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A phase I trial of tipifarnib with radiation therapy, with and without temozolomide, for patients with newly diagnosed glioblastoma

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Abstract

Purpose—To determine the maximum tolerated dose (MTD) of tipifarnib in combination with conventional radiotherapy (RT) for patients with newly diagnosed glioblastoma (GBM). 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 on EIAED, and on treatment with TMZ; Group B – any patients receiving EIAED, but no TMZ.

Methods and Materials—After diagnostic surgery or biopsy, treatment with tipifarnib started 5–9 days before initiating RT, twice daily, in four-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, 20 patients in Group B. In Group A and Group A-TMZ cohorts, patients achieved the intended MTD of 300 mg bid with DLTs including rash and fatigue. For Group B, the MTD was determined as 300 mg bid, half the expected dose. DLTs included rash and 1 intracranial hemorrhage. Thirteen of the 20 patients evaluated in Group A-TMZ were alive at one 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 GBM and not on EIAED.

Keywords

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, 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). FTIs were originally developed to block the post-translational activation of Ras proteins but subsequently were found to inhibit farnesylation of other targets such as Rho. Additionally, effects of this agent include inhibition of proliferation in tumors both with and without Ras mutations as well as effects on antiangiogenesis, apoptosis, and tumor microenvironment(7–9). Several pre-clinical 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 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 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): MTD was 600 mg bid for 21 days every 4 weeks in patients on EIAED, 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 (AUC) from 0–12 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 on or off EIAED favored those not on 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 glioblastoma.

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

prior to enrollment. Eligibility criteria also included KPS ≥60 and adequate hematologic and organ function. Patients were excluded from the study if they had significant existing medical problems, were pregnant or breast feeding. 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 (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 stay on 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 B. Later, in April 2005, as data revealed that combination treatment of radiotherapy and temozolomide (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 temozolomide. These patients on 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 be off the EIAED for a minimum of 2 weeks prior to enrollment.

Study Design

This study is a phase I dose-escalation trial to establish the MTD for tipifarnib in combination with radiation alone or chemoradiation in patients on or off EIAEDs. The study was also designed to define the safety profile of tipifarnib taken twice a day in this patient population. A secondary, exploratory objective was to assess antitumor activity against newly diagnosed glioblastoma as measured by PFS and overall survival (OS). See Figure 1 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 twice a day 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 5–9 days prior to 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 three 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 three additional patients would be opened at the next dose level as per Table 2. If one patient experienced a DLT, three more patients would be added to that dose cohort. The MTD was defined as the dose at which no more than one in six 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 B15.

Radiation Therapy

Radiotherapy was given by external beam to a partial brain field in daily fractions for 2 Gy, to a planned total dose of 60 Gy. 3D 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 MRI T2 or FLAIR abnormality plus a 2 cm margin receiving 46 Gy in 23 fractions, and a final cone-down volume defined by the T1 MR enhancement plus surgical cavity with a 1 cm margin receiving an additional 14 Gy. RT-QA 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/m2 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: Since DLT was determined over a 10-week period, after radiation, chemotherapy was not re-initiated until patients had been on trial for at least 10 weeks with the next planned cycle of tipifarnib. The first post radiation cycle was administered at 150mg/m2 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/m2 daily at 5/28 dosing.

Patient Evaluation

Pretreatment evaluation included a medical history and physical examination. Baseline tumor measurements by magnetic resonance imaging (MRI) or computed tomography (CT) were obtained within 21 days before study entry. Baseline hematologies and chemistries 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 prior to each cycle after completion of radiation therapy. MRI/CT was performed 4 weeks after the 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.

DLT was evaluated according to the National Cancer Institute Common Toxicity Criteria version 3. DLT 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 due to toxicity. Patients with progression prior to 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 due to death, or deteriorating condition.

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 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 US centers that were 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 grade 3 and 4 toxicities for each group whose attributions were possible, probable 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 also had similar rash characteristics. The rash resolved after discontinuation of tipifarnib and 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 one patient became non-compliant and withdrew from study prior to the evaluation period but had no toxicity.

Group B—Tipifarnib dose started at 400 mg bid and deescalated to 300mg 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 300mg bid, and 1 of 6 patients had a DLT of grade 3 CNS hemorrhage. In this cohort, 1 patient was replaced due to tumor progression and death prior to 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 one subject 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 1 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 one year after protocol registration and 13 patients survived beyond one 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 (PBMN) cells(22–23), one of the presumed anti-tumor 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 concomittant temozolomide 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 therapy. Grade 3 rash is the predominate DLT in this group. This rash was not limited to the radiation field only, but rather a rash 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 are related more to EIAED being given with radiation therapy rather than tipifarnib itself. We did not collect information on the type of rash, or 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.

Other than rash, CNS 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 3–4 toxicities of hematologic cytopenias and pulmonary embolism, but these DLTs were predominately limited to the Group A-TMZ cohorts.

Although the primary endpoint of this study was not clinical efficacy, we felt it might be insightful to report some of the clinical outcomes of the 20 patients treated in Group A-TMZ cohort as 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 on possible additive or inhibitory effect of tipifarnib on chemoradiation. Since 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 post-operative changes or radiographical pseudoprogression(27). The addition of temozolomide 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 use of new imaging criteria such as the RANO criteria(31).

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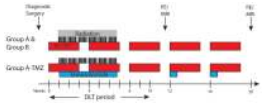

Figure 1.
Phase I Trial Schema. Abbrev.: R115777=tipifarnib, PE= physical examination, DLT=dose limiting toxicity evaluation.

Table 1

Patient Characteristics

	Group A		Group B	All
	No TMZ	With TMZ	No TMZ	
Number of Patients	10	20	21	51
Gender: 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: Median (Range)	52 (38–61)	52 (37–74)	58 (39–73)	54 (37–74)

Table 2

R115777 Dose Levels

Group A and Group A-TMZ			
Dose Level	**Dose**	**Schedule**	**Days Administered**
−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
Group B			
Dose Level	**Dose**	**Schedule**	**Days Administered**
−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

Table 3

Grade 3 and 4 adverse events

	Group A								Group B			
	No TMZ				with TMZ				No TMZ			
R115777 mg dose bid (No.)	**200 (3)**		**300 (7)**		**200 (7)**		**300 (13)**		**400 (4)**		**300 (17)**	
	No.	**AE Grade**	**No.**	**AE Grade**	**No.**	**AE Grade**	**No.**	**AE Grade**	**No.**	**AE Grade**	**No.**	**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

*AE occurring in same patient

DLT denoted as bold and shaded

^only one patient had rash develop in initial 10-week evaluation period

Table 4

DLTs

Cohort Groups	Dose Level	Patient #	DLT	DLT Type
Group A	1	3	none	NA
	2	7	one	Rash
Group B	2	4	two	Rash
	1	17	one	CNS Hemorrhage
Group A w/TMZ	1	7	one	Fatigue
	2	13	one	Rash