The Role of Avastin in the Management of Recurrent Glioblastoma

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KEYWORDS

• Recurrent glioblastoma • Treatment malignant glioma • Angiogenesis • Angiogenic switch • VEGF • Antiangiogenic • Bevacizumab • Avastin • Radiation necrosis

Glioblastoma multiforme (GBM) is a malignant cerebral neoplasm of glial cell origin, accounting for 17% of all primary central nervous system tumors.[1] It has been classified by the World Health Organization as a grade IV malignancy and, thus, associated with rapid disease progression and a universally fatal outcome.[2] The prognosis for patients diagnosed with GBM is dismal, with an estimated 5-year survival rate of only 3.4%.[1] The current standard of treatment of newly diagnosed glioblastomas entails aggressive surgical resection with postoperative radiotherapy and chemotherapy, consisting of temozolamide, an oral alkylating agent.[3,4] Such treatment has improved the overall survival to a median of 12 to 15 months, compared with the previously sited 8 to 10 months.[5,6] However, although patients are living longer with this disease, recurrence proves to be unavoidable, with one study quoting an overall median survival of 6.25 months.[7]

The propensity for glioblastomas to recur can, in part, be explained by their ability to promote endothelial vascular proliferation.[6] The marked increase in vascular density largely accounts for their aggressive and invasive behavior.[8] These neoplasms exhibit an overexpression of vascular endothelial growth factor (VEGF), a promoter of angiogenesis.[9] Increased VEGF expression results in microvascular proliferation and accelerated tumor growth and has been linked to poor prognosis.[8,10]

Novel therapies aimed at arresting angiogenesis and tumor growth have come to play an integral role in the management of recurrent GBM. One such therapy is bevacizumab (Avastin), a recombinant monoclonal immunoglobulin (Ig) G_1 antibody that received Food and Drug Administration (FDA) approval in 2009 for the treatment of recurrent GBM.[11] Avastin acts by inhibiting the binding of VEGF to endothelial cell receptors. It is thought through inhibition of VEGF binding, tumor neovascularization, and, thus, tumor growth can be minimized. The proposed effect of the drug is supported by its radiographic findings of decreased contrast enhancement of tumors on magnetic resonance imaging (MRI).[11] However, the correlation of reduced tumor burden, as seen on imaging, with a progression-free survival (PFS) is uncertain. It is argued that Avastin's ability to neutralize VEGF results in the stabilization of the blood-brain barrier, which can prevent radiographic enhancement and, thus, mask tumor growth.[11] This article reviews the use of Avastin, its clinical applications, and its role in the treatment paradigm of recurrent GBM.

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ANGIOGENESIS

The Angiogenic Switch

Angiogenesis is the process by which new blood vessels sprout from existing blood vessels.[12] Although angiogenesis is essential in normal vascular development, it can also be seen in many pathologic processes, including tumorigenesis.[13,14] New blood vessels develop in response to a hypoxic environment and the increased demand for oxygen and nutrients.[12,15] However, in pathologic conditions, this neovascularization is persistent and does not resolve by the reestablishment of adequate vascular perfusion.[12,15] In this setting, there is a transition from a physiologic prevascular environment to a pathologic vascular setting. This model of tumor angiogenesis was first introduced by Dr Judah Folkman in 1971 and is commonly referred to as the angiogenic switch (**Fig. 1**).[13,16,17]

The angiogenic switch provides 2 distinct advantages to tumor cells. The first and perhaps more significant benefit is the direct blood supply afforded to tumors by this neovascularization. In general, tumors that have access to a sufficient blood supply will continue to have exponential growth.[18] As described by Dr Folkman, there is a highly interdependent relationship between tumor cells and endothelial cells within the capillaries of a neoplasm, such that their rates of growth are contingent on each other.[16] The second advantage of neovascularization is the ability for tumor vessels to indirectly support malignant cells in an environment called the vascular niche.[19] This niche consists of small nests of dormant neoplastic cells. Neighboring endothelial cells supports these quiescent cells, yet their dormancy maintains a resistance to treatments, such as radiation and chemotherapeutic agents. Thus, neovascularization, which occurs in response to the angiogenic switch, provides tumors with a distinct growth advantage and proliferative autonomy when compared with normal cells.[14]

The mechanism by which this angiogenic switch occurs is a complex series of events. As tumors enlarge and compress neighboring blood vessels, there is a decrease in blood supply leading to hypoxia.[20] Tumors growing to a size as small as 1 to 2 mm can outgrow the local blood supply, triggering an angiogenic process.[12,15] The decreased partial pressure of oxygen tension in the tissue induces an upregulation of a transcription factor, hypoxia-inducible factor (HIF).[21] During times of normal oxygenation, HIF is kept at low levels by ubiquitin proteasome-dependent protein degradation, mediated by various tumor suppressor genes.[21] In cases of tumorigenesis, however, there is a loss of tumor suppressor function and HIF levels remain elevated.[12,15] This condition results in increased expression of proangiogenic factors, such as VEGF, basic fibroblast growth factor (FGF), and transforming growth factor-β, and a concomitant decrease in antiangiogenic factors, including interferon-α and thrombospondin-1.[13] The result is the stimulus for the angiogenic switch, which allows the growth of new capillaries and consequently the continued growth of a malignant tumor.[13]

Vascular Endothelial Growth Factor

VEGF has been shown to play a key role in the regulation of both normal and abnormal angiogenesis and it is commonly overexpressed in solid

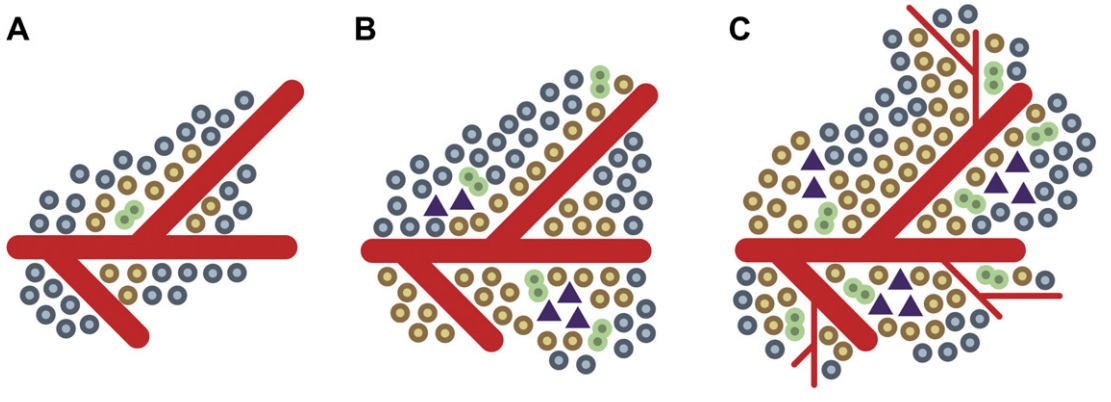

Fig. 1. Angiogenesis in high-grade gliomas. Tumor growth begins with malignant cells inhabiting regions adjacent to normal blood vessels (*A*). As the number of tumor cells increase at a rapid rate, as occurs in high-grade gliomas, the cells outgrow their previous blood supply and become hypoxic and necrotic (*B*). The hypoxic environment stimulates new blood vessel development, which in turn promotes further tumor growth (*C*). The blood vessels are depicted in red, the tumor cells are yellow, normal cells are blue, mitotic cells are green, and necrosis is demonstrated with purple triangles. (*Data from* Bergers G, Benjamin L. Tumorigenesis and the angiogenic switch. Nat Rev Cancer 2003;3(6):401–10.)

tumors.[14] VEGF is a member of the VEGF/platelet-derived growth factor gene family.[13] It binds to 2 tyrosine kinase receptors, VEGF receptor-1 (VEGFR-1 or Flt-1) and VEGF receptor-2 (VEGFR-2 or Flk-1/KDR). Both of these receptors predominantly occupy the surface of vascular endothelial cells.[13] When VEGF binds to the VEGFR-2 receptor, it signals downstream pathways, such as the phosphatidylinositol 3′OH kinase/AKT, to induce angiogenesis, vascular permeability, and mitogensis.[22] In contrast, the binding to the VEGFR-1 receptor is thought to have negative feedback on VEGFR-2 signaling, monocyte migration, and endothelial cell secretion of proteases and growth factors.[12,15]

In one study, levels of VEGF and other proangiogenic factors were quantified by enzyme-linked immunosorbent assay in patients with primary and recurrent malignant gliomas. Twelve patients with primary GBM, 26 patients with recurrent GBM, and 7 patients with recurrent anaplastic astrocytoma underwent surgery for tumor resection and placement of an Ommaya reservoir into the resection cavity. Intracavitary fluid was drawn from the Ommaya reservoir between 2 to 12 weeks, before receiving chemotherapeutic treatment, and VEGF levels within the fluid were measured. The VEGF levels in the plasma of patients were also evaluated and compared with the plasma levels in 23 healthy controls. The VEGF levels in the plasma of patients were found to be higher than that of the controls ($P = .04$). When comparing the plasma and intracavitary VEGF levels in patients, the intracavitary levels proved to be higher. Finally, the VEGF levels were highest in the intracavitary fluid of patients with recurrent GBM, followed by patients with primary GBM. Intracavitary levels were lowest in patients with recurrent anaplastic astrocytomas. The study also showed a trend toward longer survival with lower intracavitary VEGF levels in the patients with recurrent glioblastomas.[23] As a result, more therapies are aimed at inhibiting the activity of VEGF and, thus, arresting angiogenesis, (**Fig. 2**).

Avastin

One of the more recognized antiangiogenic drugs available is Avastin, a recombinant monoclonal IgG_1 antibody derived from the murine VEGF monoclonal antibody.[6,9,14] The protein sequence is composed of 7% murine VEGF-binding residues incorporated into a human IgG framework constituting the other 93% of the protein sequence.[24] Experimental studies with Avastin show neutralization of all isoforms of human VEGF.[13] Treatment with Avastin results in a dose-dependent inhibition of tumor growth and a reduction in tumor density, diameter, and permeability.[13] For instance, patients who received greater than or equal to 0.3 mg/kg of intravenous Avastin demonstrate nondetectable serum levels of VEGF.[25]

In addition to neutralizing VEGF, Avastin has also been found to return tumor vasculature to a more physiologic state.[26] In nonmalignant blood vessels, there is a delicate balance between proangiogenic and antiangiogenic signaling mechanisms. This balance allows for the development of proper support structures, such as pericytes and basement membranes.[10] In tumors, however, the proangiogenic state is favored, resulting in aberrant blood vessels, irregular basement membranes, and discontinuous endothelial lining.[10,13] In effect, there is a leaky and unorganized vascular network with hyperpermeable membranes, which ultimately increases pressure in the interstitial space within tumors.[13,27] As a result, there is impaired delivery of oxygen and cytotoxic agents from the blood to

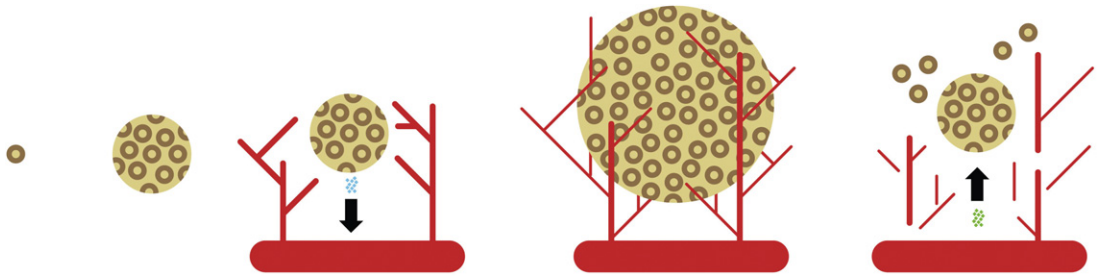

Fig. 2. Angiogenic switch and antiangiogenic theory. Tumor growth begins with a dormant nest of tumor cells, which slowly proliferate. As the tumor grows, it secretes proangiogenic factors and induces neovascularization. Tumor growth will continue as long as there is a sufficient network of blood vessels to support this growth. This process is the angiogenic switch. Antiangiogenic agents aim to inhibit the proangiogenic factors. (*Data from* Bergers G, Benjamin L. Tumorigenesis and the angiogenic switch. Nat Rev Cancer 2003;3(6):401–10.)

the tumor. Moreover, the hypoxic environment may impair the effects of any chemotherapy and radiation that is delivered to tumor cells.[13,28] By restoring the function of abnormal tumor vessels, Avastin indirectly promotes the delivery of cytotoxic agents to tumor cells while reducing leakage into the interstitial space.[13,24,29]

As alluded to earlier, anti-VEGF treatment may also enhance the effects of radiation in addition to chemotherapy. Gorski and colleagues[30] determined a dose-dependent increase in VEGF levels in tumors treated with ionizing radiation both in vitro and in vivo using mouse models. In the in vitro model, VEGF levels were initially 3 times higher in tumors concomitantly irradiated than in those that were not, and levels remained elevated for 14 days ($P = .032$).[30] The in vivo mouse model further demonstrated this synergy, showing no inhibition of tumor growth with anti-VEGF therapy alone, 68.8% inhibition of tumor growth with radiation alone, and 83.4% inhibition of tumor growth with a combined therapy ($P = .046$).[30]

AVASTIN IN CLINICAL TRIALS

Results in Other Malignancies

Angiogenesis is a common pathologic process in several types of malignancies. Similarly, the use of Avastin has been applied to the treatment of other, nonglial neoplastic processes. In 2004, the drug was FDA approved as a first-line agent with 5-florouracil chemotherapy for the treatment of colorectal cancer. In 2006, Avastin was approved as a second-line treatment with 5-fluorouracil/leucovorin/oxaliplatin -4 for colorectal cancer and as a first-line treatment of patients with unresectable or metastatic nonsquamous, non–small cell lung cancer in combination with carboplatin and paclitaxel. The approval for colorectal and lung cancer was based on randomized clinical trials that showed a statistically significant improvement in overall survival. In 2008, the FDA approved Avastin, in conjunction with paclitaxel, as a first-line treatment of metastatic breast cancer because of a single clinical trial in an accelerated approval process.[31] However, in 2010, the FDA began efforts to revoke their approval of the drug for the treatment of breast cancer after data from 5 randomized clinical trials failed to show improvement in overall survival or quality of life.[31]

Glioblastoma

The development of agents targeting VEGF for the treatment of GBM has also been under investigation. Initial trials with Avastin showed promising response rates, and the drug was thought to be a breakthrough in the treatment of glioblastoma.[32,33] In 2009, Avastin was granted accelerated FDA approval as a single-agent therapy for patients with recurrent glioblastoma. A phase II, noncomparative, multicenter trial (AVF3708 g) evaluated the efficacy of Avastin alone and in combination with irinotecan in patients with recurrent glioblastoma. All patients included in this study had histologically confirmed glioblastoma at either their first or second recurrence previously treated with radiotherapy and temozolomide. Patients were stratified by Karnofsky score and by first or second relapse. They received Avastin 10 mg/kg intravenously every other week and were observed for 6 months. Outcomes were compared with historical data with patients with 6-month PFS receiving either salvage therapy or irinotecan.[32]

The 2 primary endpoints in this study were 6-month PFS and objective response rates. The 6-month PFS was defined as the percentage of patients who were alive and progression free at the end of the 24-week period. The objective response rate was defined as either a complete or partial response seen on MRI taken at least 4 weeks apart. This study showed a 6-month PFS of 42.6% in the Avastin alone group and 50.3% in the Avastin and irinotecan group. Additionally, there was no reported investigator-determined clinical progression. These results were significantly superior to the historical controls.[32]

Based on the results of this trial, Genentech applied for accelerated approval of Avastin for monotherapy of recurrent glioblastomas. When the FDA reviewed this study, it reanalyzed the data using an exact 6-month cutoff instead of the 5.52-month cutoff used in the published study, which changed the PFS to 36.0%. The FDA did not include the results of the Avastin and irinotecan arm because that could have confounded the results. Additionally, the FDA excluded the objective response rate data from the trial because they determined that the characteristic histology of pseudopalisading necrosis of glioblastomas gives the tumor an irregular configuration that cannot be accurately measured on MRI. The FDA refused to grant accelerated approval based on these results alone until a confirmatory study with randomized controls rather than historical controls proved Avastin's efficacy.[31]

A single-arm single-site study was performed on patients with histologically confirmed recurrent glioblastoma previously treated with radiotherapy and temozolomide. In the study, patients received Avastin, 10 mg/kg every 14 days on a 28-day cycle. Patients who were noted to have progression of tumor growth during the study were asked to participate in a companion trial with the addition of irinotecan. MRI and positron emission tomography (PET) scans were performed at treatment

onset and then again after 4 weeks. The primary end point in this study was PFS at 6 months, which was found to be 29%, with a median PFS of 16 weeks. Based on the Macdonald criteria, the overall response rate was 35%. In assessing the fludeoxyglucose F 18 uptake measured by PET scan 4 weeks after the start of treatment, this uptake was diminished in 49%, equal to the baseline in 37% and increased compared with the baseline in 14% of patients. In this study, Avastin was generally well tolerated.[33]

Adverse Events

Inhibition of VEGF by Avastin occurs throughout the body and is not specific to tumor angiogenesis.[5] Its effects on normal vascular function and angiogenesis have lead to reports of several serious adverse events.[34] Perhaps the most commonly reported and often the most devastating complication is intracranial hemorrhage. Severe hemorrhage is estimated to occur 5 times more frequently in patients treated with Avastin than those receiving standard chemotherapy.[34] Wound infection and wound healing are additional potential complication because the drug may preclude adequate blood for wound healing.[34] A large cohort study analyzed the incidence of wound complications in patients undergoing abdominal surgery for colon cancer and found it to be directly related to the interval between surgery and the initiation of treatment.[35]

In the initial AVF3708 g trial of Avastin therapy in patients with glioblastomas, 98.8% of the patients experienced adverse events, with 26.2% of patients in the Avastin arm experiencing serious complications.[32] The most common findings were fatigue (45.2%), headache (36.9%), and hypertension (29.8%). A total of 46.4% of the patients in the Avastin-only arm of the study experienced grade 3 or higher adverse events. The most common of these were hypertension (8.3%), convulsion (6%), and fatigue (3.6%).[32] A total of 18 patients discontinued Avastin during this study because of the adverse events, which included cerebral hemorrhage, fatigue, seizure, myocardial infarction, reversible posterior leukoencephalopathy, infection, gastrointestinal perforation, and others.[32] In the National Cancer Institute 06-C-0064E trial, the most frequent adverse events were thromboembolism (12.5%), hypertension (12.5%), hypophosphatemia (6%), and thrombocytopenia (6%).[33]

EVALUATION OF CLINICAL EFFICACY

The Macdonald Criteria

Despite the promising therapeutic benefits of Avastin and other antiangiogenic treatments for the treatment of glioblastoma, several questions remain unanswered. Perhaps the most debated issue is the correlation between radiographic PFS and the clinical outcome of patients. Many studies that examine the efficacy of Avastin use as their end point the radiographic PFS and the objective response rate as determined by the Macdonald criteria.[11,32,36] The Macdonald criteria measure the response rate of glioblastomas to treatment, based on the size of contrast enhancement on T1-weighted MRI.[36] This size is determined by calculating the product of the maximal cross-sectional diameter of the enhancing tumor in 2 dimensions. Tumor progression is defined as a 25% increase in the 2-dimensional size.[36] In this way, 4 categories are analyzed, including a complete response (CR), a partial response (PR), stable disease, and progressive disease.[36] Using the Macdonald criteria, such studies demonstrate an improvement in PFS with Avastin compared with historical controls.[32] In part, it was the ability of Avastin to reduce contrast enhancement as early as 24 hours after the first dose that generated the enthusiasm for the drug and the approval for its use.[11] In fact, the Oncologic Drugs Advisory Committee stated: "objective response could be an adequate surrogate for clinical benefit under the proper parameters."[11]

The Macdonald criteria also factors into its determination of PFS the neurologic condition of patients and their use of steroids.[36] Steroid use is of particular importance because both steroids and Avastin have been shown to reduce vasogenic edema.[37] Reduction in surrounding edema not only improves radiographic findings but it also affects clinical symptoms because GBM-associated edema may contribute to the morbidity and mortality associated with the disease.[38] Decreased cerebral edema, even in the absence of tumor reduction, has been shown to have survival benefits.[37] Consequently, without recognizing the confounding effects of steroids, clinical and radiographic improvement can be erroneously attributed to Avastin. However, Avastin is attributed to the reduction in vasogenic edema independent of steroids by restoring a normal tumor vasculature and decreasing vessel permeability. In fact, multiple studies have shown a decrease in steroid dependence for patients on Avastin.[32,33]

Response Assessment Neuro-Oncology Working Group

Although not part of the Macdonald criteria, evaluation of the fluid attenuated inversion recovery (FLAIR) sequences on MRI may aid in measuring tumor response to antiangiogenic therapy. Some patients, after being treated with anti-VEGF agents,

develop tumor progression that is infiltrative but does not enhance on postcontrast T1-weighted images.[39] However, such changes may be evident as increased signal attenuation on the FLAIR sequences on MRI.[39] It is thought that this is caused by the normalization of blood vessels by antiangiogenic therapy, which may mask tumor enhancement without affecting tumor growth and progression.[39] To develop a better method in evaluating neuro-oncology patients, the Response Assessment Neuro-Oncology (RANO) Working Group was established.

In addition to many other items, the RANO Working Group took into account the nonenhancing portions of tumor.[40] The changes seen on the T2/FLAIR that are suggestive of infiltrative tumor are mass effect, infiltration of the cortical ribbon, and location outside the radiation field.[40] One criticism of the RANO criteria is that it does not specify the degree of T2/FLAIR changes necessary to constitute progression. However, like T1 contrast enhancement, T2/FLAIR signal abnormality is nonspecific and may be a result of the effects of radiation, demyelination, ischemic injury, changes in corticosteroid doses, infection, seizures, and postoperative changes.[39] The Macdonald and RANO criteria and their primary differences are highlighted in **Table 1**.

The Macdonald Criteria Revisited

Much controversy exists regarding the validity of these methods for assessing tumor size and growth. In 2010, Wen and Macdonald and colleagues[36,40] reported the several limitations of the Macdonald criteria that have since been recognized since its original implementation. Primarily, the irregular shape of a glioblastoma makes calculating its 2-dimensional shape very difficult and inaccurate while also causing a strong interobserver variability.[40] In addition, only the primary area of tumor burden and not the infiltrative disease can be visualized with contrast enhancement.[8] As stated previously, the decreased contrast enhancement on MRI is thought to result in decreased permeability of the blood-brain barrier caused by the known effect of Avastin to normalize abnormal tumor vessels.[11,41] As such, this antitumor response may be more appropriately termed a pseudoresponse.[41,42] Furthermore, peripheral tumor cells and tumor cells that have invaded normal brain parenchyma are supplied by nontumoral vessels, which do not enhance with contrast.[8] Contrast enhancement can also be influenced by several factors, such as corticosteroid dose, radiologic technique, treatment-related inflammation, seizure activity, postsurgical changes, ischemia, subacute radiation effects, and radiation necrosis.[40] Finally, after initial chemoradiation for glioblastoma, a transient increase in size known as pseudoprogression can occur in 20% to 30% of patients without actual tumor progression, which eventually resolves.[40] Consequently, patients with pseudoprogression included in clinical studies for recurrent gliomas could result in a falsely high response rate.[40]

Norden and colleagues[42] compared both the PFS and overall survival of patients treated with cytotoxic chemotherapy protocols with gimatecan and edotecarin as compared with patients treated with Avastin. The investigators' primary aim was to determine if treatment with Avastin results in a true survival benefit. In this study, the chemotherapy group displayed a PFS of 33%, 11%, and 6% at 3, 6, and 9 months respectively, with a median PFS of 8 weeks. In the Avastin group, the median PFS was 22 weeks with 70%, 40%, and 21% at 3, 6, and 9 months. These results showed a significant difference between the 2 treatment modalities with a P value of 0.01. However, the results do not hold for overall survival. In the chemotherapy group, median overall survival is 39 weeks, with 89%, 65%, and 54% at 3, 6, and 9 months, whereas the median overall survival for the Avastin group was only 37 weeks, with 91%, 74%, and 53% at 3, 6, and 9 months. The investigators in this study and several others concluded that Avastin improves PFS but has no significant effect on overall survival.[43]

Treatment After Avastin

Besides radiographic findings, another point of contention regarding patients with recurrent GBM previously treated with Avastin involves re-recurrence and disease progression after therapy. Under these circumstances, decision making becomes increasingly difficult because few treatment options remain.[44] Patients that received standard Avastin therapy had a mean time to disease progression of 4 months.[45] In retrospective analyses, there is no significant difference in the rate of distant recurrences between patients treated with Avastin and those who were not.[46] In fact, repeated studies demonstrate that patients previously treated with Avastin had extremely poor responses to any further treatment.[33] Kriesl and colleagues[33] studied a cohort of 19 patients with tumor progression treated with Avastin as a monotherapy or in combination with irinotecan.[33] None of the patients responded to either monotherapy or combination therapy and their median PFS was 30 days. In a prospective phase II study, Khasraw and colleagues[47] treated patients with recurrent GBM with daily temozolomide. They showed that

Table 1
Macdonld and RANO criteria

	Macdonald Criteria (using Contrast-Enhanced T1-Weighted Images)	RANO Criteria
Complete response	Imaging: complete absence of enhancing disease for a minimum of 4 wk with no new lesion formation Steroid dose: no corticosteroids Clinical assessment: clinical improvement	Imaging: complete absence of enhancing disease for a minimum of 4 wk with no new lesion formation T2/FLAIR images: stable or improved nonenhancing lesions Steroid dose: no corticosteroids Clinical assessment: clinically stable or improved
Partial response	Imaging: a 50% reduction in cross-sectional area from baseline of all measurable enhancing lesions for a minimum of 4 wk with no new lesion formation Steroid dose: stable or reduced corticosteroid dose Clinical assessment: clinically stable or improved	Imaging: A 50% reduction in cross-sectional area from baseline of all measurable enhancing lesions for a minimum of 4 wk with no new lesion formation; stable nonmeasurable lesions T2/FLAIR: stable or improved nonenhancing lesions Steroid dose: stable or reduced corticosteroid dose Clinical assessment: clinically stable or improved
Stable Response	Imaging: Does not meet criteria for CR, PR, or progression Clinical assessment: clinically stable	Imaging: does not meet criteria for CR, PR, or progression T2/FLAIR: stable nonenhancing lesions Steroid dose: stable or reduced corticosteroid dose
Progression	Imaging: an increase in cross-sectional area from baseline of 25% of enhancing lesions or the development of any new lesions Clinical assessment: clinical deterioration	Imaging: an increase in cross-sectional area from baseline of 25% of enhancing lesions or the development of any new lesions T2/FLAIR: increase in nonenhancing lesions Steroid dose: stable or increased corticosteroid dose Clinical assessment: clinical deterioration

Data from Wen P, Macdonald D, Reardon D, et al. Updated response assessment criteria for high-grade gliomas: response assessment in neuro-oncology working group. J Clin Oncol 2010;28(11):1963–72.

patients who previously received Avastin had a 6-month PFS of 14% compared with 36% in patients who did not receive prior treatment.[47]

Despite these reported failed treatments, there is no consensus as to why the use of Avastin yields resistance to future treatments. Some investigators have found that patients with progression after Avastin therapy developed perivascular fibrosis, which limited the amount of subsequent drug delivery to the tumor.[45] It has also been postulated that antiangiogenic therapy alters the phenotype of the tumor, creating a highly infiltrative compartment that is independent of angiogenesis.[44] In a separate hypothesis, treatment with Avastin and other antiangiogenic drugs results in hypoxia and a central region of tumor necrosis, whereas the remaining neoplastic tissue is preserved. The viable tumor surrounding the central necrotic core is, thus, unaffected by the antiangiogenic affects of the drug, leaving it free to infiltrate adjacent non-neoplastic parenchyma.[45] Because of hypoxia and metabolic deprivation, the still-viable cells in the periphery become increasingly invasive and grow outwards toward already-existing blood vessels. This process of anti-VEGF–treated tumors being able to form invasive satellite tumors is known as their ability to coopt existing vessels.[48] This process may explain why antiangiogenic treatment may even cause an increase in tumor invasion that is not seen radiographically and an accelerated resistance to alternate therapies.[45]

OTHER ANTIANGIOGENIC DRUGS

Although much attention has been directed at Avastin and its role in the treatment of recurrent GBM, numerous antiangiogenic drugs are also under investigation. **Table 2** lists several of these agents and their target of action. Cilengitide is a cyclic argininеglycine-aspartic acid-containing peptide inhibitor of αVβ3 and αVβ5 integrin receptors, which is necessary for tumor invasion and migration through cellular matrix interactions. A phase II trial with 81 patients with recurrent glioblastoma randomized patients to either 500 mg or 2000 mg of cilengitide twice weekly. In this study, the median overall survival was 9.9 months in the cohort receiving the 2000-mg dose compared with 6.5 months in the cohort receiving 500 mg (results not significant). Patients receiving cilengitide tolerated the medication well with no significant toxicities. The most common adverse event from treatment was fatigue (n = 3) and the most common serious adverse event was convulsion (n = 2).[43]

Aflibercept is a recombinant fusion protein of the extracellular domains of VEGF fused to the Fc portion of immunoglobulin G1. The drug binds to both VEGF and placental growth factor (PIGF). PIGF is a key mediator in angiogenesis by enhancing the activity of VEGF signaling by activation of VEGF receptor 1 and contributes to the angiogenic switch in cancer. PIGF levels are markedly increased in patients with recurrent glioblastoma. The North American Brain Tumor Coalition phase II trial was the first clinical trial of aflibercept in recurrent glioblastoma. Despite promising phase I results, the primary end point of this trial was not met because only 7.7% of patients were alive and progression free at the end of 6 months.[45]

Another antiangiogenic therapy, XL184, is a tyrosine kinase inhibitor that affects several receptors, including VEGF receptor 2. A recent phase II cohort study of patients with progressive glioblastoma treated with XL184 showed an overall response rate of 30% (11/37), with a medial PFS of 16 weeks. However, there was no response to XL184 in the patients who had previously been treated with another antiangiogenic compound, although the median PFS was the same in both groups. The most common serious adverse effects associated with XL184 were fatigue (20%), transaminase elevation (12%), and thromboembolic events (10%). The results with XL184 are encouraging and may hold promise in future trials.[44]

Like XL184, cediranib is an oral receptor tyrosine kinase inhibitor but it blocks all VEGF receptors. In a phase II study, 31 patients with recurrent glioblastoma were administered 45 mg/d of cediranib until their tumor progressed or there was unacceptable drug toxicity. At the end of the study, 25.8% of the patients were alive and progression free after 6 months, with 56.7% of patients showing a partial radiographic response. The grade 3/4 toxicities include hypertension (4/31), diarrhea (2/31), and fatigue (6/31).[49]

Table 2
Antiangiogenic agents and their targets

Antiangiogenic Agent	Target
Avastin	VEGF
Thalidomide	Basic FGF
Vatalanib	VEGF receptor, platelet-derived growth factor receptor
Cilengitide	Integrin receptors
Aflibercept	VEGF, placental growth factor
XL 184	Receptor tyrosine kinase
Cediranib	VEGF receptor, receptor tyrosine kinase
Sunitinib	Receptor tyrosine kinase
CT-322	VEGF receptor-2

Data from Beal K, Abrey L, Gutin P. Antiangiogenic agents in the treatment of recurrent or newly diagnosed glioblastoma: analysis of single-agent and combined modality approaches. Radiat Oncol 2011;6:2.

OTHER APPLICATIONS OF AVASTIN

Intra-arterial Avastin

The role for Avastin and other antiangiogenic agents is not limited to intravenous administration for the treatment of malignancy. In 2009, neurosurgeons at New York-Presbyterian Hospital/Weill Cornell Medical Center were the first to inject intra-arterial (IA) Avastin directly into the tumor bed.[50] In this procedure, known as superselective IA cerebral infusion, an angiogram is performed to identify the abnormal vasculature supplying the tumor. IA mannitol is then injected in an effort to disrupt the blood-brain barrier. Avastin is subsequently injected into the arterial vessels supplying the tumor, with the goal of improving penetration of the drug to the tumor bed without increasing the overall systemic effects of the drug.[50]

The first clinical study to assess the safety and efficacy of superselective IA cerebral infusion was conducted from 2009 to 2010 in patients with recurrent glioblastomas.[51] The study included 20 patients divided into 2 groups according to their prior treatment. Ten patients never received prior treatment with Avastin, whereas 10 patients were previously treated with intravenous Avastin. In the study, all participants were given IA mannitol

followed by escalating doses of 2 to 15 mg/kg of IA Avastin. The radiographic effects of the therapy were assessed with MRI before treatment, immediately after therapy, and 28 days later.[51]

Radiographic assessment was based on the RANO working group's study, evaluating the area and volume of T1 contrast enhancement and peritumoral FLAIR signal changes. In the Avastin-naive group, there was a median reduction of area and volume of tumor enhancement by 34.7% and 46.9% respectively. In comparison, the median reduction of area and volume in the comparison group was 15.2% and 8.2% respectively ($P = 0.02$ and 0.06 respectively). There was no significant difference between groups regarding the reduction of tumor perfusion on MRI. The signal attenuation on FLAIR was increased in 2 (10.5%) patients and stable in 8 (42.1%) patients in the Avastin-naive group compared with the previously treated group in which 3 (30%) patients had increased signal and 7 (70%) patients had stable findings on FLAIR.[51]

In this study, IA Avastin was observed to be relatively safe, with no grade 3, 4, or 5 adverse events reported.[51] The grade 2 adverse events were seizures in 2 patients and an acneiform rash in 1 patient. Two patients with a history of pulmonary embolus had new-onset pulmonary emboli during the observation period. One procedure-related stroke with the inflation of the endovascular balloon was reported.[51]

Although this study had a small sample size, it demonstrated the safety and efficacy of IA Avastin for the treatment of recurrent GBM. All of the patients in the group not previously treated with Avastin and two-thirds of the patients who had been previously treated with Avastin showed a meaningful reduction in tumor size according the RANO group's study.[51] These results are also superior to the 50% response rate to intravenous Avastin.[52] Additional investigation into IA Avastin is ongoing.

Treatment of Radiation Necrosis

Avastin may also have applications outside the inhibition of tumor growth. Radiation necrosis is a result of injury to the local tissue, which may occur after radiation therapy. The characteristic appearance of radiation necrosis on MRI is difficult to distinguish from tumor itself, with an area of central necrosis and surrounding vasogenic edema.[53] Radiation necrosis is caused by endothelial cell injury, resulting in a breakdown of the blood-brain barrier with subsequent edema and hypoxia.[54] The hypoxia induces an upregulation of VEGF that causes increased vessel permeability and tissue necrosis.[54] Therefore, it is theorized that radiation necrosis may respond to treatment with Avastin. A randomized, controlled, double-blinded study comparing Avastin with a placebo control showed that patients treated with Avastin for radiation necrosis had a 59% decrease in the edema as seen on FLAIR on MRI. This result is in stark contrast to the 14% increase in edema on FLAIR sequences in the placebo group.[55] Additionally, there was a 63% decrease in contrast enhancement seen on T1-weighted postcontrast MRI in the Avastin group compared with a 17% increase in enhancement in the placebo group. Although the study sample was small, these results are very promising for the treatment of radiation necrosis.[55]

SUMMARY

The development of antiangiogenic therapy for malignancy is an ever-evolving area of research. With regard to glioblastoma, Avastin is the most studied and is currently approved for recurrent disease. The significant reduction in tumor enhancement on MRI in early studies generated significant excitement concerning the ability of Avastin to improve overall survival in this difficult patient population. However, as Avastin continues to be studied, it is evident that although there is an increase in PFS there is no change in overall survival as compared with historical controls. Currently, several therapies targeting the different mediators of angiogenesis, including endothelial cell growth factor ligands and receptors, placental growth factor, fibroblast growth factor, and angiopoietins, are under investigation. As data from these studies are evaluated, it will become evident which antiangiogenesis inhibitors display efficacy and in what combination chemotherapeutic regimen they should be administered.

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