Enzastaurin in the Treatment of Recurrent Glioblastoma: A Promise That Did Not Materialize

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Glioblastoma multiforme (GBM) is the most common primary malignant brain tumor and represents one of the toughest therapeutic challenges in oncology. On recurrence after radiation therapy and temozolomide, median survival historically has ranged from 4 to 7 months. Interest in antiangiogenic approaches in the treatment of gliomas was founded on preclinical work demonstrating the dependency of these tumors on intense angiogenic activity, and culminated with the recent accelerated approval of the anti-vascular endothelial growth factor (VEGF)–A humanized monoclonal antibody, bevacizumab, in May 2009 in the United States. This approval was based on the durable progression-free survival (PFS; range, 3.9 to 4.2 months) and response rate (range, 19.6% to 25.9%) observed in patients with recurrent GBM treated with bevacizumab monotherapy. However, the modest median overall survival (OS) of 7.8 to 9.2 months, highlights the need for further improvement of efficacy. Several ongoing phase II/III investigations testing large molecule VEGF inhibitors (bevacizumab, aflibercept), or small molecule kinase or integrin inhibitors (such as enzastaurin, cediranib, pazopanib, sorafenib, sunitinib, vandetanib, XL-184, dasatinib, cilenitide) are in progress, both in the newly diagnosed and recurrent disease setting. Many of these clinical trials are testing combination regimens with antiangiogenesis agents to determine the optimal incorporation of angiogenesis inhibition in GBM treatment and to prevent or overcome the development of bevacizumab resistance.

In this issue of Journal of Clinical Oncology, Wick et al report on the results of a randomized phase III trial of enzastaurin versus lomustine, a nitrosourea commonly employed in this setting, in patients with recurrent GBM. Enrollment was terminated at 266 patients after a planned interim analysis for futility. Despite excellent trial design and conduct, results were disappointing. Median PFS (1.5 v 1.6 months; hazard ratio, 1.28), the trial’s primary end point, 6-month PFS (11.1% v 19%; P = .03), and OS (6.6 v 7.1 months; hazard ratio, 1.2) did not differ significantly between the enzastaurin and lomustine arms. Objective response was observed in 2.9% and 4.3% of the patients, respectively. Enzastaurin is a potent and selective inhibitor of protein kinase C (PKC)–β. Binding of the VEGF-A ligand with the VEGF receptor (VEGFR) 2/Flik-1/KDR high affinity receptor is thought to represent the most important ligand/receptor interaction regulating glioma angiogenesis, and PKC–β mediates VEGFR2 signaling through MEK and MAP kinase activation. Furthermore, by being downstream of phosphoinositide-3-kinase (PI3K) and by activating Akt through phosphorylation, PKC–β interacts with the phosphatase and tensin homolog (PTEN)/PI3K/Akt pathway, another key signaling pathway in gliomagenesis. After promising preclinical data demonstrating antiangiogenic and antiproliferative effects in glioma models at clinically achievable concentrations, a phase II trial of enzastaurin in heavily pretreated patients with recurrent GBM showed an objective radiographic response rate of 26% at the interim analysis, and the phase III trial was activated.

Despite the strong preclinical rationale and a promising response rate in a single institution phase II trial, why did enzastaurin fail to fulfill its promise in the phase III setting? One possibility could be that drug concentrations sufficient to block the target pathway and inhibit angiogenesis were not achieved in the CNS tumors, despite the fact that the enzastaurin dose utilized was known to produce a biologically active concentration in plasma. Higher doses would not likely have been feasible since a phase I trial attempting to escalate the enzastaurin dose resulted in significant hematologic toxicity. The very low objective response rate (2.9%) to enzastaurin observed in this phase III trial supports this hypothesis. Even in the absence of a significant antitumor effect, one would have expected decreased contrast enhancement on magnetic resonance imaging as a consequence of reduced vascular permeability associated with VEGFR2 inhibition, if enzastaurin had been able to block VEGFR2 signaling in the recurrent GBM tumors. Given the importance of drug delivery, trials of neoadjuvant administration of novel therapeutic agents before surgery with subsequent assessment of the drug effect in the surgical specimen, or use of functional imaging when applicable, to assess target inhibition, as part of the early development steps of novel antiglioma agents remain important.

Another possibility pertains to complementary angiogenesis pathways, bypassing PKC β inhibition and negating its antitumor effect in patients. VEGF-A ligand binding to other receptors, such as VEGFR1/Flt-1, and VEGFR2 signaling, via a nonPKC–β–dependent pathway, such as T-cell–specific adaptor/VEGFR–associated protein or fibroblast growth factor 2 upregulation, at the presence of enzastaurin could represent such alternatives. Overlapping molecular pathways could also have negated the effect of an enzastaurin–mediated decrease in Akt phosphorylation/activation of the PI3K/Akt pathway. The overlapping molecular networks driving glioma proliferation help explain why less-specific targeted agents might be associated with higher antitumor activity. The two further developed antiangiogenesis agents in glioma treatment are either targeting the VEGF ligand (bevacizumab), or in the case of the tyrosine kinase...
inhibitor cediranib (response rate, 56%; PFS at 6 months, 26%) are blocking multiple angiogenesis related receptor kinases (VEGFR2, VEGFR1, VEGFR3, c-Kit, platelet-derived growth factor receptor), with the inhibitory signaling still predominantly occurring via VEGFR2.

Independent of possible explanations regarding the negative outcome of this phase III trial, this study underscores one of the major current challenges in glioma therapeutics—what should be the criteria for determining enzastaurin activity? Although the final analysis of the phase II single-agent enzastaurin trial has not been published yet, as Wick et al. discuss, a median PFS of 1.3 months, a 6-month PFS of 7%, and median OS of 4.4 months was observed in this trial, pointing to possible prematurity of phase III testing, before single-agent activity being convincingly demonstrated.

Response rate (the criterion used in the case of enzastaurin), using the currently accepted response criteria, can be particularly misleading as an indicator of antitumor activity of antiangiogenic agents. Improvement in T1 gadolinium enhancement likely represents reduced vascular permeability with or without true antitumor effect. Pseudoprogress with development of progressive, infiltrative nonenhancing tumor can further confound interpretation. Overall, there is poor correlation between response rate and other outcomes such as 6-month PFS and OS in malignant glioma trials. End points, such as 6-month PFS, and OS, likely represent more robust primary endpoints to confirm efficacy that justifies the launching of a phase III trial. Furthermore, in a rapidly evolving landscape of therapeutic algorithms in glioma treatment, a regimen tested in a phase II trial should either demonstrate significant improvement compared to appropriate historic controls or, even better, this evidence should be provided through comparative randomized phase II designs. This can be increasingly important in recurrent glioma trials, due to lack of appropriate historic control data sets in the post-bevacizumab era.

Might there still be a role for enzastaurin in the treatment of gliomas? In this phase III trial reported by Wick et al, enzastaurin’s modest activity (median PFS and median OS) appeared to be comparable to lomustine. Single-agent tolerance of enzastaurin at the employed dose was also satisfactory. It would therefore still be worth incorporating enzastaurin in rationally designed combinatorial regimens, especially if based on a strong mechanistic rationale or preclinical demonstration of synergistic activity. Based on preclinical data indicating synergistic antiangioma activity in combination with radiotherapy, enzastaurin is being tested in combination with temozolomide and radiation in patients with newly diagnosed GBM. For patients with recurrent glioma, trials with enzastaurin in combination with bevacizumab or carboptatin are also ongoing.

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