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Review Article

Bevacizumab: A Review of Use in High Grade Gliomas

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Abstract

Malignant gliomas are the most common type of primary malignant brain tumors in adults. They have a grave prognosis that is attributed to their high proliferative index and increased vascular proliferation. The latter is primarily mediated by the secretion of Vascular Endothelial Growth Factor (VEGF) by tumor cells, which leads to the development of an increased number of abnormal blood vessels in and around the tumor. There has been evidence of radiographic response with clinical improvement by targeting this signaling pathway using VEGF/VEGF receptor inhibitors, primarily bevacizumab (BEV), a monoclonal antibody against VEGF, which has been approved by the Food and Drug Administration (FDA) for treatment of recurrent gliomas. Though it extends progression-free survival (PFS) and decreases the reliance on steroids, BEV has not been shown to confer a survival benefit in patients with malignant glioma. We have reviewed the available literature to demonstrate the effectiveness and drawbacks of BEV therapy reinforcing the need for research into newer, better-tolerated and more effective modalities.

ABBREVIATIONS

VEGF: Vascular Endothelial Growth Factor; BEV: Bevacizumab; FDA: Food and Drug Administration; PFS: Progression-Free Survival; GBM: Glioblastoma Multiforme; RT: Radiotherapy; TMZ: Temozolomide; OS: Overall Survival; HIF: Hypoxia-Inducible Factor; MAPK: Mitogen-Activated Protein Kinase; PI3K: Phosphoinositide 3-Kinase; FGF: Fibroblast Growth Factor (FGF); PDGF: Platelet-Derived Growth Factor; MRI: Magnetic Resonance Imaging; IRI: Irinotectan (IRI); MGMT: O-6-Methylguanine-DNA Methyltransferase; PD-1: Programmed Cell Death-1; PET: Positron Emission Tomography; HGF: Hepatocyte Growth Factor; TGF: Transforming Growth Factor; Ang: AvγIopoietin; PTP1B: Protein Tyrosine Phosphatase 1B

INTRODUCTION

Gliomas are classified into low grade (grades I and II) and high grade (grades III and IV) [1]. Grade IV (glioblastoma multiforme/GBM) is the most aggressive type with the poorest prognosis and is characterized by high mitotic activity, hypoxia and necrosis, cellular polymorphism and microvascular proliferation [2]. The current standard of care for high-grade glioma is maximal safe resection followed by radiotherapy (RT) and temozolomide (TMZ) chemotherapy, followed by TMZ monotherapy, the so-called Stupp protocol [3]. This combination affords an overall survival (OS) and progression free survival (PFS) of 14.7 months and 6.9 months respectively [3].

The mechanism of microvascular proliferation and angiogenesis in gliomas appears to be driven by both hypoxia-dependent (mediated by hypoxia-inducible factor (HIF)-1α) [4] and -independent (via the Mitogen-activated protein kinases (MAPKs) and Phosphoinositide 3-kinase (PI3K) pathways) [5] mechanisms mediated by pro-angiogenic factors like VEGF, fibroblast growth factor (FGF), and platelet-derived growth factor (PDGF) [6]. VEGF appears to be the one of the most important pro-angiogenic factors whose level of expression is higher in areas of hypoxia and correlates with tumor grade [7]. The VEGF gene includes six subtypes (VEGF-A, B, C, D, E and placental growth factor PIGF), of which VEGF-A has been best characterized and is known to be associated with higher glioma grades and poorer prognosis [6,8]. New tumor vasculature, however, is both structurally and functionally abnormal [9] leading to leakage of fluid with resultant edema and gadolinium enhancement on magnetic resonance imaging (MRI). Bevacizumab (BEV) is a monoclonal antibody composed 93% of human IgG1 and 7% VEGF complementarity-determining regions, which binds the six forms of VEGF [10]. By binding VEGF, BEV directly inhibits neovascularization and thereby plays a role in the decrease in tumor size and growth. Angiogenesis is critically important in the growth of high-grade glioma, and offers many therapeutic targets for therapy. Our goal in this review is to describe the potential risks and benefits of BEV in the treatment of primary or recurrent high-grade gliomas.

Recurrent GBM

The FDA approval of BEV with irinotectan (IRI) in colorectal cancer prompted two single-arm Phase II prospective studies for their use in patients with malignant gliomas who had recurred after receiving standard therapy with RT and Temozolomide. The BRAIN trial was designed with two cohorts of 35 patients

with known GBM and prior treatment with standard therapy, the initial cohort of 23 patients receiving both BEV and IRI every 14 days. Once this was deemed safe, a second cohort of 12 patients was treated with IRI for 4 doses in 6 weeks and BEV every 3 weeks [11]. The results seemed promising with a 6 month PFS of 46% (95%CI 32-66%) and median PFS of 24 weeks (95%CI 18-36 weeks) with no statistical difference between the cohorts. The 6-month OS was 77% (95%CI 64-92%) and median OS of 42 weeks (95%CI 35-60 weeks). Twenty patients (57%) had at least partial response and six of them showed no residual high-grade tumor after 1 year. However, there were quite a few complications including thromboembolism (4), grade 2-3 proteinuria (2), sepsis (1) and intracranial hemorrhage (1). Thirteen patients went on to have progression of the disease and four patients dropped out voluntarily citing fatigue as the major side effect.

A second study involved a cohort of 32 patients with recurrent glioma (23 Grade IV and 9 Grade III) treated with BEV and IRI [12]. This regimen demonstrated 63% radiographic response (20 patients; 14 Grade IV and 6 Grade III) and a PFS period of 23 weeks (95%CI 15-30 weeks). The 6-month PFS was 38% (95%CI 24-59%) for the whole group with a 6-month OS of 72% (95%CI 58-89%). These results were better than other anti-angiogenic therapies like thalidomide (which weakly inhibits VEGF and FGF) which demonstrated a 6% response and median PFS of 10 weeks [13]. The complications, however, were significant with thromboembolism (3), ischemic stroke (1), and proteinuria (2); including two deaths in the patients with stroke and pulmonary embolus. Twelve patients had progression of disease and two dropped out due to fatigue.

With improvement in PFS and an acceptable side effect profile at a moderate efficacy, BEV was FDA approved for use as a combination with IRI or alone in recurrent high-grade glioma 2009. Subsequently, the BELOB trial investigated the use of BEV with or without Lomustine in patients with a first recurrence of GBM. Using Response Assessment in Neuro-Oncology Criteria (RANO), an improvement in 9 month OS (38% BEV alone, 43% lomustine alone, vs. 59% for combination therapy) was seen [14]. The EORTC-2601 trial, on the other hand, compared lomustine monotherapy to BEV plus lomustine combination therapy and though PFS was improved (4.2 months vs. 1.5 months), no significant difference in OS (9.1 months vs. 8.6 months) was noted [15].

Newly Diagnosed GBM

There was a hope that BEV could be an important drug in the treatment of gliomas and this lead to trials investigating BEV as first line therapy with TMZ. In a single-arm, multicenter Phase II trial of combined RT, TMZ and BEV in 70 patients with newly diagnosed glioblastoma, patients received concurrent administration of daily TMZ and biweekly BEV with RT followed by TMZ for 5 days every 4 weeks and continued biweekly BEV [16]. The control group received RT/TMZ followed by TMZ for 5 days every 4 weeks and BEV at recurrence. The study group showed improved PFS (13.6 months vs. 7.6 months) without improved OS (19.6 months vs. 21.1 months). The groups showed expected post RT adverse effects including neutropenia, fatigue, venous thrombosis, hypertension and proteinuria. However, the group receiving BEV showed increased incidence of cerebrovascular ischemia, wound infections, GI perforations, GI bleeds, and CNS hemorrhage. The higher risk of ischemia was observed with a pattern suggestive of involvement of small vessels, including lenticulostriate perforating arteries and potentiation of radiation-induced occlusive arteriopathy.

The RTOG 0825 study was a large randomized, placebo-controlled, double-blinded trial of 637 patients in which patients (following radiotherapy and daily TMZ) received BEV or placebo from week 4 of RT continued for 12 weeks [17]. There was no significant overall survival benefit of adding BEV (15.7 months vs. 16.1 months respectively, hazard ratio (HR) 1.13) though PFS was slightly improved (10.7 months vs. 7.3 months, HR 0.79). The treatment effects after adjustment for O-6-methylguanine-DNA methyltransferase (MGMT) resistance status were unchanged and statistically insignificant. Serious adverse effects were more prevalent in the BEV group and included hypertension (4.2 vs. 0.9%), thromboembolism (7.7 vs. 4.7%), wound dehiscence (1.5 vs. 0.9%), visceral perforation (1.2 vs. 0.4%), serious hemorrhage (1.5 vs. 0.9%) and serious neutropenia (10.0 vs. 5.1%). In addition, patients who had progression in the BEV group reported poorer quality of life and worse neuro-cognitive decline.

The AVAglio study likewise compared BEV to placebo in combination with standard radiation and temozolomide chemotherapy. Again, PFS was improved (10.6 months vs. 6.2 months) but no improvement in overall survival (16.8 months vs. 16.7 months). BEV did, however, appear to decrease dependence on steroids and prolong cognitive function in this study [18-26].

Immunotherapy

Recently tumor immunity is also thought to play a significant role with studies suggesting that anti-angiogenic factors increase delivery of tumor effector cells into the tumor [27]. There are suggestions that combination immunotherapy can play a key role in resistance to anti-angiogenic therapy as well. This has opened new avenues to the research in the use of immunomodulators in new diagnosis of GBM. Immune checkpoint inhibitors have been FDA approved for use in melanoma and lung cancer and this has led to a trial of anti-PD-L1 antibody with standard radiotherapy in newly diagnosed GBM (NCT02336165) and CheckMate143 (NCT02017717) evaluating the safety and efficacy of Anti-PD-1 (Programmed Cell Death-1) antibody vs. BEV in recurrent gliomas. Dendritic cell vaccines and peptide vaccines are also under investigation. In a phase II trial testing standard therapy with dendritic cell vaccine (AV0113) [28], there is report that a subgroup receiving the vaccine as a second line to BEV showed improved OS compared to the control group (535 ± 155 days vs 406 ± 224 days), while there was no difference reported in patients receiving only standard therapy without BEV. Similar reports from another phase II trial with use of peptide vaccine (rindopepimut against EGFRvIII) where there was prolonged median OS (12 mo. vs. 8.8 mo., HR 0.47) and improved 6-month PFS (26% vs. 11%) [29]. Additional trials are underway looking at heat shock protein vaccines, Wilms tumor protein vaccines and engineered T cells use [30]. Oncolytic viral therapy is a novel approach and offers quite some advantages with lack of cross-reactivity with chemo, synergism, immune response [31], and several oncolytic viruses are currently being tested.

Pseudoprogression

An inflammatory reaction known as "pseudoprogression" can occur weeks to months following chemo-radiation in which MRI shows increased enhancement and edema that mimics true progression [32]. This may progress to radiation-induced necrosis which also mimics recurrent tumor on imaging. MGMT promoter methylation increases the probability of pseudoprogression [33] but there is no reliable biomarker study to differentiate tumor progression from pseudoprogression. Distinguishing pseudoprogression from true tumor progression remains a challenge in neuro-oncology and, though magnetic resonance spectroscopy, magnetic resonance perfusion, and Positron Emission Tomography (PET) scans have all been employed to diagnose pseudoprogression, none has a sensitivity of greater than 70-80% [34]. The use of BEV may also act as a confounding factor in such a diagnosis due its pseudoresponse. Differentiating between tumor progression and pseudoprogression has important clinical implications as each is managed very differently: pseudoprogression might require temporary cessation of chemo-radiation while tumor progresion requires continued therapy.

There is no consensus for treatment of pseudoprogression, though corticosteroids, anticoagulation, and hyperbaric oxygen have all been advocated. Surgery remains an option in symptomatic patients with radiation necrosis and surgery not only provides a tissue diagnosis but also reduces mass effect and edema. BEV has been shown to reduce contrast enhancement and improve T2/FLAIR sequences on MRI in patients with demonstrated radiation necrosis and reduce reliance on corticosteroids [35]. Its use has been advocated in symptomatic patients based on the results of a randomized double blind placebo controlled trial [36] and patients with recurrent radiation necrosis may respond to repeated BEV therapy [37].

Bevacizumab resistance

Though it affords improved PFS, BEV does not provide a survival benefit for patients with malignant glioma. There are several possible reasons for resistance to BEV. Besides VEGF, other molecules are known to be involved in neovascularization, including FGF, hepatocyte growth factor (HGF), PDGF, transforming growth factor (TGF)-α, ενδογλιν, ανδ Ανγιοποιετιν (Ang)−2 [38]. Effεχτιωελψ blocking angiogenesis would therefore require inhibiting multiple pathways and there are studies underway looking at blocking VEGF with BEV along with Ang-2 [39], integrins [40], and endoglin [41]. In addition to redundant angiogenic pathways, tumors employ other mechanisms to satisfy their metabolic needs including the poorly understood mechanism of co-option of normal blood vessels, and the differentiation of tumor stem cells into an endothelial phenotype.

A perhaps more clinically significant consequence of VEGF inhibition is the transformation of glioma cells from a proliferative to a migratory phenotype, a process seen by BEV treatment in other cancers, as well [42]. By inducing a hypoxic environment by inhibiting angiogenesis, BEV therapy leads to upregulation of hypoxia-inducible factors [43] and a transition to a more invasive, mesenchymal phenotype. Glioma cell lines with resistance to BEV show increased expression of mesenchymal markers and increased invasion *in vitro* [44]. Furthermore, tumors isolated from patients resistant to BEV likewise show upregulation of hypoxia and mesenchymal markers [45]. Microarray analysis of BEV-resistant GBM showed increased expression of the receptor tyrosine kinase, c-Met, which activates various intracellular pathways that promote angiogenesis, cell growth and invasion via HGF-dependent signaling [46]. VEGFR-2 forms a heterodimeric complex with c-Met. Binding of VEGF, recruits protein tyrosine phosphatase 1B (PTP1B), which dephosphorylates and inactivates c-Met, thus suppressing HGF-mediated growth and invasion. C-Met is also expressed on endothelial cells and HGF signaling may represent a non-VEGF dependent pro-angiogenic signaling cascade [47].

Future directions

BEV has improved PFS in patients with malignant glioma when used in conjunction with surgery, radiation- and temozolomide chemotherapy. Angiogenesis is a complex process, offering many potential targets for therapy, and several trials are currently underway to maximize antiangiogenic therapy by combining BEV with other agents. Many small molecule tyrosine kinase inhibitors have been investigated without much success and a study is currently underway using an agent (buparlisib) which targets the PI3K pathway known to be involved in both angiogenesis and invasion (NCT01339052). Trebananib, an ihnibitor of the angiopoietin/Tie-2 signaling pathway is being investigated in combination with BEV (NCT01609790), and an antibody targeting endoglin, an accessory receptor for transforming growth factor (TGF)-β involved in tumor-mediated angiogenesis, has been combined with BEV as well (NCT01648348). In an attempt to induce apoptosis in endothelial cells, a Fas-expressing transgenic adenovirus, VB-111, has been developed for use with BEV in patients with recurrent GBM (NCT02511405) with encouraging overall survival benefit. Because c-Met appears to be a key player in mediating BEV resistance, it makes an especially attractive target for therapy in patients. INC280 is a small molecule Met inhibitor that has been shown to reduce migration and adhesion in ovarian cancer cell models and is currently under investigation in combination with BEV for recurrent glioma (NCT02386826). Onartuzumab, a monoclonal antibody directed against cMet, was combined with BEV (NCT01632228), though it showed no improvement in PFS or overall survival [48]. Finally, an upcoming trial will determine the benefit of combining BEV with Optune Tumor Treating Fields in BEV-refractory recurrent GBM (NCT02743078).

CONCLUSIONS

High-grade gliomas are the most aggressive brain malignancies with a poor prognosis and near universal fatality despite treatment with surgery, radiation- and chemotherapy. The standard of treatment with surgery followed by combination chemo-radiotherapy seems to have a fair overall survival and progression free survival. Targeting angiogenesis with agents like BEV makes good clinical sense and affords a definite radiographic response, but the degree to which this corresponds to clinical improvement is open to debate. In addition to its implication in vasculopathy and possible neurotoxicity, there is also growing concern that BEV could play a role in transition of

the proliferative to migratory phenotype in glioma cells thereby promoting tumor infiltration. BEV has not shown significant improvement of overall survival when used as a first line agent and there is a need for better understanding of the resistance to VEGF/VEGF-R antagonists. Targeting several pathways or combination chemotherapy with BEV and other agents such as immunomodulators may help overcome resistance and to maximize benefit. Additional studies are therefore warranted for other newer agents to be used on a large scale.

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