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# New developments in targeted molecular therapies for glioblastoma

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**“...combination therapy represents an attractive therapeutic strategy...”**

Glioblastoma multiforme is the most common type of malignant primary brain tumor in adults. Each year it is estimated that there are over 10,000 cases of the tumor diagnosed in the USA [1,2]. Despite optimal treatment with surgery and radiation therapy with concomitant and adjuvant temozolomide, median survival is usually less than 15 months [3]. Until recently, there was no effective therapy for these tumors when they recurred, with a 6-month progression-free survival (PFS6) of only 8–15% [4,5].

In recent years, there has been significant progress in understanding the molecular pathogenesis of glioblastomas [6,7]. This has resulted in increasing interest in the therapeutic potential of targeted molecular therapies [8,9]. Unfortunately, the results with single agents inhibiting receptor tyrosine kinases, such as the EGF receptor (EGFR) and PDGF receptor, or signal transduction pathways components, such as farnesyltransferase or mTOR, have been disappointing [8,9]. Response rates have, generally, been less than 10–15% with no prolongation of PFS6. Reasons for these poor results include coactivation of multiple tyrosine kinases [10] and redundant signaling pathways, limiting the activity of single agents. In addition, penetration of many agents across the blood–brain barrier is poor and compounded by active efflux of drugs via P-glycoprotein and other pumps. Attempts to define subsets of patients that respond to specific agents have also met with limited success. Initial studies suggested that EGFR inhibitors appear to be more effective in tumors with EGFRvIII mutations and intact phosphatase and tensin homolog deleted on chromosome 10 [11], while tumors with increased activity of the PI3K/Akt pathway, as determined by increased phospho-Akt, generally do not

respond [12]. However, recent studies have failed to validate the utility of EGFRvIII mutations and intact PTEN as markers of responsiveness to EGFR inhibitors [13].

**“The recent availability of more potent and often irreversible inhibitors ... has led to renewed interest in targeted molecular therapies.”**

In an attempt to improve the effectiveness of targeted molecular therapies, there is growing interest in using multitargeted agents that inhibit several kinases, combinations of agents inhibiting complementary targets, such as EGFR and mTOR, and combinations of targeted agents with radiotherapy and chemotherapy. The utility of these approaches remains to be determined, but preliminary results suggest that many combinations of targeted agents are poorly tolerated. For example, the North American Brain Tumor Consortium recently completed accrual to a Phase I/II trial of erlotinib (EGFR inhibitor) and temsirolimus (mTOR inhibitor) [14]. The maximum tolerated dose of temsirolimus when used in combination was only 15 mg once weekly compared with the single-agent dose of 170 mg once weekly. This large reduction potentially results in administration of subtherapeutic doses of the drug. Nonetheless, combination therapy represents an attractive therapeutic strategy and other agents may potentially be better tolerated. The recent availability of more potent and often irreversible inhibitors with improved brain penetration, for example, EGFR inhibitors (e.g., BIBW2992), agents that inhibit critical targets (e.g., PI3K, Akt and c-Met), agents that inhibit multiple

targets (e.g., heat-shock protein 90 and NF- $\kappa$ B) and agents that promote apoptosis or inhibit DNA repair enzymes (e.g., O6-methylguanine-DNA-methyltransferase or poly-[ADP-ribose]-polymerase) has led to renewed interest in targeted molecular therapies. In addition, given the increasing importance of stem cells in gliomagenesis [15] and mediating resistance to therapy [16], there is also significant interest in molecular therapies targeting stem cell pathways, such as notch and sonic hedgehog. The lessons learned from the previous generation of trials has led to improved study design [17]. Many trials now incorporate a pharmacodynamic component, in which patients requiring re-operation are pretreated with the targeted agent. Examination of the tumor specimens provides an indication of the drug's ability to penetrate into the tumor across the blood-brain barrier and inhibit putative targets *in vivo* [17]. Ideally, clinical trials would include an enriched population of patients whose tumor expresses that molecular target of interest. However, this approach remains a challenge given that there is a lack of validated molecular markers predicting response. There is also increasing interest in novel trial designs incorporating strategies, such as sequential accrual, factorial design or 'pick the winner' designs in an attempt to test multiple combinations efficiently and eliminate ineffective regimens more rapidly.

In contrast to the relatively disappointing results with other targeted molecular therapies, there has been real progress with agents that inhibit angiogenesis. Over three decades ago, Judah Folkman proposed the hypothesis that inhibition of angiogenesis may, potentially, be an effective treatment for cancers [18]. Glioblastomas are among the most vascularized tumors in the body and represent a particularly attractive target for this therapeutic strategy. These tumors secrete a variety of angiogenic factors, such as VEGF, PDGF, basic FGF (bFGF)/FGF2 and HGF/scatter factor, which contribute to neovascularization [19]. In addition, VEGF is an important cause of the increased vascular permeability and peritumoral edema that contributes significantly to the morbidity associated with these tumors [19].

Studies with early antiangiogenic agents, such as thalidomide, produced only minimal benefits, with response rates of less than 10% and no prolongation of PFS. However, the recent availability of more-potent antiangiogenic agents, especially those targeting VEGF and its receptors (VEGFR), has led to important progress in the treatment of glioblastomas [19–22]. Bevacizumab (Avastin<sup>®</sup>) is a humanized monoclonal antibody that binds VEGF, preventing it from activating its receptors, especially VEGFR2 and, therefore, abrogating subsequent biologic effects. Bevacizumab has been evaluated alone and in combination with various chemotherapeutic agents in recurrent glioblastomas with encouraging results. In one Phase II study, the combination of bevacizumab and irinotecan produced a response rate of 57% and a PFS6 of 46% in recurrent glioblastomas [23]. By comparison, ineffective therapies provide response rates of less than 10% and PFS6 of 15% in glioblastomas [4]. Although the high response rates may be partly the result of reduced vascular permeability and contrast enhancement as a result of VEGF inhibition, the improvement in PFS6 suggests that there is also a real anti-

tumor effect. The regimen was generally well tolerated, with a low incidence of intracerebral hemorrhage. These preliminary findings have been confirmed by a large multicenter randomized Phase II study of 167 patients with recurrent glioblastomas who were treated with bevacizumab alone or in combination with irinotecan [21]. Patients receiving bevacizumab alone had a response rate of 28.2% and a PFS6 of 42.6%, while patients receiving bevacizumab in combination with irinotecan had a response rate of 37.8% and a PFS6 of 50.3% [21]. However, median survival was similar between the two groups (9.2 months for bevacizumab alone and 8.7 months for the combination), making it unclear whether the use of irinotecan provides any additional benefit. Patients treated with bevacizumab also experienced a significant reduction in peritumoral edema and the need for corticosteroids, significantly improving the quality of life of patients. This study, again, confirmed that bevacizumab was well tolerated, with a low incidence of intracranial hemorrhage. As a result of these studies, bevacizumab, often combined with irinotecan, is increasingly used for the treatment of patients with recurrent glioblastomas.

**“...bevacizumab, often combined with irinotecan, is increasingly used for the treatment of patients with recurrent glioblastomas.”**

Aflibercept (VEGF-Trap) is a soluble hybrid receptor, composed of portions of VEGFR-1 and -2 fused to an immunoglobulin G1 Fc domain. As with bevacizumab, it is designed to deplete circulating VEGF, but has significantly greater affinity for VEGF than bevacizumab itself. A Phase II study conducted by the North American Brain Tumor Consortium was recently completed with response rates similar to those obtained with bevacizumab [24].

There are also encouraging results with inhibitors of VEGFRs. In a Phase II trial study of a potent pan-VEGFR inhibitor, cediranib (AZD2171; Recentin<sup>™</sup>), in patients with recurrent glioblastomas, response rates in excess of 50% were observed and the PFS6 was increased to approximately 25% [25]. At the time of tumor recurrence, serum levels of bFGF/FGF2, SDF1 $\alpha$  and circulating endothelial cells were increased, together with Tie2, suggesting that these may be contributing to resistance to VEGFR inhibition. Studies with other inhibitors of VEGFR, such as vandetanib (ZD6474; Zactima<sup>™</sup>), sorafenib (Nexavar<sup>®</sup>), sunitinib (Sutent<sup>®</sup>), pazopanib (GW786034), vatalanib (PTK787) and CT322, in glioblastomas are in progress.

In comparison to drugs targeting VEGF or VEGFR, agents inhibiting other angiogenic pathways have produced less success. Drugs that inhibit PDGF receptors, such as imatinib mesylate (Gleevec<sup>®</sup>), were ineffective, due partly to its poor penetration across the blood-brain barrier [26,27]. Cilengitide, a drug that inhibits  $\alpha_v\beta_3$  and  $\alpha_v\beta_5$  integrins has shown modest activity in glioblastomas [28], and studies combining it with other agents are in progress [8].

Since antiangiogenic agents can potentially have synergistic effects with radiation therapy, there is significant interest in combining these agents with radiation therapy [29]. Two

Phase III trials evaluating the benefits of adding bevacizumab to radiation therapy and temozolomide for the treatment of newly diagnosed glioblastomas will begin in the near future. These studies will help determine the safety of bevacizumab in newly diagnosed glioblastomas and whether it is more effective as first-line treatment or at recurrence. Given the vascular niche of normal neural stem cells and its potential disruption with antiangiogenic therapy, it will be important to determine if the addition of agents such as bevacizumab to radiation therapy increases the risk of delayed neurocognitive impairment.

**“In contrast to the relatively disappointing results with other targeted molecular therapies, there has been real progress with agents that inhibit angiogenesis.”**

After over two decades of minimal progress in the treatment of recurrent glioblastomas, antiangiogenic therapies, such as bevacizumab, represent an important but limited advance. In addition, by reducing peritumoral edema, these agents frequently allow patients to decrease or eliminate their need for corticosteroids, improving their quality of life. The risk of hemorrhage with these agents is modest but they are associated with other complications, such as an increased risk of venous thromboembolism, impaired wound healing, proteinuria and hypertension. These agents are also very expensive, and important issues regarding their economics remain to be resolved.

As experience with antiangiogenic agents accumulates, it is clear that the benefits are only transient, and most tumors eventually progress after a number of months. In a subset of patients, these tumors recur, not as enhancing masses, but with a more infiltrative phenotype resembling gliomatosis [30]. This raises the possibility that by inhibiting angiogenesis, anti-VEGF and anti-VEGFR agents force tumor cells to co-opt and grow along existing blood vessels, changing their natural

history [31,32]. Unfortunately, most conventional therapies are generally ineffective for patients who progress on bevacizumab and subsequent survival is often limited. As a result, it is unclear whether the improvements in PFS produced by these agents translate into a significant increase in overall survival. In order to improve on the advances made with bevacizumab and other anti-VEGF/VEGFR agents, it will be critical to identify the mechanisms that determine intrinsic resistance of subsets of glioblastomas to these agents, as well as the mechanisms that develop during therapy that allow the tumor to eventually progress after an initial response. These mechanisms of ‘evasive resistance’ are thought to include upregulation of alternative proangiogenic signals, such as FGF-1 and -2, SDF1 $\alpha$ , ephrins and angiopoietins, leading to revascularization, protection of the tumor vasculature either by recruiting proangiogenic inflammatory cells or by increasing protective pericyte coverage, as well as co-option of normal vasculature and invasion into surrounding tissue [33]. Combining agents targeting VEGF with inhibitors of FGF, SDF1 $\alpha$ , ephrins or Tie2 may, potentially, lead to improved tumor control. Given the increasing importance of invasion as a mechanism of resistance, combining antiangiogenic agents with drugs that inhibit invasion also holds great promise [34]. These approaches will hopefully allow us to build on the recent progress that has occurred with the introduction of potent antiangiogenic agents, such as bevacizumab.

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