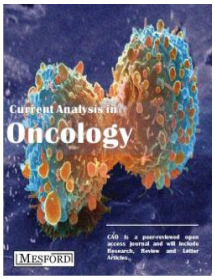
Bevacizumab in the Treatment of Brain Metastases, Is There Still a Role? An Updated Review of the Literature



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Abstract:

Brain metastases account for more than 50% of all brain tumors. The incidence of brain metastases has been increasing in recent years, with better imaging studies and with the improvement of cancer directed therapies. Growth and survival of tumor cells depend largely on angiogenesis and the development of adequate blood supply. Bevacizumab is a humanized monoclonal antibody against vascular endothelial growth factor used to treat different types of solid tumors; however, due to concerns for intracerebral hemorrhage, patients with brain metastases were not included in initial trials. In recent years, several trials studied the efficacy and safety of bevacizumab and other vascular endothelial growth factor inhibitors have shown promising results in patients with brain metastases. Significant advances have been made for non-small cell lung cancer that is the most lethal cancer and the cancer that most commonly metastasizes to the brain. Melanoma has also shown good responses to these therapies. There are small case series about the use of anti-angiogenesis therapy in renal cell carcinoma, colorectal carcinoma, hepatocellular carcinoma and other malignancies. The treatment for central nervous system metastases is slowly evolving, and the hopes of better response, and eventually improvement in survival, are increasingly anticipated.

We present an updated review of the literature discussing the most recent applications and safety of anti-angiogenesis treatment in patient with brain metastases.

Publication History: Received: 02 May 2019 | Revised: 09 July 2019|Accepted: 09 July 2019

Keywords:
Bevacizumab, brain metastases, lung cancer, VEGF, angiogenesis, antiangiogenic therapy.

INTRODUCTION

Brain metastases (BM) account for more than 50% of all brain tumors [1]. The majority of central nervous system (CNS) metastases are parenchymal, however metastases to leptomeninges are not uncommon [2]. The risk of BM ranges from 6-22% and the primary cancers that most commonly are associated to BM are lung (45% of BM), breast (15%), melanoma (10%), and colorectal cancer (5%) [3, 4]. If left untreated the median survival is 2 months [4].

There are reports of rising incidence of BM in various clinical scenarios [5, 6]. Improvement in cancer therapies has led to better survival outcomes but also to an increase in the number of patients with cancer recurrence in sanctuary sites, such as the brain, demonstrating the lack of effectiveness of chemotherapy and other therapeutic modalities in the CNS [2, 5, 7]. Additionally, more sensitive diagnostic studies are now incorporated into staging, allowing more frequent diagnoses of BM earlier in the disease course [5, 6].

Growth and survival of tumor cells depend largely on angiogenesis and the development of adequate blood supply [8, 9]. Bevacizumab is a humanized recombinant monoclonal IgG1 antibody against vascular endothelial growth factor (VEGF) that was first approved by the United Stated Food and Drug Administration (FDA) in 2004 for metastatic colorectal cancer, in 2006 for non-small cell lung cancer (NSCLC), since then it has also been approved for glioblastoma multiforme (GBM), kidney, and ovarian cancer [8]. However, due to concerns for excess risk of central nervous system (CNS) hemorrhage, most of the initial trials using bevacizumab for metastatic solid tumors excluded patients with BM [10]. Growing experience and increasing safety data on the use of bevacizumab spurred interest in the use of other anti-angiogenic agents for BM. The evolving question resides not only in whether bevacizumab or other anti-angiogenic agents are effective or safe as primary treatment for brain metastases, but also whether bevacizumab can and should be continued when disease progresses after standard systemic therapy. To better understand the mechanisms of BM via angiogenesis and the utility of angiogenesis inhibitors in BM a literature review was published by our group in this journal in 2012; since then practice-changing information has been published, we present an updated review of the literature [5].

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METHODS

The databases PubMed and Cochrane were comprehensively searched for studies that referred to the use of bevacizumab in patients with BM, we collected data from January of 2012 to January of 2019. The annual meeting abstracts from the American Society of Medical Oncology (ASCO), European Society of Medical Oncology (ESMO), and American Thoracic Society (ATS) were also searched. The search was limited to English publications in human subjects, case reports were excluded (Table **1**).

Table 1. Methods.

Records Identified in Database Search (Duplicates Removed)	**1546**
Abstracts selected	178
Full text articles selected	46
Studies included	39

The following search terms were used: CNS metastases, brain metastases, angiogenesis inhibitors and CNS metastases, angiogenesis of brain metastases, bevacizumab and brain metastases, bevacizumab and brain metastases and melanoma, bevacizumab and brain metastases and lung cancer.

Two reviewers independently performed the initial search, deleted duplicate records and reviewed the titles and abstracts for relevance. Then the selected publications were obtained as full text for a second independent review to identify eligible studies.

BRAIN MALIGNANCIES AND ANGIOGENESIS

Angiogenesis in Brain Tissue

Angiogenesis requires a delicate balance between pro and anti-angiogenic factors all of which plays a vital role in normal brain development [8, 11]. Substances originating from both extracellular as well as intracellular sources mediate pro- and antiangiogenic signaling [11]. (Table **2**).

Table 2. Pro and Anti-Angiogenic Factors.

Pro-Angiogenic	Anti-Angiogenic
VEGF	Angiostatin
Acid fibroblast growth factor	Endostatin
Basic fibroblast growth factor	Thrombospondin-1
Placental growth factor	Endothelial monocyte-activating polypeptide 2
Angiopoietin-2	Protamine
Angiopoietin-like 4	Platelet factor 4
Interleukin 8 / CXCL8	Angiostatic steroids
Hypoxia-inducible 1 alpha	Notch ligand delta-like 4
Hepatic fibrinogen/angiopoietin-related protein	Interferon

The prototype proangiogenic factors include VEGF, acidic fibroblast growth factor (FGF), basic fibroblast growth factor, placental growth factor, insulin growth factor, angiopoietin-2 and interleukins [11]. Low oxygen induces expression of hypoxia inducible factors (HIF-1) in glioma that lead to high levels of expression of VEGF mRNA and other pro-angiogenic factors [11]. HIF-1 and nuclear factor kappa (NF-kB activates Interleukin-8, chemokine with proangiogenic activity [12]. The integrin family, particularly 3-integrins, are upregulated in tumors and associated blood vessels; they mediate endothelial and cellular spread and migration [12]. Recent studies suggest that 3-integrins may play a dual pro- and anti-angiogenic role depending on which cell matrix they are bound [13].

Intracellular signaling mechanisms have similar complex effects on vascular development. For instance, activation of Ras/Raf/ protein kinases, as well as phosphatase and tensin homolog/mammalian target of rapamycin (PTEN/mTOR) pathways affect regulation of cell proliferation, migration and permeability [14, 15]. Receptor activators angiopoetin 1 and receptor antagonist angiopoetin 2 complement the actions of VEGF [14]. The angiopoietin 1/ angiopoietin 2 balance may also serve as a prognostic marker in primary glioblastoma [21]. The Notch pathway is a critical regulator of tumorous angiogenesis that can affect cell growth and differentiation either negatively or positively [16]. Notch has become an important therapeutic target because of its close interaction with VEGF [17]. Binding of VEGF to the VEGF receptor leads to activation of Notch signaling and conversely, inhibition of Notch leads to up-regulation of VEGF receptor expression [17, 18]. Angiostatin, endostatin, PEX, pigment epithelial-derived factor (PEDF) and thrombospondin (TPS)-a and mediate inhibition of angiogenesis and can be used as potential targets.

Angiogenesis and Brain Metastases

Most BM are thought to develop via homogenous spread [19]. BM depend on blood supply, Folkman first elucidated that tumors grow to only a pin head size in the absences of angiogenesis [20]. Vessel growth can occur by either sprouting or non-sprouting processes [21]. Sprouting occurs when new capillaries form from pre-existing vessels [21]. Non-sprouting angiogenesis on the other hand, is produced by proliferation of endothelial cells within walls of a vessel which leads to enlargement of pre-existing vessels [21].

Rapidly progressing BM tend to use nonsprouting angiogenesis that directly correlates with expression of VEGF mRNA [9]. Subsets of tumors may co-opt host vasculature for their growth initially, with later regression of host vessels, again inducing hypoxia and stimulating significant VEGF expression [11, 22]. To challenge Folkman's theory, Kusters et al. demonstrated that melanoma cells injected into internal carotid artery can grow without inducing the angiogenic switch by pre-existing vessels; proving that metastatic tumors stay in the peri-vascular space rather than infiltrating into tissue compared to primary brain tumors [23].

The blood brain barrier (BBB) presents a unique and specific challenge for pathogenesis and consideration for treatment of BM [24]. The complex structure of the BBB is created by specialized tight junction between the endothelial cells with no fenestration with astrocytes, pericytes and extracellular matrix [24, 25]. The BBB was designed to restrict permeability of blood vessels and suppress substance movement into the brain to protect central nervous system (CNS) function [24, 25]. However, this function also poses a primary obstacle for effective drug delivery to the brain. During tumorigenesis, blood vessels become dilated and require high concentration of VEGF for their growth; this process interrupts normal delivery of nutrients, oxygen and drug supply to the brain tissue and causes irreversible damage.

TARGETING ANGIOGENESIS IN PRIMARY BRAIN TUMORS

GBM is the most common primary brain tumor in adults and is usually rapidly fatal [26].The pathogenic mechanisms of primary brain gliomas are well described and this has allowed the design of effective treatment strategies allowing some improvement in the survival of patients with GBM [26].

Standard therapy for primary gliomas is considered to be surgery, followed by concomitant radiation and temozolomide with 6 months of maintenance temozolomide [26].

Patients with GBM and non-methylated O6-methylguanine-DNA methyltransferase (MGMT) have a particularly short median survival of 12.6 months and they often do not benefit of standard therapy with temozolomide; targeted therapy with anti-VEGF drugs has been explored in this group of patients [27]. The GLARIUS trial showed that the combination of irinotecan and the VEGF inhibitor bevacizumab lead to an improvement in progression free survival (PFS) at six months from 42.6 to 79.3% when compared with temozolomide, however the combination did not improve overall survival (OS) and quality of life was similar in both groups [27].

Bevacizumab with or without irinotecan has also been studied in the setting of recurrent GBM [28, 29]. Friedman *et al.* randomized 167 patients with recurrent GBM to receive bevacizumab alone or in combination with irinotecan, the estimated 6-month PFS was 42.6 and 50.3% respectively, and OS was 9.2 and 8.7 months respectively [29]. Sixty five percent of patients receiving both drugs experienced grade 3 and 4 adverse events (most common convulsion, neutropenia and fatigue), in the bevacizumab group 46% had grade 3 and 4 adverse events (most common hypertension, convulsion) [29].

Based on increased rates of grade 3 and 4 toxicities with irinotecan-based regimens, the question was raised regarding the true benefit of adding irinotecan to bevacizumab as treatment for glioblastoma. Fine and colleagues conducted a study with bevacizumab alone and the response rate was similar, about 60% [30]. These results were recapitulated by other studies comparing bevacizumab monotherapy in comparison with combination arms, with short term benefit in PFS which did not translate into improvement in overall survival [29]. Kreisl et al. studied 48 heavily pretreated patients with recurrent GBM, patients received bevacizumab as monotherapy and then after tumor progression they were treated with bevacizumab plus irinotecan, 35-71% of patients showed radiographic response with bevacizumab alone there were not objective radiographic responses in the patients that received both drug [31]. The most common adverse effects of bevacizumab were thromboembolic events, hypertension, hyperphosphatemia and thrombocytopenia [31]. The data from the previously reported trials has been extrapolated to patients with BM.

USES OF ANTI-VEGF THERAPY IN PATIENTS WITH BRAIN METASTASES

The incidence of BM has increased as a result of use of better neuroimaging and improvements in systemic therapies [6]. Limited therapeutic options exist for patients with parenchymal BM and until 2017 guidelines for management of BM were not available [6]. Whole brain radiation therapy and stereotactic radiosurgery improved response and progression free survival of patients with BM [32-34]. Chemotherapy has been the mainstay for treatment of solid tumors and some regimens are used to control systemic disease and BM. Apart from systemic chemotherapy, few other CNS directed chemotherapy regimens have been tested in patients with BM. Most of them have been extrapolated from experience GBM. Chemotherapy in combination with radiation has also been explored in brain metastases from other primary sites and has yielded greater response than either chemotherapy or radiation alone; unfortunately, no survival advantages have been seen [35].

Based on previous studies showing good outcomes with bevacizumab in solid tumors and GBM, multiple trials have been published since 2012 trying to assess anti-VEGF therapy efficacy and safety in patients with BM. Significant advances have been made for NSCLC that is the most lethal cancer and the cancer that most commonly metastasizes to the brain; the NSCLC trials are summarized in Table **3** [36]. There are also multiple ongoing trials summarized in Table **4** [37].

Most large studies are for patients with lung cancer and melanoma. There are small case series about the use of anti-VEGF therapy in renal cell carcinoma, colorectal carcinoma, hepatocellular carcinoma and other malignancies [38]. The guidelines from the European Society of Neuro-Oncology (EANO) from 2017 recommend using bevacizumab for radiation necrosis; they also describe some benefit in patients with NSCLC based on the BRAIN trial [6, 39].

Bevacizumab is a monoclonal antibody that binds VEGF-1 and is approved for treatment of metastatic colorectal, lung ovarian and kidney cancer as well as GBM, given that this drug showed promising outcomes more targeted therapies have been developed [8]. Ramucirumab is a fully human IgG1 monoclonal antibody that targets VEGF-2, it was first approved in 2014 for previously treated gastric cancer based on the REGARD and RAINBOW studies that showed that remucirumb as monotherapy or in combination with paclitaxel are associated with good outcomes in patients with gastric-junction adenocarcinoma [40, 41]. The drug is also approved

Table 3. Anti-VEGF Therapy in Non-Small Cell Lung Cancer.

Study	Author, Year	Type of Study	Treatment	Patients with BM N (%)	Comments/Outcomes
PASSPORT	Socinski, 2009 (55)	Phase 2	First-line: bev with platinum-based doublet therapy or erlotinib. Second-line: bev with single-agent chemotherapy or erlotinib, until progression or death	115 (100)	Safety trial, CNS hemorrhage grade 2+ was reported in 0 patients. 34% of patient progressed. Median treatment duration 85 days
SAiL	Crino, 2010 (53)	Phase 4	First line: Bev plus standard chemotherapy for up to six cycles, followed by single-agent bev until disease progression	281 (12.7)	CNS hemorrhage grade 3-5 in less than 1%. Of note BM was an exclusion criterion, the patients reported developed BM during treatment
BeTa	Herbst, 2011(64)	Phase 3	First line: erlotinib with bev, or erlotinib with placebo	37 (11.6)	No improvement in OS
ATLAS	Johnson, 2013 (56)	Phase 3	First line: bev with placebo or bev with erlotinib	29 (3.9)	Addition of erlotinib to bev improved PFS (3.7 vs 4.8 months) but no OS
REVEL	Garon, 2014 (42)	Phase 3	Second line: docetaxel and ramucirumab or docetaxel and placebo	Not reported, patients with BM not excluded	No CNS hemorrhage reported
ARIES	Lynch, 2014 (65)	Prospective cohort	There were no protocol-defined treatments or assessments. The dosing of bev and chemotherapy, and the choice of chemotherapy regimen, was at the discretion of the treating physician	150 (8.8)	CNS hemorrhage grade 3-5 in 3 patients (0.2%)
ERACLE	Galetta, 2015 (66)	Phase 3	First line: cisplatin, pemetrexed and pemetrexed maintenance or carboplatin with paclitaxel and bev with bev maintenance	2 (3.4)	Underpowered study, quality of life did not differ between groups
PRONOUNCE	Zinner, 2015 (67)	Phase 3	First line: carboplatin, pemetrexed and pemetrexed maintenance or carboplatin with paclitaxel and bev with bev maintenance	32 (17.9)	PFS and OS did not differ between groups
BRAIN	Besse, 2015 (39)	Phase 2	First line: bev plus carboplatin and paclitaxel. Second line: bev plus erlotinib	91 (100)	One grade 1 intracranial hemorrhage occurred and resolved without sequelae

Abbreviations: OS: overall survival, PFS: progression free survival, Bev: bevacizumab, CNS: central nervous system, BM: brain metastases, OS: overall survival, PFS: progression free survival

Table 4. Ongoing Trials for Bevacizumab in Brain Metastases [37].

Trial	Phase	Institution or Sponsor
Bevacizumab with etoposide and cisplatin in breast cancer patients with brain and/or leptomeningeal metastases	II	National Taiwan University Hospital
Safety evaluation of a combination of brain radiation therapy and bevacizumab for treatment of brain metastasis	I	Centre Francois Baclesse
Bevacizumab, etoposide and cisplatin followed by whole brain radiotherapy in breast cancer in brain metastases (A-Plus)	II	National Taiwan University Hospital
Pemetrexed/cisplatin with or without bevacizumab in brain metastases from non-squamous non-small cell lung cancer	II	Sun Yat-sen University
Pembrolizumab plus bevacizumab for treatment of brain metastases in metastatic melanoma or non-small cell lung cancer	II	Yale Univesrity

Fractionated stereotactic radiosurgery with concurrent bevacizumab for brain metastases: a phase I dose-escalation trial	I	National Taiwan University Hospital
Bevacizumab and erlotinib in lung cancer with brain metastases	II	National Taiwan University Hospital
Bevacizumab in patients with recurrent brain metastases who have failed whole brain radiation therapy	II	Northwestern University

for the second line for metastatic non-small lung cancer (NSCLC) in combination with docetaxel based on the REVEL trial that compared docetaxel and deocetaxel plus ramucirumab, the combination arm had improvements in OS and PFS; it is important to mention that patients with stable, treated BM were included in this study [42]. Aflibercept is a fusion protein that consists of human VEGFR-1 and VEGFR-2 extracellular domains fused to hinge affinity human IgG1 Fc domain, this drug has been most widely used in colorectal cancer, the VELOUR trial that showed that adding afilbercept to FOLFIRI in previously treated patients was associated to better outcomes; additionally, two trials have shown some benefit in patients with NSCLC however this did not include patients with BM [43-45]. Some multi-targeted small molecules with anti-anigogenic properties have also been used with promising results, the most widely studied are sunitinib (approved for renal cell carcinoma (RCC), neuroendocrine pancreatic cancer and being studied for NSCLC with BM) and sorafenib (approved for RCC, liver and thyroid cancer, also being studied for NSCLC) [46].

In case of breast cancer, bevacizumab was first granted an "accelerated" FDA approval in 2008 based on the results of the E2100 trial that showed benefits of the combination of weekly paclitaxel and bevacizumab as first line treatment of HER-2 negative metastatic breast cancer; however, after two years the FDA reversed this decision due to safety concerns and no any added benefit in PFS. Since then the use of bevacizumab in breast cancer has fallen out of favor [47, 48].

SAFETY OF ANTI-VEGF THERAPY IN PATIENTS WITH BRAIN METASTASES

Given the encouraging data on the use of bevacizumab in GBM, further expansion of its use in BM was deemed worthy of exploration. However, patients with BM were excluded during the initial registration trials of bevacizumab in solid tumors; based on a previous report patients with BM have been excluded from 76% of phase I and II trials and 82% of randomized studies [49]. The initial reluctance regarding the use of bevacizumab in patients with brain metastases was based on a report of a patient with hepatocelluar carcinoma (HCC) who had undiagnosed BM who subsequently developed intracranial hemorrhage in a phase I study while on bevacizumab [50]. Patients with HCC are also more prone to develop coagulopathy associated mucosal and systemic bleeding, with consequent increased rate of spontaneous intracerebral hemorrhages [51].

Carden et al. provided an elegant review that included 57 eligible trials on the risk of intracranial bleeding during anti-VEGF therapy with bevacizumab, sorafenib, sunitinib and a varietynof other agents [49]. Among the phase I and II trials that excluded patients with CNS metastases, only 2 episodes in 1,755 patients (< 1%) of CNS bleeding was observed [49]. Similarly, in phase I and II studies that did not exclude patients with intracerebral metastases, only one episode of bleeding was observed in the 524 patients treated with anti-VEGF therapy (< 1%) (49). Of the 11 randomized phase III trials identified which included 5,476 patients, 9 of the 11 studies excluded patients with brain metastases; of the two studies that included patients with brain metastases, bleeding was observed in only 1 patient (< 1%), which correlated with a similar rate of bleeding in the control arm of these studies [49]. Similarly, of the 9 studies that excluded brain metastases, only one study reported 1% of CNS bleeding in the bevacizumab arm [49]. This analysis provided insight into the paucity of significant risk of intracranial bleeding in patients with BM who receive anti-angiogenic therapy.

These findings are shown in several other studies, the use of bevacizumab does not appear to increase the rates of intracranial bleeding as shown in a review of 13 randomized controlled trials by Dr. Besse et al [52]. In the retrospective analysis, the rate of cerebral hemorrhage was 3.3% in the bevacizumab-treated group compared with 1% in the non-bevacizumab group [52]. Mortality rates were similar in both groups [52]. The SAiL and the ATHENA were two large open-labeled single arm studies in lung and brain cancer respectively, both reported only 0.9% of patients developing cerebral hemorrhage [53, 54]. Based on these findings, more recent studies have incorporated bevacizumab in solid tumors like colon and lung, especially in those who have BM.

While these studies are retrospective, several prospective studies using anti-angiogenic therapy have also been conducted. The PASSPORT study was a phase II open label multicenter trial to answer the question of safety of using bevacizumab in patients with NSCLC and previously treated BM [55]. Patients received bevacizumab with platinum-based doublet therapy or erlotinib depending on the investigator, followed by single agent bevacizumab therapy until disease progression [55]. None of the patients developed more than grade 2 CNS hemorrhage although there were 2 grade 5 toxicities, both were pulmonary hemorrhages that led to death, concluding that bevacizumab added to chemotherapy appeared to be safe from the intracranial bleeding standpoint [55]. Another prospective trial looking at the safety of bevacizumab with or without erlotinib in patients with NSCLC was the ATLAS trial, which included 714 patients with stable BM, showed an incidence of grade 2 intracranial bleeding of about 0.8%; the addition of erlotinib had a mild impact of PFS but not in OS and had increase in toxicities [56].

Given these data, it appears as though patients with BM are at a similar risk of developing cerebral hemorrhage, independent of bevacizumab therapy, thereby supporting the safety of the use of bevacizumab in the treatment of BM. An interesting approach with anti- VEGF inhibitors is to combat radiation-induced cerebral necrosis and reduce steroid use in these patients [57, 58]. Cerebral radiation necrosis (CRN) results from the death of endothelial cells leading to vasogenic edema, hypoxia that leads to an increase VEGF production [59]. Small series of patients suffering from CRN were treated with bevacizumab with improved outcome [57].

AREAS OF UNCERTANTY

Even though significant advances have been made in the last 7 years, several questions remain unanswered. Among them is that while treatment with bevacizumab brings about longer PFS survival, similar benefits in overall survival are small or lagging. Another concern is the challenge of determining progression using traditional staging techniques. Imaging modalities can be difficult to interpret since restoration of vessels may interfere with contrast penetration to the tissue [60]. It has been proposed that treatment does not affect tumor growth, but changes the pattern of progression to a more invasive angiogenesis-independent phenotype [60, 61]. While anti-angiogenic therapy was initially thought to be free of development of resistance as seen in cytotoxic agents, there have been several mechanisms of anti-angiogenic resistance proposed [62]. Another concern is that the restoration of the BBB could theoretically render insufficient penetration of chemotherapy [63]. Despite these challenging issues, the use of angiogenesis inhibitors remains a valid approach to treating primary brain tumors and exploration of its use in metastatic brain tumors.

CONCLUSIONS

Antiangiogenic agents are showing promising results in patients with primary brain tumors. Drugs are well tolerated with manageable and dose-dependent toxicity profile and large studies have shown that the risk for intracerebral hemorrhage is not increased in patients with BM. The treatment for CNS metastases is slowly evolving, and the hopes of better response, and eventually improvement in survival, are increasingly anticipated.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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