment hold ≥ 6 months</th>
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<tbody>
<tr>
<td>1</td>
<td>m</td>
<td>22</td>
<td>6</td>
<td>Dysphagia/airway</td>
<td>Cervical</td>
<td>Yes</td>
<td>8</td>
<td>75–85</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>2</td>
<td>m</td>
<td>15</td>
<td>14</td>
<td>Dysphagia/airway</td>
<td>Cervical</td>
<td>Unknown</td>
<td>11</td>
<td>75–85</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>3</td>
<td>m</td>
<td>25</td>
<td>12</td>
<td>Spastic paraparesis</td>
<td>Cervical</td>
<td>Yes</td>
<td>24</td>
<td>5 q3</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>4</td>
<td>m</td>
<td>22</td>
<td>17</td>
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<td>Yes</td>
<td>36</td>
<td>5 q3</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>f</td>
<td>34</td>
<td>23</td>
<td>Ataxic gait, Paraparesis</td>
<td>Cervical and thoracic</td>
<td>Yes</td>
<td>36</td>
<td>5 q3</td>
<td>Yes</td>
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<td>Yes</td>
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<tr>
<td>6</td>
<td>m</td>
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<td>17</td>
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<td>Cervical</td>
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<td>5 q3</td>
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<tr>
<td>7</td>
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<td>38</td>
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<td>No</td>
</tr>
<tr>
<td>8</td>
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<td>Yes</td>
<td>16</td>
<td>5 q3</td>
<td>Yes</td>
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</tr>
</tbody>
</table>

1 In addition to symptomatic ependymoma, patient also had progressive vestibular schwannoma.
2 Immunohistochemical staining of pretreatment surgical specimen revealed the ependymoma was negative for VEGFR-1 and positive for VEGFR-2.
3 Immunohistochemical staining of pretreatment surgical specimen revealed the ependymoma was positive for VEGFR-1 and VEGFR-2.

Clinical and radiographic response

All eight patients had subjective improvement in neurologic function as rated by both the patient and the care team. Improved neurological symptoms included dysphagia (#1–2), sensory deficits (#3–8), weakness (#3–6), bladder and bowel dysfunction (#3), pain (#3, 6–8), and ataxia (#4–6).

Half of patients experienced radiographic response of ependymoma, seen within 3–6 months after treatment initiation. In all four patients with a radiographic response (#4–7), the cystic compartments of the ependymoma demonstrated the greatest decrease in size. Importantly, there were no instances of pseudoresponse—the resolution of contrast enhancement—noted in any patients. (14) There was no obvious relationship between the degree of tumor shrinkage and perceived clinical benefit. For example, patient 3, who showed no significant radiographic change in tumor size, demonstrated improvement of ataxia, paraparesis, and urinary incontinence such that he regained bladder control and ambulation.

Treatment breaks

In five of eight patients, treatment was held for ≥6 months. In three patients (#1, 4, and 7), symptomatic improvements noted during treatment were lost during treatment hold, but returned within a few months when drug was restarted. Radiographic progression was noted in patient 4 during treatment hold (Fig. 1), but was followed by a reduction in tumor size to the baseline volume after restarting bevacizumab. After stopping treatment, patients 2 and 8 presented with radiological relapse and increasing back pain.

Toxicity

Toxicity related to bevacizumab treatment was mild. One patient had a single episode of abdominal pain with hematochezia for which bevacizumab was held for 2 months. Symptoms improved, work-up was negative, and he was able to resume drug without complication. There were no grade 3 or 4 adverse events related to bevacizumab.

Immunohistochemistry

Upon immunohistochemical investigation, all tumors investigated showed expression of
VEGF-R2 in all parts of the tumor (Fig. 2). Four of five tumors showed expression of VEGFR-1 in tumor cells, and in two of five cases, the receptor was detected in endothelial cells. Staining ranged from scattered single cells over patchy expression to strong labeling of large tumor areas (Fig. 3). In one case, (patient 3) the staining was negative. This patient experienced clinical improvement but no radiographic response.

**Discussion**

This is the first case series to investigate the effect of bevacizumab on symptomatic spinal ependymomas in patients with NF2. All eight patients showed clinical improvement, despite significant neurological impairments at baseline. Continued treatment with bevacizumab was necessary to maintain neurological improvement. In our experience, clinical and radiographic improvement occurred within 3–6 months of treatment and clinical relapse occurred about 6 months after treatment discontinuation. Interestingly, some individuals had discordant radiographic changes in vestibular schwannomas and ependymoma, pointing to the heterogeneity of NF2-related tumors.

Shrinkage of tumors was primarily noted in the cystic portions of ependymomas, suggesting that the primary effect of bevacizumab is on vascular permeability rather than on tumor cells. The clinical improvement after treatment onset may be explained by an anti-edema effect of bevacizumab. In previous studies on vestibular schwannoma treated with bevacizumab, there was a correlation between tumor shrinkage and

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**Figure 1.** Spinal ependymoma (SE) in the cervical cord with a large cystic compartment (cy) of patient 4, shown with T2-weighted sagittal MRI (Siemens Avanto 1.5T). (A) Before treatment with bevacizumab. (B) After 6 months of treatment. (C) Six months after discontinuation of treatment. (D) After retreatment.

**Figure 2.** Immunohistochemical demonstration of VEGFR2 in spinal ependymoma of NF2 patients. Varying expression of VEGF-R2 in three samples of NF2-associated ependymomas, in both the vasculature and the tumor tissue.
change in the apparent diffusion coefficient value, a radiological marker for edema (8).

We found a slight endothelial expression and strong tumor tissue expression of VEGFR-1 in 4 of 5 NF2-associated spinal ependymomas. Our findings agree with that of Chan et al. (15), who reported that five of six sporadic ependymomas investigated by in situ hybridization for VEGFR-1 and VEGFR-2 expression had slight-to-strong expression of mRNA of both receptors.

From our case series, patient 3 showed no significant expression of VEGF-R1 prior to treatment, which could explain the lack of radiographic response in this patient. However, this patient still displayed significant clinical improvement despite the lack of tumor shrinkage. For this reason, we believe that clinical improvement, rather than radiographic response, should be used to assess the benefit of bevacizumab for patients with NF2.

Because of the small sample size, our data cannot be generalized to all NF2 patients with symptomatic spinal ependymomas. Ependymomas were evaluated by linear measures and not by volumetric measurement, so small changes in tumor size might not have been detected. The patients presented in this case series were selected for bevacizumab treatment due to severe symptoms associated with their spinal ependymomas; however, many NF2 patients with ependymomas have few or no clinical impairments, making drug treatment unnecessary.

Taken together, these findings suggest bevacizumab improves clinical symptoms related to NF2-related spinal ependymoma in selected patients, with a less robust effect on tumor size. Further investigation is warranted to study the mechanisms and potential benefit of bevacizumab as a novel option for the treatment of symptomatic ependymomas in NF2 patients.

Acknowledgment
None.

Conflicts of interest
The authors declare they have no conflict of interests.

Sources of funding
No funding.

Declaration
This study was conducted in full accordance with the Declaration of Helsinki.

References