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Phase I Pharmacokinetic Study of the VEGFR Tyrosine Kinase Inhibitor Vatalanib (PTK787) plus Imatinib and Hydroxyurea for Malignant Glioma

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Abstract

Background—We determined the maximum tolerated dose (MTD) and dose-limiting toxicities (DLT) of the oral vascular endothelial growth factor receptor (VEGFR) inhibitor, vatalanib, when administered with imatinib and hydroxyurea on a continuous daily schedule among recurrent malignant glioma patients.

Methods: All patients received 500 mg of hydroxyurea twice daily. Imatinib was dosed at 400 mg per day for patients not taking enzyme-inducing antiepileptic drugs (EIAEDs; stratum A) and at 500 mg twice-a-day for patients taking EIAEDs (stratum B). Vatalanib was escalated from 500 mg to 1250 mg twice daily in successive cohorts, independently for each stratum. Pharmacokinetics of each drug were assessed.

Results: Thirty-seven recurrent patients, including 34 (92%) with glioblastoma and 3 (8%) with grade 3 malignant glioma, were enrolled. Nineteen patients (51%) were taking EIAEDs. The MTD of vatalanib for all patients was 1000 mg twice-a-day. DLTs were hematologic, gastrointestinal, renal and hepatic. No patients developed intracranial hemorrhage. Concurrent administration of imatinib and hydroxyurea did not affect vatalanib exposure, but EIAEDs decreased vatalanib and imatinib plasma exposures.

Conclusion: Vatalanib doses up to 1000 mg twice-a-day combined with imatinib and hydroxyurea are well tolerated. Strategies to target tumor blood vessel endothelial cells and pericytes by inhibiting VEGFR and PDGFR, respectively, are safe among recurrent malignant glioma patients and may enhance anti-angiogenesis activity.

Keywords

Malignant glioma; imatinib mesylate; vascular endothelial growth factor; platelet-derived growth factor; vatalanib; hydroxyurea

INTRODUCTION

The current standard of care for patients with newly diagnosed glioblastoma (GBM), the most common primary adult central nervous system tumor, includes radiotherapy plus temozolomide (TMZ), based on a modest survival benefit compared to radiotherapy alone. However, recurrence remains universal, with a median progression-free survival (PFS) of only 6.9 months.¹ Patients with grade 3 malignant glioma (MG) fare somewhat better, with median survival between 2 and 5 years.² Following recurrence, there is no established, effective treatment. Therefore, more active therapies to improve survival for newly diagnosed MG patients, and beneficial salvage therapies for patients following progression are critically needed.

Recently, encouraging clinical benefit for patients with recurrent MG has been reported with anti-angiogenic strategies targeting vascular endothelial growth factor (VEGF) signaling. Agents utilized in this approach include cediranib (AZD2171),³ a VEGFR tyrosine kinase receptor inhibitor, and bevacizumab (Avastin), a humanized anti-VEGF monoclonal antibody, administered with or without irinotecan.⁴⁻⁶

Vatalanib (PTK787) is an orally bioavailable, amino-phthalazine derivative that potently inhibits VEGFR1 (Flt-1), VEGFR2 (KDR) and VEGFR3 (Flt-4) and can also inhibit PDGFR β at an IC₅₀ that is approximately twice that of imatinib.^{7, 8} In preclinical models, vatalanib significantly diminishes VEGF-mediated glioma growth by inhibiting neovascularization.⁹ In phase I studies, daily administration of vatalanib, with or without chemotherapy, were well tolerated and associated with modest clinical benefit among patients with recurrent MG.^{10, 11} Subsequent studies have demonstrated that twice-daily dosing of vatalanib is also well-tolerated and associated with more consistent drug concentrations compared to once-daily dosing.¹²

Imatinib mesylate (Gleevec®, formerly STI-571) has established activity against hematologic and solid organ malignancies via effective inhibition of selective receptor tyrosine kinases including Bcr-Abl, c-KIT, c-fms and PDGFR.¹³ Imatinib has been evaluated in patients with MG based on frequent, increased expression and activity of PDGF and PDGFR.¹⁴⁻¹⁶ Although preclinical studies confirm significant activity,¹⁷ clinical benefit with single-agent imatinib in MG is limited.^{18, 19} In contrast, a more substantial clinical benefit has been described when imatinib is combined with hydroxyurea, a ribonucleoside reductase inhibitor.²⁰⁻²² A possible mechanism underlying this combination includes complementary anti-angiogenic activities. Specifically, imatinib inhibits pericyte stabilization and down-regulates VEGF,²³ while protracted, daily hydroxyurea may act as a “metronomic” cytotoxic against tumor endothelial cells.²⁴ Therefore, we postulated that vatalanib may enhance the activity of imatinib plus hydroxyurea. We escalated the dose of vatalanib administered twice daily, with daily dosing of imatinib and hydroxyurea, to determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of this regimen among recurrent MG patients.

MATERIALS AND METHODS

Protocol Objectives

The primary objective of this study was to define the MTD and DLT of vatalanib when administered twice daily with imatinib and hydroxyurea to adults with recurrent MG. Secondary objectives included: to define other toxicities associated with the regimen; to evaluate the pharmacokinetics of vatalanib, imatinib, and hydroxyurea when co-administered to this patient population; and to document antitumor activity.

Patient Eligibility

Patients were required to have a histologically confirmed diagnosis of grade 3 or 4 MG that was recurrent. Patients with prior low-grade glioma were eligible if histologic transformation to MG prior to enrollment was confirmed. Patients were also required to: be ≥ 18 years of age; have a Karnofsky performance status (KPS) $\geq 60\%$; be on a stable corticosteroid dose for ≥ 1 week; have satisfactory hematologic (hemoglobin >9 g/dl; absolute neutrophil count >1000 cells/ μ l; platelet count $>100,000$ cells/ μ l) and biochemical results (serum creatinine, BUN, AST and bilirubin < 2.0 times the upper limit of normal); have recovered from all expected toxicity related to previous therapy; and provide written informed consent. At least 4 weeks had to have elapsed since prior surgical resection, radiotherapy, or chemotherapy (6 weeks for nitrosoureas).

Exclusion criteria were: treatment with prior PDGFR- or VEGFR-directed agents; >3 episodes of progressive disease; pregnancy or nursing; intra-tumoral hemorrhage (except post-operative grade 1); significant concurrent medical illness; prior malignancy; concurrent warfarin use; $\geq$ grade 2 peripheral edema, pulmonary or pericardial effusion or ascites; and prior stereotactic radiosurgery or radioimmunotherapy unless there was obvious radiographic disease progression or biopsy-proven recurrence.

Treatment Design

Imatinib and vatalanib were provided by Novartis Pharmaceuticals (Florham Park, NJ); hydroxyurea was prescribed. Study medications were taken at the same time each day and after a light snack, if possible. Vatalanib was administered alone for the first 7 days of cycle 1 to facilitate pharmacokinetic analyses. Thereafter, all three study medications were administered every day as described below. Patients and caregivers were carefully taught how to administer study medications and were asked to complete daily dose administration diaries.

Prior studies confirmed that the metabolism of vatalanib and imatinib are significantly increased by concurrent use of CYP3A-inducing anti-epileptic drugs (EIAEDs) such as phenytoin, carbamazepine, phenobarbital, oxcarbazepine and primidone.^{10, 11, 19, 22} Therefore, patients were accrued independently to two strata: stratum A included patients not taking EIAEDs; stratum B included patients taking EIAEDs. Imatinib was administered at 400 mg/day to patients on stratum A and at 500 mg twice-a-day to those on stratum B. Hydroxyurea was administered at 500 mg twice-a-day to all patients. The starting dose of vatalanib was 500 mg twice-a-day for stratum A and 750 mg twice-a-day for stratum B. Subsequent dose levels increased vatalanib by 250 mg twice-a-day (Table 1). Cohorts of 3–6 patients were treated per dose level until DLT was observed. Each cycle was 28 days, except for cycle 1 which was 35 days so that pharmacokinetic studies could be performed.

Dose Escalation and Statistical Considerations

Vatalanib dose was escalated in successive cohorts of three patients as long as DLT did not occur. If one instance of DLT was observed among the initial three evaluable patients, an

additional three patients were treated at that dose level. Dose escalation then continued as long as no DLT occurred in these additional patients. If two instances of DLT were observed at a dose level, the MTD was surpassed, and a total of six patients were treated at the previous level to assure its tolerability. MTD was defined as the highest dose causing DLT during cycle 1 in no more than one of six patients.

Non-hematologic DLT included $\geq$ grade 3 attributable toxicities, except for alopecia, and nausea, vomiting or diarrhea that responded to standard medical therapy. Hematologic DLT included either grade 4 neutropenia or grade 3 thrombocytopenia. Any toxicity resulting in a >14 -day delay to re-treat was also considered DLT.

Time to progression (TTP) and overall survival (OS) were measured from treatment initiation and analyzed by the Kaplan-Meier method including 95% confidence intervals (CIs).

Toxicity Evaluation

Toxicity was graded according to the National Cancer Institute Criteria for Adverse Events, Version 3.0. Patients were evaluated by physical examination before each cycle. In addition, blood pressure was measured weekly for the first cycle and then on days 1 and 14 of subsequent treatment cycles. A complete blood count with differential was obtained weekly, and serum electrolytes, BUN/creatinine and liver function tests were obtained monthly. A urinalysis was performed prior to the first cycle, as was a beta human chorionic gonadotropin test in women with reproductive potential. Patients who experienced DLT or unacceptable toxicity were followed weekly until toxicity resolved.

Response Evaluation

Response was evaluated by neurologic examination and contrast-enhanced MRI prior to the start of every other treatment cycle and was graded using modified Macdonald criteria. Complete response (CR) required disappearance of all enhancing tumor on consecutive MRIs at least 6 weeks apart, with corticosteroid discontinuation and neurologic stability or improvement. Partial response (PR) required $\geq 50\%$ reduction in product of largest perpendicular diameters of enhancing tumor with stability or improvement of neurologic status and corticosteroid requirement. Progressive disease (PD) was defined as a $\geq 25\%$ increase of enhancing tumor or new lesion. Stable disease (SD) was defined as any assessment not meeting CR, PR, or PD criteria.

Dose Modification and Retreatment Criteria

Re-treatment required adequate hematologic and biochemical parameters (defined in eligibility criteria) and resolution of any treatment-related grade ≥ 3 toxicity to grade ≤ 1 . Dose modification was performed for DLTs during study drug administration. For initial hematologic DLTs, hydroxyurea was reduced to 500 mg once a day, while subsequent hematologic events required a 25% imatinib dose reduction. Imatinib was also reduced by 25% for grade ≥ 3 rash or edema. Vatalanib was reduced by 25% for grade ≥ 3 non-hematologic events and discontinued for grade 4 hypertension.

Study therapy was discontinued for PD, > 2 dose reductions due to toxicity, grade ≥ 2 hemorrhage or noncompliance.

Pharmacokinetic Analysis

Blood samples for vatalanib pharmacokinetics were collected in heparinized tubes on day 7 (steady state vatalanib alone) and day 35 of cycle 1 before treatment, and at 1, 2, 3, 4, 6, 8 and 24 hours after the morning dose. Plasma was prepared by centrifugation and

immediately frozen at -20 °C. Plasma concentrations of vatalanib were determined by high-pressure liquid chromatography-mass spectrometry (LC-MS). A 0.25 mL aliquot of plasma, 15 µl of 10 µg/ml internal standard (CGP80805, (4-chloro-phenyl)-[4-2, 6-dimethyl-pyridylmethyl phthalazin-1-yl]) amine, molecular weight, 374.87), 500 µl 0.1 N NaOH, and 5.5 ml *t*-butylmethyl-ether were pipetted into a 10-mL conical glass tube. The tube was shaken in an overhead shaker for 10 minutes. After 5 minutes of centrifugation at 4,000 rpm, the organic layer was transferred into another tube and evaporated to dryness under a nitrogen stream at 40 °C. The residue was redissolved in 100 µl of mobile phase, and 75 µl were injected into the HPLC system. The isocratic mobile phase, consisting of 5 g ammonium acetate dissolved in 1,250 ml distilled water, and 600 ml of acetonitrile, brought to pH 6.5 with phosphoric acid, was pumped at 0.4 ml/minutes. Chromatographic separation was achieved with an Inertsil column, (5 µm, 125 × 2 mm i.d.,) (Phenomenex, Torrance, CA). The lower limit of quantification was 2.5 ng/mL, with a concentration range of 2.5 to 10,000 ng/mL. At concentrations of 20, 800, and 8,000 ng/ml, the intraday variability (percent coefficient of variation [CV%]) was 0.7, 1.4, and 1.3, respectively. At concentrations of 20, 800, and 8,000 ng/ml, the interday variability (CV%) was 1.3, 2.0, and 1.6, respectively. The CV% for the assay sensitivity at 2.5 ng/ml was 4.0.

Blood samples for imatinib and hydroxyurea pharmacokinetics were collected in heparinized tubes on days 8 and 35 of cycle 1 before treatment, and at 0.5, 1, 1.5, 2, 4, 6, 8 and 24 hours after the morning dose. Plasma was prepared by centrifugation and immediately frozen at -20 °C. Plasma concentrations of imatinib and its active metabolite, CGP74588, were determined with a validated LC-MS assay.²⁶ Plasma concentrations of hydroxyurea were determined with a validated HPLC assay.²²

Plasma pharmacokinetic parameters of vatalanib were extracted from the data using standard non-compartmental methods (WinNonlin Professional 4.1, Pharsight, Mountain View, CA), whereas the parameters for imatinib, CGP74588 and hydroxyurea were estimated non-compartmentally using the LaGrange function²⁷ as implemented by the LAGRAN computer program.²⁸ The maximum concentration normalized for dose ($C_{\max}/D$) and time to reach the maximum concentration ($t_{\max}$) were determined by visual inspection of the plasma concentration *versus* time curves. Area under the concentration *versus* time curve (AUC) was calculated with extrapolation to infinity for the first dose, or extrapolation until the next dosing time (either 12 hours or 24 hours) for doses at steady-state. The AUC was used to calculate clearance (CL/F) and volume of distribution (V/F).

Statistical analyses for pharmacokinetics were performed using SPSS 15.0 for Windows (SPSS Inc., Chicago, IL). Per analyte, only the data from patients with full pharmacokinetic profiles on both days of pharmacokinetic sampling were used in the subsequent statistical analyses. The pharmacokinetic parameter estimates of vatalanib determined in the absence (day 7) and presence (day 35) of imatinib and hydroxyurea were compared (after logarithmic transformation) with a two-tailed, paired *t*-test, where a $P < 0.05$ was considered significant. The difference between day 7 and day 35 vatalanib $t_{\max}$ were analyzed (untransformed) by the two-tailed exact Wilcoxon signed rank test. The pharmacokinetic parameter estimates of vatalanib in patients taking EIAEDs and patients not taking EIAEDs were compared (after logarithmic transformation) with a two-tailed, *t*-test, where a $P < 0.05$ was considered significant. The untransformed values for vatalanib $t_{\max}$ were analyzed by the exact two-tailed Wilcoxon signed rank test. Pharmacokinetic parameter estimates of imatinib, CGP74588, and hydroxyurea on day 8 and day 35 were compared with the same statistical tests described for comparison of day 7 and day 35 vatalanib pharmacokinetic parameters.

RESULTS

Patient Characteristics

Thirty-seven patients with MG were enrolled at Duke University Medical Center between July, 2005 and December, 2006 (Table 2). Eighteen patients (49%) were not taking EIAEDs (stratum A) and 19 (51%) were taking EIAEDs (stratum B). Patient characteristics did not differ substantially between strata. Thirty-four patients had GBM (92%), and 3 (8%) had anaplastic astrocytomas (AA). All patients had progressive disease after at least radiotherapy and chemotherapy including TMZ. Enrolled patients had received a median of 2 prior chemotherapy agents (range, 1–6) and had experienced a median of 1 episode of prior progressive disease (range, 1–3).

As of September 1, 2008, 8 patients (22%) remain alive, and 1 patient (3%) continues to receive treatment on study in cycle 29.

Dose-Limiting and Non-Dose-Limiting Toxicities

Table 3 summarizes toxicities that occurred among $\geq 10\%$ of patients including all DLTs. One hundred and forty-eight courses of imatinib, hydroxyurea, and vatalanib were administered, including 80 to patients on stratum A and 68 to patients on stratum B.

Overall, up to 1000 mg twice-a-day of vatalanib was well tolerated when combined with imatinib plus hydroxyurea. Grade ≥ 3 hematologic toxicities were uncommon and resolved promptly with study drug interruption. Only two episodes of grade 3 thrombocytopenia occurred, whereas grades 3 or 4 neutropenia complicated 3% of administered courses, respectively. The most frequent non-hematologic toxicities included hypertension (9% of courses) and fatigue (8% of courses). Eleven patients (30%) experienced grade 2 hypertension, and 2 patients (5%) developed grade 3 hypertension. All episodes of hypertension responded to appropriate medical therapy. Grade 3 fatigue, which persisted throughout the course of therapy, was experienced by two patients while grade 4 fatigue was not observed. Approximately 5% of courses were complicated by grade 2 nausea/emesis or mucositis that responded to appropriate medical therapy, whereas reversible grade 3 transaminase elevation occurred after 3% of courses. Diarrhea, infection, and rash, all limited to grade 2, also complicated 3% of administered courses, and responded to appropriate medical therapy. Of note, no patients developed CNS hemorrhage.

Three patients were not eligible for DLT assessment; two patients took an incorrect dose of vatalanib during cycle one, and one patient voluntarily withdrew after the first eleven days of cycle one. Only one DLT occurred among stratum A patients and included reversible, grade 3 thrombocytopenia at dose level 3. In contrast, three patients in stratum B experienced four DLTs. One patient at dose level 2 developed reversible grade 3 hypertension and grade 3 transaminase elevation. Two patients treated at dose level 3 experienced DLT consisting of reversible grade 3 fatigue and rash, respectively. These results confirmed the MTD of vatalanib to be 1000 mg twice a day when administered with imatinib and hydroxyurea for patients on stratum B. Dose escalation for patients on stratum A beyond the MTD established for stratum B patients was not performed for safety concerns. Specifically, vatalanib exposures and potential associated toxicity were predicted to be higher for patients not taking EIAEDs compared to those taking EIAEDs.^{10, 11} Therefore, vatalanib dose escalation for stratum A above the MTD for stratum B was not performed, and the recommended vatalanib dose for all patients, irrespective of whether or not they are taking EIAEDs, was defined as 1000 mg twice-a-day when administered with imatinib and hydroxyurea.

Outcome

The median follow-up for all patients was 108 weeks (95% CI, 99–134 weeks). The median OS, median PFS and 6-month PFS rate for all GBM patients were 48 weeks (range 35–68 weeks), 12 weeks (9–22 weeks) and 25% (12–40%), respectively and did not differ significantly between patients based on EIAED stratum. All patients were evaluable for response. Nine patients (24%) achieved a radiographic PR, (Figure 1), and eighteen (49%) patients achieved SD. Progressive disease was noted at initial evaluation in ten patients (27%).

Pharmacokinetics

The number of patients with full plasma pharmacokinetic profiles on both the first and second days of pharmacokinetic sampling as well as overall pharmacokinetic results for vatalanib, imatinib, CGP74588 and hydroxyurea are summarized in Table 4A-D. The smaller percentage of patients taking EIAEDs who had full pharmacokinetic data on both days of sampling primarily reflected the failure to obtain pharmacokinetic samples in most of those patients and incomplete pharmacokinetic sampling in others.

There was no significant effect of vatalanib dose on vatalanib pharmacokinetic parameters. The use of EIAEDs had a significant effect on vatalanib day 7 pharmacokinetics, decreasing C_{max}/D and increasing CL/F approximately 3-fold, and, surprisingly, increasing V/F more than 3-fold, while not significantly affecting the plasma $t_{1/2}$. Similar effects were seen on day 35, although the differences did not reach statistical significance because of higher inter-patient variability. There was no difference in either stratum between vatalanib pharmacokinetics on day 7 when vatalanib was administered alone, and on day 35 when vatalanib was co-administered with imatinib and hydroxyurea.

The use of EIAEDs decreased imatinib C_{max}/D and increased CL/F , but not V/F , as previously reported.²² Although imatinib and hydroxyurea were co-administered on both days 8 and 35, the effect of hydroxyurea on imatinib pharmacokinetics became fully apparent at day 35 and was characterized by an increase in C_{max}/D and decreases in CL/F and V/F as previously described.²² These effects were more pronounced in the patients taking EIAEDs, in whom hydroxyurea almost neutralized the effect of EIAEDs on imatinib pharmacokinetics. The effects of EIAEDs and hydroxyurea on CGP74588 pharmacokinetics were similar to those on imatinib, but are harder to interpret, as both formation and elimination of CGP74588 are mediated by metabolism. There was no relevant effect of EIAEDs or time on hydroxyurea pharmacokinetics.

DISCUSSION

Recent studies suggest that targeting angiogenesis represents an important advance in the treatment of MG patients. Vredenburgh demonstrated that the humanized anti-VEGF monoclonal antibody, bevacizumab, in combination with the topoisomerase I inhibitor irinotecan was associated with radiographic response rates of 67% and 61% among patients with recurrent anaplastic glioma and GBM, respectively. Furthermore, 6-month PFS rates were 56% and 30% for patients with recurrent grade 3 and grade 4 MG, respectively. The median OS was 40 weeks for recurrent GBM patients.^{4, 5} These results compare favorably with those achieved using TMZ in patients with first recurrence of anaplastic glioma and GBM, respectively.^{29, 30} Smaller series of recurrent MG patients treated with bevacizumab plus irinotecan demonstrate comparable rates of radiographic response and outcome benefit.^{31, 32} In addition, preliminary results of a randomized, multi-center clinical trial comparing bevacizumab to bevacizumab plus irinotecan among recurrent GBM patients, demonstrate prolonged survival relative to previously reported salvage therapy approaches.⁶

In addition, Batchelor recently demonstrated that single-agent cedarinib, a pan-VEGFR tyrosine kinase inhibitor, achieved a radiographic response rate of 50% and a median PFS of 16 weeks among recurrent GBM patients.³ Furthermore, using a constellation of sophisticated imaging modalities, the authors demonstrated that patients treated with cedarinib exhibited radiographic findings consistent with the hypothesis that anti-angiogenic agents can transiently normalize tumor vasculature.³³

Preclinical studies suggest that targeting PDGFR signaling, an important mediator of pericyte stabilization of tumor blood vessels,^{34, 35} may complement the anti-tumor activity of VEGF inhibitor therapy.^{23, 36-38} Clinical studies evaluating agents with dual inhibitory effects on VEGFR and PDGFR also show encouraging activity in select cancers.^{3, 39, 40} We conducted the current study to evaluate the safety and toxicity of the VEGFR inhibitor vatalanib in combination with standard doses of imatinib, a potential PDGFR inhibitor, in recurrent MG patients. Hydroxyurea was included in the current regimen because prior studies suggest it may enhance the anti-tumor activity of imatinib in recurrent MG patients.²⁰⁻²² In the current study, vatalanib was well tolerated up to the MTD of 1000 mg twice-a-day when administered on a continuous dosing schedule. Although the spectrum of toxicities appeared similar between both strata, toxicity frequency appeared increased for patients on EIAEDs. The explanation for this observation may involve the higher percentage of patients treated at second or third recurrence for stratum B rather than pharmacokinetic factors. In fact, although stratum B patients received higher doses of vatalanib and imatinib, clearance was increased and overall exposures were decreased relative to patients not on EIAEDs. Of note, intratumoral hemorrhage was not observed among patients treated with this regimen.

Day 7 vatalanib plasma pharmacokinetic data in patients not taking EIAEDs agreed with previous reports of single-agent vatalanib.^{12, 41, 42} The effect of EIAEDs on vatalanib AUC, C_{max} and CL/F agree with earlier reports of the effects of EIAEDs on imatinib pharmacokinetics.^{19, 22} This was not unexpected as both vatalanib and imatinib are cleared by CYP metabolism. Day 35 vatalanib plasma pharmacokinetic data did not differ substantially from that obtained on day 7 suggesting that concurrent imatinib and hydroxyurea administration did not affect vatalanib metabolism. Chronic dosing of hydroxyurea affected the pharmacokinetics of imatinib, as previously reported.²² The hypothesized mechanism of this alteration was inhibition of CYP enzymes. It is therefore surprising that the pharmacokinetics of vatalanib, also cleared primarily by CYP3A metabolism,⁴² were not affected by hydroxyurea therapy. The basis for this lack of effect on vatalanib is unclear, but might reflect compensatory routes of elimination for vatalanib, as opposed to imatinib.

Although the radiographic response rate, median PFS and 6-month PFS are encouraging, particularly because all patients in this study had failed prior TMZ therapy, efficacy conclusions are clearly limited by small sample size and dose escalation design. Furthermore, potent VEGFR inhibitors such as vatalanib can rapidly diminish permeability and subsequent contrast enhancement making evaluation of radiographic response difficult.^{12, 43} In the present study, we defined the MTD of vatalanib when administered with imatinib and hydroxyurea. Furthermore, our study demonstrates that combining potential inhibitors of VEGFR and PDGFR, two key regulators of tumor vascular endothelial cells and pericytes, can be achieved safely in patients with recurrent MG. Further clinical evaluation of this strategy may improve the anti-tumor benefit associated with anti-angiogenic regimens solely targeting VEGFR.

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Abbreviations List

AA	anaplastic astrocytoma
CI	confidence interval
CR	complete response
DLT	dose-limiting toxicity
EIAEDs	enzyme-inducing antiepileptic drugs
GBM	glioblastoma multiforme
ITT	intent-to-treat
KPS	Karnofsky performance status
MG	malignant glioma
MTD	maximum-tolerated dose
OS	overall survival
PD	progressive disease
PDGF	platelet-derived growth factor
PDGFR	platelet-derived growth factor receptor
PFS	progression-free survival
PR	partial response
SD	stable disease
TMZ	temozolomide
TTP	time to progression
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor

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Figure 1.

Baseline and post-treatment MRIs of a recurrent GBM treated patient with vatalanib, imatinib and hydroxyurea. Post-contrast axial T-1 weighted (upper) and fluid-attenuated inverted recovery (FLAIR) (lower) sequences at baseline (left) and after 17 cycles.

TABLE 1

Dose Escalation Schedule

Dose Level	Stratum A ¹			Stratum B ²		
	Vatalinib (mg/day)	Imatinib (mg/day)	Hydroxyurea (mg bid)	Vatalinib (mg/day)	Imatinib (mg bid)	Hydroxyurea (mg bid)
1	500	400	500	750	500	500
2	750			1000		
3	1000			1250		

¹ Stratum A: patients not on CYP3-A inducing anti-epileptics (EIAEDs: phenytoin, phenobarbital, carbamazepine, oxcarbazepine, primidone)

² Stratum B: patients on EIAEDs

TABLE 2

Patient Characteristics

	STRATUM A (No EIAEDs ^a)	STRATUM B (On EIAEDs ^a)	ALL
No. of patients(%)	18(49)	19(51)	37
Median age(yrs)	53.4	52.0	53.0
Range	26.2 – 73.4	31.8 – 75.7	26.2 – 75.7
Male(%)	11(61)	14(74)	25(68)
Histology(%)			
GBM	18(100)	16(84)	34(92)
AA	0	3(16)	3(8)
KPS(%)			
90–100	10(56)	10(53)	20(54)
80	8(44)	7(37)	15(41)
70	0	2(10)	2(5)
Surgery(%)			
GTR	2(11)	0	2(5)
None	16(89)	19(100)	35(95)
Prior XRT (%)	18(100)	19(100)	37(100)
Prior Chemotherapy Agents(%)			
1	4(22)	6(32)	
2	6(33)	7(37)	
3	4(22)	4(21)	
4	2(11)	2(11)	
≥ 5	2(11)		
No. prior progressions(%)			
1	13(72)	10(53)	
2	5(28)	7(37)	
3		2(11)	

KPS–Karnofsky Performance Status

GTR–gross total resection

XRT–Radiation therapy

^aEIAEDs enzyme-inducing anti-epileptic drugs (phenytoin, phenobarbital, carbamazepine, oxcarbazepine or primidone)

Table 3

Toxicity > 10% patients by dose level, stratum.

Dose Level	1				2				3				Total(%)
Stratum	A		B		A		B		A		B		
#Patients	5		6		6		7		7		6		37
#Cycles	24		28		25		22		31		18		148
Grade	1/2	3/4	1/2	3/4	1/2	3/4	1/2	3/4	1/2	3/4	1/2	3/4	
Diarrhea	1	0	2	0	1	0	1	0	1	0	0	0	6(16)
Fatigue	0	0	2	0	2	1	3	1	1	0	1	1*	12(32)
Hypertension	0	0	3	0	3	1	1	1*	1	0	3	0	13(35)
Infection	0	0	0	1	0	0	0	0	2	0	1	1	5(14)
Mucositis	0	0	3	0	2	0	0	0	0	0	0	2	7(19)
Nausea/Emesis	0	0	2	0	1	0	1	0	2	0	2	0	8(22)
Neutropenia	2	0	0	1	0	0	2	0	5	1	2	4	17(46)
Rash	0	0	1	0	2	0	0	0	1	0	1	2*	7(19)
Thrombocytopenia	0	0	0	0	2	0	0	0	1	1*	1	1	6(16)
Transaminase	0	0	0	0	0	1	0	1*	0	1	3	0	6(16)
Elevation													

* Dose-limiting toxicity

TABLE 4

Plasma Pharmacokinetics

Agent	Stratum	Day	C _{max} /D(ng/mL/mg)	t _{max} (h)	t _{1/2} (h)	AUC _{0-12 / 0-12} (ng/mL* h/mg)	CI/F(L/h)
Imatinib	A(N=14)	8	Mean(Range) 4.46(1.20-9.25)	Mean(Range) 3.64(1.50-4.00)	Mean(Range) 10.7(6.9-25.0)	Mean(Range) 22.4(5.40-52.7)	Mean(Range) 23.9(7.59-74.1)
		35	6.05(4.50-9.25)	4.21(1.00-6.00)	10.6(2.10-18.7)	47.9(19.4-75.0)	9.78(5.33-20.6)
	P day 8 vs 35		0.011	0.461	0.840	0.0004	0.0004
	B(N=9)	8	2.78(0.60-4.00)	2.11(1.00-4.00)	3.99(3.00-5.70)	10.1(2.80-18.0)	66.5(27.8-178.6)
		35	4.20(1.60-8.40)	2.56(0.00-4.00)	4.58(1.20-8.80)	39.4(10.4-62.1)	16.4(8.05-48.1)
	P day 8 vs 35		0.295	0.500	0.932	0.0003	0.0003
	P stratum A vs B	8	0.040	0.006	0.0000006	-	0.0004
		35	0.008	0.029	0.001	-	0.034
Vatalinib	A(N=15)	7	3.12(0.72-5.03)	1.86(0.97-3.00)	3.80(1.35-8.54)	11.1(2.23-16.1)	122(62.0-448)
		35	2.82(0.82-7.38)	2.45(1.00-4.42)	2.62(1.44-5.13)	10.4(3.28-25.5)	137(39.3-305)
	P day 7 vs 35		0.289	0.088	0.050	0.437	0.436
	B(N=8)	7	1.15(0.40-2.46)	1.79(1.00-3.17)	5.13(1.47-14.4)	4.51(1.31-12.1)	377(82.3-765)
		35	1.91(0.16-6.52)	2.13(0.00-4.00)	3.30(1.25-5.88)	6.75(0.73-17.7)	368(56.5-1371)
	P day 7 vs 35		0.735	0.375	0.329	0.494	0.494
	P stratum A vs B	7	0.001	0.779	0.550	-	0.001
		35	0.088	0.451	0.527	-	0.073
CGP74588	A(N=14)	8	0.77(0.25-1.25)	3.43(2.00-6.00)	13.5(2.40-30.7)	5.29(1.00-14.2)	-
		35	1.48(0.75-4.25)	3.57(1.00-8.00)	18.4(2.20-52.8)	17.8(3.20-52.1)	-
	P day 8 vs 35		0.0005	0.938	0.263	0.000007	-
	B(N=6)	8	0.77(0.40-1.60)	2.83(1.00-4.00)	4.42(1.40-6.50)	2.97(1.30-5.40)	-
		35	1.50(0.80-2.80)	3.25(1.50-6.00)	5.25(1.50-11.7)	24.7(8.40-54.4)	-
	P day 8 vs 35		0.004	0.750	0.926	0.002	-
	P stratum A vs B	8	0.866	0.392	0.002	-	-
		35	0.824	0.845	0.005	-	-
			-	-	-	-	-

Agent	Stratum	Day	C _{max} /D (ng/mL/mg)	t _{max} (h)	t _{1/2} (h)	AUC _{0-12 / 0-12} (ng/mL* h/mg)	CI/F (L/h)
			Mean (Range)	Mean (Range)	Mean (Range)	Mean (Range)	Mean (Range)
Hydroxyurea	A (N=14)	8	18.5(6.80–29.6)	1.29(0.50–2.00)	4.84(1.60–12.5)	50.4(9.50–91.1)	15.2(5.50–52.5)
		35	19.4(5.60–32.6)	1.30(0.50–4.00)	3.29(1.40–6.80)	41.7(13.0–84.5)	15.4(5.90–38.4)
	P day 8 vs 35		0.931	0.441	0.020	0.246	0.248
	B (N=6)	8	16.5(7.60–35.0)	1.80(0.50–4.00)	3.5(2.70–5.40)	37.38(18.1–60.4)	16.4(8.3–27.6)
		35	19.0(7.80–31.4)	0.90(0.50–1.50)	7.12(2.50–21.5)	41.4(17.0–70.1)	15.4(7.10–29.4)
	P day 8 vs 35		0.615		0.415	0.723	0.718
	P stratum A vs B	8	0.467	0.554	0.373	0.517	0.516
		35	0.848	0.852	0.123	0.964	0.965