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Case Report

Everolimus and Bevacizumab in the Management of Recurrent, Progressive Intracranial NF2 Mutated Meningioma

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Abstract
Meningiomas are primary CNS tumors that arise from the arachnoid layer of the meninges. Genomic sequencing has revealed that NF2 mutations are the most common genetic alteration seen in meningiomas. Meningiomas although usually low grade, can sometimes progress to high grade. A patient who had several recurrences of meningiomas since childhood presented with recurrent headaches. Imaging showed that he had another recurrence of a meningioma. He underwent surgery for resection of the meningioma and histopathology showed NF2 mutation. He was started on everolimus and bevacizumab with good effect. Studies have shown that NF-2 mutated meningiomas have a good response to everolimus and bevacizumab with increased progression-free survival time and progression-free survival time at 6 months.

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Introduction

Meningiomas are the most common primary central nervous system (CNS) tumors making up 36.8% of all CNS tumors. There is an increase in incidence after the age of 65 and they are more common in women than in men [1].

Meningiomas are tumors that arise from the arachnoid cap cells, the outer layer of the arachnoid layer. Intracranial meningiomas are more common than spinal meningiomas, with intracranial meningiomas accounting for approximately 90% of all meningiomas [1]. The majority of meningiomas are non-malignant, with the Central Brain Tumor Registry of the United States (CBTRUS) survey report from 2010–14 showing that meningiomas with ICD-O-3 codes, 0 (benign) or 1 (uncertain), accounted for 98.7% of meningiomas [1].

Genomic sequencing in different studies has revealed that NF2 mutations are the most common genetic alteration seen in meningiomas, with mutations in TRAF7, KLF4, AKT1, and SMO being seen in NF-2 independent meningiomas [2, 3]. The tumor suppressor gene NF2, located on chromosome 22q12, encodes a protein called merlin. Loss of function results in absence of activity of the tumor suppressor protein merlin, which results in multiple tumors [4]. Meningiomas, although usually low grade, can sometimes progress to high grade tumors and several genetic abnormalities have been implicated.

The treatment of meningiomas is usually surgery and stereotactic radiation. However, there has been no recommended standards of therapy for recurrent meningiomas. There have been studies that have shown the effectiveness of bevacizumab and everolimus in the treatment of meningiomas [5, 6].

We present a case of NF-2 associated recurrent malignant meningioma which was subsequently treated with bevacizumab and everolimus.

Case Presentation

Reported patient is a 41-year-old male with a known history of meningioma that was first diagnosed at the age of 13 years for which he underwent resection of a right skull-based meningioma. He had a recurrence of his disease in 2007, at the age of 30 years. He had multiple surgeries for resection of his recurrent meningioma and subsequently right cranioplasty in 2009. In 2013, he developed a left frontal meningioma which was excised. His post-operative course was complicated by infection of the surgical site and he underwent removal of his right temporalis Medport which was placed in January, 2015. He also underwent debridement of the right zygomas and lateral maxilla with removal of the infected maxillary hardware in November, 2015.

The patient had progressively worsening right sided headache and magnetic resonance imaging (MRI) performed in April, 2017 showed recurrence of meningioma in the right middle fossa. While under consideration for enrollment in a clinical trial, survellance imaging showed that his meningioma tumor burden was rapidly progressing. Patient had a generalised tonic clonic seizure and an MRI peformed six months after his recent recurrence showed that the infratemporal component of meningioma had significantly enlarged and was extending intracranially through the foramen ovale. The middle cranial fossa component had also enlarged and measured 2.4 cm by 2.9 cm by 1.5 cm. The tumor resulted in severe compression of the right temporal lobe with associated progressive vasogenic edema throughtout the temporal white matter and orbitofrontal white matter. He was started on levetiracetam and a decision was made to proceed with surgical resection. Postoperative MRI showed plaque like dural

thickening along the anterior frontal and temporal convexities but no residual meningioma in the operative bed.

Histopathological analysis revealed that this was a WHO Grade II meningioma. Foundation 1 genetic testing revealed NF2 mutation. His tumor was microsatellite proficient and mutation burden was low. As recent phase II clinical trials have shown promising results with combination therapy with bevacizumab and everolimus in patients with NF2 mutated meningiomas, patient consented to proceed with this regimen. MRI performed after 4 cycles of combination treatment with bevacizumab and everolimus showed no new enhancing mass in the operative bed or the rest of the brain.

Discussion

Meningiomas are classified into three grades based on the WHO criteria, Grade I (benign), Grade II (atypical) and grade III (anaplastic). This classification is based on the cellular atypia and the degree of invasiveness of the tumor [7]. The majority of meningiomas have mutations in the tumor suppressor gene, NF2, which in turn encodes the tumor suppressor protein, merlin. Merlin belongs to the FERM protein family, which includes ezrin, radixin and moesin. Merlin acts as a tumor suppressor protein and regulates receptor mediated signalling pathways which control cell proliferation [4]. The pathways which are regulated include mTOR, hippo, PI3k/AKt among others [4]. Loss of tumor suppressor function of merlin causes the formation of multiple tumors in the CNS including schwannomas and meningiomas. Recent genomic studies have also revealed mutations in AKT1, SMO, TRAF7 and KLF4 [2, 3]. AKT1 mutations cause increased downstream activation of the mTOR pathway. SMO mutations cause alteration in the Hedgehog signalling pathway which can lead to increased number of meningiomas. TRAF7 and KLF4 mutations are responsible for maintaining the pluripotency of cells [2, 3].

Meningiomas are most commonly benign [1]. The prognosis of grade III meningioma is poor with the average survival after diagnosis being usually less than 2 years [8]. Meningiomas can undergo progression to malignant meningiomas. Goutagny and colleagues demonstrated that TERT promoter mutations were common in meningiomas undergoing malignant transformation [9]. TERT promoter mutations cause increased TERT expression which in turn helps maintain telomere length, a key event in the progression of malignancy [9]. NF2 related tumor progression has been associated with gain and loss of alleles. The most commonly associated allelic losses other than 22q losses are 1p, 10q and 14q, and the most common gains are 1q, 9q, 12q and 15q [10, 11].

The initial treatment of meningiomas is surgery and, if needed, radiation. There have been no well-defined guidelines for the treatment of recurrent, aggressive meningiomas. Meningiomas, like any tumor are dependent on angiogenesis. Reszec and colleagues demonstrated that vascular endothelial growth factor (VEGF) expression is more predominant in higher grade meningiomas, especially recurrent and anaplastic meningiomas. This finding has been similar to other studies as well [12]. Meningiomas also seem to have increased activity of the mTOR pathways. Thus, inhibitors of the mTOR pathway such as everolimus have also been under study for the treatment of meningiomas. Everolimus has been shown to be effective in the prevention of progression of meningioma [13]. VEGF inhibitors, especially bevacizumab have been under trial for the treatment of meningiomas. There have been retrospective studies which have evaluated the efficacy of bevacizumab in the treatment of meningiomas. In one retrospective study, the mean progression free survival (PFS) time was found to be 26 weeks and the progression free survival time at 6 months (PFS6) was found to be 43.8%. None of the

patients achieved complete or partial response. Stable disease was the best response obtained [14]. Another retrospective study by Lou and colleagues, showed that when bevacizumab was used in patients with recurrent meningiomas, the PFS was 17.9 months and the PFS6 was 85.7%. 1 of the 14 patients in the study attained a partial response, with stable disease being the next best outcome [15]. A recent phase II trial using bevacizumab and everolimus, showed favourable results as well, with PFS being 22 months. The study also showed that grade II/III meningiomas had a longer PFS than grade I meningiomas (22 vs 17.5 months) [5]. This could be explained by the fact that higher grade meningiomas were more vascular and had increased VEGF expression and increased activation of the mTOR pathway [5]. These studies, although promising are limited by the small sample sizes. Further studies with larger sample size will be able to clarify the effectiveness.

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Author Contributions

Vinay Mathew Thomas – responsible for writing the first draft of the manuscript, and making subsequent recommended changes in the manuscript.

Poorva Bindal – responsible for writing the drafts of the manuscript and also editing the manuscript.

James J. Vredenburgh – responsible for overseeing the whole project, making recommendations for editing throughout the project and responsible for the final approval of the manuscript before submission.

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