HHS Public Access

Author manuscript

Mt Sinai J Med. Author manuscript; available in PMC 2019 December 03.

Published in final edited form as:

Mt Sinai J Med. 2010 ; 77(6): 655–666. doi:10.1002/msj.20223.

Malignant Gliomas: New Translational Therapies

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Abstract

Malignant gliomas are the most common primary brain tumors in adults and carry a dismal prognosis. Despite aggressive therapy with maximal safe surgical resection, radiation and chemotherapy, these tumors invariably are refractory to or become resistant to treatment and recur. Gliomas are highly infiltrative cancers and display remarkable genetic heterogeneity making them challenging to treat. Recent progress has been made in understanding the molecular and genetic composition of these tumors and from this, promising new targets for therapy have emerged. In particular, anti-angiogenesis therapies have led to modest success in disease control. In addition, the growing body of research in cancer immunology as well as cancer stem cells has made inroads in our understanding of tumorgenesis. Translational research has been particularly crucial to the development of these therapies as much preclinical and clinical work is needed to develop the rationale for treatments, to develop biomarkers of drug activity and to elucidate mechanisms of resistance. This brief overview will discuss some of the pivotal advances made in the pursuit of improved outcomes and survival for patients with this devastating disease.

Keywords

angiogenesis; epigenetics; glioblastoma; glioma stem cells; immunotherapy; malignant glioma; molecular profiles; signal transduction pathways; translational research; tyrosine kinase inhibitors

Malignant gliomas are the most common primary brain tumors in adults, with an incidence of 7 per 100,000 in the United States.[1] The World Health Organization (WHO) grading system is a widely accepted scale used to categorize these tumors, with the 2 chief histopathologies being anaplastic astrocytoma (AA), WHO grade III tumors; and glioblastoma (GBM), WHO grade IV.[2] Anaplastic oligodendrogliomas and mixed oligoastrocytomas are also WHO grade III tumors, but less common than AAs. Glioblastomas are the most aggressive of the primary brain tumors and exhibit steadfast resistance to treatment. Although survival has improved for many other solid tumors, it remains poor for patients with malignant gliomas. The current standard of care for GBM was determined by a large phase III trial published in 2005 conducted by the European Organization for Research and Treatment of Cancer (EORTC) and National Cancer Institute of Canada (NCIC).[3] Stupp *et al*. randomized patients with newly diagnosed glioblastomas to

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DISCLOSURES

Potential conflict of interest: Nothing to report.

either radiation therapy (RT) alone or RT with temozolomide, an oral chemotherapy. Patients who received combination therapy had improved progression-free survival (PFS) and overall survival (OS) when compared with the RT-alone group (Table 1). More recent follow-up from this trial corroborates the durabil-ity of these findings. In patients receiving both RT and chemotherapy, 3-, 4-, and 5-year survival was improved compared with those receiving RT alone (Table 2).[4] Although the addition of chemotherapy proved beneficial in these patients, progression of disease remains nearly universal.

Several factors contribute to the resistance of these tumors to treatment. Gliomas are diffuse by nature, with infiltrating tumor cells invading adjacent areas of normal brain. Thus, surgical resection is inadequate for local control, and these reservoirs of residual tumor undoubtedly lead to recurrent disease. Although somewhat sensitive to high-dose radiation, treatment of gliomas with radiotherapy is limited by normal tissue toxicity to the normal brain. Chemotherapy, the linchpin of treatment for most cancers, has had only modest effects on improving outcomes for gliomas. This is in part due to the protective nature of the blood brain barrier (BBB), which can preferentially exclude chemotherapeutics and other targeted therapies. In addition, malignant gliomas are among the most genetically heterogeneous cancers, making it difficult to achieve durable responses.

Fortunately, significant advances in basic and clinical research have been made in recent years toward understanding the genetics of these tumors, as well as the abnormal cell-signaling pathways that lead to these cancers. This brief review will highlight some of the recent developments that have resulted from the interchange between preclinical and clinical efforts. Substantial research has been devoted to elucidating the genetic and molecular profiles of gliomas, and new therapies, such as those directed against angiogenesis, have appreciably changed the outcomes and course of this disease. Basic research in tumor immunology and cancer stem cells has also contributed to our understanding of gliomagenesis. Yet despite promising results in the preclinical setting, many of these treatments have not yet resulted in the anticipated clinical responses. As such, translational research is particularly valuable to understanding why the discoveries that occur in the laboratory have not yet been borne out in the clinic.

CLASSIFICATION OF MALIGNANT GLIOMAS

Brain tumors have classically been diagnosed and graded by pathological evaluation of cellular elements. Anaplastic astrocytomas are characterized by pleomorphic cells, nuclear atypia, and mitosis. Glioblastomas exhibit these same features, as well as necrosis and vascular proliferation. Yet despite having consistent histologic descriptions, patient outcomes and response to treatment can be quite varied. It is clear that the current classification systems are inadequate to fully characterize these tumors. Underlying genetic variability exists among these tumors, and it is likely that each has a distinctive profile. It is hoped that identifying subgroups among malignant gliomas will lead to more predictable responses to treatment within these groups, and to more personalized therapies for individual patients.

There have been large-scale efforts made toward understanding the genetic and molecular profiles of gliomas, and glioblastomas in particular. The Cancer Genome Atlas is a coordinated effort of the National Cancer Institut[3] and the National Human Genome Research Institute aimed at determining the principal genome alterations leading to malignancy. Glioblastomas were the first cancers to be studied under The Cancer Genome Atlas.[5] Interpretation of DNA, mRNA, and micro RNA profiles of hundreds of primary glioblastoma tissue samples is ongoing and has led to the categorization of these tumors into 4 main types: classical, mesenchymal, neural, and proneural.[6] Validation of these subgroups is challenging, and the clinical applications are as yet uncertain.

The Glioma Molecular Diagnostic Initiative is another large-scale effort to develop a classification schema based on unbiased gene-expression profiles. Previous classification schemas have been stratified by a priori histological classes or candidate genes. In contrast, the Glioma Molecular Diagnostic Initiative relies only on molecular data without premeditated stratification to create its framework. From this, 2 major groups of gliomas are predicted: glioblastoma-rich and oligodendroglioma-rich. These have been further separated into 6 subtypes.[7] These data are being collected to be assimilated into a comprehensive molecular/clinical database for public use.[8] The efforts toward unlocking the molecular signatures of malignant gliomas are in progress with the ultimate goal of defining a new classification model with both prognostic and predictive value.

EPIGENETICS

Epigenetics refers to changes in gene expression or phenotype that do not occur as a result of changes in DNA. Methylation of DNA is a primary mechanism of epigenetic changes in gene expression, and it has been recognized that hypomethylation of genes occurs in many malignancies. The DNA repair protein O6-methylguanine-DNA methyltransferase (MGMT) has been implicated in resistance to chemotherapeutic agents,[9-11] and epigenetic silencing of the MGMT gene by methylation of its promoter region has been correlated with better responses to alkylating agents.[12,13] Methylation leads to loss of MGMT expression and chemotherapy-induced damage to malignant cells is left unrepaired, leading to apoptosis. An important corollary to the previously described EORTC study reports MGMT methylation occurring in 46 of 206 patients.[13] This was found to be an independent prognostic factor, and OS was significantly improved in those patients with promoter methylation who received combination therapy compared with those patients who received RT alone or who were not methylated (see Table 3).

Several strategies have been employed in an attempt to overcome MGMT expression, including adding O6-benzylguanine (O6-BG), an irreversible inhibitor of MGMT, to chemotherapy. Although preclinical studies were promising,[14,15] clinical trials using this agent have not shown clear benefit.[16-18] Quinn *et al.* reported results from a phase II study of temozolomide in combination with O6-BG in patients with recurrent malignant gliomas on temozolomide. The overall objective response rate was 9%, and the median PFS was 7.9 weeks in this group.[16] The disappointing clinical outcomes may in part be due to the additive toxicity of O6-BG to cytotoxic agents, potentiating bone marrow suppression and requiring substantial dose reductions. In this study, the dose of temozolomide was decreased

by 50%, and in another phase II study using carmustine in combination of O6-BG, an 80% dose reduction in carmustine was necessary.[18]

Another strategy to overcome MGMT-mediated chemotherapy resistance is the use of alternative dosing schedules. Dose-dense or metronomic schedules both lead to more prolonged exposure to temozolomide, and can potentially deplete MGMT. Tolcher *et al.* used 2 different dosing schedules (7 days on/7 days off or 21/28 days consecutively), and took serial blood samples to evaluate for MGMT activity.[19] Both dosing schedules resulted in reducing MGMT activity, but with recovery of function during the rest period. Clarke *et al.* conducted a randomized phase II trial of dose-dense or metronomic temozolomide following standard chemoradiation in newly diagnosed glioblastomas.[20] There was some suggestion that patients with unmethylated MGMT may have benefited from the dose-dense regimen because their median OS was improved compared with those unmethylated patients in the EORTC trial (15.4 months versus 12.7 months).

Methylation status of MGMT has not yet been fully validated as a molecular marker of response, and as such current recommendations for temozolomide treatment are not based on this parameter. A large phase III trial conducted by the Radiation Therapy Oncology Group is currently under way comparing standard temozolomide dosing schedule to 21/28-day dosing, and patients have been stratified by MGMT methylation status prior to randomization. The results of this multi-institutional trial may help to validate the clinical significance of MGMT status.

TARGETED MOLECULAR THERAPIES

Intracellular signal transduction pathways determine all the key aspects of tumor biology, including proliferation, motility, apoptosis, and angiogenesis.

Many of these pathways are regulated by the interaction of growth factors and their cell-surface receptors. Tyrosine kinases (TKs) are a major class of membrane receptors that are often deregulated in cancer, and therefore they have become prominent targets of pathway inhibition. Most agents that target TKs are either small molecule TK inhibitors (TKIs) or monoclonal antibodies (mAbs). As the growth pathways for malignant gliomas are identified, corresponding targeted therapies have been developed. Two major pathways have emerged as promising candidates: the epidermal growth factor (EGF) and its receptor, EGFR; and the angiogenesis pathway involving vascular endothelial growth factor (VEGF). Vascular endothelial growth factor is a key mediator of the angiogenesis pathway and EGFR is a promoter of multiple factors in cell proliferation, invasiveness, and angiogenesis.

Epidermal Growth Factor Pathway

Overexpression or overactivity of EGFR has been associated with numerous malignancies and has become a prominent focus in cancer research. Activation of EGFR launches a host of downstream signaling cascades leading to cell proliferation, motility, and adhesion. In malignant gliomas, EGFR signaling is increased via overexpression or mutation in 40%–50% of all tumors, but not so in normal brain tissue.[21,22] In addition, EGFRvIII is a specific EGFR mutant that is constitutively active, is present in 20%–30% of glioblastomas, and may

be associated with worse OS.[23-25] Some preclinical data suggest that EGFR inhibition slows tumor proliferation and inhibits glioma invasion. This profile makes EGFR an attractive target for glioma treatment. The most common approaches to anti-EGFR therapy include the use of mAbs, small-molecule TKIs, and peptide vaccination.

Small-molecule TKIs act by blocking adenosine triphosphate binding in the intracellular catalytic domain of EGFR tyrosine kinase. Agents such as gefitinib and erlotinib are prototypes of these drugs and have been studied in multiple clinical trials as single-agent therapy as well as in combination with standard chemotherapy for malignant gliomas (see Table 4). Rich *et al.* reported minimal responses with gefitinib, and no improvement in OS in 53 patients with recurrent glioblastomas.[26] In addition, EGFR expression on tumor tissue was not found to be a predictor of response or OS. Erlotinib has activity against both EGFR and EGFRvIII. Results with erlotinib have also been mixed, with studies reporting response rates of 0% to 25%.[27]

These results demonstrate that the promise of EGFR inhibition in the preclinical setting has yet to translate to significant clinical responses. The reason for this is unclear, although curiously the current data suggest there is no clear correlation between EGFR expression and tumor response in the clinical setting.[26] One potential explanation for this observation is that there are other genetic determinants that modify the susceptibility of glioma cells to EGFR inhibition. For instance, there is some evidence that tumors with EGFRvIII and intact phosphatase and tensin homolog (PTEN; a tumor-suppresser gene) are more susceptible to EGFR inhibitors; however, this has yet to be validated.[28] As is true of all agents, another confounding variable in the clinical effectiveness of EGFR inhibitors is drug delivery. Both the anatomical microarchitecture of the blood-brain barrier (BBB) as well as drug efflux transporters on the endothelial cells that constitute the BBB combine to impede drug penetration into normal cerebral as well as tumor tissue. The extent of pathway inhibition is critical to determining a clinical response, and is dependent on the ability of the agent to reach its target in vivo.[29] Accurate measurements of drug levels in tumor tissue are difficult to assess in this population given the invasiveness of brain-tissue sampling. Finally, the activation of alternate pathways that bypass the EGFR signaling by direct downstream signaling activation likely also contributes to resistance to EGFR-targeted therapies. In fact, preclinical models have demonstrated that multiple kinase inhibition may be required to optimally suppress tumor growth.[30]

Antiangiogenesis and Vascular Endothelial Growth Factor

Contrary to the variable results we have seen with EGFR inhibition, the strategy of antiangiogenesis for malignant gliomas has yielded moderate success. Cancer-related blood vessels have been studied since the 1800s, but it was Dr. Judah Folkman's work in the early 1970s that established tumors were restricted in growth and would only reach a size of 1–2 mm^3 unless they were able to generate an autonomous blood supply.[31-33] Folkman recognized that inhibiting the growth of blood vessels could lead to effective cancer treatment and postulated that antiangiogenesis would be a viable avenue to tumor inhibition.

Malignant gliomas are highly vascularized, and as such are well suited for treatment with antiangiogenesis agents. The process is driven by multiple factors, including VEGF, platelet-

derived growth factor (PDGF), stem cell factor-1, and basic fibroblast growth factor (bFGF).[34-36] The VEGF pathway, however, is clearly central to the promotion of neovascularization and it has been the principal target of most antiangiogenic therapies.

The mechanism of action for anti-VEGF therapy is likely multifold and has not been clearly proven. Two of the more commonly discussed hypotheses include (1) direct inhibition of endothelial cell proliferation, leading to decreased blood vessel formation and hypoxic cell death, and (2) normalization of the tumor vasculature, leading to decreased interstitial pressure and subsequent enhanced delivery of chemotherapeutic agents.[35,37] Batchelor *et al.* presented early clinical and imaging data supporting the use of antiangiogenesis agents in glioblastoma.[38] Using AZD2171, a TKI against the VEGF receptor, they demonstrated normalization of tumor blood vessels in patients with recurrent GBMs. The radiographic response rate was 56%, and patients were often able to reduce or discontinue steroid use as a result of dramatic reduction in peritumoral edema. The authors also measured blood vessel size, permeability, contrast enhancement, and edema at serial time points using dynamic contrast-enhanced magnetic resonance imaging (MRI). These factors were correlated with serum biomarkers of response such as circulating endothelial and progenitor cells. As a corollary to these findings, a recent follow-up to this same study describes changes in several serum biomarkers: VEGF, placental growth factor, and stromal cell–derived factor-1α were increased after VEGF blockade, whereas matrix metalloproteinase (MMP)-10 was decreased. An increase in both plasma MMP-2 and urinary MMP-9/neutrophil gelatinase–associated lipocalin was associated with poorer outcomes.[39]

Bevacizumab is a humanized mAb against VEGF and was the first commercially available angiogenesis inhibitor. It was approved by the US Food and Drug Administration in February 2004 for use in metastatic colorectal cancer when used with standard chemotherapy treatment. Early data on the activity of bevacizumab in malignant gliomas was reported in 2005.[40] An unprecedented 9 of 21 patients with recurrent malignant glioma had radiographic response with the combination of bevacizumab and CPT-11, a topoisomerase inhibitor. Following this, there have been multiple studies demonstrating the utility of bevacizumab in treating malignant gliomas (see Table 5).[40-43] In 2009, bevacizumab received accelerated approval from the FDA for treatment of recurrent glioblastomas, based on 2 phase II trials.[41,42] The use of VEGF inhibitors has significantly impacted outcomes for patients with progressive disease or patients who have failed standard therapy. In the wake of the responses seen with bevacizumab, other inhibitors of angiogenesis have been studied, including TKIs targeted against VEGF, PDGF, and stem cell factor-1.

Despite the relative success in improving response rates with VEGF inhibitors, gliomas ultimately escape the effects of antiangiogenesis therapies. Insight into the mechanisms of resistance has shown that levels of several growth factors, including bFGF and stromal cell derived factor-1α were increased at the time of tumor progression.[38] These pathways may serve as alternative routes for angiogenesis in the presence of VEGF inhibition. There are also emerging data that blood vessel stability relies on pericyte-endothelial cell interactions that are promoted by PDGF. In the setting of anti-VEGF therapy PDGF signaling is increased, and thereby is a potential target for therapy in conjunction with VEGF inhibitors.

[44] Finally, there is increasing evidence to suggest that anti-VEGF therapy alone may trigger a distinctive pattern of recurrence characterized by enhanced infiltrative growth and co-opting of existing blood vessels.[45-48] Thus, it is highly plausible that even if complete antiangiogenic blockade can be achieved, tumor progression will eventually occur through individual glioma cell invasion along preexisting normal cerebral vasculature. Thus, antiangiogenic treatment may change the pathogenesis of end-stage disease from one of a large tumor mass causing mass effect, cerebral edema, and focal cerebral destruction to a diffuse encephalic clinical picture as a result of widely infiltrative individual glioma cells, as is seen in the condition gliomatosis cerebri.

IMMUNOTHERAPY

In theory, the immune system is the ideal mechanism for the treatment of highly infiltrative gliomas. Ideally, the host's innate immune cells would identify specific tumor antigens and launch a directed response against any disseminated cells while leaving normal cells unharmed. Strategies to exploit the immune system include passive immunotherapy using mAbs, or active immunotherapy using tumor vaccines. Both tactics depend on the successful activation of lymphocytes against tumor antigens. Although the intellectual rationale for these approaches is valid, significant clinical success has yet to be seen. Clinical trials using vaccines have been far more prevalent and are the main focus of this discussion.

The central nervous system (CNS) had long been thought of as an "immune-privileged" sanctuary separated from the general circulation by the BBB, and devoid of native immune cells or lymphoid tissue. It is now known that although the immune responses generated in the CNS are generally less efficient than systemic responses, there is ample activity, as witnessed by the vigorous immune reactions seen in the setting of CNS infections and autoimmune diseases. Although resident antigen-presenting cells (APCs) have yet to be identified it has been postulated that microglia may assume this role in the brain.[49,50] Early preclinical studies demonstrated that glioma cells expressing interferon-gamma transplanted into brain tissue lead to priming of microglia and tumor rejection.[51]

The model of immune activation is dependent on uptake of antigens by APCs, which then travel through lymphatic channels to reach lymph nodes. Once there, APCs with their associated antigen trigger activation of T cells. These primed lymphocytes then travel to the tumor and initiate cell death. The identification of many tumor-associated antigens has spurred the development of vaccine therapies mediated by T cells. There are numerous sources for vaccine antigens, including cancer cell lysates and specific peptide or proteins related to the cancer. These antigens need not be limited to those involved with the oncogenesis of the tumor, but any antigen specific to malignant cells and absent in normal tissue. The 2 major types of vaccines discussed below, dendritic cell (DC) vaccines and peptide vaccines, have both been studied in clinical trials.

Dendritic Cell Vaccines

Dendritic cells function as APCs, and once activated they travel to lymphoid tissue where they initiate T cell and B cell responses. They are so named for their dendrite-like projections and have no relation to neurons. Most current DC vaccine strategy involves

harvesting peripheral autologous DCs from patients and exposing them ex vivo to tumor cell antigens or lysates. These DCs are then reintroduced to the patients with the intent of inducing an endogenous immune response. Preclinical studies using DC vaccines have yielded encouraging results.[52,53] An early phase I trial proved the safety of dendritic cell vaccines in humans.[54] Patient-derived DCs and glioma cells were pulsed together, then injected intradermally. There were no clear tumor responses, but interferon-gamma expression was detected in the peripheral blood monocyte cells of a few patients. In another phase I dose-escalation study, Liau *et al.* treated 12 GBM patients with DCs pulsed with autologous tumor peptides.[55] Although the study was not powered to measure efficacy, patients did have improved PFS (15.5 months) and OS (23.4 months) compared with historical controls.

Although DC vaccine trials have gained popularity, there has been little proof of clinical benefit in the form of measurable MRI changes. It is uncertain if the responses seen in many of these trials may be restricted to specific a population. In the previous phase I study by Liau *et al.*, tumor burden and evidence of disease progression at the time of vaccination were significant factors in determining OS and presence of tumor infiltration by T cells.[55] Only those patients who had no radiographic evidence of disease progression at the time of vaccination were shown to mount a systemic cytotoxic T-cell response, and only those with minimal tumor burden exhibited tumor-infiltrating lymphocytes. Moreover, the actual ability of DCs to successfully prime T cells against tumor antigens is still in question. There is no direct evidence of the mechanism by which the T-cell priming may occur, and there has been some recent data that implicates DCs in the brain as inhibitors of T-cell priming.[56] Even if reactive T cells are primed against the proper antigens, they may have no impact on tumor growth. Rosenberg *et al.* demonstrated this in melanoma patients where normal tumor growth persisted despite the presence of up to 30% of T cells displaying antitumor activity.[57] The use of supplemental treatments to enhance the effects of DC vaccination has been explored, and includes the addition of cytokines[58] and adjuvant chemotherapy.[59]

Peptide Vaccines

A concern with the use of nonspecific autologous tumor extracts is the danger of inducing autoimmune disease.[60] To circumvent this risk, tumor-specific antigens have been explored as candidate targets. The advantage of peptide vaccines lies in the ease of access to synthetically produced tumor associated peptides, and the decreased risk of induced autoimmune states. The obvious disadvantage with this technique is the lack of specificity for individual gliomas, which can be widely heterogeneous. EGFRvIII is the prototype for a tumor-specific antigen, and an early phase I study with a vaccine using autologous DCs pulsed with the peptide fragment of EGFRvIII (PEPvIII) demonstrated improved OS in 12 newly diagnosed GBM patients.[61] Following this, preclinical data demonstrated that direct vaccination with the PEPvIII was sufficient to inhibit tumor growth, and subsequent phase II trials were conducted without DCs, using peptide-based vaccines.[62,63] A phase II trial incorporated direct vaccination with the PEPvIII fragment in 18 patients with newly diagnosed, EGFRvIII+ GBMs. Compared with historical matched controls, PFS was improved from 6.3 to 14.2 months.[64] A subsequent phase II trial treated 21 patients with the same histology using monthly intradermal vaccinations with concurrent temozolomide. The

PFS was reported as 16.6 months, compared with the PFS in historical controls of 14.3 months.[65]

Despite encouraging preliminary results in these clinical trials, the true clinical efficacy of vaccine therapy is highly questionable. Peptide vaccines have been studied far more extensively in systemic cancers such as melanoma and prostate, breast, cervical, and colorectal cancers. In a rigorous review of these clinical trials, Rosenberg *et al.* reported only a 4% objective response rate, all of which occurred in melanoma trials exclusively.[66] They argue that the use of surrogate endpoints such as tumor necrosis or tumor lymphocyte infiltration do not adequately describe true effectiveness. Likewise, actual MRI responses are rarely seen in vaccine trials of recurrent glioma. Advocates of vaccines in gliomas have pointed to the longer PFS and OS seen in patients treated in the small phase I/II vaccine trials completed to date, compared with that seen in historical controls. The almost universal problem in interpreting these data, however, is that the patients treated on these vaccine trials tend to be highly selected, with very favorable prognostic factors, compared with the nonselected historical controls, making comparisons problematic.[67]

There are a number of reasons for skepticism regarding the ability of the current generation of crude vaccines to be clinically effective. Gliomas are poorly antigenic and they have an innate ability to induce immunosuppression mediated by regulatory T cells (Tregs). These factors are thought to be the major impediments to the success of immunotherapy. Glioma-driven immunosuppressive factors include transforming growth factor β, interleukin 10 (IL-10), and prostagladin E2 (PGE2).[68,69] Tregs expressing CD25 are increased in GBMs and may be pivotal in hindering immune responses. Thus, there is evidence that the local microenvironment of these tumors does not support a robust immune activation response. Bai *et al.* demonstrated that paradoxically, T cells may be simultaneously activated and tolerized in microenvironments of the same tumor.[70] Strategies to overcome glioma-induced immunosuppression and enhance vaccine efficacy include targeting immunosuppressive factors such as transforming growth factor β.[71]

STEM CELL THERAPY

Stem cells are characterized by the ability for extensive self-renewal and differentiation into diverse lineages. In contrast to the historically accepted stochastic model of cancer development and progression, the cancer stem cell model hypothesizes that most cancer cells within a tumor are not clonogenic and that only a small subpopulation of cells within the tumor truly possesses the capability to self-renew, proliferate, and (potentially) differentiate, as is seen in normal stem cells. Such tumor/cancer stem cells have been implicated as the principal governors of tumor initiation, growth, and resistance to treatment.[72-74]

Glioma stem cells were first isolated using the stem cell marker CD133[74,75]; however, more recent data has shown that the early neural stem cell marker SSEA-1 (CD15) is a more reliable marker of glioma stem cells.76 Like normal neural stem cells (NSCs), cancer stem cells rely on well-orchestrated interactions within the microenvironment in order to flourish. Crucial signaling pathways for NSCs such as PI3K, notch, and Wnt are active in glioma stem cells as well,77 and represent potential novel therapeutic targets.

Notch receptor proteins are found on cell membranes, and once activated the intracellular portion is cleaved by γ-secretases, a class of integral membrane proteins, freeing it to associate with transcription factors that activate several genes essential for maintenance and renewal of neural stem cells Abnormal notch signaling has been implicated in glioma growth and progression,[78,79] and animal studies show blockade through inhibition of γ-secretases can restrict stem cell activity in vitro and tumor formation in vivo.[80,81] Notch inhibition with γ-secretase inhibitors is a new strategy under evaluation in early phase I clinical trials.

Sonic hedgehog homolog (SHH) is a crucial regulator of neurogenesis and the propagation of neural stem cells in the cerebellum.[82-84] SHH signaling has also been shown to regulate growth of medulloblastomas and gliomas,[85,86] and inhibition of this pathway may lead to reductions in glioblastoma stem-like cells, and increased responsiveness to therapy.[87] Although there is no controversy regarding the role that SHH plays in the biology of medulloblastomas, its role in gliomas remains controversial. The clinical development of SHH inhibitors, such as GDC-0449, is currently in phase I and II trials for medulloblastomas and other solid tumors where SHH appears to play an important role (ie, prostate cancer).

Although the identification of cancer stem cells has shifted our paradigm of oncogenesis and broadened the scope of therapeutic considerations, understanding their role in gliomagenesis is still in its relative infancy. Current research is ongoing in identifying optimal stem cell markers, tracking these cells in vivo, and sparing normal NSCs from the effects of targeted and cytotoxic therapies.

CONCLUSION

In recent years, basic and preclinical studies have revealed multiple new mechanisms of gliomagenesis and corresponding targets for treatment. Yet for the most part these discoveries have not translated to impressive improvements in response or survival for patients. Although this impasse is reached in many other disciplines of medicine, the challenges of conducting translational research for brain tumors are distinct. To begin with, the CNS circulation is essentially separated from the rest of the body by the BBB; drug delivery is therefore unpredictable and unreliable. Ideally we would analyze tumor tissue in order to confirm adequate concentrations of our agents; however, the difficulties of accessing brain tumor samples compared with other tumor samples in systemic cancers make this a difficult task. This also impedes our validation of biological effects in vivo, a crucial step in the assessment of new interventions and therapies. Finally, the validity of our endpoints for malignant glioma clinical trials is uncertain. The question of whether PFS or OS is the more appropriate endpoint for malignant glioma trials has long been debated. Moreover, the use of antiangiogenic therapies has changed patterns of enhancement and recurrence on imaging. Our current standard of radiographic response, Macdonald's criteria,[88] measures the enhancing tumor volume in 2 dimensions, and has proven inadequate to describe the changes seen with these newer therapies.

Nevertheless, much is being learned from the translational research now being undertaken to connect these basic science discoveries to clinical trials. Mechanisms of treatment resistance are better appreciated, and it has become increasingly apparent that inhibition of a single

pathway or target is unlikely to affect tumor growth to the degree where durable clinical benefit is attained. Directed therapy against multiple pathways and growth factors is likely necessary, and with the prodigious number of potential targets available, the challenge will be in ascertaining the optimal combinations of drugs for individual patients. Parallel to this is the task of determining the unique molecular and genetic profiles of individual patient tumors so that the most effective therapies can be selected for those individuals. Developments in other arenas of brain tumor diagnosis and treatment such as neuroimaging, surgery, and radiation therapy are also evolving. Finally, great progress has been made in uncovering the molecular and genetic constitution of these tumors. Collectively, these advances have laid the foundation for significant improvements in treatments and outcomes for brain tumor patients.

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Table 1.

Outcomes by Randomized Treatment Regimen for Newly Diagnosed Glioblastomas[3].

	Treatment (mo)	
Outcomes	**RT**	**RT + TMZ**
OS	12.1	14.6
PFS	5.0	6.9

Abbreviations: OS, overall survival; PFS, progression-free survival; RT, radiation therapy; TMZ, temozolomide.

Table 2.

Long-Term Follow-Up of the EORTC-NCIC Trial[4].

	Survival (%)			
Treatment	**2-year**	**3-year**	**4-year**	**5-year**
RT	10.9	4.4	3.0	1.9
RT + TMZ	27.2	16.0	12.1	9.8

Abbreviations: EORTC-NCIC, European Organisation for Research and Treatment of Cancer-National Cancer Institute of Canada; RT, radiation therapy; TMZ, temozolomide.

Table 3.

O6-Methylguanine-DNA Methyltransferase Promoter Methylation Status and OS for Newly Diagnosed Glioblastomas[13].

	OS (mo)	
Promoter Status	**RT**	**RT + TMZ**
Methylated	15.3	21.7
Unmethylated	11.8	12.7

Abbreviations: OS, overall survival; RT, radiation therapy; TMZ, temozolomide.

Table 4.

Phase II Clinical Trials With EGFR Inhibitors in Patients With Glioblastoma.

Authors	No. of Patients	Radiographic Response Rates (%)	PFS (mo)	OS (mo)
Gefitinib				
Rich *et al.*[26]	57	0	2.0	9.9
Lieberman *et al.*[89]	38	13	2.0	—
Uhm *et al.*[90]	96	—	6.8	12.8
Franceschi *et al.*[91]	16	0	2.1	6.2
Erlotinib				
Vogelbaum *et al.*[92]	16	25	5.2	—
Raizer *et al.*[93]	31	0	2.3	—
Cloughesy *et al.*[94]	48	8	—	—
Van den Bent *et al.*[95]	54	4	1.8	7.7

Abbreviations: EGFR, epidermal growth factor receptor; OS, overall survival; PFS, progression-free survival.

Table 5.

Clinical Trials With Bevacizumab in Patients With Malignant Gliomas.

Authors	No. of patients	Radiographic Response Rates (%)	PFS (mo)	OS (mo)
Stark-Vance[40]	21	43	—	—
Friedman *et al.*[41]	Bev alone: 85	28	4.2	9.2
	Bev + CPT-11: 82	38	5.6	8.7
Kreisl *et al.*[42]	48	35	4.0	—
Vredenburgh *et al.*[43]	35	57	—	—

Abbreviations: Bev, bevacizumab; CPT, irinotecan; OS, overall survival; PFS, progression-free survival.