CCR 20th Anniversary Commentary: Bevacizumab in the Treatment of Glioblastoma—The Progress and the Limitations

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Vredenburgh and colleagues conducted the first phase II study of bevacizumab plus irinotecan in recurrent malignant glioma, confirming the safety and efficacy of bevacizumab. This study, which was published in the February 15, 2007, issue of *Clinical Cancer Research*, was a stepping stone for subsequent research, leading to regulatory approval of bevacizumab for recurrent glioblastoma. *Clin Cancer Res; 21(19); 4248–50. ©2015 AACR.*

See related article by Vredenburgh et al., Clin Cancer Res 2007; 13(4) February 15, 2007;1253–9

Background and Previous Research

Gliomas account for almost 80% of primary malignant brain tumors, and glioblastoma is the most common subtype (1). Median survival for patients with newly diagnosed glioblastoma is 8 to 15 months, while recurrent disease is associated with a median survival of 3 to 9 months (2). Further, fewer than 4% of patients live for more than 5 years following glioblastoma diagnosis, with most deaths occurring within 2 years (1).

Malignant gliomas are considered among the most angiogenic of cancers and are mostly fueled by vascular endothelial growth factor (VEGF) signaling (3). The main VEGF isoforms (VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E, VEGF-F, and placental growth factor) and several other active VEGF variants are secreted by tumor cells. Several hypoxia-dependent and -independent mechanisms also yield VEGF in the tumor microenvironment. Expression of VEGF receptors (VEGFR-1, VEGFR-2, and VEGFR-3) and coreceptors, although low in the normal brain, is markedly increased in glioblastoma. Ligand binding activates VEGFRs, triggering downstream intracellular signaling, which promotes endothelial cell proliferation, survival, activation, invasion, migration, and permeability.

Increased VEGF expression has been found to predict glioma aggressiveness and poorer outcome (2). Both microvessel grade and microvessel count have been significantly correlated with postoperative survival in newly diagnosed and previously treated patients with glioblastoma (4). Patients with low-grade astrocytomas that overexpress VEGF were also found to have a significantly shorter mean overall survival (OS) and earlier time to recurrence than those with VEGF-negative tumors (5). Further, low-grade gliomas can demonstrate an "angiogenic switch," which is defined as an induction of transformation to high-grade gliomas via proangiogenic mediators and new blood vessel formation (3).

Glioblastoma is challenging to treat and is frequently associated with a rapid and fatal clinical course. In patients with newly diagnosed disease, optimal treatment consists of surgical resection with adjuvant concurrent chemoradiotherapy with temozolomide, followed by 6 to 12 months of temozolomide (6). The prognosis is better for patients who undergo gross total resection, rather than those with subtotal resection or patients unable to undergo surgery (7). In recurrent disease, salvage therapies have been limited and result in minimal improvement in OS. This overwhelming need for improved treatments has driven the development of novel drugs that target glioblastoma biology, specifically anti-VEGF therapies.

Bevacizumab is a recombinant humanized monoclonal antibody that binds all VEGF isoforms, causing reduced tumor vascularization and inhibiting tumor growth (2). Early studies showed improved outcomes when bevacizumab was administered with chemotherapy in colorectal, lung, breast, and renal cancers (3). In preclinical studies, bevacizumab was also shown to inhibit human glioblastoma growth in xenograft models (2). In February 2004, the FDA approved bevacizumab in combination with irinotecan-based chemotherapy for metastatic colorectal cancer.

Irinotecan is a topoisomerase I inhibitor, which prevents relaxation of supercoiled DNA and results in decreased RNA transcription and DNA replication (1). Several factors make irinotecan attractive in malignant glioma management. First, topoisomerase I and II activity has been shown to be significantly augmented in malignant gliomas following DNA damage. These drugs also readily cross the blood–brain barrier and have a different mechanism of action than alkylating agents, such as temozolomide. In studies, irinotecan has shown modest activity as a single agent in recurrent glioblastoma, including a 5% to 15% radiographic response (RR) rate and a median progression-free survival (PFS) of 12 weeks (3). Early data also showed possible synergy with anti-VEGF therapies with acceptable toxicity.

Despite its promise, there was initial hesitancy to use bevacizumab in patients with glioblastoma after a single report of a fatal cerebral hemorrhage in a patient with hepatocellular carcinoma and previously undiagnosed brain metastasis (3). In fact, patients

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with brain metastasis from solid tumors have routinely been excluded from bevacizumab clinical trials following this report. Nonetheless, an early retrospective series of heavily pretreated patients with recurrent glioblastoma who received bevacizumab with irinotecan, modeled after the colorectal cancer experience, showed acceptable safety and unprecedented activity with RR in 43% and stable disease in 52% of patients (8).

These results prompted two single-arm, prospective phase II studies led by Vredenburgh and colleagues (2, 9). Their first major finding was that the safety profile of bevacizumab in recurrent glioblastoma was similar to that in patients with other cancers. Particularly, only 1.5% of patients experienced intracerebral hemorrhage. The second major finding was confirmation of the significant antitumor activity of bevacizumab and irinotecan. RR was observed in 60% of patients, the 6-month PFS rate was 38% to 46%, and the median OS was 40 to 42 weeks. To put these findings in perspective, previous salvage therapy for patients with recurrent glioblastoma resulted in an RR of 5% to 10%, 6-month PFS of 9% to 15%, and OS of 22 to 26 weeks (3). Finally, many patients with an RR in these studies showed neurologic improvement and were able to taper chronic steroids.

These studies also highlighted the phenomenon of pseudoresponse. Contrast enhancement on brain MRI is regulated by the vascular permeability of cerebral vasculature (2). As a direct result of antipermeability effects of bevacizumab on the blood–brain barrier, contrast enhancement of tumors on MRI is diminished. As such, a decrease in contrast enhancement and tumor dimensions following bevacizumab therapy may not represent true tumor response, but a secondary steroid-like effect. In early studies, tumor response was measured with MRI, including both postcontrast and T2/FLAIR sequences (i.e., modified Macdonald criteria). RRs were correlated with patient clinical improvement and results from neurologic examinations. These responses were also sustained and associated with improved PFS. Newer alternative MRI sequences, such as diffusion or perfusion sequences, may be preferred as these modalities show changes in tumor vasculature in patients being treated with bevacizumab.

A follow-up phase II study (BRAIN study) was an open-label, multicenter, noncomparative trial that randomly assigned patients with recurrent glioblastoma to single-agent bevacizumab or bevacizumab plus irinotecan (10). The toxicity profile of bevacizumab was consistent with previous data, although patients who received irinotecan had more adverse events. In the single-agent bevacizumab versus bevacizumab-plus-irinotecan groups, the objective RRs were 28.2% and 37.8%, 6-month PFS rates were 42.6% and 50.3%, and median OS durations were 9.2 months and 8.7 months, respectively. Again, these data represented significantly improved outcomes compared with previous salvage therapy. However, outcomes for bevacizumab plus irinotecan were similar to those for single-agent bevacizumab. On the basis of this study, as well as a study by Kreisl and colleagues (11), the FDA granted accelerated approval to single-agent bevacizumab for patients with recurrent glioblastoma in May 2009, with a rapid process from an investigator-sponsored trial to FDA approval.

Subsequent Research

Interestingly, use of bevacizumab in newly diagnosed glioblastoma demonstrated improved PFS, but failed to show a difference in OS. One phase III trial (AVAglio) randomly assigned patients to receive either bevacizumab or placebo in addition to standard chemoradiotherapy. The median PFS durations were 10.6 months for the bevacizumab group and 6.2 months for the placebo group, while OS did not differ significantly (12). Baseline health-related quality of life and performance status were maintained longer in the bevacizumab group, and the glucocorticoid requirement was lower. Another randomized phase III trial (RTOG 0825) revealed a PFS duration of 10.7 months in the bevacizumab group versus 7.3 months in the placebo group, but again no difference in OS (13). However, increased symptom burden, worse quality of life, and decline in neurocognitive function were more frequent in the bevacizumab group. The lack of OS advantage in both studies may be explained, in part, by the high crossover rate that plagued both trials.

In the newly recurrent setting, multiple combination therapies with bevacizumab have been investigated. One such trial (BELOB) was an open-label phase II study of patients with a first recurrence of glioblastoma after chemoradiotherapy, who were randomly assigned to treatment with lomustine, bevacizumab, or a combination of both (14). The 9-month OS rates were 43% in the lomustine group, 38% in the bevacizumab group, and 63% in the combination group. Combination therapy was well tolerated. A follow-up health-related quality-of-life study did not show any negative effects of bevacizumab, whether alone or in combination with lomustine.

In patients with a second relapse of glioblastoma, treatment options are very limited. One retrospective study examined bevacizumab continuation compared with non-bevacizumab therapy among patients with recurrent glioblastoma who had previously been treated with bevacizumab-containing regimens (15). The median OS durations were 5.9 months versus 4.0 months, while the 6-month OS rates were 49.2% versus 29.5% for patients who continued bevacizumab. Similarly, an unmet clinical need is in initially unresectable glioblastoma, which is associated with a poor prognosis, with a median OS of 6 to 10 months (7). A phase II trial of upfront bevacizumab and temozolomide for unresectable or multifocal glioblastoma yielded partial responses in 24.4% and stable disease in 68.3% of patients (7). Toxicities were consistent with those seen in the adjuvant setting using these agents.

Several potential mechanisms of resistance to anti-VEGF agents have been identified. One major mechanism involves upregulation of alternative angiogenic factors following VEGF inhibition, such as PDGF/PDGFR-β, FGF, SDF-1α, and angiopoietin-1 (Ang-1)/Tunica interna endothelial cell kinase homolog (Tie-2; ref. 3). Others include increased mobilization of pericytes, secretion of endothelial cell survival factors, and induction of a more invasive phenotype by the glioma cells with host blood-vessel appropriation and gliomatosis (3). These factors contribute to rebound angiogenesis following initial tumor suppression. Current research is focusing on agents that would be able to thwart anti-VEGF tumor escape. Other promising areas of research include combination therapies of anti-VEGF inhibitors with vaccine strategies, immune checkpoint inhibitors, and other treatment modalities, such as newer radiotherapy techniques.

In summary, bevacizumab clearly appears to have activity in glioblastoma, providing a window into glioblastoma biology. In the newly diagnosed setting, studies do not justify routine use due to a lack of OS benefit and conflicting quality-of-life results. However, bevacizumab is approved for use after first glioblastoma recurrence and may be of clinical benefit in newly diagnosed patients with unresectable disease or those with high steroid

needs. Future exploration of clinical strategies to circumvent mechanisms of resistance with novel agents or combination regimens may prove highly valuable.

Disclosure of Potential Conflicts of Interest

A. Desjardins is a consultant/advisory board member for Genentech. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: N. Mar, A. Desjardins, J.J. Vredenburgh
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