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CLINICAL STUDY

Phase II study of tivozanib, an oral VEGFR inhibitor, in patients with recurrent glioblastoma

Jayashree Kalpathy-Cramer[1] · Vyshak Chandra[1] · Xiao Da[1] · Yangming Ou[1] · Kyrre E. Emblem[1,3] · Alona Muzikansky[2] · Xuezhu Cai[1] · Linda Douw[1,4] · John G. Evans[1] · Jorg Dietrich[2] · Andrew S. Chi[6] · Patrick Y. Wen[5] · Stephen Stufflebeam[1] · Bruce Rosen[1] · Dan G. Duda[2] · Rakesh K. Jain[2] · Tracy T. Batchelor[2] · Elizabeth R. Gerstner[2]

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Abstract Targeting tumor angiogenesis is a potential therapeutic strategy for glioblastoma because of its high vascularization. Tivozanib is an oral pan-VEGF receptor tyrosine kinase inhibitor that hits a central pathway in glioblastoma angiogenesis. We conducted a phase II study to test the effectiveness of tivozanib in patients with recurrent glioblastoma. Ten adult patients were enrolled and treated with tivozanib 1.5 mg daily, 3 weeks on/1 week off in 28-day cycles. Brain MRI and blood biomarkers of angiogenesis were performed at baseline, within 24–72 h of treatment initiation, and monthly thereafter. Dynamic contrast enhanced MRI, dynamic susceptibility contrast MRI, and vessel architecture imaging were used to assess vascular effects. Resting state MRI was used to assess brain connectivity. Best RANO criteria responses were: 1 complete response, 1 partial response, 4 stable diseases, and 4 progressive disease (PD). Two patients were taken off study for toxicity and 8 patients were taken off study for PD. Median progression-free survival was 2.3 months and median overall survival was 8.1 months. Baseline abnormal tumor vascular permeability, blood flow, tissue oxygenation and plasma sVEGFR2 significantly decreased and plasma PlGF and VEGF increased after treatment, suggesting an anti-angiogenic effect of tivozanib. However, there were no clear structural changes in vasculature as vessel caliber and enhancing tumor volume did not significantly change. Despite functional changes in tumor vasculature, tivozanib had limited anti-tumor activity, highlighting the limitations of anti-VEGF monotherapy. Future studies in glioblastoma should leverage the anti-vascular activity of agents targeting VEGF to enhance the activity of other therapies.

Keywords Glioblastoma · Anti-angiogenesis · MRI · Progression-free survival · Overall survival · Tivozanib

Introduction

The formation of new blood vessels is essential for the growth of solid malignant tumors and vascular endothelial growth factor (VEGF) is one of the critical drivers of tumor angiogenesis—the growth of new capillaries from pre-existing blood vessels [1–3]. Targeting VEGF has been a strategy in several cancers—particularly in glioblastoma (GBM), which are highly vascularized tumors [4–6]. Currently, bevacizumab, a monoclonal antibody targeting VEGF, is FDA approved as salvage therapy for recurrent GBM. The drawbacks of bevacizumab are that most tumors progress within 4–5 months despite initial radiographic responses [7]. Moreover, the drug is given intravenously

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✉ Elizabeth R. Gerstner
egerstner@partners.org

1 Martinos Center for Biomedical Imaging, Charlestown, USA

2 Stephen E. and Catherine Pappas Center for Neuro-Oncology, Massachusetts General Hospital Cancer Center, Yawkey 9E, 55 Fruit Street, Boston, MA 02114, USA

3 The Intervention Centre, Oslo University Hospital, Oslo, Norway

4 Department of Anatomy and Neuroscience/VUmc CCA Brain Tumor Center Amsterdam, VU University Medical Center, Amsterdam, The Netherlands

5 Dana-Farber Cancer Institute, Boston, USA

6 Laura and Isaac Perlmutter Cancer Center, NYU Langone Medical Center, New York, USA

every 2 weeks and has a long high-life. A more efficacious, oral alternative would be highly desirable.

Tivozanib (AV-951, AVEO Pharmaceuticals, Inc. MA, USA) is a tyrosine kinase inhibitor with potent activity against all 3 VEGF receptors—VEGFR1 (IC_{50} 0.21 nM), VEGFR2 (IC_{50} 0.16 nM), and VEGFR3 (IC_{50} 0.24 nM)—as well as c-Kit (IC_{50} 1.63 nM) and platelet derived growth factor receptor (PDGFR; IC_{50} 1.72 nM). The agent has been studied in several cancer types with some initially positive results in early phase studies, but has not been studied in recurrent GBM [8–11]. We designed a phase II trial of tivozanib in recurrent GBM to determine treatment activity in this patient population. The trial included correlative MRI and blood biomarker studies to investigate tumor vascular changes and more global functional brain connectivity with resting state MRI to determine the relationship between these parameters and GBM response to tivozanib.

Materials and methods

Study overview

This was an open-label, non-randomized, single arm, phase II study of oral tivozanib in adult patients with recurrent GBM (NCT01846871) to examine treatment efficacy. The Dana-Farber/Harvard Cancer Center institutional review board (IRB) approved this trial. Prior to enrollment, all patients signed an informed consent document. Patients received tivozanib 1.5 mg daily by mouth for the first 3 weeks of every 4-week cycle, and there was no maximal length of therapy. Patients were treated until there was radiographic or clinical evidence of disease progression or unacceptable toxicity. The primary endpoint was the proportion of patients alive and progression free at 6 months (PFS6). Secondary endpoints included assessment of drug toxicity, radiographic response rate, steroid use, and blood and imaging correlative biomarkers. A Simon two-stage design was employed with 80% power and required that 5 subjects enroll in stage I. The study terminated if none of the initial 5 subjects was free of progression and alive at 6 months. An additional 13 patients would be enrolled if the first stage met the pre-specified endpoint. RANO criteria were used to determine response to therapy [12]. The study was funded by a general research grant from the National Comprehensive Care Network.

Patient eligibility

Patients with recurrent GBM (WHO grade IV) who met the following criteria were eligible for this study: histologically confirmed GBM that had progressed or recurred (based on imaging or surgery), age ≥18 years, Karnofsky performance status ≥60, measurable disease (at least one lesion ≥1 cm on MRI), at least 3 months since radiation, stable steroid dose for at least 5 days prior to baseline MRI, ≤3 prior tumor relapses, and mini-mental score >15. Exclusion criteria included major surgical procedures within 28 days of therapy initiation, concurrent administration of other experimental agents, prior anti-VEGF agents, history of allergic reactions to compounds similar to tivozanib, pregnancy/breastfeeding, concurrent treatment with CYP450 enzyme modulators, significant cardiovascular disease, concurrent malignancy, significant inter-current illness, and significant intratumoral hemorrhage.

Correlative imaging studies

All patients underwent advanced MRI scans on a 3T magnet (Skyra, Siemens Inc, Malvern, PA). The scanning protocol included resting state (rs) functional MRI, dynamic contrast enhanced (DCE), dynamic susceptibility contrast (DSC), as well as routine clinical sequences (pre-/post-contrast T1, diffusion-weighted imaging, and FLAIR). The MRIs were obtained at the following time points: within 14 days before starting treatment, 24–72 h after first treatment, and then monthly after the start of treatment. See Supplemental Information for details of the imaging acquisition and analysis plan.

Correlative blood biomarker studies

Serial blood monitoring was performed for all patients to assess circulating levels of plasma biomarkers of angiogenesis and inflammation. The blood was processed as previously described [11]. Briefly, plasma samples were collected in EDTA-containing tubes, separated by centrifugation, aliquoted and stored at −80 °C until ELISA measurements were performed. The following molecular markers were collected: VEGF, placental growth factor (PIGF), soluble (s)VEGFR-1, and fibroblast growth factor using the Human Angiogenesis Panel 1 Kit (K15190D); Interleukin-1β, IL-6, IL-8, and tumor necrosis factor (TNF)-α using the Human Proinflammatory-4 Kit (K15025A); stromal cell derived factor (SDF1)-α, CAIX, sVEGFR2, sTie-2, Ang-1, Ang-2, and collagen IV using ELISA kits.

Statistical analysis

The primary endpoint of the study was to determine the proportion of patients with recurrent GBM alive and progression free for 6 months (PFS6) after start of tivozanib therapy. In additional to the endpoints above, other secondary endpoints included assessment of median overall survival (OS), median progression free survival (PFS),

and radiographic response using RANO criteria. The probability of survival was estimated using the Kaplan–Meier method, while the proportion of PFS6 was estimated using binomial distribution along with a 95% confidence interval. The imaging and blood biomarkers were correlated to OS and PFS using Cox proportional hazard models. Changes in the imaging and blood biomarker parameters were expressed as an absolute difference from baseline measurements. Since the imaging and blood biomarker analyses were exploratory, no statistical adjustment was made for multiple testing. All *P* values were reported as 2-sided and statistics were calculated using SAS (version 9.4, SAS Institute).

Previous studies had indicated that the relative size of the abnormal enhancing volume to the abnormal FLAIR hyperintense volume could be predictive of OS as well as suggestive of the underlying genotype of the tumor [13]. After separating our participants based on median value, we looked at a binary variable of high and low enhancement proportion groups and evaluated PFS and OS as a function of this proportion of enhancing volume to abnormal FLAIR volume.

For the rs-MRI, limited data was available. Therefore, we explored the association between global functional connectivity and tumor volume (enhancing and abnormal FLAIR hyperintensity volumes separately) using non-parametric Kendall's Tau correlation coefficients. This analysis does not take into account that some of the measurements were from the same patient, but at a different time point, but gives an indication of the overall association between tumor volume and functional connectivity strength.

Results

Patient characteristics

Ten patients with recurrent GBM were enrolled between August 2013 and January 2014. All 10 patients were enrolled in a single cohort (study over accrued beyond the pre-planned 5 initial patients because of rapid accrual across the 2 participating Dana-Farber/Harvard Cancer Center sites), and the baseline participant characteristics are outlined in Table 1. Since none of the first 5 patients enrolled were alive and progression free at 6 months, the study was halted for futility per the pre-planned stopping rule.

Toxicity

Two participants (20%) were taken off study because of toxicity (skin toxicity and muscle weakness). There were no unexpected grade 3 or 4 toxicities as all toxicities were expected based on the published toxicity spectrum of anti-VEGF activity of tivozanib (Table 2). There was no clear association with increased or decreased steroid use within the first month of treatment (Table 1).

Table 1 Baseline patient characteristics

	Total (N = 10)
Age	
Median	62
Range	51–74
Gender	
Male (%)	4 (40)
Female (%)	6 (60)
Karnofsky performance status	
Median	90
Range	80–100
Mini mental score	
Median	29
Range	17–30
Prior treatments	
RT + TMZ	10
Other CTX[a]	4
Repeat surgery	2
Steroid dosage[b]	
On steroids at baseline	4
Decreased dosage	3
Increased dosage	4
No change	4
Molecular status	
IDH1	
Mutant	1
Wildtype	6
Not tested/unknown	3
MGMT	
Methylated	1
Unmethylated	7
Not tested/unknown	2
EGFR	
Positive	7
Negative	3

[a]Other CTX include: dacomitinib, semustine, etoposide, everolimus

[b]Within the first month of treatment

Response

As seen in Table 3, best RANO criteria responses were: complete response (1), partial response (1), stable disease (4), and progressive disease (4). The median duration of response was 3.6 months (1.7–3.8 months). Eight patients were taken off study for progressive disease. Only 1 patient was alive and progression free at 6 months (last patient

Table 2 Grade 3 or 4 toxicities possible or likely related to treatment (total number of patients = 10)

Toxicity	Tivozanib
Elevated ALT/AST	1 (10%)
Cerebral edema	1 (10%)
Hypertension	1 (10%)
Decreased lymphocyte	1 (10%)
Seizure	2 (20%)
Colonic perforation	1 (10%)

Table 3 Clinical responses

	Total (N = 10)
Best RANO criteria response	
CR (%)	1 (10)
PR (%)	1 (10)
SD (%)	4 (40%)
PD (%)	4 (40%)
PFS-6 (%)	1 (10%)
Median PFS (95% CI)	2.3 months (1.5–4.0)
Median OS (95% CI)	8.1 months (5.2–12.5)

enrolled). Median PFS was 2.3 months (1.5–4.0 months) and median OS was 8.1 months (5.2–12.5 months).

Imaging biomarker analysis

When compared to baseline, we found significant decreases in the following MRI biomarkers: median K^{trans} (a maker of vascular permeability), relative cerebral blood flow (rCBF), relative tissue oxygenation (SO2), and median ADC within the contrast-enhancing tumor after 2 cycles of therapy (all $p < 0.05$) (Table 4). However, there were no significant changes in vessel caliber, tumor volume or median relative cerebral blood volume (rCBV). There was no association between the change in MRI parameters from baseline to 24–72 h after therapy with OS or PFS, as seen previously with other anti-VEGFR therapies (Supplemental Table 1) [14]. A higher proportion of enhancement at baseline compared to the volume of FLAIR hyperintensity at baseline was predictive of shorter PFS ($p = 0.045$) (Supplemental Fig. 1).

Since seven patients had multiple rs-fMRI measurements, only correlations between tumor volume and connectivity were explored using all subjects and time points ($n = 27$). Global connectivity showed a trend towards positive correlation with both contrast enhancing tumor volume (Kendall's Tau = 0.254, $p = 0.064$) and FLAIR tumor volume (Kendall's Tau = 0.225, $p = 0.100$).

Table 4 Change in MRI parameters within the contrast enhancing tumor

Variable	Baseline	Cycle 1 day 2 vs. baseline	Pre-cycle 2 vs. baseline	Pre-cycle 3 vs. baseline	Pre-cycle 3 vs. baseline p value[a]
Volume (cc)	17.37 (5.18, 31.11)	−2.012 (−6.08, −0.79)	−2.75 (−5.68, 3.19) (N = 9)	−3.53 (−18.28, 1.76) (N = 8)	0.70
Median ADC	0.0013 (0.0011, 0.0015)	−0.00009 (−0.00014, −0.00005)	−0.00024 (−0.00032, −0.00011)	−0.00023 (−0.0003, −0.00004)	**0.028**
Median K^{trans}	0.032 (0.026, 0.054)	−0.01468 (−0.025, −0.010)	−0.024 (−0.032, −0.022)	−0.030 (−0.045, −0.022)	**0.0019**
Median rCBV	0.68 (0.52, 0.75)	0.0078 (−0.063, 0.13)	−0.085 (−0.24, −0.05)	−0.055 (−0.24, 0.049)	0.16
Median rCBF	0.67 (0.57, 0.71)	0.0081 (−0.063, 0.14)	−0.12 (−0.19, −0.068)	−0.15 (−0.25, −0.062)	**0.036**
Vessel caliber	1.22 (0.91, 1.47) (N = 8)	−0.016 (−0.033, 0.21) (N = 9)	−0.16 (−0.24, 0.073)	0.038 (−0.18, 0.79)	0.32
Relative O_2 saturation	0.64 (0.55, 0.68)	−0.057 (−0.11, −0.00003) (N = 9)	−0.0041 (−0.060, 0.063)	−0.097 (−0.12, −0.017)	**0.033**

Bold values are statistically significant

Data are shown as median (interquartile range) values and are compared to baseline value

[a]p value from t test; not adjusted for multiple testing. N = 10 unless otherwise noted

Blood biomarker analysis

Evaluation of plasma biomarkers showed significant decreases in sVEGFR2 and increases in PlGF and VEGF (Table 5). None of the blood biomarkers were associated with OS or PFS (Supplemental Table 2).

Discussion

Despite being overall well tolerated, tivozanib did not extend PFS or OS in patients with recurrent GBM compared to historical controls that included FDA approved treatments or other investigational agents. GBM is characterized by a rich vasculature and can respond to bevacizumab, but tivozanib did not appear to have a significant impact in our study [7]. Most patients were not able to decrease their steroid dose suggesting a limited clinical benefit as well.

Due to the intricate relationship between tumor perfusion, vascular permeability, and drug delivery, longitudinal monitoring of vascular parameters is necessary to assess the impact anti-angiogenic therapy is having on tumor growth and its microenvironment. Our correlative blood

Table 5 Average change in blood biomarker parameters

Plasma biomarkers	Baseline (N = 10)	Pre-cycle 2 (N = 8)	Pre-cycle 3 (N = 8)	Pre-cycle 3 vs. baseline P value
CAIX	51.25 (25.11, 76.14)	31.83 (14.00, 54.59)	14.74 (5.06, 56.93)	0.17
sMET	1012.90 (873.90, 1109.70)	−42.60 (−106.70, 6.05)	−114.15 (−257.90, 27.00)	0.25
SDF1α	1947.71 (1577.50, 2169.81)	65.07 (−170.24, 322.77)	131.80 (−97.03, 447.77)	0.26
sVEGFR2	9841.90 (8768.90, 11657.90)	−2334.40 (−3947.45, −1737.15)	−3586.30 (−4669.85, −3181.25)	**0.0001**
Ang2	1554.25 (1343.50, 1748.70)	−396.15 (−575.00, −221.15)	−352.60 (−597.60, −5.70)	0.19
IFNγ	5.96 (3.81, 6.68)	−0.16 (−1.42, 1.59)	−0.25 (−2.70, 0.48)	0.64
IL-10	0.34 (0.27, 0.52)	−0.07 (−0.15, 0.02)	−0.05 (−0.17, 0.00)	0.35
IL-6	1.13 (0.72, 1.62)	0.21 (0.00, 0.63)	0.06 (−0.69, 0.77)	0.87
IL-8	4.58 (3.55, 5.76)	1.13 (0.63, 2.18)	1.85 (1.02, 10.95)	0.090
TNF-α	1.24 (1.61, 1.58)	−0.08 (−0.44, 0.35)	−0.13 (−0.50, 0.27)	0.64
bFGF	15.39 (8.81, 21.35)	−0.08 (−0.44, 0.35)	−0.13 (−0.50, 0.27)	0.64
PlGF	38.63 (36.25, 44.88)	30.65 (15.84, 86.05)	75.93 (24.29, 109.50)	**0.0056**
sFLT1 (sVEGFR1)	55.10 (51.06, 68.32)	2.47 (−5.75, 18.25)	2.89 (−12.77, 19.09)	0.67
sTie2	5765.44 (3526.98, 6395.42)	−274.38 (−500.67, 42.31)	−378.21 (−582.44, 553.04)	0.91
VEGF-A (VEGF)	82.36 (56.50, 92.85)	50.32 (31.72, 71.34)	108.95 (35.40, 241.87)	**0.020**
VEGF-C	60.00 (60.00, 71.89)	0.00 (0.00, 4.13)	0.00 (0.00, 53.03)	0.24
VEGF-D	1144.42 (738.14, 1216.76)	99.87 (−66.71, 166.97)	93.53 (−129.70, 425.30)	0.26

Bold values are statistically significant

Data are shown as median values

(interquartile range in pg/ml) at baseline (pre-treatment), and the change (+ or −) at the 2 time-points after tivozanib. Comparison for Pre-cycle 3 vs. baseline was made using *t* test

and imaging analyses showed that tivozanib had an impact on the functional status of the tumor vasculature as evidenced by decreases in K^{trans} (permeability/surface area), ADC (resolving edema), rCBF (tumor perfusion), and SO2 (tumor oxygenation). Similar changes in imaging biomarkers, as well as specific changes in plasma biomarkers (i.e. decreased sVEGFR2 and increased PlGF and VEGF) have been seen in GBM as well as other cancers using a variety of anti-VEGFR agents, suggesting that these markers are useful in monitoring the pharmacodynamic effects of anti-angiogenic agents [15–18]. Prior studies with cediranib, a VEGFR TKI, have suggested a benefit in tumor control with increase in tumor perfusion, an increase not seen in the current study and underscoring the lack of activity with tivozanib [15, 16].

Reduction of abnormal tumor vessel calibers has been proposed as a potential biomarker of response in previous studies of anti-angiogenic agents [19]. The lack of change in vessel caliber after tivozanib may indicate the limited efficacy of this drug in changing the structure of blood vessels and thus limiting its potential as a durable anti-angiogenic agent in GBM. Therefore, tivozanib appeared to have some impact on the function of the vasculature but without any impact on vascular structure (as measured by vessel caliber), tumor control (contrast enhancement) or steroid dose that has been seen with other anti-angiogenic agents given as monotherapy in recurrent GBM [20, 21]. On the other hand, combination of FOLFOX chemotherapy with tivozanib recently showed efficacy in patients with advanced gastrointestinal malignancies [8]. Whether a similar combination strategy would be more effective in recurrent GBM is not known.

To investigate the link between enhancing tumor volume and outcome, we explored the ratio of the baseline enhancing tumor volume to the FLAIR hyperintensity volume based on prior data suggesting that the relative size of the abnormal enhancing volume to abnormal FLAIR volume was predictive of overall survival [13]. In our study, a larger enhancing tumor with smaller surrounding FLAIR hyperintensity was associated with worse PFS possibly suggesting that these tumors have a less leaky but still abnormal vasculature. Controlling cerebral edema is a particularly important benefit of effective anti-VEGF therapy so less leaky tumors may be less likely to respond to anti-VEGF therapy—a hypothesis that should be further explored as there is a need to identify the subset of patients more likely to respond to anti-angiogenic therapy [22].

One method of investigating global aspects of brain functioning is using functional connectivity based on rs-fMRI. Recent studies have shown global effects of local neurological diseases such as glioma [23]. Functional connectivity refers to the coupling between blood oxygenation level dependent (BOLD) fluctuations of different regions in the resting brain [24]. In glioma patients, global measures of functional connectivity relate to symptoms such as epilepsy and cognitive deficits [25–27]. In our study, we found a trend towards correlations between global connectivity and tumor volume but were underpowered to detect a difference. These findings suggest that changes in global connectivity may go hand in hand with changes in tumor volume. Previous studies have not related tumor volume to connectivity, particularly not using rs-fMRI. However, neurophysiological studies have shown that increased functional connectivity may be a detrimental correlate of epileptic seizures and cognitive deficits [25–27]. Although a certain level of connectivity is deemed necessary for cognitive functioning, hyperconnectivity may facilitate seizure spread as well as hamper global integration of the network. Future studies with larger cohorts should further investigate these longitudinal associations between tumor growth and connectivity, as well as the use of connectivity as a biomarker.

The conclusions of our study are limited by the small sample size. However, many of our findings were consistent with prior studies and highlight the importance of correlative endpoints such as imaging or blood biomarkers to better understand the physiological impact drugs have on tumor growth.

In summary, despite having an impact on the tumor vascular function, as indicated by imaging and blood biomarkers, tivozanib monotherapy showed limited clinical efficacy in recurrent GBM. Rational biomarker-based combinations of tivozanib with other therapies may be warranted to take advantage of the functional vascular changes in recurrent GBM. Exploring the complex interactions between vascular structure and function will be critical in moving anti-angiogenic therapy forward in this disease.

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Compliance with ethical standards

Conflict of interest R. K. J. owns equity in Enlight, Ophthotech, SynDevRx, and XTuit and serves on the Board of Directors of XTuit and the Boards of Trustees of Tekla Healthcare Investors, Tekla Life Sciences Investors, Tekla Healthcare Opportunities Fund, and Tekla World Healthcare Fund, and received grants from MedImmune and Roche. D. G. D. received grants from Merrimack, Bayer and HealthCare Pharmaceuticals.

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