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Anti-angiogenic therapy in glioblastoma multiforme

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SUMMARY

Glioblastoma multiforme is the most common brain malignan-cy in adults. It is also highly aggressive and characterized by very poor prognosis. Surgical resection of the tumor remains the basic treatment that significantly improves survival. Moreover, adjuvant chemoradiotherapy is the standard-of-care. Glioblastoma multiforme has a very complex genetic profile; various genetic abnormalities have been discovered in cells of this type of tumor. Despite growing interest in tar-geted therapies in oncology, no breakthrough offering suc-cessful treatment of glioblastoma multiforme has occurred. Owing to the tumor's rich vasculature, antiangiogentic the-rapies seem promising. An association between carcinogene-sis and tumor vasculature was observed in 1970s. At present, the only FDA-approved drug targeting antiogenesis-stimula-ting factor is bevacizumab. In recent years, more and more new antiangiogenic therapies have been investigated in both monotherapy and combined treatment of glioblastoma mul-tiforme with different success rates. This article presents an overview of the most explored therapies.

Key words: angiogenesis, glioblastoma multiforme, targeted therapies

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INTRODUCTION

Primary brain tumors constitute a highly diver-sified group of neoplasms. In adults, the most common are tumors originating from the astro-glia [1]. Glioblastoma multiforme is the most common brain malignancy worldwide. Median survival is 12–15 months from diagnosis in patients receiving standard treatment, which makes it one of the most malignant cancers. Only 3–5% of patients survive longer than 3 years [2]. The pathogenesis of glioblastoma is highly complex as mutations contributing to its occurrence result in alterations in not only one, but several cell signaling pathways respon-sible for cell proliferation, differentiation and apoptosis [2]. Glioblastoma multiforme (GBM) may be primary (de novo) or secondary, pro-gressing from lower grade astrocytomas. De-pending on the manner of their occurrence, these tumors have different genetic and epige-netic profiles that affect prognosis. Secondary GBM is more prevalent in younger patients with the mean age of diagnosis being 40 years of age. Moreover, its growth progresses more slowly and prognosis is better [3,4]. These tumors are characterized by more frequent occurrence of suppressor gene *TP53* (tumor protein p53) mutation and, above all, gene *IDH1* (isocitrate dehydrogenase (NADP(+)) 1) mutation, which results in greater Hif-1-alpha expression contributing to tumor progression, for instance via angiogenesis activation. *IDH1* mutations are reported for over 80% of secon-dary tumors and less than 5% of primary tu-mors [3,5]. In about 90% of cases, glioblasto-ma multiforme is of *de novo* nature and is characterized by faster clinical manifestation. It is mainly detected in older individuals with the mean age of diagnosis being 55 years. The most common genetic disorders found in these tu-mors include: loss of chromosome 10q hetero-zygosity, *EGFR* (epidermal growth factor recep-tor) gene amplification, suppressor *p16* deletion and mutation in the suppressor *PTEN* gene (phosphatase and tensin homolog deleted on chromosome ten) [4,6]. A more recent classifi-

cation of glioblastoma multiforme is based on a study on genetic signatures and distinguishes four subtypes: proneural, neural, classical and mesenchymal. They differ in gene mutations and thus the response to treatment [7].

Infiltrating and diffuse growth is an impor-tant feature of GBM as it prevents radical tu-mor resection and is conductive to its rapid regrowth [8]. GBM treatment requires an inter-disciplinary approach. Radical tumor resection with adjuvant radiotherapy combined with chemotherapy using temozolomide is aimed at as standard management [9,10]. Methylguani-ne methyltransferase (*MGMT*, O-6-methylgu-anine-DNA methyltransferase) promoter methy-lation is a positive prognostic and predictive factor. It is more common in secondary than in primary tumors (73% vs 43%) and may be associated, for instance, with concurrent *IDH1* mutation [11]. GBM cells that have methylated *MGTM* promoter are characterized by better response to radiotherapy and chemotherapy with temozolomide [12,13]. Tumor vascular tu-re increases with tumor grade. GBM is charac-terized by the richest vascular network of all brain tumors [14]. This rich vasculature is lin-ked with high expression of proangiogenic factors. High grade tumors are frequently ac-companied by overexpression of vascular endo-thelial growth factor (VEGF), transforming growth factor beta (TGF-ß), cathepsin B and epidermal growth factor receptor (EGFR) inc-luding its activating mutations (EGFRvIII) [15]. In GBM, newly emerging blood vessels take the form of characteristic structures resembling renal glomeruli [16]. These vessels have an irregular course, abnormal interconnections and blind branches, thus being incapable of delive-ring sufficient oxygen to glioblastoma cells. Hypoxia, on the other hand, creates a „vicious circle" in the form of abnormal angiogenesis

[7]. Glioblastoma cells initially settle healthy host blood vessels which are used for GBM growth. Subsequently, they trigger the forma-tion of their own blood vessels [14]. There are reports stating that glioblastoma stem cells can imitate endothelial cells or pericytes [17,18,19]. These neoplastic pericytes are found in the brain, even beyond the tumorous lesion [19]. Tumor growth and development was for the first time correlated with the neoangiogenesis in 1971 by an American scientist, Jugah Folk-man [20]. Therapy targeted at proangiogenic factors in the treatment of glioblastoma helps normalize or reduce the abnormal vascular network and decrease tumor edema [21].

VEGF

Vascular endothelial growth factor (VEGF) is highly proangiogenic and plays a crucial role in the regulation of new vessel formation [22]. Glioblastoma cells exhibit significant overe-xpression of this factor compared with healthy tissues, which leads to irregular tumor vascula-ture. The main VEGF-stimulating factor is hypo-xia. Chronic oxygen deficiency induces the pro-duction of hypoxia-inducible factor 1 (HIF-1) which is a transcription factor that promotes VEGF production and release [2,23]. The VEGF family proteins are associated with specific recep-tors, such as VEGFR-1, VEGFR-2, VEGFR-3, neuropilin-1 and neuropilin-2. VEGF activation promotes endothelial cells in new vessels to activate the angiogenesis pathway. This induces proliferation, growth and migration of endothe-lial cells and increases vascular permeability [22].

BEVACIZUMAB

Bevacizumab is a recombinant human monoc-lonal antibody that neutralizes VEGF-A activi-ty and shows antiangiogenic action [24]. It has been approved by the FDA in 2009 as second-line therapy for recurrent glioblastoma multi-forme based on two phase II clinical trials [25,26]. Patients with GBM recurrence after first-line therapy (surgery with adjuvant chemo-radiotherapy with temozolomide) received be-vacizumab (10 mg/m^2) every two weeks. After tumor progression, the antiangiogenic therapy was combined with chemotherapy using irino-tecan. The treatment response rate and 6-month progression-free survival (PFS) improved com-pared with a historical control group [25,26]. According to the MacDonald criteria, the radio-logical response to bevacizumab monotherapy reached 28–35%. When bevacizumab was ad-ded to treatment after tumor progression, the MRI response based on the MacDonald crite-ria was not noted [25,26]. Other studies con-ducted to assess bevacizumab monotherapy in glioblastoma multiforme compared to histori-cal controls, for example a prospective phase II trial and a retrospective analysis, confirmed its activity; the response rates were 25% and 42%, respectively, and six-month progression-free su-rvival (PFS-6) reached 32% and 42%, respec-tively [27,28]. The rationale behind the use of the combination of chemotherapy with bevaci-zumab is the improvement of tumor vasculatu-re by regression of the pathological vascular

network. This could increase cytostatic penetration and cause a synergistic effect of bevacizu-mab with standard chemotherapy [29]. It has also been attempted to implement bevacizumab in first-line treatment along with chemoradio-therapy with temozolomide. However, overall survival (OS) did not improve, and the treat-ment induced more adverse effects, such as thromboembolic events, hypertension problems, bleeding and wound healing complications [30,31]. In both studies, PFS was longer for the bevacizumab group compared to the placebo group, for instance 10.6 months vs 6.2 months [30,31]. In a phase II randomized multicenter trial called GLARIUS, conducted in patients with newly diagnosed glioblastoma multiforme with unmethylated *MGMT*, PFS was longer for bevacizumab + irinotecan combination compa-red with temozolomide + radiotherapy. Me-dian PFS for chemoradiotherapy with temozo-lomide reached 5.9 months, while for bevaci-zumab + irinotecan – 9.7 months. OS showed no statistically significant differences ($p>0.05$)
[32]. It has also been reported that a VEGF level reduction might sensitize the vascular endothelium to radiotherapy [33]. Anti-VEGF antibo-dies may reduce edema around the tumor by eliminating cancer cell hypoxia, thereby increasing radiosensitivity of tumor cells [34]. Moreover, a combination of hypofractionated stereotactic radiotherapy with bevacizumab in the treatment of recurrent glioblastoma multiforme resulted in a complete response rate of 50%, PFS-6 of 65% and mean overall survival (mOS) of 12.5 months [35]. However, there are also studies that show no significant increase in OS of patients with recurrent glioblastoma multi-forme after bevacizumab implementation com-pared to chemotherapy with lomustine [36,37]. A phase II trial, BELOB, indicated improved OS for bevacizumab + lomustine compared with bevacizumab monotherapy in the treatment of recurrent glioblastoma multiforme. Nine-month overall survival reached 38% for patients tre-ated with bevacizumab in monotherapy, 43% for patients receiving lomustine monotherapy, and 88% for the bevacizumab + lomustine combination [38]. It has been shown that bevacizumab may decrease the need for corticosteroids and improve the quality of life in pa-tients with the recurrent disease [39]. It has also been attempted to combine bevacizumab with a different platelet-derived growth factor (PDGF), tandutinib, in a phase II trial enrolling patients with recurrent glioblastoma. However, the efficacy of this therapy was comparable to that of bevacizumab monotherapy, and the combination of the two angiogenesis inhibitors was linked with greater toxicity [40]. Bevacizumab failure in glioblastoma treatment is of multifaceted background. Animal tests have revealed that, over time, glioblastoma cells may travel along normal vascular network, thereby contributing to the occurrence of distant satel-lite tumors [41,42]. VEGF stimulates mainly normal angiogenesis, while the neoplastic one is promoted by a range of other factors, such as platelet-derived growth factor (PDGF), tu-mor necrosis factor alpha (TNF-alpha), fibro-blast growth factor (FGF), hepatocyte growth factor (HGF), interleukin-8 (IL-8), interleukin-6 (IL-6), and transforming growth factor ß (TGF-ß). That is why, new targets for antian-giogenic therapy are being searched [7]. PDGF is not only involved in abnormal angiogenesis, but its receptor expression is found in gliobla-stoma cells and it contributes to tumor growth by an autocrine loop [43]. PDGF helps stabi-lize a newly emerged vessel and promotes migration of tunica adventitia cells and vascu-lar smooth muscle cells [44].

Sunitinib is an oral small-molecule kinase inhibitor targeted at VEGFR, platelet-derived growth factor receptor (PDGFR) and tyrosine kinase c-Kit, FMS-like tyrosine kinase-3 (FLT3), colony stimulating factor 1 receptor (CSF-1R) and neurotrophic factor receptor for glioblasto-ma (RET) [45]. In a preclinical trial, sunitinib, owing to its antiangiogenic properties, exhibi-ted anti-proliferative effects and prolonged survival in mice with orthotopic glioblastoma multiforme (GBM) [46]. However, in one of the phase II trials, sunitinib was not found effecti-ve (dosage: 37.5 mg/m^2 daily until progression or unacceptable toxicity) in second-line treat-ment of 21 patients with grade III and IV glio-blastoma. Sunitinib is not as potent as bevaci-zumab in selective inhibition of VEGF/VEGFR signaling, which might explain the predominan-ce of the latter drug in GBM treatment [47]. In another study conducted in patients with recur-rent glioblastoma multiforme or gliosarcoma after first-line treatment and bevacizumab the-rapy, sunitinib failed to significantly increase PFS. This does not confirm the assumption that angiogenesis inhibitors suppressing several si-gnaling pathways that contribute to tumor cell proliferation might be more effective [45]. Moreover, a study enrolling patients with non-resectable glioblastoma multiforme treated with sunitinib before and during radiotherapy sho-wed no PFS or OS benefits, either [48].

Pazopanib is yet another tyrosine kinase inhibitor with antiangiogenic properties. It is targeted against VEGFR, PDGFR-α and ß, FGFR (fibroblast growth factor receptor) and stem cell factor receptor (c-KIT). In a phase II trial, pazopanib administered to patients with recurrent glioblastoma multiforme and gliosar-coma had no influence on PFS, but partial radiological response by the MacDonald crite-ria was noted [49]. Another phase II trial eva-luating combined treatment using pazopanib and lapatinib in patients with recurrent gliobla-stoma and confirmed tumor PTEN/EGFRvIII mutations showed no anti-tumor efficacy of this combination in the form of no PFS benefit [50].

Imatinib is a tyrosine kinase inhibitor that, apart from suppressing tyrosine kinase Bcr-Abl, which is used in the treatment of chronic my-eloid leukemia, also exhibits potent inhibitory effects towards PDGFR. There are phase II trials enrolling patients with recurrent glioblastoma multiforme treated with standard chemoradio-tehrapy where imatinib mesylate and hydroxy-urea demonstrated some minimal effects against tumor cells. One of the study's endpoints was PFS-6 achieved in five of 31 GBM patients (16%). In some patients treated with imatinib, contrast enhancement in MRI was reduced de-spite deteriorated neurological condition. PDGFR is expressed on both endothelial cells and pericytes and therefore imatinib may lead to the normalization of abnormal vascular perme-ability with no genuine anti-tumor effect. The drug was well-tolerated by patients [51,52].

Cediranib is a potent inhibitor of all three endothelial growth factor receptors (VGEFR-1,-2,-3). One of the phase II trials reports quite encouraging treatment outcomes. Recurrent GBM patients treated with cediranib achieved partial radiological response in brain MRI with PFS-6 at the level of 25.8% [53]. Another stu-dy evaluating cediranib demonstrated a reduc-tion of the vasogenic edema around the tumor and, as in the studies on bevacizumab, this enabled corticosteroid dose reduction in GBM patients [54]. However, in a phase III trials, treatment outcomes were not as encouraging any more. There was no benefit to PFS after monotherapy or combined treatment with lo-mustine in patients with recurrent glioblastoma multiforme [55].

Cilengitide is a cyclic peptide targeted aga-inst integrins α, which are present in blood vessels and GBM cells, and take part in angio-genesis. Cilengitide blocks neoangiogenesis as well as suppresses tumor cell invasion and pro-liferation [56]. In a phase II trial (CORE), the activity of cilengitide in patients with newly diagnosed glioblastoma multiforme with unme-thylated *MGMT* promoter showed activity in the form of slight overall survival and PFS improvement [57]. In a phase I/II trial, the addition of cilengitide to standard chemoradio-therapy with temozolomide in patients with glioblastoma multiforme with *MGMT* promo-ter methylation also yielded encouraging out-comes in the form of improved PFS and OS
[58]. Unfortunately, in the phase III CENTRIC trial, OS and PFS did not improve upon the administration of temozolomide combined with cilengitide to patients with newly diagnosed glioblastoma multiforme with *MGMT* promo-ter methylation undergoing adjuvant radiothe-rapy. Integrins remain an interesting anti-can-cer therapy target and they do require more investigation [59]. In antiangiogentic therapy, it has been attempted to use antisense oligonuc-leotides in order to inhibit TGF-ß2 expression. A phase II trial in which TGF-ß2 suppression was achieved by administering trabedersen (AP12009) to patients with grade III/IV gliobla-stoma showed no statistically significant survi-val benefit in AP12009 patients as compared with the standard chemotherapy group. This issue surely requires more studies [60,61]. Another interesting goal of antiangiogenic the-rapy is suppression of HIF-1-dependent path-ways, such as m-TOR inhibitors. One of them is temsirolimus which, when administered in monotherapy to patients with recurrent gliobla-stoma multiforme in phase II trials, did not cause PFS or OS improvement [62,63]. The combination of temsirolimus with standard radiotherapy was evaluated in a phase I trial. However, the treatment occurred too toxic due to higher risk of bacterial infections [64]. Moreover, another phase II trial evaluating temsirolimus combined with radiotherapy in patients with glioblastoma multiforme with *MGMT* promoter methylation did not reveal any PFS or OS benefit as compared with stan-dard chemoradiotherapy [65].

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