F1000 MEDICINE REPORTS

Published: 09 December 2009

New therapies for recurrent glioblastomas

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F1000 Medicine Reports 2009, **1**:94 (doi:10.3410/M1-94)

Abstract

Glioblastomas are the most common and deadliest form of malignant primary brain tumor. Until recently, therapies for tumors that recur after standard treatment have been largely ineffective. Recent phase II studies with the humanized monoclonal antibody against vascular endothelial growth factor bevacizumab suggest that this agent is active in recurrent glioblastomas, producing response rates of 26-40% and prolonging 6-month progression-free survival to 36-50%. As a result of these studies, the US Food and Drug Administration recently granted accelerated approval for bevacizumab as a treatment for recurrent glioblastomas.

Introduction and context

Glioblastomas are the most common malignant primary brain tumor, with an annual incidence of approximately 3-4 per 100,000 [1]. Standard therapy involves maximal surgical resection, followed by radiotherapy, together with concomitant and adjuvant temozolomide [2,3]. Unfortunately, despite these therapies, glioblastomas inevitably recur with a median time-to-progression of 6.9 months [3]. Following recurrence, the 6-month progression-free survival (PFS6) is only 9-16% [4-6], and median survival is approximately 5-7 months [4,5].

Therapy for recurrent glioblastomas may involve surgery, reirradiation, chemotherapy, or novel agents, including antiangiogenic therapies [7]. Until recently, these therapies were largely ineffective. Reoperation has a role in a minority of patients but rarely prolongs survival [8,9]. The role of radiotherapy for recurrent glioblastomas is controversial [10]. Some reports suggest that fractionated stereotactic reirradiation [11] and stereotactic radiosurgery [12] may be beneficial, but selection bias may have influenced these results. Chemotherapy wafers and conventional chemotherapies have only limited activity. Nitrosoureas such as lomustine produce PFS6 rates of approximately 19% [7,13]. Dose-dense or metronomic regimens of temozolomide may also have modest activity in patients who fail standard temozolomide therapy [14,15].

Recent advances

There has been significant progress in understanding the molecular pathogenesis of glioblastomas in recent years [16-18]. This has resulted in increasing interest in the therapeutic potential of targeted molecular therapies [2,19]. Unfortunately, the results with single agents inhibiting receptor tyrosine kinases such as the epidermal growth factor receptor and platelet-derived growth factor (PDGF) receptor or with signal transduction pathway components such as mammalian target of rapamycin have been disappointing [19,20]. Reasons for these poor results include co-activation of multiple tyrosine kinases [21] and redundant signaling pathways, limiting the activity of single agents. In addition, penetration of many agents across the blood-brain barrier is poor and is compounded by active efflux of drugs via P-glycoprotein and other pumps. Attempts to define subsets of patients who respond to specific agents have also met with limited success [22-24]. Strategies to improve on the effectiveness of targeted agents using multitargeted agents that inhibit several kinases, combinations of agents inhibiting complementary targets, combinations of targeted agents with radiotherapy and

chemotherapy, and agents that inhibit critical final common pathways are in progress [25].

In contrast to the disappointing results with targeted therapies directed at tumor cells, there has been significant progress with agents that inhibit angiogenesis. Glioblastomas are very vascular tumors and represent a particularly attractive target for this therapeutic strategy. These tumors secrete a variety of angiogenic factors such as vascular endothelial growth factor (VEGF), PDGF, and basic fibroblast growth factor (bFGF), which contribute to neovascularization [26]. In addition, VEGF is an important cause of the increased vascular permeability and peritumoral edema that contribute significantly to the morbidity associated with these tumors [26].

The recent availability of potent antiangiogenic agents targeting VEGF and its receptors (VEGFR) has led to important progress in the treatment of glioblastomas [26,27]. Bevacizumab, a humanized monoclonal antibody that binds VEGF, preventing it from activating its receptors (especially VEGFR2) and abrogating subsequent biologic effects, has been evaluated alone and in combination with various chemotherapeutic agents in recurrent glioblastomas with encouraging results. In an early phase II study, the combination of bevacizumab and irinotecan produced a response rate of 57% and a PFS6 of 46% in recurrent glioblastomas [28]. 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 antitumor effect. The regimen was generally well tolerated, with a low incidence of intracerebral hemorrhage. These preliminary findings were confirmed by a multicenter randomized phase II study of 167 patients with recurrent glioblastomas who were treated with bevacizumab alone or in combination with irinotecan [29]. Patients receiving bevacizumab alone had a response rate of 28.2% and a PFS6 of 42.6%, whereas patients receiving bevacizumab in combination with irinotecan had a response rate of 37.8% and a PFS6 of 50.3% [29]. In reviewing this trial for purposes of approval, the US Food and Drug Administration (FDA) analyzed data from the bevacizumab monotherapy arm only and determined that the response rate was 26% and the PFS6 was 36% [30]. Median survival was similar between the two groups, 9.2 months for bevacizumab (Avastin®) alone and 8.7 months for the combination, making it unclear whether the use of irinotecan provided any additional benefit. Patients treated with bevacizumab experienced a significant reduction in peritumoral edema and the need for corticosteroids. This study again confirmed that bevacizumab was well tolerated, with a low incidence of intracranial hemorrhage.

A second phase II trial of bevacizumab monotherapy was conducted in 48 heavily pretreated recurrent glioblastoma multiforme patients [31]. The investigators determined that the response rate was 35%, PFS6 29%, and median overall survival 31 weeks. On FDA review, the response rate was 19.6% [30]. Fifty-eight percent of patients reduced their corticosteroid doses by an average of 59% [31]. As a result of these two studies, on 5 May 2009 the FDA granted accelerated approval for bevacizumab for the treatment of patients with recurrent glioblastomas.

Since antiangiogenic agents can potentially have synergistic effects with radiotherapy, there is significant interest in combining these agents with radiotherapy [32]. Two phase III trials evaluating the benefits of adding bevacizumab to radiotherapy and temozolomide for the treatment of newly diagnosed glioblastomas are in progress. 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.

In addition to bevacizumab, other agents that bind VEGF, such as aflibercept (VEGF-Trap [33]), are under active investigation. There is also significant interest in inhibitors of VEGFR such as cediranib [34], vandetanib, sorafenib, sunitinib, pazopanib, and CT322 in glioblastomas. In comparison with drugs targeting VEGF or VEGFR, agents inhibiting other angiogenic pathways have been less successful. Cilengitide, a drug that inhibits $\alpha v\beta 3$ and $\alpha v\beta 5$ integrins, has shown modest activity in glioblastomas, and studies combining it with other agents are in progress [19,35].

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 [36]. 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 [37,38]. Unfortunately, most of the conventional therapies are generally ineffective for patients who progress on bevacizumab and subsequent survival is often limited [39]. As a result, it is unclear whether the improvements in progression-free survival produced by these agents translate into a significant increase in overall survival [40]. 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 which allow the tumor to eventually progress after an initial response. These mechanisms of resistance are thought to include upregulation of alternative proangiogenic signals such as bFGF 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 [41]. Combining agents targeting VEGF with inhibitors of other angiogenic molecules such as bFGF or with drugs that inhibit invasion may hold promise. Other novel therapies undergoing evaluation for glioblastomas include viral gene therapies [42,43], immunotherapies [44], and convection-enhanced delivery of targeted immunotoxins [45], but their value remains to be determined.

Implications for clinical practice

After over two decades of minimal progress in the treatment of recurrent glioblastomas, bevacizumab represents an important but limited advance. This agent undoubtedly increases progression-free survival and improves quality of life, but how much it prolongs survival remains unclear. Whether the drug should be used alone or in combination with chemotherapeutic agents and which ones should be used also remain unclear. Although most of the studies have been performed with irinotecan, it is possible that combining bevacizumab with lomustine may be more effective. It is also unclear whether bevacizumab should be used at first relapse or whether patients should be treated with other therapies or enrolled into clinical trials first and bevacizumab reserved for subsequent progression. Given the difficulty in evaluating agents after bevacizumab failure, it seems prudent to evaluate these agents first in bevacizumab-naïve patients.

Abbreviations

bFGF, basic fibroblast growth factor; FDA, US Food and Drug Administration; PDGF, platelet-derived growth factor; PFS6, 6-month progression-free survival; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

Competing interests

PYW receives research support from Genentech, Inc. (South San Francisco, CA, USA), AstraZeneca, (London, UK/Södertälje, Sweden), Amgen, Inc. (Thousand Oaks, CA, USA), Novartis International AG (Basel, Switzerland), Bayer Schering Pharma AG (Berlin-Wedding, Germany), Exelixis (South San Francisco, CA, USA), and Boehringer-Ingelheim GmbH (Ingelheim, Germany).

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