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REGULAR ARTICLE

Vascular endothelial growth factor blockade: A potential new therapy in the management of cerebral arteriovenous malformations

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Abstract Cerebral arteriovenous malformations (AVMs) occur universally in 1.1 per 100,000 people. These malformations are the cause of serious neurological morbidity or even death when they bleed. AVMs are not necessarily static congenital abnormalities. They can undergo internal changes due to angiogenesis resulting in vascular remodelling. They can even regrow after successful therapy. Vascular endothelial growth factors (VEGFs) play an important role in angiogenesis. Drugs that block the action of VEGF on vascular endothelial growth factor receptors (VEGFRs) on the endothelial cell surface are available. This blockade causes an anti-angiogenetic effect. Anti-angiogenic drugs are widely used as adjuvant therapy in the management of cancers because they suppress the formation of new blood vessels required by the tumour for growth. For similar reasons, they are used in the treatment of age-related macular degeneration.

The present treatment options for AVMs are surgery, embolisation and irradiation either on their own or in combination. Irradiation with stereotactic radiosurgery (SRS) offers the advantage of being non-invasive, but it relies on the late radiation effects to achieve its therapeutic goal of complete obliteration. This latent time (1–3 years), during which the risk for a bleed remains, is an inherent drawback of SRS. The histopathology of surgical specimens of post-SRS AVMs demonstrates a role of endothelial cells in repairing the radiation damage. Suppressing their activity post SRS by a VEGF blockade has the potential to enhance the radiation damage and hence speed up the obliteration process and reduce the latent time. It is postulated that such a 'VEGF blockade' could be useful as an adjuvant therapy to SRS. In addition, there is also the potential for a neo-adjuvant use, whereby a VEGF blockade could cause regression in the size of the AVM, making definite therapy easier. The rationale for the VEGF-blockade concept is presented and discussed.

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Introduction

Arteriovenous malformations (AVMs) have traditionally been considered to be congenital with no postnatal changes during the patient's life. Antenatal diagnosis of the presence of cerebral AVMs is highly uncommon. If fully developed cerebral AVMs were already present at birth, it might be expected that the widespread use of computed tomography (CT) and magnetic resonance (MR) scans in newborns would show an incidence close to that found in adolescence and adults. However this is not the case. The postnatal development of an AVM is a concept supported by clinical observations. Genetic and biological studies have demonstrated that an environmental trigger, the so-called 'second hit', in addition to a genetic predisposition can lead to the development of cerebral vascular lesions [1]. All of the genes associated with vascular malformations of the brain to date have also known or plausible roles in angiogenesis and vascular remodelling [2,3]. An uncontrolled local angiogenesis process, starting after a double hit, could explain the development of AVMs into the entities as seen when they become clinically manifest usually around the age of 4 years or later. This development during childhood and adolescence is a possible explanation as to why this is the period in life when most AVMs are diagnosed, as they rapidly develop together with the growth of the rest of the body [4,5].

During most part of adult life they remain physiologically active and undergo vascular remodelling on the basis of ongoing neo-angiogenesis [6,7]. This can lead to further growth or, more rarely, complete regression [8–16]. Forces that influence this ongoing vascular remodelling are: feeding artery pressures, venous drainage, flow patterns and vascular steal [17,18]. This remodelling is reflected by elevated vascular endothelial growth factor A (VEGF-A) expression in human brain AVMs, [19,20] elevated VEGF plasma levels [21] and active VEGF production by AVM endothelial cells [22]. AVM endothelial cells also significantly overexpress the vascular endothelial growth factor receptors (VEGFRs) 1 and 2, and AVM brain endothelial cells proliferate faster and migrate more quickly [23].

The sprouting of new blood vessels or angiogenesis is a normal physiological process that is most important during embryonic development. This process also happens in adult life during wound healing and during muscle development from exercise and in the formation of collateral vessels to bypass blocked vessels. During malignant tumour development, angiogenesis plays a role in producing extra blood vessels to increase the tumour blood supply [24]. This angiogenetic process is mediated by a signal protein called VEGF. This has actually been found to be a family of factors with the most important one being VEGF-A [25]. Other members are placenta growth factor (PGF), VEGF-B, VEGF-C and VEGF-D. These members of the VEGF family bind to VEGFRs on the cell surface, whereby they activate intracellular pathways. Two such receptors have been identified, namely VEGFR-1 and VEGFR-2, of which VEGFR-2 seems to mediate almost all of the signalling [24,25].

Present treatment options for AVMs are: (a) surgery for those lesions that are resectable and (b) radiation therapy under the form of stereotactic radiosurgery (SRS) for those lesions that are irresectable or when the patient refuses surgery. Embolisation is helpful in making the surgery easier but is not always successful on its own [26,27].

SRS, by gamma knife and linear accelerator- or cyclotron-produced charged particles, is a well-established treatment option [28]. However, lesions most effectively treated have volumes < 15 cc or a maximum diameter of ± 3 cm. As the AVM volume increases, it becomes more and more difficult to obtain an optimal balance between successful obliteration and radiosurgical complications [29]. Even when radiosurgery can be given with a small risk of side effects, there is always a latent period (1–3 years) between the irradiation procedure and the eventual obliteration. During this time the patient remains at risk for a bleed, and only when the AVM is completely obliterated can the patient be considered cured [28].

The pathophysiological events after radiosurgery have been well documented in surgical specimens post radiosurgery and consist initially of endothelial cell death and denudation of the vessel wall surface followed by a reactive subsequent increased endothelial cell proliferation in an attempt to repair the denudation of the vessel wall [30]. The remaining areas of denudation then trigger a thickening of the intima layer by proliferation of smooth muscle cells [31]. These changes in turn lead to thrombosis of the AVM vessels. If this process is sufficiently extensive it leads to complete obliteration [32,33].

The hypothesis

Current traditional methods for treating brain AVMs are based on the concept that they are congenital and do not undergo change during the patient's life. However that is not necessarily the case and there is evidence that AVMs are dynamic entities undergoing vascular remodelling driven by angiogenesis. The process of angiogenesis is well understood and is stimulated by activating cellular membrane receptors. Monoclonal antibodies that block these interactions have been developed for oncological use. They block the tumour-induced angiogenesis needed for tumour growth and are routinely used in the treatment of certain cancers.

A similar VEGF blockade has potential in the management of AVMs by suppressing the ongoing angiogenesis, a process that is responsible not only to maintain the AVM but also to repair the radiation-induced damage. Such a VEGF blockade could be used as adjuvant therapy following the irradiation procedure to suppress the repair process by proliferating endothelial cells and therefore speed up the thrombotic process responsible for obliteration. This would reduce the latent period and the time at risk for a new bleed, and in turn would have significant clinical and health economic implications. A neo-adjuvant use would be aimed at suppressing the ongoing vascular remodelling and reducing the vascular density and to possibly make the AVM smaller and more manageable for surgical or radiosurgical interventions.

Evaluation of the hypothesis

Drug-based anti-angiogenesis therapy is well established in oncology [34,35].

Tumours are dependent on new blood vessel formation for their growth and they actively promote angiogenesis by releasing VEGFs in their immediate environment to achieve this. A treatment strategy to interfere with this angiogenesis has long been seen as a way to help in the eradication of tumours. A variety of drugs exist that have proven anti-angiogenesis