Phase II trial of pazopanib (GW786034), an oral multi-targeted angiogenesis inhibitor, for adults with recurrent glioblastoma (North American Brain Tumor Consortium Study 06-02)

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The objective of this phase II single-arm study was to evaluate the efficacy and safety of pazopanib, a multi-targeted tyrosine kinase inhibitor, against vascular endothelial growth factor receptor (VEGFR)-1, -2, and -3, platelet-derived growth factor receptor-α and -β, and c-Kit, in recurrent glioblastoma. Patients with ≤2 relapses and no prior anti-VEGF/VEGFR therapy were treated with pazopanib 800 mg daily on 4-week cycles without planned interruptions. Brain magnetic resonance imaging and clinical reassessment were made every 8 weeks. The primary endpoint was efficacy as measured by 6-month progression-free survival (PFS6). Thirty-five GBM patients with a median age of 53 years and median Karnofsky performance scale of 90 were accrued. Grade 3/4 toxicities included leukopenia (n = 1), lymphopenia (n = 2), thrombocytopenia (n = 1), ALT elevation (n = 3), AST elevation (n = 1), CNS hemorrhage (n = 1), fatigue (n = 1), and thrombotic/embolic events (n = 3); 8 patients required dose reduction. Two patients had a partial radiographic response by standard bidimensional measurements, whereas 9 patients (6 at the 8-week point and 3 only within the first month of treatment) had decreased contrast enhancement, vasogenic edema, and mass effect but <50% reduction in tumor. The median PFS was 12 weeks (95% confidence interval [CI]: 8–14 weeks) and only 1 patient had a PFS time ≥6 months (PFS6 = 3%). Thirty patients (86%) had died and median survival was 35 weeks (95% CI: 24–47 weeks). Pazopanib was reasonably well tolerated with a spectrum of toxicities similar to other anti-VEGF/VEGFR agents. Single-agent pazopanib did not prolong PFS in this patient population but showed in situ biological activity as demonstrated by radiographic responses. ClinicalTrials.gov identifier: NCT00459381.

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Glioblastoma is the most frequent and aggressive primary brain tumor in adults and despite maximal safe resection and chemoradiotherapy followed by adjuvant temozolomide, its prognosis remains poor with a median survival of approximately 15 months. Almost all patients ultimately develop progressive tumors after initial standard treatment, after which median survival is only about 6 months. Clearly, novel therapeutic strategies and new therapeutic agents are needed.
Glioblastomas are among the most vascular tumors and current clinical research strategies are greatly focused on antiangiogenic agents. Glioblastomas have increased expression of vascular endothelial growth factor (VEGF), a protein produced by tumor and stromal cells. VEGF binds to VEGF receptors (VEGFRs) and promotes endothelial cell proliferation and migration. Recently, based on positive findings of phase II clinical trials, the FDA granted accelerated approval of single-agent bevacizumab, a monoclonal antibody against VEGF, for recurrent glioblastomas. However, factors other than VEGF play a significant role in glioblastoma angiogenesis. One such mechanism involves platelet-derived growth factor (PDGF) and its receptor PDGFR, which is commonly overexpressed in tumor endothelial cells and pericytes. Experimental studies suggest that PDGF/PDGFR is involved in pericyte recruitment and tumor vessel maturation in gliomas. More recently, stem cell factor (SCF) was found to be expressed in human glioma specimens in a tumor grade and angiogenesis-dependent manner. High SCF expression was shown to be an independent and more powerful negative prognostic factor in glioblastoma than VEGF expression. In addition, SCF secreted by glioma cells and host reactive astrocytes in combination with endothelial cell expression of its receptor, c-Kit, was shown to be a potent angiogenic factor in vivo, independent of VEGF.

Pazopanib (GW786034) is a second generation tyrosine kinase inhibitor that targets VEGFR-1, -2, and -3, PDGFR-α, PDGFR-β, and c-Kit. Pazopanib has shown activity and good tolerability in several cancer preclinical models and in patients with advanced renal cell carcinoma and soft-tissue sarcomas. An agent with multiple antiangiogenic targets, such as pazopanib, is attractive because it may have better antitumor activity than drugs that target a single angiogenic pathway. Therefore, we conducted a single-arm phase II clinical trial of pazopanib for recurrent glioblastoma with the goal of evaluating its efficacy and toxicity.

**Methods**

**Eligibility Criteria**

Patients ≥18 years old with histologically confirmed glioblastoma or gliosarcoma and unequivocal radiographic tumor progression were eligible. Patients could have had treatment for no more than 2 prior relapses. Additional eligibility criteria included Karnofsky performance scale (KPS) ≥60, adequate bone marrow function (white blood cell count ≥3000/µL, absolute neutrophil count ≥1500/µL, platelet count ≥100 000/µL, hemoglobin ≥10 g/dL), adequate liver function (bilirubin and AST <2.5 times the upper limit of normal), adequate renal function (creatinine <1.5 mg/dL or creatinine clearance ≥60 mL/min), normal coagulation tests (prothrombin and partial thromboplastin time ≤1.2 times the upper limit of normal) and life expectancy >8 weeks. At least 6 weeks must have elapsed from radiation therapy, 2 weeks from any investigational agent, 4 weeks from cytotoxic drugs, 6 weeks from nitrosoureas, 3 weeks from procarbazine, 2 weeks from vincristine, and 1 week from noncytotoxic agents such as interferon, tamoxifen, thalidomide, or cis-retinoic acid. Patients could undergo resection for recurrent disease prior to enrollment, and residual disease was not required for eligibility. Patients had to be on a stable dose of corticosteroids for at least 5 days before obtaining their baseline magnetic resonance imaging (MRI) scan.

Patients with prior interstitial brachytherapy or stereotactic radiosurgery needed to undergo PET, thallium scan, MR spectroscopy, or surgical documentation of progressive disease. Patients on anticoagulation therapy or enzyme-inducing antiepileptic drugs or who had undergone prior therapy with VEGF/VEGFR inhibitors were ineligible. Patients with a serious or non-healing wound, ulcer, or bone fracture; abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess within 4 weeks of enrollment; cerebrovascular accident within 6 months; myocardial infarction, cardiac arrhythmia, unstable angina, cardiac angio-plasty or stenting, or venous thrombosis within 3 months; or QTc prolongation or other significant ECG abnormalities or class III or IV New York Heart Association heart failure were ineligible. Patients who were pregnant or nursing were ineligible, and birth control methods were required although oral contraceptives were not considered reliable due to potential drug interactions. HIV positive patients on antiretrovirals were also ineligible. The protocol was approved by the institutional review board of each participating institution and all patients provided written informed consent before enrollment.

**Endpoints**

The primary efficacy endpoint was progression-free survival at 6 months (PFS6). PFS was calculated from the date of radiographic progression or the date of treatment for clinical decline. PFS for patients who
died on treatment or within 30 days of the end of treatment without documented progression was based on the date of death. All other patients without documented progression were censored at the date of last follow-up prior to start of other treatment. Overall survival (OS) was calculated from study registration until the date of death or patients were censored at the last date known to be alive. Radiographic response was assessed with standard criteria using largest cross-sectional diameters of measurable lesions (Macdonald criteria) or scored evaluations (Levin criteria). Determinations of complete or partial response required stable or decreasing dose of corticosteroids. Histologic diagnosis and brain MRI scans with stable disease or responses were centrally reviewed. Toxicity was evaluated using the National Cancer Institute Common Toxicity Criteria version 3.0.

Advanced MRI Studies

Patients (n = 11) who were treated at the Clinical Center of the National Institutes of Health underwent advanced MRI studies. These patients underwent MRI scanning at baseline and every 4 weeks thereafter. In addition to standard brain MRI studies, dynamic contrast-enhanced MRI (DCE-MRI) were obtained and the transfer constant (Ktrans) from the tumor to the tissue was computed voxel by voxel. To compute cerebral blood volume (CBV), gradient-echo dynamic susceptibility contrast MRI (DSC-MRI) was also obtained. The baseline 3D T1 images were used as a reference to which the other images and parametric maps were rigidly co-registered and analyzed.

Statistics

At the time the protocol was written, the sample size was selected based on historical data from 8 consecutive phase II clinical trials for recurrent malignant gliomas that were deemed negative and showed a PFS6 of 15% (95% confidence interval [CI]: 10%–19%) for GBM. This phase II single-arm trial was sized to discriminate between a PFS6 of 15% (P0) and 35% (P1). With accrual of 32 GBM patients, the trial would be considered successful if at least 8 patients achieved the PFS6 mark. This design provided greater than 90% probability of rejecting if the true PFS6 was 15% and 92% probability of declaring success if the true rate was 35%. A maximum of 35 patients were to be accrued to compensate for those who might not be evaluable. The primary endpoint was the number of patients known to have PFS >6 months. In addition, estimation of both PFS and OS was conducted using Kaplan–Meier analyses.

Results

Patient Characteristics

Patients were accrued from June 2007 to January 2008 at 4 member institutions of the North American Brain Tumor Consortium and follow-up extended through June 2009. Thirty-five patients (63% men) with median age of 53 years (range: 29–73 years) and median KPS of 90 (range: 60–100) were accrued, all of whom were eligible. All patients had completed radiotherapy a median of 10 months (range: 1–169) prior to enrollment. Patients also had received a median of one prior chemotherapy regimen (range: 1–3) before study entry. Eight patients underwent resection for the progression prior to enrollment (Table 1).

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Toxicity

All 35 patients received at least one dose of pazopanib and were evaluable for toxicity (Table 2). The most common adverse events were hypertension (37%), fatigue (34%), and elevated ALT (40%). Hematologic toxicities were usually mild. Four patients (11%) discontinued treatment as a result of toxicities; 3 due to thrombotic/embolic events and 1 due to CNS hemorrhage. One patient died of pneumonia with a normal WBC and another developed communicating hydrocephalus and withdrew consent but both events were deemed unrelated to pazopanib. Eight patients required dose reductions due to toxicity.

Outcomes

All 35 patients were included in an intent-to-treat analysis for PFS and OS and 34 patients had follow-up scans and were evaluable for objective radiographic response (ORR). Three patients were censored for PFS, all less than 2 weeks after study registration. Thirty patients
have died and 5 surviving patients were followed for at least 44 weeks.

Only 1 patient had a PFS/C21 6 months (PFS6 3%; 95% CI: 0.001% to 15%). Median PFS was 12 weeks (95% CI: 8–14 weeks) and median OS was 35 weeks (95% CI: 24–47 weeks, Fig. 1). There were 2 partial responses (ORR = 5.9%; 95% CI: 0.7%–21%) according to the Macdonald criteria. The best radiographic response was progressive disease in 11 patients (32%), whereas 21 patients (59%) had stable disease, although 2 of these were in patients who were followed <2 weeks and 5 others had progressed by the first protocol-specified scan at 8 weeks. In addition, 9 of 21 patients whose best response was stable disease according to the Macdonald criteria had a partial response by Levin criteria (Fig. 2). Six of the 9 patients with Levin criteria responses had a partial response at the 8-week scan, whereas 3 had radiographic response only on scans within the first 4 weeks of treatment. These 9 patients had reduction in contrast enhancement, vasogenic edema, and mass effect but the reduction in the products of the tumor diameters was <50%. In a subset of patients who underwent DSC and DCE-MRI scans, Levin’s partial response was often accompanied by decrease in relative CBV (rCBV) and Krans, a measurement of vessel permeability and total vessel surface (Fig. 2).

**Discussion**

In this phase II clinical trial, single-agent pazopanib did not prolong PFS in patients with recurrent glioblastomas. The primary endpoint of PFS6 was only 3% and did not show improvement compared with a PFS6 of 9% derived from several negative phase II trials conducted by our consortium. As a comparison, phase II trials of single-agent bevacizumab in a similar patient population found a PFS6 of 29%–43%. On the basis of demonstration of durable objective response rates observed in these 2 single-arm trials, the FDA
recently granted accelerated approval of bevacizumab for recurrent glioblastoma. It is unclear whether failure of pazopanib and other multi-targeted tyrosine kinase inhibitors to show significant responses in glioblastoma can be explained by inadequate dosing. It has been suggested that multi-targeted drugs have more off-target side effects and are not tolerated at higher and potentially more effective doses. Independent of this speculation, the fact remains that our patients were treated at the maximum tolerated dose and thus we can only conclude that pazopanib lacks efficacy in this disease at clinically tolerated doses. The lack of efficacy of pazopanib in our trial, however, does not necessarily reflect a failure of the class of multi-targeted tyrosine kinase inhibitors in glioblastoma. For example, a phase II trial of cediranib, a pan-VEGFR tyrosine kinase inhibitor with PDGFR-α, PDGFR-β, and c-Kit activity, achieved a more promising PFS6 of 28% in recurrent glioblastoma and a randomized phase III of cediranib is ongoing.

Pazopanib was reasonably well-tolerated in patients with recurrent glioblastoma. Similar to other anti-VEGF/VEGFR drugs, arterial hypertension was frequent, but usually mild, easily controllable, and reversible with cessation of pazopanib. In contrast to pure anti-VEGF drugs such as bevacizumab, pazopanib can cause mild myelosuppression as reported with other multi-targeted tyrosine kinase inhibitors. One patient discontinued treatment due to CNS hemorrhage and 3 patients discontinued due to thrombotic/embolic events, both known complications of anti-VEGF/VEGFR therapy but also of malignant gliomas. Thus, the relationship of these significant adverse events to pazopanib is unclear.

Despite failing to meet our predetermined landmark of success, our study did demonstrate that pazopanib has biological activity in situ in patients with glioblastoma as evidenced by the anti-VEGF/VEGFR toxicity profile and the decreased contrast enhancement seen on MRI, often with diminished vasogenic edema and mass effect, in 11 of 34 (32%) evaluable patients. As has been the case in other trials of VEGF/VEGFR inhibitors, however, it is impossible to know for certain whether the MRI responses seen with pazopanib resulted from stabilization of a leaky blood–brain barrier or a direct antitumor effect. The DCE-MRI findings in a select subset of pazopanib-treated patients did demonstrate decreased tumor CBV and decreased Ktrans, a measurement of tumor vessel permeability. It has previously been suggested that such findings represent drug-mediated normalization of abnormal tumor blood vessels, as similarly reported in glioblastoma patients treated with cediranib and bevacizumab. Whether tumor vessel normalization is truly occurring or the drug is merely inhibiting the blood vessel hyperpermeability effects of VEGF is unknown. Nevertheless, the very rapid induction and short duration of response to pazopanib is strongly suggestive of a primary vascular permeability effect rather than a direct antiangiogenic and antitumor effect.

VEGF/VEGFR inhibitors differ from traditional cytotoxic agents in that even in the absence of a direct antitumor effect, clinical benefit can still be achieved through the reduction in vasogenic edema, resulting in improved...
neurologic status, and diminished dependence on corticosteroids. Furthermore, independent of antitumor activity, a significant decrease in vasogenic edema can result in a survival benefit as described in the early studies of corticosteroids in patients with malignant glioma; resolution of edema has also been reported in preclinical studies with cediranib. Finally, it has been suggested that anti-VEGF-mediated tumor vascular normalization may improve the delivery of cytotoxic drugs by decreasing tumor interstitial pressure thereby providing a rationale for combination therapy. Thus, for optimizing regimens for glioblastoma, it may still be useful to identify VEGF/VEGFR inhibitors that have clinical biological activity for future use in combination with other agents or as antiedema agents, even if those specific drugs do not have single-agent antitumor activity.

The clinical significance of PDGF/PDGFR and SCF/c-Kit signaling blockade in gliomas remains to be elucidated. PDGF/PDGFR is an interesting target because it is not only involved in gliomaangiogenesis, but is also expressed in glioma cells and linked to glioma tumor growth through an autocrine loop. c-Kit is overexpressed in gliomas, but no activating receptor mutations such as those described in gastrointestinal stromal tumors have been reported. In fact, prior studies with imatinib, a PDGFR and c-Kit inhibitor, failed to show significant clinical activity in malignant gliomas, although its lack of activity may have been related to its poor penetration across the blood–brain barrier.

One of the difficulties in translating laboratory findings to clinical studies is the limitation of commonly used glioma preclinical models. Most preclinical studies evaluating glioma angiogenesis are based on standard orthotopic xenografts grown in immunodeficient mice. These tumors generally do not have an intact blood–brain barrier within the tumor, are encapsulated, and by nature require neoangiogenesis to grow. In contrast, human gliomas grow in situ as highly infiltrative tumors, often behind a partially or fully intact blood–brain barrier, and may not have high intrinsic proangiogenic activity secondary to cooperation of the normal pre-established brain vasculature.

There are emerging preclinical data suggesting that inhibition of the VEGF pathway can promote vessel cooption and increase tumor invasiveness. If this is confirmed in the clinic, these drugs may, in fact, have deleterious effects in some patients. Given that human glioblastomas are biologically heterogenous, further studies are needed to identify patients who will most likely benefit from antiangiogenic therapy.

Despite the limitations of preclinical screening and the results of clinical trials to date, it still remains plausible that inhibiting additional angiogenic pathways in conjunction with the VEGF/VEGFR pathway may ultimately result in enhanced tumor control compared with VEGF/VEGFR inhibition alone. Additional preclinical studies using improved glioma models (genetically modified mice, glioma initiating/stem cells) along with ongoing clinical trials of other multikinase inhibitors, including phase II clinical trials of sunitinib (a VEGFR, PDGFR, and c-Kit tyrosine kinase inhibitor), a phase I/II trial of tandutinib (another PDGFR and c-Kit inhibitor), and a phase II trial of tandutinib plus bevacizumab, will provide further data regarding the value of simultaneously inhibiting multiple angiogenic targets in glioblastoma.

Conflict of interest statement. None declared.

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References


33. Rubenstein JL, Kim J, Ozawa T, et al. Anti-VEGF antibody treatment of glioblastoma prolongs survival but results in increased vascular coop-