

Antibody Targeted Therapies in Meningiomas: A Critical Review

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Abstract

Surgical resection being the most successful approach for meningiomas is not always possible pertaining to its inapproachable locations of tumors. Radiation therapy is sometimes restricted by neurotoxicity and tumor size, while chemotherapy regimens have been minimally effective as treatment option in meningiomas. Therefore, treatment of the remaining subset of aggressive, unapproachable or refractory meningiomas remains challenging. This makes it a topic of concern to explore more strategies for its management. Recent practices have shown increased interests in the utilization of monoclonal antibodies. Among the most prospective are TRAIL therapy followed by antibodies targeting receptors such as PDGFR, EDGF, VEGFR, PD-1. These therapies can be utilized to reduce the stability of meningiomas. There is a need for initiation of large scale Randomized controlled trials to improve outcomes in meningioma patients and formation of a more productive management strategy.

Keywords: Meningioma; Monoclonal antibodies; Molecular targeted therapies; Disease management; *In vitro* techniques

Introduction

The prevalence rate of intracranial meningiomas is predicted to be 97.5 in 100,000 approximately in the United States with over 138,000 individuals currently diagnosed [1]. They account for 30% of all primary intracranial tumors [2]. Meningiomas show a higher incidence in females than males with a ratio of 2:1, however higher grade meningiomas occur more frequently in males [3]. According to WHO, meningiomas have been classified into benign (Grade I), atypical (Grade II) and anaplastic (Grade III), comprising of 80%, 15%-20% and 1%-3% of all meningiomas, respectively [4]. Atypical and anaplastic meningiomas have a recurrence rate of upto 40% and 80%

respectively and require more aggressive treatment. Benign meningiomas have a 5 year recurrence rate of 5% following gross- total resection [4]. Superficially located meningiomas have been adequately treated with surgical resection and radiation therapy, however, some meningiomas are located in potentially inaccessible locations or have frequent recurrences. For these types of meningothelial tumors molecular targeted therapies are of increasing interest since the last decade. Here we review some of the most frequently documented target therapies.

NF2/mTOR

mTOR is an important mediator of Merlin's tumor suppressive activity. The growth and proliferation of NF-2 associated tumor is triggered by dysregulation of mTOR activation and it may restrict the proliferation of these neoplasms through negative feedback [3]. *In vitro* study by Gallon et al. human meningioma primary cells were targeted by mTOR inhibitor (Everolimus). The results exhibited decreased cell viability in 17 cases. However, the association of the drug with induction of Akt pathway causes anti proliferative effect of the drug to be reduced. Somatostatin receptor 2 which is frequently expressed in melanomas is targeted by Octreotide that has similar results on tumor cell viability as that of Everolimus. A combined therapy of both Everolimus and Octreotide decreased the cell viability from 24-27% to 46% on 12 randomly selected tumors, including six WHO grade II and III tumors [5].

PDGF

The platelet-derived growth factor receptors (PDGFR) α and β play a vital role in cell growth and division, making them an important target for management of meningiomas. In a phase II study conducted by The North American Brain Tumor consortium, PDGFR inhibitors (Imatinib Mesylate) were well tolerated. 19 patients were evaluated for response, out of which 9 were stable and 10 showed progression at the first scan. The overall median PFS of the patients was 2 months (range 0.7-34 months) and 6 months PFS was seen in 29.4% of

the patients. PDGFR inhibitors had the most potent response for benign meningiomas with a median PFS of 3 months (range 1.1-34 months) and 6M- PFS of 45% [6].

PI3K/AKT

PI3K/AKT pathway and MAPK pathway is atypically activated in meningiomas. The functions of these pathways are growth, differentiation and apoptosis. Activation of PI3K by KRas, causes phosphorylation Akt and activation of p70S6K through mTOR. Administration of PI3K inhibitors has shown to block PDGF stimulation which results in decrease of AKT and p70S6K phosphorylation [7]. Marvin et al, discovered high levels of phosphorylated Akt in anaplastic and atypical meningiomas but not in benign meningiomas [8]. Marianne F James et al. found that the deregulation of mTORC1 activation is responsible for the aberrant growth and proliferation of NF2-associated tumors and may reduce the growth of these lesions through negative feedback mechanisms, suggesting that rapamycin in combination with phosphoinositide 3-kinase inhibitors may be therapeutic for NF2.

EGFR-Epithelial Growth Factor Receptor

Overexpression of EGFR may promote tumor growth in meningiomas. In an ongoing phase II study of EGFR inhibitors Gefitinib and Erlotinib are used for recurrent malignant meningioma. Patients with confirmed recurrent meningiomas with no more than 2 previous chemotherapy regimens were treated with Gefitinib 500 mg/day or Erlotinib 150 mg/day until tumor progression or unacceptable toxicity. Twenty-five patients with median age 57 years (range 29-81 years) and median Karnofsky performance status (KPS) score 90 (range 60-100) were enrolled out of which, 8 patients (32%) maintained stable disease. No considerably prospective results were seen against recurrent meningioma by the use of Gefitinib and Erlotinib. The role of EGFR inhibitors alone in meningiomas is unclear. However, combination therapy of EGFR inhibitors with other targeted molecular agents may produce an effective response [9].

VEGF-Vascular Endothelial Growth Factor

Vascular endothelial growth factor (VEGF) and its receptor (VEGFR) are frequently expressed in meningiomas hence, targeting this pathway might be of significance for its treatment. Raizer et al reported VEGFR inhibitor PTK787 (Valatanib) used in Grade II and Grade III tumors. For Grade II patients the median PFS was 7.6 months and OS was 26 months, and Grade III patients, the median PFS 3.6 months and OS 23 months. The study documented stable disease in 15 patients, and 60% of the patients suffered from Valatanib induced toxicity. The study suggested targeting VEGF causes decreased tumor stability which makes this receptor beneficial in targeting meningiomas [10]. In a phase II study by Kaley et

al. a tyrosine kinase inhibitor targeting VEGFR, Sunitinib malate, was administered to 36 high-grade meningioma patients (30 atypical and 6 anaplastic). Results showed that 15 patients (42%) with recurrent or anaplastic meningioma were progression free and alive at 6 months, thus the patients meeting the primary endpoint of PFS-6 rate were 42%. Median PFS was 5.2 months (95% CI: 2.8–8.3 months), and median OS was 24.6 months (95% CI: 16.5–38.4 months). It was concluded that Sunitinib was active in recurrent/progressive atypical and anaplastic meningiomas, however significant toxicities were observed that included 1 intratumoral hemorrhage (grade 5), 3 intratumoral hemorrhages (grade 3 and 4), 2 thrombotic microangiopathies (grade 3 and 4), and 1 patient with gastrointestinal perforation (grade 3) [11].

PD-L1-Programmed Death-1Ligand

Programmed death-1ligand (PD-L1) is frequently expressed in higher grade tumors which suggest that it may play a significant biological role in the aggressive phenotype of meningiomas [12]. Treatment of meningiomas with monoclonal antibody targeting PD-L1 (Nivolumab) showed a significant decrease in size of tumor in a recent case report by Gerstein [13].

TRAIL-Tumor Necrosis Factor Related Apoptosis Inducing Ligand

When tumor necrosis factor related apoptosis inducing ligand (TRAIL) binds to a tumor cell, apoptosis inducing receptors, TRAIL-R1 and TRAIL-R2, cluster on the tumor cells and form a death inducing signaling complex. The role of TRAIL targeted therapy in meningiomas was documented by Koschny et al, in which 29.7% patients (11) showed sensitivity to the treatment whereas 32.4% (12) were intermediately resistant and 37.8% (14) were completely resistant. In the same study Bortezomib (proteasome inhibitor) markedly sensitized meningioma cells to TRAIL-induced apoptosis in 21 meningioma samples [14].

Conclusion

Our review of literature suggests that there is minimal clinically appreciable evidence of monoclonal antibodies in a treatment of meningiomas. Although TRAIL, PD-1 and motor pathway inhibitors have shown anti-tumor activity, their relevance to significant outcome in patients has not been well established. PI-3k/AKT pathway inhibitor may have some role in recurrent meningiomas. Most of the immunotherapies for meningiomas have been associated with potentially unacceptable toxicities. Hence, we can conclude in the light of above evidence that additional development is required to attain better outcomes for immunotherapies in meningiomas.

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