INHIBITORS OF ANGIOGENESIS IN BRAIN TUMORS – REVIEW

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Intoduction

Malignant glial and metastatic tumors are highly vascularized tumors and like all solid tumors, they require angiogenesis for their growth. [1] For glioblastoma (GBM) this microvascularization is very likely and those vessels have abnormal structure, shape and organization.[2] The permeability of those blood vessels is high and very variable in space and time.[3, 4] This abnormal permeability and aberrant morphologic vascularnetworkare associated with abnormal - blood flow, oxygen and nutrients delivery, and also decreased delivery of applied systemic medications.[5] The microenviorment of the tumor has zones of hypoxia, interstitial hypertension and necrosis.[6, 7, 8, 9, 10] According to *Hobbs et al.*, when the tumor'diameter reaches 1-2mm,the integrity of blood brain barrier (BBB) is structurally and functionally impaired. The abnormal permeability and efflux can be visualized on MRI/CT scan imaging as enchancement of the contrast.

Materials and methods

We gathered published materials related to mechanisms of action of VEGF inhibitors and especially in brain tumors, including data from the past decade. Also, according to the literature we defined the most appicable agents in VEGF targeted therapy. Their advantages and disadvantages, probable benefit, also according to the gathered literature. (Fig. 1)

Mechanisms of action of VEGF inhibitors

Glioblastomas use several mechanisms of forming new blood vessels. (**Fig.1**) Initially the tumor growth could appear as a "co-option" of already existed, natural blood vessels. Malignant cells - they can migrate by using already existed healthy blood vessels and can structurally destabilize them. This leads to regression of those vessels and reduction of blood flow and local hypoxia. [11] As a result – the local hypoxia stimulates the secretion of proangiogenic cytokines. [11, 12] The new vascular network can be formed by angiogenesis, where the progenitor cells derived from stem cells, penetrate in the circulation and areincorporated directly. [14]

Multiple complex and alternative molecular pathways are involved in growth and development of the new vascular web. Since there are a lot of pathways and details related to brain tumor angiogenesis, we will focus only on VEGF signaling transduction pathway. GBMs produce several pro-angiogenic factors, including VEGF [15], PDGF-b[16],HGF/SF[17,18] and bFGF [19].VEGF-A (also known as VEGF) is one of the key regulators of the tumor angiogenesis – the signaling transduction pathway of which, starts with binding of VEGF to VEGFR-2,that is mostly a membrane receptor mainly on the surface of the endothelial cells.[20, 21] Theexpression of VEGF can be increased by several factors. The hypoxic environment, increases the expression and stabilization of heterodimer transcriptional factor HIF-1b – a key

mediator synthesized in response to hypoxia, which leads to increased transcription of many genes involved in survival of the cell and the angiogenesis itself, including VEGF.[22] High levels of HIF-1b and VEGF are associated with higher malignancy grade.[15, 23] The expression of VEGF is also increased by nitric oxide (NO), acidosis, other growth factors, loss of tumor surpessor genes (e.g. **p53**) and activation of oncogenes (e.g.**v-src**).[20, 24, 25]

Binding of VEGF to VEGFR-2 leads to dimerization of the receptor which is associated with tyrosine kinase(RTK), trans-autophosphorylation of the receptor and activation of several intracellular enzymes (protein-kinases) and the result of that cascade is endothelial proliferation, migration and survival. These pathways involve ***mitogen-activated protein kinase*** (**MAPK**) and ***phosphatidyl-inositol-3'-kinase*** (**PI3K**)-Akt.[20, 26] VEGF also increases the expression of ***Delta-like ligand 4*** (**Dll4**).The (Notch) Dll signaling pathway is an important stimulator of angiogenesis and there are a lot of studies that are still running, because it can be used as a potential therapeutic target.[20] The inhibition of Dll4 leads to unproductive angiogenesis which leads to decreased perfusion, increased hypoxia and decreased tumor growth.[27, 28]

Furthermore VEGF interacts with ***angiopoetin signaling pathway***.***Angiopoethin-1*** (**ang-1**) and ***Angiopoetin-2*** (**ang-2**), a couple - agonist/antagonist with significant homologous sequence, are the main ligands, which connect and mediate the signalization through **Tie-2** – tyrosine kinase receptor expressed over the endothelial cells.[29 In the presence of VEGF, the binding of ang-2 to Tie-2, stimulates angiogenesis.[30] Future investigations related to detailed studing of these pathways may be helpful for developing new therapeutic agents.

Inhibitor mechanisms of VEGF in brain tumors.

Anti-VEGF mechanisms are not fully understood and there are several hypotheses. Classically it is considered, that VEGF inhibitors prevent developing of new vessels, which will lead to low levels of oxygen and nutrients, needed for the tumor's growth. [31] Second potential mechanism of action VEGF inhibitors, is tha there is vascular's wall normalization, according to which leads to reduction of undeveloped vessels and stabilization by perivascular cells and basal membrane. [32, 33] Thus will lead to increased delivery of concurrent chemotherapeutics and increased response to radio therapy. [32, 33]

VEGF inhibitors intrerrupt the interaction between the endothelial cells and "stem-like cells" of GBM, as well as perivascular-stem cell niche distortion, which may contributes to the death of these stem cells. [35, 36] Many anti-angiogenic agents, based on these mechanisms are being in a process of investigation for the treatment of brain tumors. (Fig. 2)

VEGF Antibodies

Bevacizumab

Bevacizumab is recombinant antibody, which neutralizes all isoforms of human VEGF.33 years after the first conception of angiogenesis of Dr. J. Folkman, Bevacizumab becomes the first developed inhibitor of angiogenesis, which is approved by FDA. [20] Some investigations show that bevacizumab may have activity against recurrent malignant gliomas. In series of patients with recurrent malignant gliomas, who are treated in a combination with

bevacizumab and conventional chemo- and radiotherapy there is 27-66% response to that therapy. [37, 38, 39, 40]. At this moment bevacizumab is approved as a drug for the treatment of recurrent glioblastomas. Many investigations are being taken to evaluate the efficacy of bevacizumab in combination with other drugs in patients with recurrent and also newly diagnosed with GBMs. [41]

VEGF 'decoys'

Aflibercept is fussive protein, composed of extracellular domeins of the VEGF-receptors 1 and 2, connected with the Fc-part of IgG1, and produced in K1 cells of Chinese hamster's ovary (CHO) through recombinant DNA technology, which mostly is studied in pre-clinical trials. Aflibercept acts as a receptor-decoy, which binds VEGF-A and PIGF, and thereby inhibits binding and activation of VEGF-receptors. [42]

Tyrosine-kinase inhibitors

Cediranib

Cediranib (Recentin) is a once-daily, orally available, highly potent and selective VEGF signalling inhibitor that inhibits all three VEGF receptors, and additionally acts against c-Kit and PDGF receptors. [43] The preclinical profile of Cediranib indicates that it has the potential to be the 'best in class' VEGF signalling inhibitor. Phase I data indicate that Cediranib is generally well tolerated, with the most common dose related adverse events being diarrhoea, hoarseness, headache and hypertension.

Cediranib inhibits vacular endothelial growth factor (VEGF) receptor tyrosine kinase (RTK). By forming a blockade at the VEGF receptors, Cediranib limits the growth of new blood vessels, which are essential to supporting tumor growth. Thus, lacking sufficient blood supply, tumor cells become starved for nutrients, slowing or halting growth and potentially improving the efficacy of other treatments. Preclinical evidence indicated that the drug had a high affinity at these sites, and was well tolerated and efficacious in animal studies. Future studies of the effect of the agent in combination with other agents, in treatment of recurrent glioblastomas, are yet to be done. [43]

Valatinib

Valatinib (PTK787) is an oral pan-VEGF,c-kit and PDGFR tyrosine kinase inhibitor, which is studied for treatment of newly diagnosed and recurrent malignant gliomas.[44] At this moment this agent is rejected, despite the results that are obtained from these studies.

Other Tyrosine Kinase Inhibitors

Sorafenib

Sofarenib (Nexavar) is a multitarget kinase inhibitor with action against a lot of kinase enzymes, including VEGFR, PDGFR, c-Kit, Ret and Raf. [45] Sorafenib has antiproliferative effect (in vitro) against cell lines of malignant gliomas. [46] At this stage of the studies related to this medication, there are good results in patients with recurrent malignant gliomas.

Investigations in combination with other VEGF inhibitors including **sunitinib** and **vandetanib** are still processing. [47]

Immunomodulatory Agents

Thalidomide & Lenalidomide

There are a lot of investigations for potential anti-angiogenic therapies in different cancers including primary and secondary. Some of this therapies include direct inhibitors tyrosine-kinases (eg. sorafenib), direct inhibitors of tyrosine kinase receptors (eg. VEGFR, EGFR, PDGFR) [48, 49] and other therapies that include immunomodulatory agents such as Thalidomide and Lenalidomide. Mechanisms of immunomodulatory agents: The Inhibition of TNF (tumor necrosis factor) [50] is thought to be the immunomodulatory effect of thalidomide, but not its anti-angiogenic activity's mechanism. The inhibition of tumors angiogenesis is unclear, but is possibly due to the inhibition of VEGF and bFGF. [51, 52]

Thalidomide

There results of monotherapy with Thalidomide in recurrent glioblastoma patients are very poor – only 5-6% have responded to radiotherapy. [51, 53, 54] There are different results in combination therapies: For some of the combination therapies there was no evidence for better response, for example the combination of thalidomide and temozolomide (Temodar) had a small effect in recurrent primary glial tumors and the radiation therapy response was also very poor. [55, 56, 57] For other combinations there was evidence for better response. The combination of thalidomide with carmustine was associated with better radiographic response -24% in phase II trial .[58]

Lenalidomide (Revlimid,Celgene)

A thalidomide analog with greater anti-angiogenic activity. The monotherapy response to Lenalidomide was poor in patients with recurrent malignant gliomas. In phase I trial of newly diagnosed glioblastomas also there was no evidence of better response to radiotherapy in combination with lenalidomide. [59, 60]

Thalidomide was evaluated also for patients with metastatic brain tumors.

In a phase III study of thalidomide in patients with multiple brain metastases there was a study that compared whole brain radiotherapy in combination with thalidomide versus whole brain radiotherapy without thalidomide. There was no evidence for better response to the radiation therapy – both groups had median survival of 3.9 months.

A phase II study of thalidomide monotherapy in patients with brain metastases from melanoma showed limited activity. [61]

The combination of thalidomide, temozolomide and whole-brain radiation therapy to patients with brain metastases from melanoma also showed little efficacy. [62]

There will be future studies of thalidomide and lenalidomide in malignant gliomas and also in metastatic brain tumors.

Discussion

Although there is a proved benefit in application of anti-angiogenic agents, most patients expirience at some point tumor progression. Tumor develop resistance to angiogenic inhibitors. [63] Mechanisms of resistance include - turning alternative pro-angiogenic pathways, protection of tumor vascular system, and ability to invade, without angiogenesis. [63] Further researches are needed to study the all the mechanisms of tumors' to develop resistance to anti-angiogenic therapy.

Conclusion

Angiogenesis is not fully understood and all its molecular pathways. The researches and trials done by now, including monotherapeutic or combined-one approach, show that anti-angiogenic agents show efficacy in the treatment of malignant primary and secondary brain tumors. The prolonged progression free period, as well as the lesser vasogenic edema, are proved to be related with application of anti-angiogenic agents. The need of more prospective trials - to validate the up-to-date results and to investigate the other targets pf pro-angiogenic pathways.

Regardless the application of angi-angiogenic drugs in primary and secondary brain tumors shows to be a promising therapeutic approach, which has the potential to have a significant impact in the treatment of brain oncologic patients. [64]

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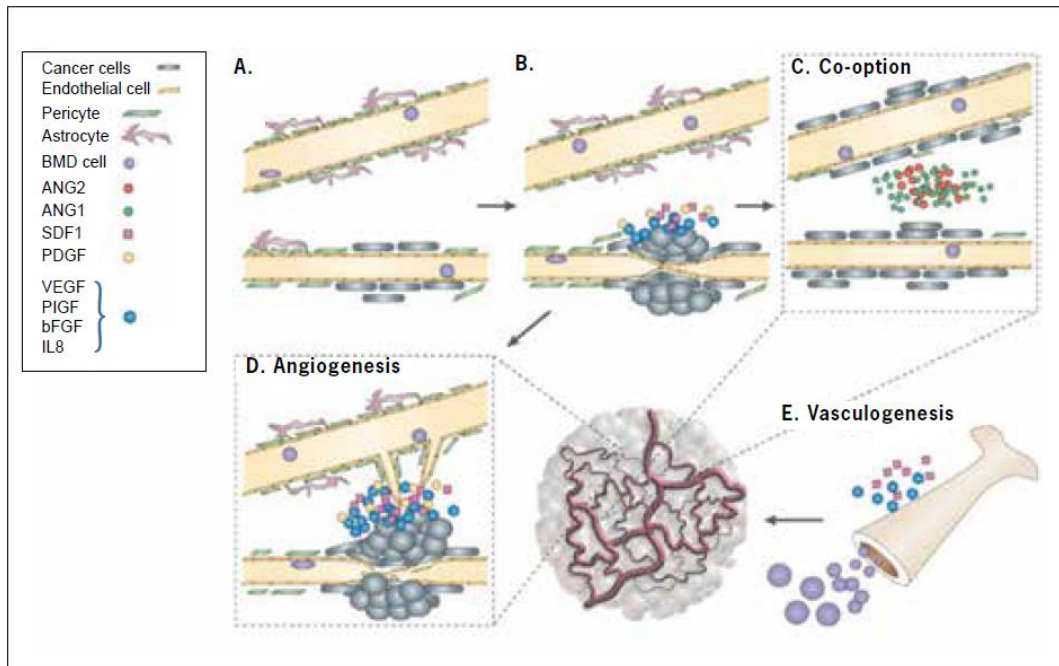
Fig.1 Schematic representation of different mechanisms of new blood vessel formation. A) Blood vessels are composed of astrocytes, pericytes, and endothelial cells. B) Tumor cells infiltrate along blood vessels. C) As the tumor grows, it co-ops normal capillaries using various cytokines. D) Blood vessels are compressed and destabilized, which decreases perfusion, and results in hypoxia. Hypoxic conditions result in increased secretion of several growth factors such as vascular endothelial growth factor (VEGF), stromal-cell-derived factor (SDF-1), basic fibroblast growth factor (bFGF), and Interleukin 8 (IL8). E) Bone-marrow-derived (BMD) cells and SDF-1 are recruited to induce vasculogenesis. Reprinted from Jain et al. Angiogenesis in brain tumours. *Nat Rev Neurosci*. 2007;8:610-622.
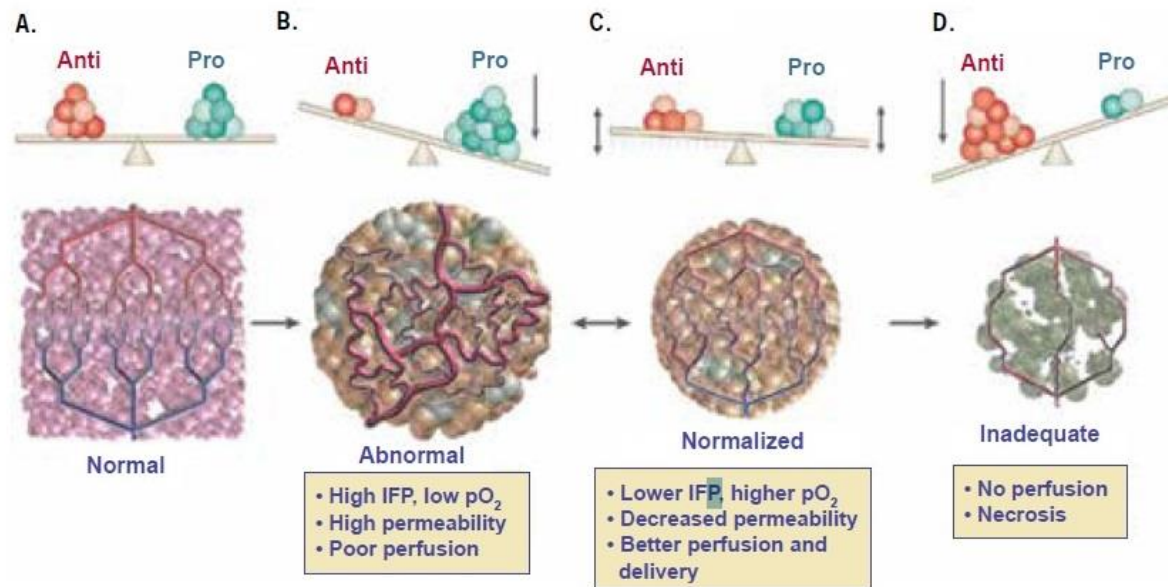
Figure 2. Schematic representation of mechanisms of anti-angiogenic treatment. A) Healthy tissues have balanced signaling from pro- and anti-angiogenic factors, and this results in an organized, effective vasculature. B) Tumors produce anti-angiogenic factors, which create a highly disorganized vascular network. C) Anti-angiogenic therapy can normalize the vasculature and allows for more effective delivery of drug. D) With potent anti-angiogenesis, the tumor is starved of nutrients and oxygen, with resulting necrosis of tumor.
IFP=interstitial fluid pressure; pO2=tissue oxygen level
Reprinted from Jain et al. Angiogenesis in brain tumours. *Nat Rev Neurosci*. 2007;8:610-622.