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CLINICAL INVESTIGATION

A PHASE I TRIAL OF TIPIFARNIB WITH RADIATION THERAPY, WITH AND WITHOUT TEMOZOLOMIDE, FOR PATIENTS WITH NEWLY DIAGNOSED GLIOBLASTOMA

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Purpose: To determine the maximum tolerated dose (MTD) of tipifarnib in combination with conventional radiotherapy for patients with newly diagnosed glioblastoma. The MTD was evaluated in three patient cohorts, stratified based on concurrent use of enzyme-inducing antiepileptic drugs (EIAED) or concurrent treatment with temozolomide (TMZ): Group A: patients not receiving EIAED and not receiving TMZ; Group A-TMZ: patients not receiving EIAED and receiving treatment with TMZ; Group B: any patients receiving EIAED but not TMZ.

Patients and Methods: After diagnostic surgery or biopsy, treatment with tipifarnib started 5 to 9 days before initiating radiotherapy, twice daily, in 4-week cycles using discontinuous dosing (21 out of 28 days), until toxicity or progression. For Group A-TMZ, patients also received TMZ daily during radiotherapy and then standard 5/28 days dosing after radiotherapy. Dose-limiting toxicity (DLT) was determined over the first 10 weeks of therapy for all cohorts.

Results: Fifty-one patients were enrolled for MTD determination: 10 patients in Group A, 21 patients in Group A-TMZ, and 20 patients in Group B. In the Group A and Group A-TMZ cohorts, patients achieved the intended MTD of 300 mg twice daily (bid) with DLTs including rash and fatigue. For Group B, the MTD was determined as 300 mg bid, half the expected dose. The DLTs included rash and one intracranial hemorrhage. Thirteen of the 20 patients evaluated in Group A-TMZ were alive at 1 year.

Conclusion: Tipifarnib is well tolerated at 300 mg bid given discontinuously (21/28 days) in 4-week cycles, concurrently with standard chemo/radiotherapy. A Phase II study should evaluate the efficacy of tipifarnib with radiation and TMZ in patients with newly diagnosed glioblastoma and not receiving EIAED.

Tipifarnib, Newly diagnosed glioblastoma, Radiation, Farnesyltransferase inhibitor, Temozolomide.

INTRODUCTION

Treatment of malignant glioma remains a major therapeutic challenge. The heterogeneity of molecular signaling pathways involved in the growth and survival of glioma make it difficult to treat this neoplasm (1, 2). Currently, there is limited chemotherapeutic treatment for glioma, and novel agents that target aberrant signaling pathways need to be evaluated. Several pathways implicated in the pathogenesis of malignant astrocytoma and its microenvironment, including amplification of the epidermal growth factor receptor or platelet-derived growth factor, and overexpression of the angiogenic vascular endothelial growth factor, can lead to activation of Ras genes (3–5). Ras genes control normal cell growth and differentiation, and overexpression of the Ras oncogene is also found in a large proportion of human cancers (5). Additionally,

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recently discovered mutations in the neurofibromatosis gene NF1 may activate Ras and play a role in the pathogenesis and progression of some high-grade gliomas (6).

Tipifarnib (R115777, Zarnestra; Johnson & Johnson Pharmaceutical Research & Development LLC, Titusville, NJ) is a potent and selective nonpeptidomimetic farnesyltransferase inhibitor (FTI). The FTIs were originally developed to block the posttranslational activation of Ras proteins but subsequently were found to inhibit farnesylation of other targets such as Rho. Additionally, the effects of this agent include inhibition of proliferation in tumors both with and without Ras mutations and also effects on antiangiogenesis, apoptosis, and tumor microenvironment (7–9). Several preclinical studies also demonstrated that FTIs can sensitize tumors to radiotherapy (8, 10) and have activity against gliomas (11,12).

Given that glioma patients face limited therapeutic options, FTIs present a new therapeutic modality with a unique mechanism of action that affects multiple tumor-promoting pathways. In pharmacokinetic (PK) Phase I studies, tipifarnib has revealed oral bioavailability with dose-proportional pharmacokinetics (13,14). Tipifarnib has also been studied in the treatment of patients with recurrent glioma (15,16). These studies found that the toxicity profile and efficacy of tipifarnib can depend on the types of antiepileptic drugs being taken by patients. Commonly, patients with glioma are prescribed enzyme-inducing antiepileptic drugs (EIAEDs) for prevention or treatment of seizures. Induction of hepatic enzymes by EIAEDs can alter the metabolism of concurrently administered chemotherapeutic agents, which might lead to reduced dosing. Patients receiving EIAEDs show decreased plasma levels of several chemotherapeutic drugs when EIAEDs are administered at conventional doses (17–19). A Phase I study using tipifarnib in recurrent glioma showed that both maximum tolerated dose (MTD) and type of dose-limiting toxicity (DLT) differed between patients taking EIAEDs compared to patients not taking EIAEDs (17): the MTD was 600 mg twice daily (bid) for 21 days every 4 weeks in patients receiving EIAED, it was double the MTD for patients not receiving EIAEDs, and the predominate DLT was rash rather than myelosuppression. Pharmacokinetic evaluation showed that the area under the plasma concentration–time curve from 0 to 12 hours at MTD was approximately halved in those receiving EIAEDs compared with those not receiving EIAEDs. However, a limited pharmacodynamic evaluation revealed that the MTD dosing scheme in patients receiving EIAEDs was adequate to inhibit farnesylation in peripheral blood mononuclear cells. Interestingly, a Phase II clinical trial for exploratory progression-free survival (PFS) analysis comparing recurrent glioblastoma (GBM) patients treated with tipifarnib at MTD receiving or not receiving EIAED favored those not receiving EIAED (16). Although these data are intriguing, the response, PFS, and survival data were modest at best.

Without clinically significant benefits as a single agent, tipifarnib might have better efficacy when combined with other cytotoxic therapies or complementary targeted molecular agents. Therefore, we conducted a Phase I clinical trial of tipifarnib with radiation or chemoradiation for the treatment of newly diagnosed GBM.

PATIENTS AND METHODS

Patient population

Eligible patients were ≥18 years of age with pathologically confirmed newly diagnosed GBM. Other than surgery, patients were not allowed any additional therapeutic intervention before enrollment. Eligibility criteria also included Karnofsky Performance Status ≥60 and adequate hematologic and organ function. Patients were excluded from the study if they had significant existing medical problems, were pregnant, or were breastfeeding. The protocol and informed consent were approved by the local institutional review board at each participating institution. All patients reviewed, signed, and provided written informed consent before enrollment.

Stratification

Three Phase I evaluations were conducted and stratified based upon use of EIAED and concomitant use of temozolomide (TMZ) (Table 1). Any patient taking one or more EIAEDs (carbamazepine, oxcarbazepine, phenytoin, fosphenytoin, phenobarbital, or primidone) was stratified to Group B and was required to continue receiving at least one EIAED for the duration of the study. All other patients were evaluated in Group A. Initially, the protocol evaluated only patients receiving tipifarnib in combination with radiation therapy alone for both Group A and Group B. Later, in April 2005, when data revealed that combination treatment with radiotherapy and TMZ chemotherapy conferred better survival for patients with newly diagnosed GBM (20), a protocol amendment changed tipifarnib to be taken concurrently with radiation therapy and TMZ. These patients receiving a combination of tipifarnib and chemoradiation were evaluated as Phase I Group A-TMZ. Patients who switched from an EIAED to a non-EIAED were required to have discontinued the EIAED for a minimum of 2 weeks before enrollment.

Table 1. Patient characteristics

	Group A		Group B	
Characteristic	No TMZ	With TMZ	No TMZ	All
Number of patients	10	20	21	51
Sex: M/F	7/3	11/9	14/7	32/19
KPS: median (range)	90 (60–100)	90 (60–100)	90 (70–100)	90 (60–100)
Race: Caucasian, no.	10	19	21	50
Age (y): median (range)	52 (38–61)	52 (37–74)	58 (39–73)	54 (37–74)

Abbreviation: KPS = Karnofsky Performance Status

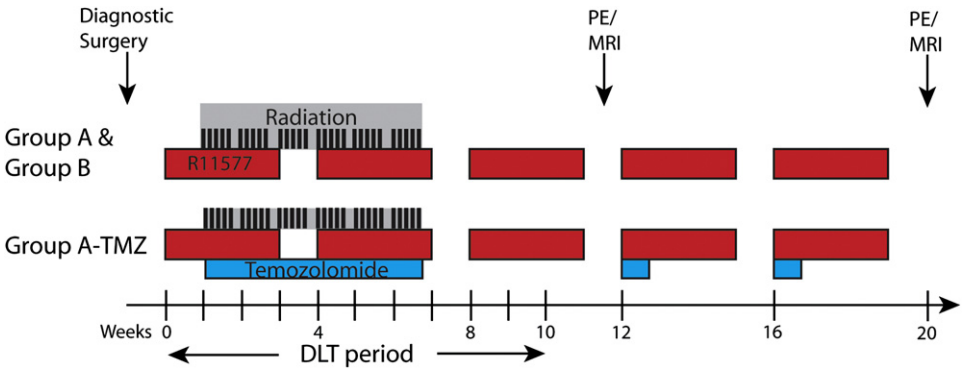

Figure. Phase I trial schema. R115777 = tipifarnib; PE = physical examination; DLT = dose-limiting toxicity evaluation.

Study design

This study was a Phase I dose-escalation trial to establish the MTD for tipifarnib in combination with radiation alone or chemoradiation in patients receiving or not receiving EIAEDs. The study was also designed to define the safety profile of tipifarnib taken bid in this patient population. A secondary, exploratory objective was to assess antitumor activity against newly diagnosed GBM as measured by PFS and overall survival. See the figure for study schema.

Tipifarnib dosing

Tipifarnib was supplied by the National Cancer Institute (Bethesda, MD) as 100-, 200-, and 300-mg tablets. Tipifarnib was given bid for 21 days followed by 7 days off in repeating 28-day cycles (21/28 days). Patients were counseled to take the study drug with food. The first dose of tipifarnib was given 5 to 9 days before starting radiation or chemoradiation. After the completion of radiation or chemoradiation, maintenance dosing of tipifarnib continued until tumor progression or unacceptable toxicities.

Dose escalation was performed in cohorts of 3 patients beginning at a starting dose of tipifarnib of 200 mg bid for Groups A and A-TMZ, and 400 mg bid for Group B. If no DLT occurred in that cohort, a subsequent cohort of 3 additional patients would be opened at the next dose level as per Table 2. If one patient experienced a DLT, 3 more patients would be added to that dose cohort. The MTD was defined as the dose at which no more than 1 in 6 patients experienced a DLT and at which the next higher dose exceeded that limit, or the maximum planned dose level. DLT was determined over the first 10 weeks of treatment (*i.e.,* time surrounding radiation or chemoradiation). A cycle of treatment was defined by tipifarnib dosing. A cycle was considered 28 days in length. The maximum dose for each group was defined by the previously described MTD for single-agent use of 300 mg bid for Group A and 600 mg bid for Group B (15).

Table 2. R115777 dose levels

Group	Dose level	Dose	Schedule	Days administered
A and A-TMZ	−2	100 mg	qd	D1–D21 every 28 days
	−1	100 mg	bid	D1–D21 every 28 days
	1	200 mg	bid	D1–D21 every 28 days
	2	300 mg	bid	D1–D21 every 28 days
	3	400 mg	bid	D1–D21 every 28 days
B	−2	200 mg	bid	D1–D21 every 28 days
	−1	300 mg	bid	D1–D21 every 28 days
	1	400 mg	bid	D1–D21 every 28 days
	2	500 mg	bid	D1–D21 every 28 days
	3	600 mg	bid	D1–D21 every 28 days

Abbreviations: qd = daily; bid = twice daily.

Radiation therapy

Radiotherapy was given by external beam to a partial brain field in daily fractions of 2 Gy, to a planned total dose of 60 Gy. three-dimensional planning techniques were routinely used, and intensity-modulated radiotherapy was not permitted. The total dose was delivered using a sequential boost technique, with the initial large field, typically defined by the magnetic resonance imaging (MRI) T2 or fluid-attenuated inversion recovery (FLAIR) abnormality plus a 2-cm margin receiving 46 Gy in 23 fractions, and a final cone-down volume defined by the T1 magnetic resonance enhancement plus surgical cavity with a 1-cm margin receiving an additional 14 Gy. Radiotherapy Quality Assurance was not performed on every patient on the trial.

Temozolomide dosing

Temozolomide was given only to patients enrolled in Group A-TMZ.

With radiation. Patients received TMZ daily at 75 mg/m^2 starting the first day of radiotherapy, and stopped the night before the last fraction of radiotherapy. Patients were instructed to take TMZ on an empty stomach (21).

Post radiation. Inasmuch as DLT was determined over a 10-week period, after radiation, chemotherapy was not begun again until patients had been in the trial for at least 10 weeks with the next planned cycle of tipifarnib. The first postradiation cycle was administered at 150 mg/m^2 for the first 5 days out of 28 days (5/28). If this was tolerated and at the investigators' discretion, subsequent cycles could be given at 200 mg/m^2 daily at 5/28 dosing.

Patient evaluation

Pretreatment evaluation included a medical history and physical examination. Baseline tumor measurements by MRI or computed tomography were obtained within 21 days before study entry. Baseline determination of hematology and chemistry were obtained within 14 days of initiation of therapy. Hematology was performed every week during the first three cycles and then twice a month for subsequent cycles. Chemistry panel was obtained every 2 weeks for the first three cycles and then once a month for subsequent cycles. Complete physical examination, including an evaluation of the skin within the radiation treatment portal, and neurologic examination were

performed each week during radiation therapy and then before each cycle after completion of radiation therapy. The MRI/computed tomography was performed 4 weeks after completion of radiation therapy and then every 8 weeks to assess response. Patients with stable or responding disease received the same dose of tipifarnib at the next cycle or a reduced dose if adverse events were observed in the current cycle. If a patient experienced a DLT, the dose on the subsequent cycle was reduced by one dose level.

The DLT was evaluated according to the National Cancer Institute Common Toxicity Criteria version 3. It was defined as any Grade 4 hematologic toxicity, any nonhematologic Grade 3 toxicity, Grade 4 radiation-induced skin changes, failure to recover from toxicities within 3 weeks from the last dose of study drug, or holding radiation therapy for more than 2 weeks because of toxicity. Patients with progression before 10 weeks were considered evaluable for DLT if they were able to undergo a DLT evaluation at 10 weeks. During the first 10 weeks, patients assigned to a treatment cohort remained at the assigned dose level until tumor progression, unacceptable toxicity, or patient request.

Tumor progression was defined as a new lesion representing tumor, clear worsening of evaluable disease, failure to return for evaluation because of death, or deteriorating condition.

Statistical considerations

The primary endpoints 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 were based on the true rate of DLT at the current dose. Overall, i.f the true underlying proportion of DLTs was 30% at the current dose, there would be a 49% chance of escalating to the next dose. However, if the proportion of DLTs was 50%, the chance of escalation would only be 17%. Once MTD was reached, 10 more patients were enrolled in Group A-TMZ and Group B to define safety further in these populations.

RESULTS

Patient characteristics

A total of 51 patients were enrolled between June 2003 and March 2007 at eight United States centers that are part of the North American Brain Tumor Consortium (Table 1). There were 10 patients in Group A, 21 patients in Group B, and 20 patients in Group A-TMZ.

Toxicity

Table 3 lists the Grade 3 and 4 toxicities for each group whose attributions were possibly, probably, or definitely related to tipifarnib. The DLTs at each dose level of each cohort are in Table 4.

Group A. Tipifarnib dose ranged from 200 to 300 mg bid. There were no Grade 3 or 4 toxicities other than one Grade 3 rash at the second dose level. Grade 3 rash was the only DLT at any dose. The rash was a maculopapular, diffuse, erythematous rash involving the trunk and extremities. Subsequent patients who developed this DLT in other groups also had similar rash characteristics. The rash resolved after discontinuation of tipifarnib and the use of antihistamines and oral corticosteroids. Radiation therapy was not affected by the rash. This treatment cohort was able to meet the predefined dosing goal of 300 mg bid. There were 7 patients enrolled to the second dose level because 1 patient became noncompliant and withdrew from the study before the evaluation period but had no toxicity.

Group B. Tipifarnib dose started at 400 mg bid and deescalated to 300 mg bid. At the first dose level, 2 patients had DLTs of Grade 3 rash. One patient was replaced after withdrawing for toxicities not attributable to study drug. The dose level was deescalated to 300 mg bid, and 1 of 6 patients had a DLT of Grade 3 CNS hemorrhage. In this cohort, 1 patient was replaced because of tumor progression and death before the 10-week DLT evaluation period. One patient did develop a Grade 3 rash after the DLT evaluation period. The MTD was defined as 300 mg bid.

Group A-TMZ. Two DLTs were defined in this group. One DLT was a Grade 4 fatigue at tipifarnib dose of 200 mg bid, and this dose level was expanded to a total of 6 patients with no further DLTs. One additional patient was added to this cohort to replace 1 patient whose toxicities were, at first, thought to be unrelated to drugs. At the next dose level of 300 mg bid, only 1 patient had a DLT of Grade 3 rash. Other probable, possible, or definite Grade 3 or 4 adverse events that occurred outside of the 10-week DLT window or in the 10-patients expansion cohort included various hematologic toxicities and one Grade 4 pulmonary embolism. This treatment cohort was able to meet the predefined dosing goal of 300 mg bid.

Clinical outcomes

Given the small number of patients in each group, significant findings cannot be derived from the outcome data. Of the 20 patients enrolled in Group A-TMZ, 5 patients are free of tumor progression at 1 year after protocol registration, and 13 patients survived beyond 1 year: 3 in the 200 mg bid cohort, and 10 in the 300 mg bid group.

DISCUSSION

This study was successful in reaching the planned dose level (300 mg bid) in Group A with or without TMZ. This dose has been shown to inhibit HDJ-2 protein farnesylation in peripheral blood mononuclear cells (22, 23), one of the presumed antitumor targets of tipifarnib. Other studies have determined the MTD of tipifarnib when dosed with radiation. One study also in newly diagnosed GBM patients used tipifarnib continuously through radiation therapy and found that 100 mg bid was the MTD (24). In our study, not only was the tipifarnib MTD higher at 300 mg bid during the 6-week radiotherapy course, the use of concomitant TMZ did not change MTD.

This study also defined the MTD for Group B, patients receiving EIAEDs, at 300 mg bid. In contrast, previous studies of single-agent tipifarnib in patients receiving EIAEDs found the MTD to be 600 mg bid (15). This unexpected lower dosing for MTD in this study might be a result of tipifarnib now being given in conjunction with radiation

Table 3. Grade 3 and 4 adverse events

	Group A								Group B			
	No TMZ				with TMZ				No TMZ			
	200 (3)		300 (7)		200 (7)		300 (13)		400 (4)		300 (17)	
R115777 mg dose bid (*n*)	*n*	AE grade	*n*	AE grade	*n*	AE grade	*n*	AE grade	*n*	AE grade	*n*	AE grade
Rash	0	0	**1**	**3**	0	0	**2**†	**3**	**2**	**3**	**1**	**3**
Granulocytopenia	0	0	0	0	0	0	2	3–4	0	0	0	0
Thrombocytopenia	0	0	0	0	1	3	1	3	0	0	0	0
Leukopenia	0	0	0	0	0	0	2	3–4	0	0	0	0
Lymphocytopenia	0	0	0	0	0	0	1	3	0	0	0	0
Dyspnea	0	0	0	0	0	0	1*	4	0	0	0	0
Pleuritic pain	0	0	0	0	0	0	1*	4	0	0	0	0
Thrombosis/Thrombus/ embolism	0	0	0	0	0	0	1*	4	0	0	0	0
Muscle weakness	0	0	0	0	1*	4	0	0	0	0	0	0
Fatigue	0	0	0	0	**1***	**4**	0	0	0	0	0	0
Dizziness	0	0	0	0	1*	4	0	0	0	0	0	0
Anemia	0	0	0	0	1*	3	0	0	0	0	0	0
CNS hemorrhage	0	0	0	0	0	0	0	0	0	0	**1**	**3**

Abbreviations: AE = adverse events; bid = twice daily; CNS = central nervous system.
Dose-limiting toxicities denoted as bold and shaded.
* Adverse events occurring in same patient.
† Only 1 patient had rash develop in initial 10-week evaluation period.

therapy. Grade 3 rash was the predominate DLT in this group. This rash was not limited to the radiation field only but rather was consistent with drug eruptions. There does seem to be a hypersensitivity and higher incidence of rash seen with seizure medications such as phenytoin during radiation therapy for brain tumors (25, 26), and perhaps the DLTs in this group were related more to EIAED being given with radiation therapy than to tipifarnib itself. We did not collect information on whether patients also discontinued their EIAEDs at the time of rash and saw resolution of the rash. Previous studies also found that the 600 mg bid dosing might not be pharmacokinetically equivalent to 300 mg bid (15); thus, future evaluations of tipifarnib will likely exclude the use of EIAED. We did not evaluate PK in this study, given the unlikely impact of radiation therapy or TMZ upon metabolism of tipifarnib. Given the skin toxicities, future trials are also not expected to limit the skin dose of radiation, but rather will track this toxicity in greater detail.

Table 4. Dose-limiting toxicities

Cohort groups	Dose level	Patient	DLT	DLT type
Group A	1	3	0	None
	2	7	1	Rash
Group B	2	4	2	Rash
	1	17	1	CNS hemorrhage
Group A w/TMZ	1	7	1	Fatigue
	2	13	1	Rash

Abbreviations: DLT = dose-limiting toxicity; CNS = central nervous system.

Other than rash, central nervous system hemorrhage and fatigue were the only other DLTs that occurred in this study. We described similar events in our previous single-agent Phase I study in recurrent GBM, where the DLTs were rash and headache (15). In comparison, the study by Moyal *et al.* (24) had different DLTs of a sudden death and two episodes of pneumonitis, one associated with Grade 4 neutropenia and the other with pulmonary embolism. During the post-DLT evaluation period, this study did report Grade 3 to Grade 4 toxicities of hematologic cytopenias and pulmonary embolism, but these DLTs were predominately limited to the Group A-TMZ cohort.

Although the primary endpoint of this study was not clinical efficacy, we thought that it might be insightful to report some of the clinical outcomes in the 20 patients treated in the Group A-TMZ cohort because this combination will most likely be the regimen for studies in future trials. Although the results seem promising when compared to historical controls (20), given the small number of patients in this cohort, no conclusions can be made about the possible additive or inhibitory effect of tipifarnib on chemoradiation. In as much as these patients were treated in the newly diagnosed setting, objective tumor responses were not reported because it would be difficult to interpret progression or response after postoperative changes or radiographic pseudoprogression (27). The addition of TMZ therapy to radiotherapy may have increased pseudoprogression (28–30), and further addition of tipifarnib may enhance these radiographic treatment effects. Clinical efficacy will need to be determined with future Phase II studies, and true tumor response may require the use of new imaging criteria such as Response Assessment in Neuro-Oncology RANO (31).

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