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Phase I study of sorafenib and tipifarnib for recurrent glioblastoma: NABTC 05-02

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Abstract

Recurrent glioblastoma (GBM) has a very low six-month progression free survival (PFS) with currently available treatments. Combination chemotherapy to target multiple cell signaling pathways is currently being investigated in order to improve prognosis for recurrent disease. The purpose of this phase I study was to determine the maximum tolerated dose (MTD) for the

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combination of tipifarnib and sorafenib for the treatment of recurrent GBM. Patients with pathologically proven WHO grade IV GBM and radiographically proven tumor recurrence were eligible for this study. Treatments included sorafenib at twice daily and escalating dosages of tipifarnib. Dose-limiting toxicity (DLT) was determined over the first 28-days of treatments, and the MTD was determined in a 3+3 study design. We enrolled 24 patients, and 21 patients completed the MTD period. The study was stopped early with no MTD determination for excessive toxicities. The last dose level reached was sorafenib at 200 mg twice a day and tipifarnib 100 mg twice a day on an alternating week schedule. The DLTs included diarrhea, lipase elevation, hypophosphatemia, and arthralgia. The combination of sorafenib and tipifarnib has excessive toxicities and full single agent dosages could not be achieved in combination.

Keywords

tipifarnib; sorafenib; recurrent GBM; combination study

Introduction

Primary malignant central nervous system tumors cause more than 13,000 deaths per year in the United States[1]. The most common as well as the most aggressive primary brain tumor is glioblastoma (GBM). Despite optimal treatment with surgery, radiation therapy and temozolomide chemotherapy, almost 90% of patients with GBM will have tumor progression by 2 years [2]. Second line treatments with either chemotherapies or biological agents usually only achieve a 6-months progression free survival (PFS) in 15–16% of patients with GBM [3,4], and slightly more, 29–45%, if treated with bevacizumab [5,6]. Thus, more effective treatments at recurrence are needed.

Several pathways are implicated in the pathogenesis of GBM including multiple abnormalities in receptor tyrosine kinase pathways. For instance, the epidermal growth factor receptor is amplified in up to 70% of GBMs[7]. Mitogen binding of these receptors leads to activation of signal transduction cascades that include activation of the Ras genes[8]. Activated Ras further triggers the kinase activity of the protein kinase Raf and subsequently the mitogen-activated protein kinase (MAPK) pathway which are key controls in cell growth, proliferation, and survival[9]. Furthermore, overexpression of the Ras oncogene is also found in a large proportion of human cancers and Ras genes play a role in cell proliferation and differentiation[10].

Several clinical trials for the treatment of GBM have used agents targeting the RAS-MAPK pathway. One strategy attempts to use farnesyltransferase inhibitors (FTIs) to block the post-translational activation of RAS, including trials using the FTI tipifarnib. Tipifarnib (R115777, Zarnestra; Johnson & Johnson Pharmaceutical Research & Development LLC, Titusville, NJ) is a potent and selective nonpeptidomimetic FTI. Additional effects of this agent include inhibition of proliferation in tumors both with and without Ras mutations as well as effects on angiogenesis, apoptosis, and tumor microenvironment[11–13]. The action of FTIs have been demonstrated in several pre-clinical studies to sensitize tumors to radiotherapy[14,11] and inhibit glioma cell proliferation[15,16].

In phase I studies, tipifarnib exhibits oral bioavailability with dose-proportional pharmacokinetics[17,18]. Several trials in recurrent glioma found that tipifarnib has a toxicity profile and efficacy that depends on the types of antiepileptic drugs being taken by patients[19,20], where patients taking enzyme inducing antiepileptic drugs (EIAEDs) would have different maximum tolerated dose (MTD) and type of dose limiting toxicity (DLT) than patients not taking EIAEDs[21]. These studies found that in patients taking EIAED, the MTD was 600 mg bid for 21 days every 4 weeks, double the MTD for patients not receiving EIAED. Also, the predominant DLT seen in the patients on EIAEDs was rash versus the myelosuppression seen in those patients not taking EIAEDs. Pharmacokinetic evaluation showed that the area under the plasma concentration-time curve (AUC) from 0–12 hours at MTD was approximately halved in those receiving EIAEDs compared with those not receiving EIAEDs. Although limited pharmacodynamic evaluation revealed that at MTD, patients receiving EIAEDs had adequate inhibition of farnesylation in peripheral blood mononuclear cells, a later phase II clinical trial found that at MTD, patients not on EIAED had possibly better progression free survival (PFS) than those on EIAED, and the survival data showed limited efficacy in both these cohorts[20].

Without clinically significant benefits as a single agent, tipifarnib may have better efficacy when combined with other cytotoxic therapies or complementary targeted molecular agents. Blocking the RAS pathway further downstream with a Raf kinase inhibitor may increase inhibition of tumor growth in preclinical models[22], e.g. blockage of RAF may inhibit further activation down the MAPK pathway.

Sorafenib (BAY 43-9006, Nexavar; Bayer) is a novel bi-aryl urea that has been previously proven to inhibit RAF1 and b-RAF kinase family members. In addition, sorafenib demonstrated potent inhibition of several receptor tyrosine kinases involved in angiogenesis including VEGFR-2, PDGFR-β and VEGFR-3[23,24,22]. Sorafenib as a single agent has been evaluated in several Phase I studies in patients with advanced refractory solid tumors[25,26] in various dosages and schedules, both intermittent and continuous. The most common drug-related toxicities have involved the gastro-intestinal tract (diarrhea, nausea, abdominal cramps) and skin (pruritus, rash and hand-foot syndrome). Other reported treatment-related adverse events were hepatic disorders (abnormal AST, ALT, bilirubin, and GGT) and elevation of pancreatic enzymes. Data from Phase I trials indicate that 400mg BID is the MTD for sorafenib.

Since combination of an FTI inhibitor and a Raf inhibitor to block both upstream and downstream RAS/Raf/Mek pathway may better block tumor growth and improve survival for patients with GBM, we conducted a phase I clinical trial of sorafenib in combination with tipifarnib to determine the maximum tolerated dosages (MTD) for this combination. This study is part of the North American Brain Tumor Consortium study 05-02, which was a multi-arms study of different combinations of target inhibition to achieve better receptor tyrosine kinase inhibition, with sorafenib as the backbone (stable dose and agent in all arms) in combination with upstream RAS inhibition (tipifarnib, reported here) or with epidermal growh factor receptor inhibition (erlotinib) or PI-3-kinase pathway inhibition (temsirolimus). The primary objective of this study included finding the best phase I combination with the least toxicity and possibly some preliminary response to move on to a phase II efficacy

study. This manuscript reports the results from the attempt to determine MTD of the combination of sorafenib and tipifarnib in patients with recurrent malignant glioma. The reports for the other arms of sorafenib with erlotinib or temsirolimus have been reported previously[27,28].

PATIENTS AND METHODS

Patient Population

Eligible patients were ≥18 years of age with recurrent histologically confirmed WHO grade IV GBM or gliosarcoma. Patients must have unequivocal radiographic evidence of disease recurrence on either MRI or CT. A baseline MRI was obtained within 14 days of treatment on no or stable steroid dosage of at least 5 days. There were no restrictions on the number of recurrences or treatments, but patients must have progressed following prior radiotherapy and be at least 42 days from completion of radiotherapy. Eligibility criteria included Karnofsky performance score (KPS) ≥60 and adequate hematologic and organ function. Patients were excluded if they had received prior sorafenib, vatalanib, AEE-788, or any farnesyl transferase inhibitors, were receiving EIADs, had grade 2 or higher peripheral neuropathy, had histories of allergy to imidazoles, or were pregnant or breastfeeding. Patients were also excluded if they had significant medical illness or any disease that may obscure toxicity or dangerously alter drug metabolism. All patients with child bearing potential were required to use adequate contraception. The protocol and informed consent were approved by the institutional review boards of all participating institutions. All patients reviewed, signed, and provided written informed consent before enrollment.

Study Design

This study was a part of a phase I sequential accrual design trial with 3 different combination therapy arms: Arm 1 – sorafenib and erlotinib; Arm 2 – sorafenib and temsirolimus; Arm – 3 sorafenib and tipifarnib. Cohorts of 3 patients were enrolled starting with the first 3 patients in arm 1, then next 3 in arm 2, and so forth. This study design aimed to allow faster enrollment and more combination targeted therapies studied than the traditional 3+3 design of just one treatment modality. The most successful combination with the least toxicity would then have been expanded to a phase II study. We are reporting Arm 3 in this manuscript. The study is a phase I dose-escalation trial to establish the MTD of the combination of sorafenib and tipifarnib. The MTD was to be determined using the 3+3 trial design. The study was also designed to evaluate the pharmacokinetics of the combination therapy.

Dosing and Escalation

Tipifarnib and sorafenib were supplied by the Cancer Therapy Evaluation Program, Division of Cancer Treatment and Diagnosis, National Cancer Institute (Bethesda, MD). Tipifarnib was given once or twice a day, depending on the treatment cohort, with food. Sorafenib was given twice a day with or without food. If given with meals, patients were instructed to take sorafenib with a moderate to low-fat meal. For the first cycle of treatment, Cycle 1, only tipifarnib was given on day 1, and sorafenib would be initiated on day 2. Treatments were maintained until unacceptable toxicity, patient withdrawal, or disease progression.

Dose escalation was performed as per Table 2 in cohorts of three patients. Sorafenib dose remained the same in all cohorts at 200 mg twice daily. The starting level, level 0, dosing for tipifarnib was 200 mg twice a day. If no DLT occurred in that cohort, a subsequent cohort of three additional patients would be opened at the next higher dose level, level 1. If one patient experienced a DLT at level 0, three more patients would be added to that dose cohort. If two patients experienced DLT at level 0, the next three patients to be enrolled onto this treatment combination would be at a lower level, level −1. The MTD was defined as the dose at which no more than 1/6 patients experienced a DLT with the next higher dose having exceeded that limit for DLTs, or if all levels did not have more than 1/6 patients with DLTs, the MTD would be the maximum planned dose level. A cycle was considered 28 days in length. DLT was determined over the first 28 days of treatment (cycle 1).

In the first version of the protocol, the starting dose for tipifarnib was given at 200 mg twice daily. Subsequently, the protocol was amended to revise the dosing schedule for a new level 0, “Revised level 0”, based on the results of a published study showing that higher tipifarnib dosing could be achieved with an alternate week schedule[29]. The Revised level 0 consisted of sorafenib at 200 mg twice daily and tipifarnib at 100 mg twice daily given on days 1–7 and 15–21 (alternate weeks) of a 28-days cycle.

Patient Evaluation

Pretreatment evaluation included a medical history and physical examination, baseline tumor measurements by MRI or CT, baseline electrocardiograms, and laboratory tests for hematologies and chemistries obtained within 14 days prior to registration. Hematology was performed every week during the first cycle and then every 2 weeks for subsequent cycles. Chemistry panel and liver function tests were obtained every week for the first cycle and then every 4 weeks for subsequent cycles. Blood pressures and adverse events were evaluated weekly for the first cycle, and complete physical examination and neurologic examination were performed every 4 weeks. Brain imaging was performed prior to every other cycle.

DLT was evaluated according to the National Cancer Institute Common Toxicity Criteria version 3. DLT was defined as any grade 4 hematologic toxicity, grade 3 thrombocytopenia lasting greater than 7 days (per protocol), any grade 3 or 4 non-hematologic toxicity (except electrolyte imbalances, diarrhea, nausea, and vomiting which require maximal medical intervention before determined to be a DLT), any intolerable grade 2 non-hematological or grade 3 hematological toxicity requiring a dose reduction during the first 28 days of treatment, or any toxicity resulting in a treatment delay of >1 week during the first 28 days of treatment.

Tumor response or progression was measured using Response Evaluation Criteria in Solid Tumor Group (RECIST) criteria. These criteria were used in order to allow for comparisons to previous trials, as this trial occurred before the more modern methods of trial response evaluations such as RANO criteria[30]. Tumor progression was defined as a new lesion representing tumor, clear clinical worsening, failure to return for evaluation due to death or deteriorating condition, 25% increase in tumor measurements, or clear worsening of any evaluable disease.

Pharmacokinetic Evaluation

For both tipifarnib and sorafenib, whole blood samples (6 ml) were collected in heparinized (Na or Li) containing, nonseparator tubes by venipuncture (heparin lock) or by central venous catheter if in place. At the time of sampling, the first 1 ml of blood diluted with heparin or saline was discarded and the 6 ml sample then withdrawn. The blood sample was kept on ice and centrifuged within 30 min at 3,000 rpm × 10–15 min. The plasma was removed, placed in appropriately labeled polypropylene storage tubes and stored at −70 degrees C. Samples for pharmacokinetic analysis were collected on day 1–2 and day 15 of cycle 1 for tipifarnib, and day 2, 15, 28–29 for sorafenib. Samples were shipped frozen on dry ice to the study pharmacologist (J.K.). Quantitative analyses were performed as previously published using liquid chromatography method with tandem mass spectrometry[19,27].

Statistical Considerations

The primary end points for this tipifarnib dose-escalation, phase I study were to define DLT and determine the MTD for dosing in a phase II trial. The dose for patients was escalated as described, and DLT, MTD, and safety were evaluated. Using this dose-escalation scheme, the probabilities of escalating to the next dose level are based on the true rate of DLT at the current dose. Overall, if the true underlying proportion of DLTs was 30% at the current dose, there would be a 42% chance of escalating to the next dose. However, if the proportion of DLTs was 50%, the chance of escalation would only be 11%. Pharmacokinetic evaluation of the drug combinations, with determination of Cmax, Tmax AUC, as well as clearance and plasma half-life was obtained during the first treatment cycle in all phase I patients.

RESULTS

Patient Characteristics

A total of 24 patients were enrolled between December 2007 and December 2009 (Table 1) into Arm 3 of this study of sorafenib and tipifarnib. The other 2 arms also completed enrollment during this time, but not reported here. All patients had pathologically confirmed GBM prior to treatment; two patients had a previous diagnosis of a WHO grade III glioma with later transformation to glioblastoma. All patients failed treatments with both radiotherapy and temozolomide chemotherapy. Most of the patients were treated in the 1st or 2nd recurrence. Patients were enrolled in 3 different dose levels in cohorts of 3, with replacement if a patient did not meet criteria for safety evaluations for DLT as defined above (Table 2). In general, most patients ended study because of disease progression, with 1 due to clinical decline without clear tumor growth, 6 for unacceptable toxicities, and 4 withdrew consent to continue study participation. We do not have progression free survival (PFS) data on those who withdrew consents or stopped due to adverse events. For the rest of the patients, median PFS was 55 days, and none had event free survival at 6 months. To date, all 24 patients have expired with a median overall survival (OS) of 4.38 months (data not shown).

Toxicities

A summary of grade 3 and 4 toxicities is provided in Table 3. At starting dose level 0, ten patients were evaluated, four of whom experienced DLTs, including lipase elevation, grade 2 hypertension, diarrhea, and emesis. This arm enrolled additional patients as the toxicities were unexpected, and the study team enrolled additional patients to confirm these toxicities.

On the lower dose level −1, two of the first three patients had to be replaced due to noncompliance with treatments. Six additional patients were evaluated (one patient had progression in the original cohort). Three of these patients experienced DLTs including grade 4 lipase elevation, grade 3 arthralgia, and hypophosphatemia.

At revised level 0 with every other week tipifarnib dosing, the first two enrolled patients developed serious adverse events (SAEs) with one grade 3 encephalopathy, headache, fever, dysphasia, and one with grade 4 thromboembolic event and grade 3 lipase elevation. Although these events were not all attributable to study drugs, safety concerns regarding frequent SAEs from this combination led to a decision to stop further enrollment into this study.

Pharmacokinetic Data

Pharmacokinetic data were obtained in most patients in the first 2 dose levels. PK studies were not performed when level 0 was revised. The levels of sorafenib and tipifarnib are reported in table 4 (and Supplementary tables for per patient data). The tipifarnib levels are comparable to historical data of single agent tipifarnib in patients not taking EIAED at MTD of 300 mg twice daily[19], and the AUC do not seem to change significantly between daily or twice daily dosing when accounting for the range of AUCs seen.

DISCUSSION

This phase I study demonstrated that the combination of tipifarnib and sorafenib was toxic even at a dose of 200 mg twice a day of sorafenib and 100mg twice a day every other week of tipifarnib. These doses are lower than those reached by prior phase I studies of single agent sorafenib or tipifarnib, including a study of single agent tipifarnib in patients with malignant glioma not receiving EIAED where the MTD was 300 mg twice daily[19,31]. Since we were unable to achieve even single agent dosage levels, we terminated the trial early and did not attempt to identify a MTD.

Given that malignant gliomas can have multiple aberrant molecular targets, combination targeted therapies are more likely to be effective than a single agent[32]. Single agent molecular targeted trials in recurrent GBM have shown little improvement in survival[16]. However, to date, combination therapeutics, including those targeting the EGFR pathway and/or PI3K pathway have yet to show a survival improvement over single agents[15]. Furthermore, as was seen in this phase I trial, the efficacy of combination therapies may also be limited by failure to achieve expected dosing levels because of increased toxicities due to overlapping target inhibition. Even in those patients who did not experience dose limiting toxicities, survival was low, and no further survival analysis was performed due to the low PFS and OS.

Our subjects experienced toxicities well-known in the side effect profiles of both drugs, including rash and diarrhea for tipifarnib, hypertension and hypophosphatemia for sorafenib, and elevated lipase for both, resulting in more frequent DLTs in combination than previously reported as monotherapy. The combination also seems to have higher frequencies of fatigue, altered mental status, and mucositis than expected with single agents. Other combinatorial studies for treatments of GBM have also resulted in increased toxicities without improved efficacy, possibly from pharmacokinetic interactions between the two drugs[28,33]. Because we did not see a change in the expected pharmacokinetics of these two agents when used in combination, the toxicities may be due to overlapping target inhibition rather than toxic levels of the drugs themselves.

Future clinical studies on combination molecular treatments should consider other strategies to achieve increased breadth of target inhibition without additional toxicity. Choice of agents for combination treatments should be based on both rational molecular targets and complementary side effect profiles. Promiscuous kinase inhibitors such as sorafenib might make particularly poor partners for combination therapy[34,35]. Other options include using alternative drug schedules, such as pulsatile dosing to achieve better CNS drug level[36,37] with the potential to limit exposure to prolonged toxicities, as seen with the currently enrolling trials using pulsatile dosing of erlotinib or lapatinib for GBM[38,39].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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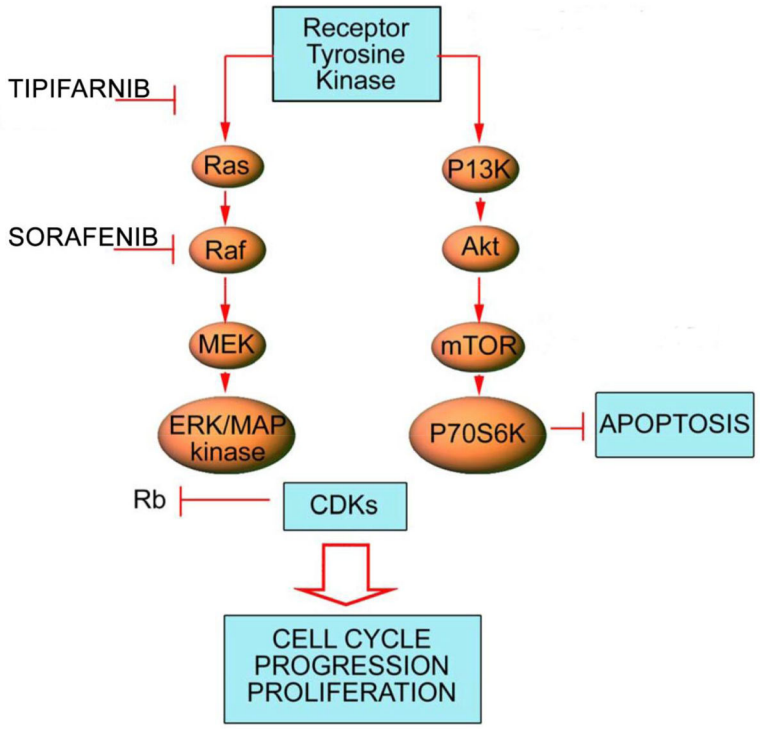

Fig. 1.
Inhibition in the RAS-MAPK pathway by tipifarnib and sorafenib

Table 1

Patient characteristics

Number	24
Male	16
Female	8
Age, median (range)	57 (27–76)
1st recurrence	18
2nd recurrence	5
3rd recurrence	1
KPS (median, range)	85 (60–100)

Table 2

Dose levels and number of enrollment and DLTs

Dose level	Sorafenib dose (mg)	Tipifarnib dose (mg)	Number enrolled	Number DLT	Number replaced
0	200 bid	100 BID d1–21	10	4	0
−1	200 bid	100 QD d1–21	9	3	3
Revised 0	200 bid	100 BID d1–7, 15–21	5	3	0

For cycle 1 only, Sorafenib was started on day 2.

DLT dose limiting toxicity, *bid* twice a day, *qd* once a day, *d1–21* taken days 1–21 of 28 days, *d1–7/15–21* taken days 1–7, break days 8–14, then taken again days 15–21 of 28-days.

Table 3

Grade 3 and 4 events attributable to combination treatment

Dose levels	0	−1	Revised 0	Total % (N=24)
Abdominal pain	1			4
Arthralgia		1		4
Diarrhea	2			8
Dysphasia			1	4
Encephalopathy			1	4
Fatigue	2			8
Fever			1	4
Headache			1	4
Hyponatremia		1		4
Hypophosphatemia	2	2		17
Infective myositis	1			4
Lipase increased	1	1	2	17
Lymphocyte count decreased	4	3		29
Serum amylase increased	1			4
Thromboembolic event			1	4
Vomiting	1			4

Number of patients with a grade 3 or 4 toxicity related to either sorafenib, tipifarnib or combination of both. The first three columns refer to number of patients with grade 3 or 4 toxicity per dose level (please refer to table 2 for dosage of drugs per dose level). Last column is the total percent of patients with a grade 3 or 4 toxicity at all dose levels.

Table 4

Pharmacokinetic data

(A) Mean levels of sorafenib/N-oxide			
Tipifarnib dose level	**Day**	**Cpmax(μg/mL)**	**AUC 0–12 (μg × h/mL)**
100 mg QD	15	3.34/0.43 (± 1.31/0.23)	30.59/4.16 (± 14.9/1.76)
	28	3.43/1.17 (± 1.46/0.85)	41.43/7.83 (± 28.82/6.6)
100 mg BID	15	4.17/0.56 (± 2.99/0.41)	12.17/0.60 (± 16.3/0.8)
	28	4.53–0.66 (± 2.38/0.32)	36.45/5.39 (± 17.2/2.71)
(B) Peak plasma concentrations of tipifarnib			
Tipifarnib dose level	T1/2 (h)		
100mg QD	6.57 ± 1.18		
100mg D1, 100mg BID D2–21	3.35 ± 1.29		
Historical[a]	3.66 ± 1.18		
Tipifarnib dose level	Day	Cpmax (ng/mL)	
100mg QD	1	209.5 ±135.85	
	15	169.5 ± 186	
100mg D1, 100mg BID D2–21	1	132.17±65.96	
	15	233.6 ± 84.83	
Historical[a]	1	634 ±374	
	15	–	
(C) Plasma concentrati ons of tipifarnib			
Tipifarnib dose level	Day	AUC0–12 (ng × hr/mL)	
100mg QD	1	814.5 ±347.57	
	15	706 ± 644.88	
	AUC (ng × h/mL)	903.5 ±377.43	
100mg D1, 100mg BID D2–21	1	631.67±431.12	
	15	390.25 ± 468.8	
	AUC (ng × h/mL)	761.5 ± 468.8	
Historical[a]	AUC (ng × h/mL)	380 ± 217	
(D) Half-life of tipifarnib			

AUC area under the curve, *Cpmax* peak plasma concentration

[a]Levels of patients not take EIAED, at Tipifarnib of 300 mg bid. Cloughesy et al. [19].