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Anti-angiogenic therapy in pediatric brain tumors: An effective strategy?

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Contents

Abstract

Brain tumors are still the leading cause of cancer morbidity and mortality among children, despite different therapeutic options including neurosurgery, chemotherapy and radiation. As angiogenesis is highly crucial in brain tumor growth and progression, numerous clinical

Abbreviations: VEGF(R), vascular endothelial growth factor (receptor); EGF(R), epidermal growth factor (receptor); LGG, low-grade glioma; HGG, high-grade glioma; DIPG, diffuse intrinsic pontine glioma; PDGF(R), platelet derived growth factor (receptor); P(I)GF, placental growth factor; Ang, angiopoietin; FGF(R), fibroblast growth factor (receptor); HGF(R), hepatocyte growth factor (receptor); MMP, matrix metalloproteinase; PRES, posterior reversible encephalopathy syndrome; HIF, hypoxia inducible factor; DLL, delta-like protein; IGF1, insulin-like growth factor 1; INF, interferon (INF); bFGF, basic fibroblast growth factor; ALK, anaplastic lymphoma kinase; RON, recepteur d'origine nantais; RT, radiotherapy; BSG, brain stem glioma; CPM, cyclophosphamide; retro, retrospective; TNF-α, tumor necrosis factor α; IL, interleukin; TZM, temozolomide; pros, prospective; CR, case report; CT, chemotherapy; PA, pilocytic astrocytoma; HCG, hypothalamic-chiasmatic glioma; CSF-1R, colony stimulating factor 1 receptor; APGD, Astellas Pharma Global Developments; MRI, magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery; PET, positron emission tomography.

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trials evaluating diverse anti-angiogenic agents have been described. In the present review, we aimed to answer the question if anti-angiogenic therapy is an effective strategy in the treatment of children with brain tumors. Although some encouraging results have been published of anti-angiogenic therapy targeting vascular endothelial growth factor (VEGF)/VEGF receptor signaling or epidermal growth factor receptor (EGFR), still more insight is warranted to be highly conclusive about the efficacy of anti-angiogenic therapy with currently potential upcoming anti-angiogenic agents in pediatric brain tumors. However, given the need for new therapeutic strategies, multi targeted therapy with anti-angiogenic agents anticipating on possible tumor escape mechanisms could be effective in the future treatment of pediatric brain tumors.

Keywords: Pediatric brain tumors; Anti-angiogenic therapy; Clinical trials; Angiogenesis; Vascular endothelial growth factor (receptor); Epidermal growth factor receptor

1. Introduction

Brain tumors account for nearly 20% of all childhood cancers and are characterized by a large diversity of morphologic entities. The most common brain tumor subtype occurring in children and young adults is glioma, representing more than 50% of all tumors [1]. Gliomas are classified into low-grade glioma (LGG), including the most frequent occurring pilocytic astrocytoma (WHO grade I) and diffuse astrocytoma (WHO grade II) and high-grade glioma (HGG), including anaplastic astrocytoma (WHO grade III) and glioblastoma (WHO grade IV). WHO grade III tumors of oligodendroglial or mixed oligoastrocytic origin are less commonly found in children [2]. Tumor vascularity is associated with a higher WHO grade, except for pilocytic astrocytoma which are as grade I astrocytoma highly vascular tumors [2–4]. Preferred sites of low-grade astrocytoma include the optic nerve, optic chiasm/hypothalamus, thalamus and basal ganglia, cerebral hemispheres, cerebellum and brain stem [2]. Overall these tumors have a good prognosis with 5-year overall survival rates of 80–90%. However, the 5-year survival rate for anaplastic astrocytomas ranges from merely 20 to 40% and is even worse for glioblastoma (5–15%) [5]. Diffuse intrinsic brain stem gliomas (DIPG) which are mainly grade III or IV astrocytomas have the most infaust prognosis [6]. The overall survival of these children remains approximately 9 months, and most patients die from the disease within 2 years [7].

Medulloblastoma, one of the embryonal brain tumor types, is the second most frequent tumor subtype after glioma. Peak occurrence is at 4 years of age with one-third of the cases are present in the first years of life [2,6]. Management of these very young patients remains challenging since the immature brain is particularly susceptible to the toxicity of current treatment options. Ependymoma is the third most common pediatric brain tumor subtype with a peak incidence between birth and 4 years of age. Ependymomas are classified into myxopapillary ependymoma (WHO grade I), grade II ependymoma (cellular, papillary, clear cell, tancytic) and anaplastic ependymoma (WHO grade III) [2], although clinical studies have failed to show a correlation between grade and clinical outcome [8,9]. 5-year overall survival was reported to be 57.1% in which supratentorial location was associated with better survival rates compared with infratentorial located tumors, although radiotherapy appears beneficial for survival in patients with infratentorial ependymoma [10].

Although the prognosis for pediatric patients with brain tumors has improved over the last few decades with diverse intensive therapeutic modalities as neurosurgery, chemotherapy and radiation, many brain tumors remain difficult to treat and are associated with a poor prognosis. The long-term survival for children with DIPG has not even changed over the last decades. Overall brain tumors are still the leading cause of cancer morbidity and mortality among children. So to reduce this morbidity as well as mortality, alternative therapeutic strategies have been developed, extrapolating from adult studies, including anti-angiogenic therapy.

In 1971, Folkman firstly proposed that tumor growth is angiogenesis-dependent, and hence, blocking angiogenesis could be a strategy to arrest tumor growth [11]. This possibility stimulated an intensive search for pro- and anti-angiogenic molecules, resulting in the identification of crucial angiogenic factors including vascular endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR) and platelet derived growth factor (PDGF). Later, various strategies inhibiting the process of angiogenesis were described, specific anti-angiogenic inhibitors were developed and tested in preclinical and clinical settings in adults and subsequently in children.

Nowadays, numerous clinical studies of anti-angiogenic therapy also in pediatric brain tumors have been described. In the present review an introduction in the process of angiogenesis and its mediators in pediatric brain tumors will be followed by a description of the general effects of and possible tumor resistance mechanisms to anti-angiogenic therapy. Next, we provide an overview of both published clinical pediatric brain tumor studies and recently started clinical trials inhibiting angiogenesis in different pediatric brain tumor subtypes. Moreover, we will evaluate clinical results and monitoring of anti-angiogenic therapy. Finally, the question if anti-angiogenic therapy is an effective strategy in the treatment of children with brain tumors and the future perspectives will be discussed.

2. Angiogenesis and its mediators in pediatric brain tumors

Vascularization of the brain begins during embryogenesis, continues into the post-natal period, and involves a