Phase II trial of sunitinib for recurrent and progressive atypical and anaplastic meningioma

Thomas J. Kaley, Patrick Wen, David Schiff, Keith Ligon, Sam Haidar, Sasan Karimi, Andrew B. Lassman*, Craig P. Nolan, Lisa M. DeAngelis, Igor Gavrilovic, Andrew Norden, Jan Drappatz, Eudocia Quant Lee, Benjamin Purow, Scott R. Plotkin, Tracy Batchelor, Lauren E. Abrey, and Antonio Omuro

Department of Neurology, Memorial Sloan Kettering Cancer Center, New York, New York (T.J.K., S.K., A.B.L., C.P.N., L.M.D., I.G., L.E.A., A.O.); Center for Neuro-Oncology, Dana-Farber Cancer Institute/Brigham and Women’s Center, Boston, Massachusetts (P.W., K.L., S.H., A.N., J.D., E.Q.L.); Department of Neurology, University of Virginia, Charlottesville, Virginia (D.S., B.P.); Department of Neurology, Massachusetts General Hospital, Boston, Massachusetts (S.R.P., T.B.)

*Current affiliation: Department of Neurology, Columbia Presbyterian Medical Center, New York, New York.

Corresponding Author: Thomas J. Kaley, MD, Department of Neurology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10065 (kaleyt@mskcc.org).

See the editorial by Marosi, on pages 7–8.

Background. No proven effective medical therapy for surgery and radiation-refractory meningiomas exists. Sunitinib malate (SU011248) is a small-molecule tyrosine kinase inhibitor that targets vascular endothelial growth factor receptor (VEGFR) and platelet-derived growth factor receptor, abundant in meningiomas.

Methods. This was a prospective, multicenter, investigator-initiated single-arm phase II trial. The primary cohort enrolled patients with surgery and radiation-refractory recurrent World Health Organization (WHO) grades II–III meningioma. An exploratory cohort enrolled patients with WHO grade I meningioma, hemangiopericytoma, or hemangioblastoma. Sunitinib was administered at 50 mg/d for days 1–28 of every 42-day cycle. The primary endpoint was the rate of 6-month progression-free survival (PFS6), with secondary endpoints of radiographic response rate, safety, PFS, and overall survival. Exploratory objectives include analysis of tumoral molecular markers and MR perfusion imaging.

Results. Thirty-six patients with high-grade meningioma (30 atypical and 6 anaplastic) were enrolled. Patients were heavily pre-treated (median number of 5 recurrences, range 2–10). PFS6 rate was 42%, meeting the primary endpoint. Median PFS was 5.2 months (95% CI: 2.8–8.3 mo), and median overall survival was 24.6 months (95% CI: 16.5–38.4 mo). Thirteen patients enrolled in the exploratory cohort. Overall toxicity included 1 grade 5 intratumoral hemorrhage, 2 grade 3 and 1 grade 4 CNS/intratumoral hemorrhages, 1 grade 3 and 1 grade 4 thrombotic microangiopathy, and 1 grade 3 gastrointestinal perforation. Expression of VEGFR2 predicted PFS of a median of 1.4 months in VEGFR2-negative patients versus 6.4 months in VEGFR2-positive patients (P = .005).

Conclusion. Sunitinib is active in recurrent atypical/malignant meningioma patients. A randomized trial should be performed.

Keywords: chemotherapy, malignant meningioma, sunitinib, tyrosine kinase.
inhibitors of platelet-derived growth factor receptors (PDGFRs; imatinib) and epidermal growth factor receptor (gefitinib and erlotinib), have all been disappointing.\(^2\)–\(^9\) Although the natural history of these tumors is not well established, the 6-month progression-free survival (PFS6) rate for these patients is poor. A phase II study of imatinib in recurrent meningioma demonstrated a PFS6 of 0% in the atypical/anaplastic cohort.\(^19\)

PDGF is a ubiquitous growth factor driving cell proliferation in normal development as well as numerous neoplasms, including meningiomas.\(^20\)–\(^25\) Administration of PDGF-BB to meningioma cells in culture results in stimulation of tumor growth, while administration of anti-PDGF-BB antibodies inhibits proliferation.\(^26\)–\(^27\)

Vascular endothelial growth factor (VEGF) is upregulated in almost all meningiomas and has been associated with neovascularization, tumor growth, and the development of edema.\(^28\)–\(^29\) Targeting VEGF with different agents has proved effective in several different cancers, including malignant gliomas.\(^30\)–\(^31\) Targeting this pathway may have therapeutic potential in meningioma.

Sunitinib malate (SU011248, Sutent, Pfizer) is an orally administered tyrosine kinase inhibitor targeting VEGF receptor (VEGFR), PDGFR, and KIT.\(^32\) Inhibiting these targets represents an attractive therapeutic approach for recurrent meningiomas. The FDA-approved and recommended dose for sunitinib in renal cell carcinoma and gastrointestinal stromal tumor is 50 mg daily for 4 of every 6 weeks. We selected this dose because meningiomas are extraparenchymal tumors. Given (i) the strong preclinical rationale for targeting PDGFR and VEGFR in meningiomas, (ii) the efficacy of sunitinib cotargeting VEGFR2 and PDGFR, and (iii) its safety in adults with other solid tumors, we investigated sunitinib in this phase II study for recurrent and progressive meningiomas that had failed prior surgery and radiation.

**Patients and Methods**

This was a prospective, multicenter, investigator-initiated single-arm phase II trial conducted at Memorial Sloan-Kettering Cancer Center, the Dana-Farber Cancer Institute, Massachusetts General Hospital, and the University of Virginia from December 2007 to February 2011. The main study cohort consisted of patients with recurrent or progressive meningioma (WHO grades II–III). An additional exploratory cohort enrolled patients with either recurrent WHO grade I meningioma, hemangiopericytoma (HPC; also known as solitary fibrous tumor [SFT] of the meninges), or hemangioblastoma.

**Patient Eligibility**

Patients were required to have either histologically proven meningioma, HPC, hemangioblastoma, or classic radiographic features of a surgically inaccessible meningioma. All patients had to have recurred despite radiotherapy, unless radiotherapy was contraindicated. There was no limit on the number of prior surgeries, radiation or radiosurgery treatments, or chemotherapy regimens. Patients who received stereotactic radiosurgery (SRS) were eligible without histologic documentation of recurrence if 2-fluoro-2-deoxy-D-glucose PET imaging demonstrated hypermetabolism. Patients were required to be ≥18 years old and have a KPS ≥60% more than 4 weeks since any prior therapy, and have an absolute neutrophil count ≥1000/mm\(^3\), platelets ≥100 000/mm\(^3\), serum aspartate transaminase (AST) and alanine transaminase (ALT) ≤2.5× laboratory upper limits of normal, creatinine ≤2.0 mg/dL, and total serum bilirubin ≤1.5. Patients were excluded if they received any other tyrosine kinase therapy in the past, were taking a cytochrome p450 enzyme-inducing antiepileptic (phenytoin, phenobarbital, carbamazepine, oxcarbazepine), or had significant heart disease or pulmonary embolus within the past 6 months, cardiac dysrhythmias of grade ≥2 of the Common Terminology Criteria for Adverse Events version 3.0, prolonged QTc interval on baseline electrocardiogram, uncontrolled hypertension, history of intracranial hemorrhage, preexisting thyroid disease, or therapeutic doses of warfarin.

**Treatment Plan**

Patients received sunitinib 50 mg daily for days 1–28 of 42, with 42 days constituting one cycle, and were treated until disease progression or intolerable toxicity. The dose of sunitinib was reduced to 37.5 mg and then 25 mg for patients who experienced grade 3 or 4 agent-related nonhematologic toxicity, including nausea, vomiting, or diarrhea that persisted despite maximal medical therapy, or grade 4 hematologic toxicity, excluding lymphopenia. Blood counts and serum chemistries were performed at 4 weeks, 6 weeks, and before each additional cycle of therapy if there was a treatment delay. Patients were assessed for response with MRI and clinical exams after cycle 1 and cycle 2, and then every other cycle until removal from study. Responses were determined using the Macdonald criteria. Treatment-related toxicities were evaluated using the National Cancer Institute Common Terminology Criteria version 3.0. The study was approved by the institutional review board of each participating site; all participants provided written informed consent.

**Statistical Considerations**

The main study cohort enrolled patients with recurrent atypical or anaplastic meningiomas, and the primary endpoint was PFS6 defined as the time from starting treatment until progression of disease or death from any cause. Any patient not known to be progression free at 6 months was assumed to have failed treatment. With a minimum sample size of 20 patients with atypical/malignant meningioma, we had 89% power to detect an improvement in the PFS6 rate from 5% to 30% with a significance level of 0.015. Secondary endpoints included radiographic response rate, median PFS, overall survival (OS), and toxicity. Survival was evaluated using Kaplan–Meier methodology and was calculated from the start of treatment.

The exploratory cohort (WHO grade I meningioma, HPC, and hemangioblastoma) with a maximum of 10 patients was analyzed descriptively.

**Correlative Studies**

MR perfusion was performed at baseline and after 2 weeks on study and then with each additional MRI assessment to determine a correlation with outcome. Immunohistochemistry (IHC)
was performed using the Envision + system (Dako) according to the manufacturer’s instructions. Heat antigen retrieval was applied to all samples using a steamer and citrate buffer. Antibodies were used as follows: PDGFRα (1:75, #3164, Cell Signaling), PDGFRβ (1:100, #3169, Cell Signaling), VEGFR2 (kinase insert domain receptor;1:75, #2479, Cell Signaling), KIT (c-Kit; 1:250, #A4502, Dako), and signal transducer and activator of transcription 6 (STAT6; 1:75, #sc621, Santa Cruz Biotechnology). The IHC results were evaluated by 2 reviewers and scored 0–3 with respect to intensity and estimated percentage of positive tumor cells.

Results

Patient Characteristics

A total of 36 patients with aggressive meningioma were enrolled onto this trial, including 30 atypical and 6 anaplastic meningiomas; 83% had supratentorial tumors (Table 1). All patients had received prior surgery, and all but 1 (because of prior cranial radiotherapy for childhood leukemia) had received radiation. Patients were heavily pretreated with a median number of 5 recurrences (range 2–10). There were 13 participants in the exploratory cohort: 4 with WHO grade I meningiomas, 6 with HPCs, and 3 with hemangioblastomas. One additional patient enrolled but withdrew consent within the first week of study and was replaced, but was included in the toxicity assessment.

Response and Outcome

At final analysis, 15 patients (42%) with recurrent atypical or anaplastic meningioma were progression free and alive at 6 months, meeting the primary endpoint. The median PFS in this cohort was 5.2 months (95% CI: 2.8–8.3 mo), and median OS was 24.6 months (95% CI: 16.5–38.4 mo) (Fig. 1). The 2-year PFS was 14.6% (95% CI: 4.4%–29.7%); the 2-year OS was 51.7% (95% CI: 29.2%–69.9%).

Of the 36 patients with aggressive meningioma, radiographic response data were available for 35. One patient achieved a complete response and 1 achieved a partial response (unconfirmed due to toxicity), both with atypical meningioma. Best radiographic responses were stable disease in 25 patients (20 atypical, 5 anaplastic) and progressive disease in 8 patients (7 atypical, 1 anaplastic). Neither age, KPS, nor prior treatment was associated with response.

Exploratory Cohort

Among the 4 patients with benign meningioma, 3 came off study after one cycle of therapy (2 withdrew consent; 1 was removed for toxicity). The 1 patient who remained on study progressed at 11.1 months and died 17.6 months after initiating study treatment with a best radiographic response of stable disease.

Among 6 patients with HPC, 3 discontinued because of toxicity, 2 withdrew consent, and 1 had progression of disease at 1.6 months. Among 3 patients with hemangioblastoma, 2 progressed at 3 and 4 months each, and the third withdrew consent within cycle 1.

Toxicity

Toxicity data are available for all 50 patients (Table 2). One grade 5 toxicity was observed: a patient with an atypical meningioma developed a fatal intratumoral hemorrhage and died 17.6 months after study treatment with a best radiographic response of stable disease.
subarachnoid extension; 2 grade 3 and 1 grade 4 CNS/intratumoral hemorrhages were also observed. Two patients developed thrombotic microangiopathy, 1 grade 3 and 1 grade 4. One grade 3 gastrointestinal perforation was also observed. Grades 1 and 2 toxicities were common (Table 3). Sixteen patients required a dose reduction, and 11 discontinued sunitinib due to toxicity.

**Correlative Studies**

**Imaging**

Dynamic susceptibility contrast MR perfusion imaging was performed on a subset of patients at study entry, repeated at 2 weeks and then with the other MRI timepoints. Evaluation was performed on 7 patients who had a baseline MR perfusion scan and at least one follow-up. Perfusion ratio was calculated and defined as the ratio of the relative cerebral blood volume (rCBV) of the tumor to the rCBV of the normal brain (contralateral white matter when available). The maximum percentage change in perfusion ratio was calculated for each patient. These 7 patients demonstrated a median maximum decrease in perfusion ratio of 45% (range 6%–55%), with all patients manifesting a decrease upon their first posttreatment scan at 2 weeks.

**Molecular Correlatives**

Thirty-five patients had sufficient tissue available for molecular correlative analysis. These included 3 WHO grade I meningiomas, 18 grade II meningiomas, 7 grade III meningiomas, 4 SFT/HPCs, and 3 hemangioblastomas. Tumor tissue studied was from newly diagnosed as well as recurrent specimens.

To evaluate whether clinical parameters might correlate with the known kinase targets of sunitinib, we performed IHC for PDGFRα, PDGFRβ, VEGFR2, and KIT. The intensity in tumor cells and percentage of positive tumor cells each were scored manually from 0 to 3, with 0 defined as no expression and 1–3 as slight, moderate, and intense expression, respectively. In all tumor types, staining for KIT was not detected in tumor cells but was noted within rare inflammatory cells within tumors of all types. Formal statistical analysis was restricted to meningiomas of all grades (n = 28) given the small numbers.
of other tumor types represented. We correlated IHC results and PFS by Kaplan–Meier analysis comparing those with no expression (score = 0) with those samples with positive expression (score = 1–3). VEGFR2 expression predicted median PFS (Fig. 2) of 1.4 months in VEGFR2-negative patients versus 6.4 months in VEGFR2-positive patients (P = .005). Similarly, VEGFR2 expression predicted median OS of 9.1 months in VEGFR2-negative patients versus 24.6 months in VEGFR2-positive patients (P = .002). Tumors were variably positive with a wide range for PDGFRα and PDGFRβ, but no significant correlation was noted of PDGFRα or -β expression with outcome measures in meningioma.

Reliable histologic discrimination of SFT from meningioma is challenging, and given the potential difference in outcome for these tumors, we validated their histology in our cohort using an additional method. Recent reports suggest that NAB2 (nerve growth factor-inducible protein A binding protein 2)-STAT6 gene fusions are present in the majority of histologically defined SFT/HPCs. IHC detection of nuclear STAT6 protein is a reliable diagnostic method for identification of SFTs with these fusions, thus we performed STAT6 IHC on all tumors. Five other tumors exhibiting STAT6 nuclear staining showed only a focal or low percentage of positive cells and consisted of atypical meningiomas and 1 hemangioblastoma.

Discussion

Molecularly targeted therapy has yet to demonstrate efficacy in treating patients with aggressive meningioma. Although PDGFR and VEGFR are highly expressed in meningiomas, no data exist demonstrating therapeutic activity from drugs designed to interfere with these pathways. Two retrospective reviews suggest possible activity with bevacizumab, and a phase II study investigating bevacizumab (NCT01125046) is nearing completion. Our trial was designed to explore the efficacy of sunitinib in a heavily pretreated and refractory population of patients with recurrent atypical and anaplastic meningiomas via inhibition of multiple targets including PDGFR and VEGFR. To our knowledge, this is the first prospective trial to demonstrate efficacy of a medical treatment for patients with aggressive meningioma. The primary efficacy endpoint was reached, with PFS6 of 42% in the primary study cohort of atypical and anaplastic meningioma patients, suggesting that this regimen warrants further investigation.

Despite apparent efficacy, considerable toxicity to sunitinib was observed. The rate of CNS hemorrhage was low (8%) and comparable to other angiogenesis inhibitor studies in patients with glioma, but 1 was fatal and 3 were serious. Other toxicities were common and significant, with 30 patients (60%) experiencing grade 3 or higher toxicity. Thirty-two percent of patients required dose reduction, and 22% of patients were removed from study for toxicity. The most common toxicity leading to dose reduction was gastrointestinal, including nausea, vomiting, and anorexia, accounting for 56% of the dose reductions. Many patients experienced grade 1 and 2 toxicities, which did not lead to removal from study or to dose reduction but still affected their quality of life. However, overall toxicity was rather similar to the prior literature on sunitinib with the exception of the CNS hemorrhages.

No activity was observed in the exploratory cohort of grade I meningiomas, HPCs, or hemangioblastomas, although the number of each was small. However, most of these patients either withdrew consent or were removed for toxicity, so assessment of benefit was very limited.

Dynamic susceptibility contrast perfusion imaging was performed in order to test the anti-angiogenic activity of the drug in these tumors. The decrease in perfusion ratio in all patients who had MR perfusion imaging demonstrates that sunitinib does reach these tumors and exerts an effect on the tumor vasculature. Whether or not this effect conveys a meaningful clinical benefit will require further investigation. However, the perfusion imaging data are intriguing and support our hypothesis that sunitinib is an active agent in these tumors.

Similarly, VEGFR2 expression was strongly associated with a response to sunitinib, further supporting the activity of the drug in aggressive meningiomas. However, our patient numbers are small and VEGFR2 expression was not evaluated in a group who did not receive sunitinib; it is possible that VEGFR2 may be a simply good prognostic marker. In addition, the prior material that was studied was not uniformly the recurrence leading to trial enrollment and, as such, may not fully represent the actual expression properties at the time of sunitinib treatment. Randomized studies are needed to fully characterize the predictive value of VEGFR2 in patients with meningiomas exposed to sunitinib.

Response assessment is challenging in this patient population. Macdonald criteria were used measuring the largest cross-sectional area of the enhancing tumor. Given that many of these tumors have irregular shapes, this measurement may be inaccurate. Improved response assessment criteria for meningioma specifically are needed for more standardized trial designs in the future.

In summary, single-agent sunitinib appears to be active in recurrent/progressive atypical and anaplastic meningiomas. The primary endpoint of this trial was met, and 42% of patients were alive and progression free at 6 months. Toxicity is a concern, but this regimen warrants further study in this population of patients. Given the lack of good historical data, this should occur in a randomized setting.

Acknowledgments

This trial was presented at the Society for Neuro-Oncology Annual Meeting in 2008, 2009 and 2010.

Funding

This work was supported by Pfizer and the Brain Science Foundation.

Conflict of interest statement. Dr. Abrey is a Global Development Leader with Roche Laboratories. No other conflicts declared.
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