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Anti-Angiogenic Therapy for Malignant Glioma: Insights and Future Directions

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1. Introduction

Malignant gliomas comprise a significant number of new cases of brain cancer diagnosed in the United States each year. Despite recent therapeutic advances, they remain associated with high morbidity and mortality rates. The current standard of care for newly diagnosed malignant gliomas includes surgical resection followed by radiotherapy with concomitant and adjuvant Temozolomide. Bevacizumab, a humanized anti-VEGF (vascular endothelial growth factor) monoclonal antibody, has recently gained FDA approval for use in the treatment of recurrent glioblastoma multiforme (GBM), based on clinical trials that revealed both efficacy and favorable side-effects. Anti-angiogenic therapy has raised new hopes, new basic and clinical questions, and has uncovered new insights into the biological and clinical behavior of these tumors. Here, we review the medical, social, and economic significance of gliomas, discuss briefly the evolution of therapeutic modalities leading to anti-angiogenesis, depict the basic mechanisms of angiogenesis, detail data from Bevacizumab clinical trials, and address new clinical issues leading to the revision of the Macdonald criteria. We close with unresolved questions and potential future directions.

2. Significance of malignant gliomas

2.1 Demographics

The annual incidence of malignant gliomas is approximately 4 to 5 per 100 thousand; they account for approximately 70% of the total number of new cases of malignant primary brain tumors diagnosed in adults in the United States each year (Wen and Kesari 2008; Wen, Macdonald et al. 2010). The overall incidence of gliomas is higher among males as compared to females (7.2 per 100,000 person-years in males versus 5.0 per 100,000 person-years in females); it is highest among Caucasians and it also increases with age (Peak and Levin 2010). Glioblastoma multiforme (GBM) is the most aggressive glioma. Stupp and colleagues reported overall survival at 2 years to be 26.5 percent among patients who received combination treatment with radiotherapy and Temozolomide and 9.8 percent at 5 years (Stupp, Mason et al. 2005; Stupp, Hegi et al. 2009). For patients diagnosed with anaplastic astrocytoma, a malignant glioma subtype, the median survival is higher at approximately 2 to 5 years (Wen and Kesari 2008). It is worth mentioning that the aforementioned survival statistics do not take into account the therapeutic effects from the current use of anti-angiogenic agents.

2.2 Economic impact

The economic impact of cancer is significant. At the present time, cancer is the second leading cause of death in the United States and, as a result of high mortality and morbidity, cancer is also a major cause of loss of productivity among American adults. In the year 2000, the U.S. annual productivity cost from cancer mortality was estimated to be 115.8 billion dollars and the projected cost for the year 2020 is 147.6 billion dollars. Death from brain cancer was estimated to be the third most costly cancer per death in the year 2010, preceded by testicular and Non-Hodgkin Lymphoma, respectively. Furthermore, death from brain cancer in men younger than 35 years of age caused the most negative impact on productivity. Another important factor to consider is the impact of cancer on caregivers and on households in general. In particular, the costs increased significantly to 232.4 billion dollars in 2000 when the value of care-giving and household activities were included; the numbers are projected to be even higher in 2020 at 308 billion dollars (Bradley, Yabroff et al. 2008). Because of its neurological morbidity, patients with brain cancer require significant care-giving and are the focus of many household activities, thus contributing to the overall cost. In particular, because almost 10 percent of GBM patients survive 5 or more years (Stupp, Hegi et al. 2009), the survivors require significant care. For example, Steinbach and colleagues have reported that patients with GBM experience neurologic impairment, psychiatric symptoms, neuro-cognitive deficits, and severe fatigue that result in significant impairment of function, including inability to work and participate in day-to-day and social activities (Steinbach, Blaicher et al. 2006). Furthermore, Hottinger and colleagues found that 85 percent of long-term survivors of GBM had at least one significant neurological deficit leading to a decline of the median Karnofsy Performance Scale (KPS) value from that at the time of initial diagnosis (from 90 to 70). This decline ultimately results in impaired day-to-day function (Hottinger, Yoon et al. 2009).

2.3 Evolution of the therapeutic strategies

In the 1970s, the Brain Tumor Study Group (BTSG), a group of neurosurgeons, neuropathologists, and radiotherapists, in conjunction with the National Cancer Institute, performed a clinical trial that evaluated the use of BCNU, 1,3-bis(2-chloroethyl)-1-nitrosurea, versus radiotherapy (both alone and in combination) versus supportive care alone. The results of this trial, published in 1978, showed only a slight but statistically-insignificant increase in the median survival times of patients treated with BCNU alone (18.5 weeks) as compared to those who received best supportive care (14 weeks). However, those who received radiotherapy alone experienced a statistically significant improvement in the median survival times (36 weeks). Moreover, as compared to the radiotherapy alone arm, the combination of radiotherapy and BCNU did not yield a statistically-significant effect on survival times. Nonetheless, the data showed a trend for better survival at 2 years (Walker, Alexander et al. 1978). After this trial, BCNU became the drug most commonly used as adjuvant therapy with radiation. Since then, many trials were conducted to investigate the effects of the addition of various chemotherapeutic agents to radiotherapy (Levin, Wara et al. 1985; Prados, Scott et al. 1999). The standard of care for newly diagnosed GBM changed in 2005, after the results of a large phase III clinical trial of post-operative radiotherapy with concomitant and adjuvant Temozolomide (Stupp, Mason et al. 2005).

Temozolomide is a second generation alkylating agent developed in the 1980s which is rapidly and completely absorbed via oral administration; it also has excellent penetration

into many tissues, including the brain. Another key advantage of Temozolomide is that it does not require enzymatic demethylation in the liver in order to be converted into its active species. Instead, it is spontaneously activated at physiological pH in aqueous solution (Stupp, Gander et al. 2001).

Three key phase II clinical trials collectively supported the conclusion that Temozolomide is effective against malignant gliomas (Stupp, Gander et al. 2001). The first was conducted by Yung and colleagues in patients with malignant astrocytomas at first relapse. The results revealed 6- and 12-month progression-free survival (PFS) rates of 46 and 24 percent, respectively; the median PFS time was 5.4 months. This study not only supported the use of Temozolomide as a single agent in the treatment of malignant astrocytoma, but it also revealed that it is well-tolerated. The most commonly reported adverse events were nausea and vomiting, which were easily controlled with standard anti-emetic therapy (Yung, Prados et al. 1999). Brada and colleagues studied Temozolomide in patients with GBM at first relapse. The results showed a 6-month PFS rate of 18 percent and a median PFS time of 2.1 months. This study also revealed that Temozolomide has a favorable side-effect profile (Brada, Hoang-Xuan et al. 2001). In 2000, Yung and colleagues compared Procarbazine versus Temozolomide in GBM patients at first relapse. This trial revealed a statistically-significant improvement in 6-month PFS rates, 21 percent for Temozolomide verses 8 percent for Procarbazine (Yung, Albright et al. 2000).

In 2005, Stupp and colleagues published the results of a randomized, multi-center, phase III clinical trial that compared concomitant and adjuvant Temozolomide with radiotherapy to radiotherapy alone in patients with newly diagnosed GBM. This study demonstrated an increase in mean survival time of 2.5 months, which was both clinically and statistically significant. It also demonstrated that at 2 years, the radiotherapy plus Temozolomide group had a survival rate of 26.5 percent, as opposed to a 10.4 percent survival rate in the radiotherapy group alone (Stupp, Mason et al. 2005). Again, the 5 year survival rate for the combination therapy group was 9.8 percent versus 1.9 percent for the radiotherapy alone group (Stupp, Hegi et al. 2009). Alkylating chemotherapeutic agents, including Temozolomide, induce DNA lesions that are repaired by the O^6-methylguanine-DNA methyltransferase (*MGMT*) protein. Thus, high levels of *MGMT* activity diminish their therapeutic effects. Interestingly, Temozolomide-treated patients whose *MGMT* promoter elements were epigenetically silenced by methylation, had a statistically-significant improvement in overall survival times (Hegi, Diserens et al. 2005). Promoter methylation lowers *MGMT* levels/activity, thus impairing the ability of the cancer cells to repair and survive the DNA damage.

3. Angiogenesis

3.1 History
The idea of anti-angiogenesis as a concept for therapy of tumors was first proposed by Dr. Folkman in the 1970s (Folkman 1972). This subject has continued to be studied in terms of the development of targeted therapies and by elucidating the mechanism of action.

3.2 Summary of angiogenesis
Angiogenesis is the process by which the vascular system is formed through growth of new capillaries from pre-existing vessels. Angiogenesis plays a critical role in key physiologic

processes such as embryogenesis, regeneration, and wound healing. And although angiogenesis is usually regarded as a formative process, it is also involved in various pathologic processes, including age-related macular degeneration, rheumatoid arthritis, and tumor growth and development, which is the focus of this chapter (Wang, Fei et al. 2004).

Of note, there are 2 types of angiogenesis: sprouting and splitting, and in this discussion, the term "angiogenesis" will refer to the sprouting type. The process of angiogenesis can be briefly summarized as follows. First, there is vasodilation, in response to nitric oxide, and increased permeability of the existing vessels. This step is then followed by degradation of the existing vessel's basement membrane and subsequent migration of endothelial cells to this area. After the endothelial cells arrive, they begin to proliferate and mature into capillaries via a balance of both growth and inhibition. The final steps involve the recruitment of pericytes and vascular smooth muscle cells that form a new network of mature vessels (Shinkaruk, Bayle et al. 2003).

3.3 Molecular signals of angiogenesis, VEGF

Although there is a great diversity in the factors and signals that contribute to angiogenesis, the chemical signal that seems to play the most critical role in the process is Vascular Endothelial Growth Factor, or VEGF. VEGF is a pro-angiogenic growth factor that is secreted by many cells, including mesenchymal, stromal, and especially tumor cells. VEGF induces the migration of the endothelial precursor cells to sites of angiogenesis and is also responsible for the proliferation and differentiation of these cells. The VEGF gene is located on chromosome 6p12 and the gene family is composed of 5 members, namely VEGF-A, VEGF-B, VEGF-C, VEGF-D, and placental-derived growth factor (PlGF). Of these, VEGF-A, B, and PlGF are involved in proliferation of the vascular system and VEGF-C and D are involved in the development of the lymphatic system (Ahluwalia and Gladson 2010). VEGF primarily signals through its receptor VEGFR2, which is a tyrosine kinase receptor, expressed by many cells, including endothelial cells, endothelial cell precursors, and tumor cells. The interaction between VEGF and VEGFR2 is heavily involved in both the physiologic and pathologic effects of VEGF (Jain, di Tomaso et al. 2007)
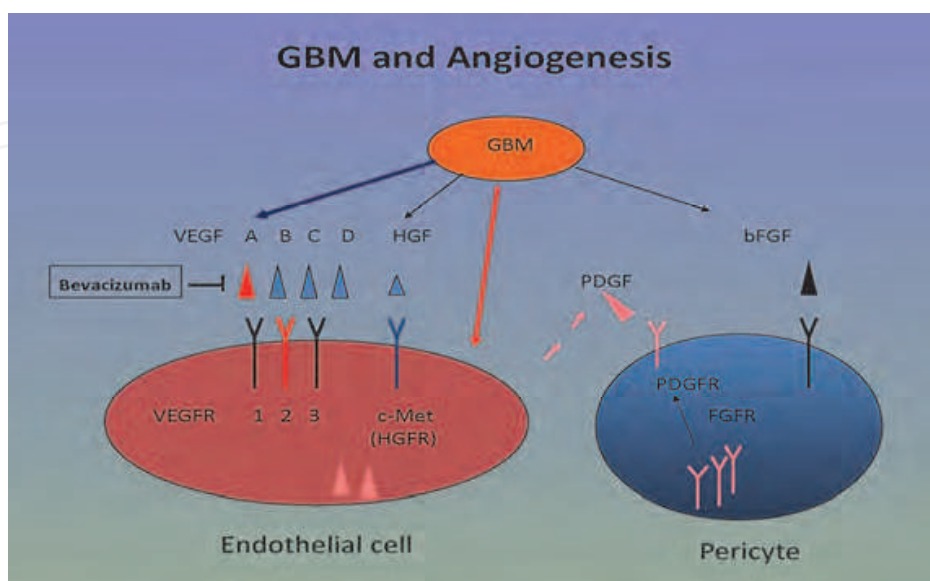

Fig. 1. GBM tumors influence multiple pathways of angiogenesis.

GBM cells secrete angiogenic molecules including VEGF, Hepatocyte Growth Factor (HGF), and basic Fibroblast Growth Factor (bFGF), which interact with their respective receptors on either endothelial cells or pericytes. Specifically, VEGFA interacts with VEGFR2, HGF with c-Met, and bFGF with FGFR. Bevacizumab is believed to block the interaction of VEGF with its receptors. Endothelial cells secrete PDGF, which promotes recruitment of pericytes. bFGF/FGFR interaction promotes PDGFR expression leading to enhanced recruitment of pericytes. The red arrow illustrates the fact that tumor-derived endothelial cells arise from the GBM tumor.

Other chemical signals that play an important role in angiogenesis are fibroblast growth factor, HGF, tumor necrosis factor-alpha (TNF-α), transforming growth factor-beta (TGF-β), angiopoietins, and platelet derived growth factor (PDGF). The function of these signals ranges from involvement in extracellular matrix degradation to endothelial proliferation and migration and then ultimately to neo-vessel stabilization and maturation (Martin and Jiang 2010; Ucuzian, Gassman et al. 2010).

3.4 Details of angiogenesis

In the first steps of angiogenesis, the vessels become leaky and dilate. Then, there is proteolytic degradation of the endothelial cell's basement membrane. This degradation is mainly carried out by matrix metalloproteinases (MMPs), which are zinc-dependent extracellular matrix (ECM) endopeptidases that work to expose the endothelial cells to other signaling factors important for regulation of angiogenesis and migration of endothelial cells (Ahluwalia and Gladson 2010; Gialeli, Theocharis et al. 2011). These factors bind to specific receptors on the endothelial cells, such as the integrin cell adhesion receptors, which promote endothelial cell survival, proliferation, and migration. This process proceeds through specific cooperation with other angiogenic pathways that originate from VEGFR2 and FGFR. Next, pericytes are recruited to help form a new endothelial cell basement membrane and provide stabilization of the growing neo-vessel (Ahluwalia and Gladson 2010). Please see Figure.

The controlled and precise development of endothelial cells into patterned vessels is thought to be controlled by the fundamental Notch pathway that regulates cell differentiation in many mammalian cell-types. Delta-Notch signaling is a form of cell-to-cell communication that plays a role in determining differentiation of cells within similar groups. The Notch pathway in mammals is comprised of 4 Notch trans-membrane receptors (Notch 1-4) and 5 membrane-bound Notch ligands. Of these, Notch 1, 3, and 4 receptors and ligands Delta-like 1 (DLL1), Delta-like 4 (DLL4), and Jagged1 play a role in angiogenesis (Thurston and Kitajewski 2008). Of note, Notch signaling regulates angiogenesis by simultaneously activating and repressing vessel sprouting. In particular, DLL4 is a selective inhibitor of VEGF; signals downstream from DLL4 and Notch 1 repress vessel sprouting by restricting the response of tip cells to VEGF. Tip cells are specialized endothelial cells located at the leading edge of blood-vessel sprouting (Jain, di Tomaso et al. 2007).

Circulating endothelial precursors (CEPs), which are bone marrow-derived, were previously recognized as the main source of vascular endothelial cells. Recently, Soda and colleagues examined endothelial cells in tumor samples collected from human GBM xenografts implanted in immunodeficient mice as well as in GBM tumors induced in $p53^{+/-}$ heterozygous mice by lentiviral delivery of oncogenes. Unexpectedly, their findings showed the presence of tumor derived endothelial cells (TDECs) suggesting that the endothelial cells transdifferentiated from the neuroectoderm, not from the CEPs. This data also suggests that

this process may be independent of signaling from VEGF and FGF and may help to explain resistance mechanisms to anti-VEGF therapy (Soda, Marumoto et al. 2011).

3.5 Targeting angiogenesis

Dr. Folkman observed that brain tumors appear to be highly dependent on endothelial cell proliferation and hypothesized that anti-angiogenic therapy may be particularly useful in the treatment of brain cancer (Folkman 1972). Angiogenesis is crucial for supplying tumors with nutrients, oxygen, and growth factors time (Khasraw and Lassman 2010). Malignant tumors in general, and gliomas in particular, are very vascular and they secrete VEGF (Peak and Levin 2010). Thus, VEGF is a prime target for anti-angiogenic therapy, leading to the development of Bevacizumab (Ahluwalia and Gladson 2010).

4. Anti-angiogenesis

4.1 Introduction to bevacizumab

Bevacizumab (Avastin) is a recombinant humanized monoclonal antibody that targets VEGF; it was the first anti-angiogenesis agent to be approved by the United States Food and Drug Administration (FDA) in 2004. Bevacizumab was initially approved for use in metastatic colorectal cancer. Nevertheless, its clinical use has been extended to other cancers, including lung, breast, renal cell, and glioblastoma (Van Meter and Kim 2010).

Study and Publication Year	Agents Studied	No of Patients	Radiographic Response Rate, %	6-mo PFS, %	Median PFS Time (months)	Median OS Time (months)
Vredenburgh, Desjardins et al. 2007	Bevacizumab + Irinotecan	35	57	46	6	10.5
Friedman, Prados et al. 2009	Bevacizumab + Irinotecan	82	37.8	50.3	5.6	8.7
Reardon, Desjardins et al. 2009	Bevacizumab + Etoposide	27	23	44.4	4.5	11.6
Gutin, Iwamoto et al. 2009	Bevacizumab + Radiation	20	50	65	7.3	12.5
Sathornsumetee, Desjardins et al. 2010	Bevacizumab + Erlotinib	25	48	29.2	4.5	11.2
Verhoeff, Lavini et al. 2010	Bevacizumab + dose-intense Temozolomide	23	20	6.7	2.6	3.9
Hasselbalch, Lassen et al. 2010	Bevacizumab + Cetuximab + Irinotecan	43	26	33	4	7.5

Table 1. Prospective Phase II Clinical Trials of Bevacizumab + Other Therapies for Recurrent GBM. PFS = Progression Free Survival, OS = Overall Survival.

4.2 Mechanism of action of bevacizumab

Bevacizumab has 6 VEGF binding residues that neutralize the ability of VEGF to bind to its target receptors on endothelial cells. This neutralization has been shown to have efficacy not only in *in vitro* studies, but also in *in vivo*. In 2004, Willet and colleagues treated 6 patients with primary and non-metastatic colorectal cancer with adjuvant Bevacizumab in a phase I clinical trial. The results revealed significant reduction in tumor blood volume and perfusion and micro-vascular density (MVD) (Willett, Boucher et al. 2004); thus yielding positive evidence of the anti-angiogenic effects of Bevacizumab in human cancer.

The therapeutic effects of Bevacizumab against cancer have been illustrated by several clinical trials. In 2004, Hurwitz conducted a randomized double-blinded phase III clinical trial of Bevacizumab plus irinotecan, fluorouracil, and leucovorin (IFL) versus IFL plus placebo in colorectal cancer. Subjects treated with Bevacizumab experienced significant prolongation in 1-year survival rates (74.3 percent vs. 63.4 percent), in the median duration of PFS time (10.6 months vs. 6.2 months), in response rates (44.8 percent vs. 34.8 percent), and in the median duration of response time (10.4 months vs. 7.1 months) (Hurwitz, Fehrenbacher et al. 2004). In 2007, Giantonio reported that the addition of Bevacizumab led to a significant prolongation of the median duration of survival time of patients with recurrent metastatic colorectal cancer (12.9 months versus 10.8 months) (Giantonio, Catalano et al. 2007).

Study and Publication Year	Agents Studied	No of Patients	Overall Radiographic Response Rate, %	6-mo PFS, %	Median PFS Time (months)	Median OS Time (months)
Kreisl, Kim et al. 2009	Bevacizumab single agent	48	35	29	4	7.8
Friedman, Prados et al. 2009	Bevacizumab single agent	85	28.2	42.6	4.2	9.2
Raizer, Grimm et al. 2010	Bevacizumab single agent	50	NA	25	NA	6.5

Table 2. Prospective Phase II Clinical Trials of Single-agent Bevacizumab for Recurrent GBM. PFS = Progression Free Survival, OS = Overall Survival.

4.3 Clinical activity of bevacizumab against recurrent GBM

Stark-Vance treated 21 patients, 11 with GBM and 10 with other high-grade gliomas, with the combination of Bevacizumab and Irinotecan, a topoisomerase 1 inhibitor. Interestingly, 1 patient had a complete response (CR), 8 patients had partial responses (PR), and 11 patients had stable disease (SD) (Stark-Vance 2005). This observation suggested that Bevacizumab may be active against high-grade gliomas and led to prospective clinical trials (Chamberlain 2010).

Since the initial work by Stark-Vance, several phase II clinical trials have studied the therapeutic efficacy of Bevacizumab as a single-agent or in combination with chemotherapy

or radiation for recurrent GBM (see Tables 1 and 2). The results support the conclusion that Bevacizumab is effective as a single-agent for recurrent GBM. In particular, the prospective studies, detailed in Table 2, reveal 6-month PFS rates ranging from 25 to 42.6 percent and median OS times from 6.5 to 9.2 months; these outcomes are statistically significant as compared to historical controls of salvage chemotherapy (Friedman, Prados et al. 2009; Kreisl, Kim et al. 2009; Raizer, Grimm et al. 2010). Retrospective studies have also supported the same conclusion. Agha and colleagues reviewed 18 patients diagnosed with recurrent malignant gliomas with Bevacizumab alone versus salvage chemotherapy. Half of the patients in the Bevacizumab arm remained progression-free at 12 months, while all patients treated with salvage chemotherapy died within 6 months. It is also important to note that 7 of 8 patients in the group treated with Bevacizumab alone showed a radiological response as compared to 4 of 10 patients in the group treated with salvage chemotherapy (Agha, Ibrahim et al. 2010). In another retrospective analysis of 50 adult patients with GBM treated with single-agent Bevacizumab, the results revealed efficacy with 6- and 12- month PFS rates of 42 and 22 percent, respectively (Chamberlain and Johnston 2010).

On the other hand, data from prospective studies also support the idea that the addition of chemotherapy or radiation therapy to Bevacizumab does not yield a clear therapeutic benefit for recurrent GBM (see Table 1). In particular, the 6-month PFS rates ranged from 6.7 to 65 percent, the median PFS time ranged from 2.6 to 7.3 months, and the median OS time ranged from 3.9 to 12.5 months (Vredenburgh, Desjardins et al. 2007; Friedman, Prados et al. 2009; Gutin, Iwamoto et al. 2009; Reardon, Desjardins et al. 2009; Hasselbalch, Lassen et al. 2010; Sathornsumetee, Desjardins et al. 2010; Verhoeff, Lavini et al. 2010). Notably, the BRAIN study evaluated the efficacy of Bevacizumab alone and in combination with Irinotecan in patients with recurrent GBM in a phase II, non-comparative trial. The 6-month PFS rates were 42.6 percent (97.5 percent CI, 29.6 percent to 55.5 percent) and 50.3 percent (97.5 percent CI, 36.8 percent to 63.9 percent) in the Bevacizumab arm and the Bevacizumab plus Irinotecan arm, respectively. Both groups exceeded the historical 15 percent 6-month PFS rate for salvage chemotherapy and Irinotecan alone ($p < 0.0001$) (Friedman, Petros et al. 1999; Cloughesy, Filka et al. 2003; Raymond, Fabbro et al. 2003; Prados, Lamborn et al. 2006; Friedman, Prados et al. 2009). The objective response (OR) rates were 28.2 percent (97.5 percent CI, 18.5 percent to 40.3 percent) and 37.8 percent (97.5 percent CI, 26.5 percent to 50.8 percent) for the Bevacizumab and the combination groups, respectively (Friedman, Prados et al. 2009). Therefore, it is unclear whether the therapeutic benefits of adding Irinotecan exceed those of single-agent Bevacizumab. The possibility of a small therapeutic benefit may be resolved by future studies that include a larger number of patients.

4.4 Bevacizumab for treatment of primary GBM

Because of the positive results in recurrent GBM, recent research has focused on the therapeutic benefits of Bevacizumab in conjunction with Temozolomide for newly-diagnosed GBM. Lai and colleagues conducted a prospective phase II study evaluating Bevacizumab in combination with radiation therapy and Temozolomide in 70 newly diagnosed GBM patients. They compared the results to a retrospectively reviewed cohort of patients treated with standard of care of radiation therapy and Temozolomide. The findings reveal a statistically-significant improvement in PFS time, 13.6 months (95 percent CI, 11.1 to 16.5 months) versus 7.6 months (95 percent CI, 5.9 to 10.8 months) in the control group, but lack of benefit in OS times (Lai, Tran et al. 2011). These results have paved the way for 2 large, prospective, randomized phase III clinical trials in newly diagnosed GBM, sponsored

by the Radiation Therapy Oncology Group (RTOG, trial RTOG-0825) and Roche (AVAglio) (Chamberlain 2010; Chinot, de La Motte Rouge et al. 2011).

4.5 Bevacizumab associated toxicities

Bevacizumab is generally well-tolerated. Nevertheless, its potential side effects include hypertension, thrombo-embolic events, bleeding complications (including intracranial hemorrhage), fatigue, proteinuria, impaired wound healing, and bowel perforation (Dietrich, Norden et al. 2008). Hypertension appears to be related to the physiologic role of VEGF in regulating vasomotor tone and blood pressure, possibly through regulation of nitric oxide synthase expression (Facemire, Nixon et al. 2009).

In the BRAIN study discussed above, fatigue, headache, and hypertension were the most common adverse events in the Bevacizumab group, while fatigue, diarrhea, and nausea were the most common adverse events in the Bevacizumab plus Irinotecan group. The rate of grade 3 adverse events was 46.4 percent in the Bevacizumab-alone arm and 65.8 percent in the combination arm (Friedman, Prados et al. 2009). There is some evidence to suggest that the rate of grade 3 adverse events is lower when Bevacizumab is used as a single-agent, rather than in combination based regimens (Friedman, Prados et al. 2009; Chamberlain 2010). Rare complications affecting the central nervous system have been observed in GBM patients treated with Bevacizumab, namely Posterior Reversible Leuko-encephalopathy Syndrome (PRES) and optic neuropathy (Hinchey, Chaves et al. 1996; Glusker, Recht et al. 2006; Sherman, Aregawi et al. 2009).

4.6 Bevacizumab and assessment of tumor response

The Macdonald criteria, developed for 2-dimensional CT (computed tomography) scans, have been considered the standard to assess response or progression of malignant gliomas since 1990. These criteria have since been applied to MRIs (magnetic resonance images), which have replaced CT scans as the standard imaging modality. The Macdonald criteria are useful because they provide an objective radiologic assessment of tumor response and allow response rates to be compared between clinical trials, both ongoing and historical, in a standardized manner. However, their limitations have been recently noted, in particular, inter-observer variability, the difficulty of measuring irregularly shaped tumors, failure to assess the non-enhancing portion of the tumor, and the difficulty of measuring enhancing lesions in the walls of cystic or surgical cavities without also including the cyst or cavity in the tumor measurement. For example, the Macdonald criteria define tumor progression as at least a 25 percent increase in the contrast-enhancing lesion. However, enhancement is influenced by many factors, including corticosteroid dosages, anti-angiogenic agents, seizure activity, surgery, radiation-induced changes, and treatment-related inflammation, to name a few, and therefore it is problematic to equate changes in contrast-enhancing areas with tumor progression (Wen, Macdonald et al. 2010).

Other important considerations include pseudoprogession and the changes in tumor vasculature permeability caused by anti-angiogenic agents. Pseudoprogression describes a treatment-related increase in contrast enhancement that usually occurs within 12 weeks of the completion of radiation therapy; it is believed to be mediated by a transient increase in tumor vasculature permeability (Chamberlain, Glantz et al. 2007; Taal, Brandsma et al. 2008; Roldan, Scott et al. 2009; Wen, Macdonald et al. 2010). On the other hand, Bevacizumab and other anti-angiogenic drugs may cause a pseudoresponse, as early as 1 to 2 days, because of

a marked decrease in contrast enhancement due to the normalization of abnormally permeable tumor vasculature. Furthermore, by the same mechanism, Bevacizumab-treated tumors may progress by increased T2/FLAIR (fluid attenuation inversion recovery) signal without an associated increase in contrast uptake/blood brain barrier disruption (Wen, Macdonald et al. 2010). In order to address the above-mentioned limitations, the Response Assessment in Neuro-Oncology (RANO) Working Group has proposed modifications to the original Macdonald Criteria. In the modified criteria, measurements of T2/FLAIR lesions are included in the determination of response or progressive disease (see Tables 3-4). Notably, progression is defined not only by increases in enhancing lesions, but also by increases in non-measurable disease and by significant increases in non-enhancing T2/FLAIR lesions, though the term "significant" is not quantifiable (Wen, Macdonald et al. 2010). Agha and colleagues have suggested a rule for progressive disease, that is if the MRI shows greater than 25 percent increase in FLAIR then the consecutive MRI, done at one month or later, must show an increase in FLAIR or enhancing volume on a stable or higher dose of corticosteroids (Agha, Ibrahim et al. 2010)

	Macdonald Criteria	RANO Criteria
CR	Requires all of the following: 1.1 Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks, 1.2 No new lesions, 1.3 No corticosteroids, 1.4 Stable or improved clinically	Requires all of the following: 1.1 Same as MacDonald 1.1, 1.2 Same as MacDonald 1.2, 1.3 Patient must be off corticosteroids or on physiologic replacement doses only, 1.4 Same as McDonald 1.4, 1.5 Stable or improved non-enhancing (T2/FLAIR) lesions.
PR	Requires all of the following: 2.1 ≥ 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks, 2.2 No new lesions, 2.3 Stable or reduced corticosteroid dose, 2.4 Stable or improved clinically.	Requires all of the following: 2.1 Same as MacDonald 2.1, 2.2 Same as MacDonald 2.2, 2.3 Stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids, compared with baseline scan and corticosteroid dose must not be greater than the dose at time of baseline scan, 2.4 Same as McDonald 2.4, 2.5 No progression of non-measurable disease.
SD	Requires all of the following: 3.1 Does not qualify for complete response, partial response, or progression, 3.2 Stable clinically.	Requires all of the following: 3.1 Same as MacDonald 3.1, 3.2 Same as MacDonald 3.2, 3.3 Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan.

CR: complete Response, PR: Partial response, SD: Stable Disease.

Table 3. Comparison of Response Criteria, CR, PR, and SD.

In the absence of a confirming scan 4 weeks later, a CR or PR response is considered stable disease. In the RANO SD criteria, in the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show stable disease will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.

	Macdonald Criteria	RANO Criteria
PD	Any of the following: 4.1 ≥ 25% increase in sum of the products of perpendicular diameters of enhancing lesions 4.2 New lesion, 4.3 Clinical deterioration.	Any of the following: 4.1 Same as MacDonald 4.1 but compared with smallest tumor measurement at baseline or best response on stable or increasing doses of corticosteroids, 4.2 Same as McDonald 4.2 4.3 Same as McDonald 4.3 not attributable to other causes apart from the tumor or to changes in corticosteroid dose 4.4 Clear progression of non-measurable disease 4.5 Significant increase in T2/FLAIR non-enhancing lesions on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy, not due to co-morbid events. 4.6 Failure to return for evaluation as a result of death or deteriorating condition.

Table 4. Comparison of Response Criteria, PD. PD: Progressive Disease.

4.7 Bevacizumab and patterns of GBM recurrence

Interestingly, the use of Bevacizumab has raised many questions about patterns of recurrence. Unfortunately, the data from several retrospective reviews have produced conflicting conclusions that appear to be secondary to such issues as poor design (retrospective analyses) and small numbers. On one side of the argument, Wick and colleagues (n = 44), Norden and colleagues (n = 26), and Chamberlain (n = 80) argue that the majority of patients who receive Bevacizumab exhibit no change in patterns of recurrence (Norden, Young et al. 2008; Chamberlain 2011; Wick, Dorner et al. 2011). However, Norden and colleagues argue that the likelihood of diffuse or distant recurrence was higher in Bevacizumab-treated patients (Norden, Young et al. 2008). Furthermore, the results of Chamberlain reveal that the number of patients with diffuse disease increases from 5/80 (6.25 percent) at the time of first recurrence, to 9/80 (11.25 percent) at the time of second recurrence while on single-agent Bevacizumab (Chamberlain 2011). On the other end of the spectrum, Pope and colleagues reported that the incidence of diffuse disease increased from 14/67 (21 percent) to 26/67 (39 percent) and from 12/57 (21 percent) to 36/57 (63 percent) in patients treated by single-agent Bevacizumab and Bevacizumab plus Irinotecan, respectively (Pope, Xia et al. 2011). Zuniga and colleagues have also reported a diffuse pattern of recurrence of 7/38 (18.42 percent) in patients treated with Bevacizumab and Irinotecan (Zuniga, Torcuator et al. 2009). These conflicting conclusions appear to arise from the fact

that the aforementioned studies are not powered to detect differences in patterns of diffuse recurrence, which are not very large. The aforementioned ongoing phase III prospective studies that include much larger numbers of patients may address this question for newly diagnosed GBM.

The biological explanation of a change in patterns of recurrence may be justified by the "Go or Grow" mechanism as a possible explanation for the switch between a proliferative tumor phenotype and an invasive one that occurs when the tumor is exposed to a hypoxic environment (Hatzikirou, Basanta et al. 2010). The basic idea is that some GBM tumors have a molecular system that allows them to infiltrate outward in search of nutrients and, in turn, may help explain the diffuse radiographic patterns of relapse seen in patients treated with Bevacizumab.

4.8 Other anti-angiogenic agents

Other anti-angiogenic agents that have been evaluated in GBM include Vandetanib, Cediranib, Tamoxifen, Enzastaurin, and Cilengitide, to name a few. These and others have been investigated in early trials. For example, Cediranib has been shown to reduce edema and the amount of tumor enhancement on contrasted studies. Cilengitide, an inhibitor of integrin receptors, has shown activity in clinical trials, both as a single agent and in combination with other, standard chemotherapeutic regimens (Reardon, Fink et al. 2008; Ahluwalia and Gladson 2010; Khasraw and Lassman 2010; Reardon, Neyns et al. 2011).

5. Future directions

Anti-angiogenic therapies, especially Bevacizumab, offer new options and hope for better outcomes to patients, caregivers, and clinicians. However, many new important questions have been raised and remain unanswered. For example, there is evidence that abrupt discontinuation of Bevacizumab may result in rebound tumor growth and rapid clinical decline (median OS of 47.5 days after discontinuation) (Zuniga, Torcuator et al. 2009). These preliminary results should be investigated in the future as they leave the clinician with the dilemma of how to discontinue Bevacizumab. In addition, more research is needed to address treatment options when patients fail Bevacizumab.   For example, with other anti-angiogenic therapies in the pipeline, it is unknown if Bevacizumab-treated patients will respond to these agents. Furthermore, recent evidence suggest that gliomas, heavily treated with chemotherapy, mutate at a fast rate; this hypermutation phenotype is daunting as it may enhance resistance and aggressiveness (Chen, Delaloye et al. 2007).

The fact that Bevacizumab normalizes the blood-brain barrier leads to clinical conundrums, namely, the inability to judge tumor response, the possibility of decreased delivery of crucial chemotherapeutic agents, and changes in recurrence patterns (Thompson, Frenkel et al. 2011). Results by Chen and colleagues suggest that positron emission tomography (PET) using [18F] fluorothymidine (FLT) may help differentiate the anti-tumor effects of Bevacizumab from its effects on the BBB as well as serve as a predictor for survival (Chen, Cloughesy et al. 2005; Chen, Delaloye et al. 2007).

As noted above, patients with malignant gliomas experience significant morbidity related to neurologic impairment, psychiatric symptoms, neuro-cognitive deficits, and fatigue. Assessment of quality of life and, in particular, of neuro-cognitive functioning, is an important end-point in clinical trials of patients with malignant gliomas and was analyzed

in the BRAIN study. The findings reveal that the majority of patients treated with Bevacizumab experienced stable or improved neuro-cognitive function during the first 6 weeks of treatment, suggesting that Bevacizumab either preserves or improves neuro-cognitive function, and thus positively affects quality of life among patients with GBM (Friedman, Prados et al. 2009; Henriksson, Asklund et al. 2011). Future studies are needed to investigate the effects of Bevacizumab on neuro-cognitive functioning and on other aspects affecting quality of life. Notably, there is recent recognition of the need to adopt new clinical endpoints including, PFS at defined intervals, development of alternative imaging approaches, and validated metrics of patient function and well-being (Reardon, Galanis et al. 2011).

6. Conclusion

In this chapter, we discuss the financial and social impacts caused by the significant morbidity and poor prognosis that remain to be associated with malignant gliomas, despite recent advances in basic sciences and the introduction of novel therapeutic strategies, including anti-angiogenesis. Bevacizumab has therapeutic efficacy against recurrent malignant gliomas; its role in the treatment of newly-diagnosed GBM is being investigated. Importantly, the use of Bevacizumab has raised new and novel questions about the basic biology of malignant gliomas and has led to a revision of the Macdonald criteria. We expect future research to answer important clinical questions about the "Go or Grow" phenotype, the patterns of recurrence of newly diagnosed and recurrent GBM treated by anti-angiogenic drugs, the importance of rebound growth when Bevacizumab is discontinued, chemotherapeutic drug delivery when used in combination with anti-angiogenic drugs, and the hypermutation phenotype. Additional clinical questions that remain open include therapeutic options when patients fail anti-angiogenic therapy and cross-sensitivity to various anti-angiogenic agents.

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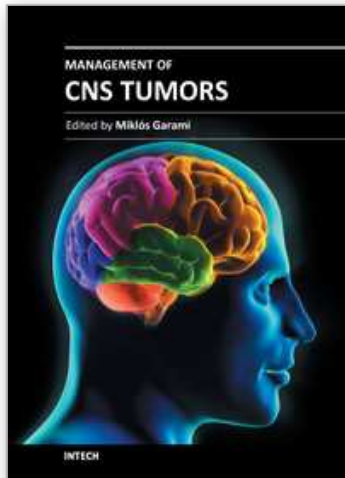
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