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Phase 1 trial of dasatinib plus erlotinib in adults with recurrent malignant glioma

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Abstract

To determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of dasatinib, an inhibitor of the Src family kinase proteins, with erlotinib, an epidermal growth factor receptor tyrosine kinase inhibitor, among recurrent malignant glioma patients. Once daily dasatinib was escalated in successive cohorts while erlotinib was administered daily at established doses based on concurrent CYP3A-inducing anticonvulsant (EIAEDS) use. Dasatinib pharmacokinetic analyzes were performed. Forty-seven patients enrolled including 37 (79 %) with grade IV and 10 (21 %) with grade III malignant glioma. Thirty patients (64 %) were at second recurrence, while 27 (57 %) had received prior bevacizumab. The dasatinib MTD was 180 mg when combined with either 150 mg of erlotinib for patients not on EIAEDs, or 450 mg of erlotinib for patients on EIAEDs. The most common DLTs were diarrhea and fatigue, while most adverse events were grade 2. Pharmacokinetic data suggests that dasatinib exposure increased with increased dasatinib dose and concurrent erlotinib administration, while concurrent EIAED use diminished dasatinib exposure. No radio-graphic responses were observed, and only one patient (2 %) remained progression-free at 6 months. We demonstrate that dasatinib plus erlotinib can be safely co-administered on a continuous, daily dosing schedule with erlotinib, and established the recommended dose level of this combination.

Keywords

Malignant glioma; Glioblastoma; Dasatinib; Erlotinib; Epidermal growth factor receptor (EGFR)

Introduction

Innovative, effective treatments are critically needed for patients with high-grade glioma, the most common, malignant primary tumor of the central nervous system. Aggressive, multimodality therapy achieves a 6.9 month median progression-free survival (PFS) and 14.7 months median overall (OS) survival for patients with newly diagnosed glioblastoma (GBM), the most common malignant glioma subtype [1]. Following recurrence, salvage therapies offer modest benefit [2–4].

Recent analyzes provide insight into the complex genetic abnormalities of GBM and underscore the critical role of aberrant signaling pathways in GBM cell proliferation, migration, angiogenesis and survival [5, 6]. The epidermal growth factor receptor (EGFR)

and Src family of kinases (SFK) contribute to these pathways and thus are attractive therapeutic targets for GBM.

Erlotinib, an oral, reversible EGFR tyrosine kinase inhibitor (TKI), is approved for recurrent non-small cell lung (NSCLC) [8] and pancreatic cancers [8]. Dasatinib, an oral BCR/ABL and Src family TKI, is approved for chronic myelogenous leukemia and Philadelphia chromosome-positive acute lymphoblastic leukemia [9]. We hypothesized that inhibition of EGFR and SFK may represent an active regimen for malignant glioma patients and designed the current phase I study to determine the maximum tolerated dose (MTD) and dose-limiting toxicity (DLT) of dasatinib when combined with erlotinib for these patients. In addition, we evaluated the impact of CYP3A enzyme-inducing anti-epileptic (EIAED) and erlotinib on dasatinib pharmacokinetics.

Patients and methods

Protocol objectives

The primary objective was to define the MTD and DLT of dasatinib plus erlotinib in adults with recurrent malignant glioma. Secondary objectives included to evaluate toxicity and to obtain dasatinib pharmacokinetic data.

Patient eligibility criteria

Patients were required to have histologically confirmed WHO grade III or IV malignant glioma that was progressive following prior radiation or chemotherapy. Additional enrollment criteria included: age at least 18 years; Karnofsky performance status (KPS) ≥ 70 ; stable corticosteroid dose for at least 1 week; hemoglobin ≥ 9 gm/dl; absolute neutrophil count (ANC) $\geq 1,500$ cells/ μ l; platelet count $\geq 100,000$ cells/ μ l; serum creatinine and bilirubin ≤ 1.5 times upper limit of normal (ULN); and serum aspartate aminotransferase (AST) ≤ 2.5 times ULN. Patients had to be ≥ 4 weeks from prior surgical resection (1 week from stereotactic biopsy), 12 weeks from prior radiation therapy (unless histologic confirmation of recurrent tumor or had new enhancing disease outside prior radiation field), 4 weeks from prior chemotherapy or investigational therapy, and recovered from toxicities associated with prior therapy. All patients provided informed consent.

Patients were excluded for: prior dasatinib or EGFR therapy; >3 prior episodes of progressive disease; pregnancy or nursing; refusal to use effective contraception if of reproductive potential; significant concurrent illness; or use of warfarin, rifampin or St. John's Wort.

Treatment plan and statistical design

Dasatinib (provided by Bristol-Myers Squibb) and erlotinib (provided by OSI Pharmaceuticals/Genentech, Inc) were orally administered on a continuous daily schedule of 28 days cycles. Dasatinib was initially administered alone for up to 7 days among patients who underwent pharmacokinetic sampling. Initial serum samples for dasatinib pharmacokinetics were obtained between days 3 and 7 of cycle one. On the following day, continuous daily erlotinib dosing began. For patients who did not undergo pharmacokinetic sampling, erlotinib began on day 1 of cycle 1 with dasatinib. Patients took dasatinib each morning with or without food. Patients were instructed to take their daily erlotinib dose as close to the dasatinib dose as possible, but 1 h before and 2 h after food.

Because erlotinib metabolism is enhanced by EIAEDs [10], patients were accrued to two strata (stratum A—patients not on EIAEDs; stratum B—patients on EIAEDs) that were independently escalated using a 3 + 3'' design. Erlotinib was dosed at 150 mg/day for

patients on stratum A, and 450 mg/day for patients on stratum B. The starting dose of dasatinib was 100 mg/day and was planned to increase to 140, 180, and 210 mg/day in consecutive cohorts for each stratum. If 1 DLT occurred among three initial patients, three additional patients were treated at that level. Dose escalation continued as long as no DLTs occurred in the additional three patients. The MTD was the highest dose causing no more than one DLT among six patients.

Dose-limiting toxicities included the following during cycle one: grade 4 neutropenia, grade 3 thrombocytopenia; grade 2 hemorrhage; >14 days delay in treatment due to related toxicity; and grade 3 related non-hematologic toxicities excluding inadequately treated grade 3 nausea or emesis. Toxicities were graded using the NCI CTC, version 3.0 and classified as study related unless attributable to tumor progression, concurrent medical condition or concomitant medication.

Prior to each cycle, patients underwent physical examination and serum chemistry panel evaluation. A complete blood count with differential was obtained weekly. A baseline urinalysis was obtained in all patients as was a beta human chorionic gonadotropin level in women of reproductive potential.

Response was assessed after each even cycle based neuro-imaging, and clinical factors that included steroid requirement and neurologic examination [11]. Kaplan–Meier curves were generated for PFS and OS, with each measured from the date cycle one began.

Dose modification and retreatment criteria

Criteria to initiate each cycle included: ANC ≥ 750 cells/ μ L; platelets $\geq 75,000$ cells/ μ L; AST and total bilirubin ≤ 2.5 times ULN; serum creatinine ≤ 1.5 times ULN and resolution of related toxicities to grade 1 except for rash, which required improvement to grade 2. Following resolution of any DLT to grade 1, dasatinib was resumed with a dose reduction by one level, and erlotinib was reduced by 50 mg/day for patients not on EIAEDs and by 100 mg/day for patients on EIAEDs. Patients who developed grade 4 rash or diarrhea, interstitial pneumonitis of any grade, or required >2 dose reductions discontinued study therapy.

Supportive care

Standard supportive care measures for rash and diarrhea were provided. Medications that inhibit CYP3A or prolong QT interval were prohibited. Gastric pH modifiers, including antacids, H-2 blockers or PPIs can affect dasatinib absorption [12]. Given the frequent administration of these medications to brain tumor patients, we attempted to limit the impact of these medications on dasatinib exposure by prescribing ranitidine (150 mg) once a day to all patients, to be taken at least 4 h after dasatinib. Routine use of other gastric pH modifiers was discouraged, but allowed with instruction to take them at least 4 h after dasatinib dosing.

Dasatinib pharmacokinetic analysis

Venous blood samples (4 mL) were collected prior to, and 0.5, 1, 2, 4, 6, 8, and 24 h after the daily dose on 1 day between days 3 and 7 of cycle 1 (prior to the initiation of erlotinib dosing), and on 28 of cycle 1. Plasma supernatants were separated by centrifugation ($1,000 \times g$ for 10 min at room temperature) and immediately frozen at -20°C . Plasma concentrations of dasatinib were determined by high-pressure liquid chromatography (HPLC) with tandem mass spectrometry detection.

Pharmacokinetic parameters, including maximum observed plasma concentration during the dosing interval ($C_{\max}$), time to reach maximum concentration ($T_{\max}$), area under the plasma concentration versus time curve from time 0 to 24 h (AUC_{0-24h}), and terminal plasma half-life ($t_{1/2}$), were derived from plasma concentration—time profiles using WinNonlin Version 5.0.1 (Pharsight Corporation, Mountain View, CA).

Erlotinib pharmacokinetic assessment was not performed; however, a recent report noted that escalating doses of dasatinib did not affect erlotinib pharmacokinetics among NSCLC patients [13].

Results

Patient characteristics

Forty-seven patients were enrolled (Table 1). Patient characteristics did not differ substantially between strata

All patients enrolled with progressive disease with approximately one-third enrolling at first, second and third recurrence, respectively. Twenty-four patients (51 %) were on dexamethasone including 16 patients on stratum A and eight patients on stratum B. The average dexamethasone dose was 3.9 mg/day (range, 0–40 mg/day). Twenty-seven (57 %) enrolled after receiving prior bevacizumab, while three had received prior VEGFR TKI. Two patients (4%) required initiation of proton-pump inhibitor therapy while on study due to gastroesophageal reflux. All patients have discontinued study therapy.

Dose-limiting toxicity

For stratum A, single patients developed DLT at each of the first three dose levels while one patient at dose level 4 developed dose-limiting diarrhea and acute renal failure, which reversed with appropriate medical therapy. For stratum B, single patients at dose level four developed fatigue and thrombocytopenia, respectively. Dose-limiting events that occurred in more than one patient included diarrhea ($n = 3$) and fatigue ($n = 2$) (Table 2). All DLTs were grade 3, except for one grade 4 event (fatigue). Dose level 3 (180 mg dasatinib) was determined to be the MTD for both strata.

Overall related toxicity

Eighty-eight courses were administered including 34 courses to patients on stratum A and 54 courses to patients on stratum B.

Rash ($n = 27$; 57 %), fatigue ($n = 17$; 36 %) and diarrhea ($n = 12$; 26 %) were the most common toxicities (Table 3). Most events were grade 2.

Pharmacokinetic analysis

Six patients from stratum A and five patients from stratum B had evaluable dasatinib plasma concentration data from both week 1 and day 28 of cycle 1 (Table 4). Three patients from stratum A received 140 mg/day dasatinib, one patient received 180 mg/day and two patients received 210 mg/day. For stratum B, three patients received 100 mg/day dasatinib while single patient were given 180 or 210 mg/day. Participation in pharmacokinetic testing was encouraged but not required, which contributed to limited compliance. Due to limited data at each dasatinib dose level, $C_{\max}$ and AUC_{INF} values were dose normalized for assessing the effect of concomitantly administered erlotinib and EIAEDs on dasatinib pharmacokinetics given that dasatinib exhibits dose proportional increases in AUC and linear elimination characteristics over the dose range of 15–240 mg/day.

In general, the dose normalized dasatinib $C_{\max}$ and AUC_{0-24h} values obtained in week 1 without co-administered erlotinib were lower in stratum B patients with concurrent use of EIAEDs compared to those in stratum A without EIAEDs (Fig. 1), suggesting that the CYP3A4 enzyme, which is a primary metabolic pathway for dasatinib in humans, was induced by EIAEDs. On average, $C_{\max}$ and AUC_{0-24h} levels obtained at day 35 of cycle 1 were 1.85 and 1.67-fold higher, respectively, than those obtained during week 1 for stratum A, suggesting that dasatinib exposures are increased by concurrent erlotinib administration (Table 4). For stratum B, the increase in $C_{\max}$ and AUC_{0-24h} on day 35 of cycle 1 were 4.21 and 2.57-fold higher than those obtained during week 1 of cycle 1. This effect was presumably due to the higher erlotinib dose (450 mg/day) and greater inhibition of dasatinib clearance by erlotinib in the presence of EIAED induction. Even with such an increase in stratum B, the dose normalized dasatinib exposure with erlotinib on day 35 of cycle 1 was still lower in general than stratum A, presumably attributed to the induction effect of concurrent EIAEDs on CYP3A4.

Outcome

For stratum A, best response was stable disease in two patients, who both progressed after 4 months, and progressive disease in all others. For stratum B, nine patients (38 %) achieved stable disease, but all progressed by 6 months except for one patient (GBM; treated on dose level 1) who progressed after 9 months of therapy.

With a median follow-up of 138.7 weeks (95 % CI, 66.0–159.9), the median PFS and PFS-6 for all patients were 4.3 weeks (95 % CI, 4.0–7.9 weeks) and 2.1 % (95 % CI, 0.2–9.8 %), respectively. Concurrent administration of EIAEDs did not appear to affect either PFS ($p = 0.15$) or OS ($p = 0.26$), respectively.

Discussion

Prospective clinical trials evaluating single-agent administration of inhibitors targeting mediators of cell signaling cascades have yielded disappointing results thus far among unselected malignant glioma patients [14–21]. Combinations of agents that inhibit separate yet interactive mediators of cell signaling cascades represent an attractive therapeutic strategy to achieve better outcome. Hence, targeting EGFR in combination with a SRC inhibitor provides an approach to inhibit key activators of the PI3/AKT and ras/MAPK pathways in malignant glioma. Recent preclinical studies support this hypothesis; specifically, dasatinib can sensitize KRAS mutant colorectal tumors to the EGFR monoclonal antibody, cetuximab [22].

Although EGFR is an attractive therapeutic target in GBM due to high rates of increased expression and EGFR gene amplification in 30–40 % [23], prospective clinical trials have demonstrated minimal anti-tumor benefit with first generation, EGFR TKIs, including erlotinib, among unselected recurrent malignant glioma patients [14–16, 18].

Although GBM cell lines and primary tumor samples lack SRC amplification or mutations [5], phosphorylated SRC and other SFK members are frequently detected [24–26]. Preclinical studies implicate SFK signaling in glioma growth, invasion and survival [24, 27–29]. Dasatinib is currently being evaluated for both recurrent and newly diagnosed GBM patients. Only one series has been published and included a retrospective cohort of 14 heavily pretreated, recurrent GBM patients who received dasatinib with bevacizumab continuation after prior bevacizumab failure. In this setting, dasatinib was inactive [30].

Our phase I study achieved its primary objective by establishing the MTD of daily dasatinib to be 180 mg when administered with erlotinib. Of note, 180 mg was also recently

determined to be the MTD in a phase I study among solid tumor patients [31]. The spectrum of toxicities, including DLTs, in our study was similar to those previously reported [9, 14, 16, 18, 32].

Our dasatinib pharmacokinetic data must be interpreted cautiously due to limited sampling. Nonetheless, we observed increased dasatinib exposure with dose and erlotinib dosing, while EIAEDs decreased exposure. Without co-administered erlotinib in week 1 of cycle 1 for three patients who were dosed with 100 mg dasatinib in stratum B, the geometric mean (CV %) $C_{\max}$ and AUC_{0-24h} of dasatinib were 13.6 (11.9 %) ng/mL and 106 (45 %) mg h/mL, respectively. These values are 71 and 51 % below the values obtained 5 days post 105 mg once per day dose of dasatinib in a Phase I dasatinib study (CA180-002, data on file), consistent with induction of CYP3A4, which is primarily responsible for dasatinib metabolism, by EIAEDs. The importance of CYP3A activity was confirmed in a recent phase I study in which dasatinib exposure was increased along with associated toxicity among patients who were co-administered ketoconazole, a known CYP3A inhibitor [31]. A recent in vitro study showed that erlotinib inhibits CYP3A in a substrate-dependent manner [33]. For three patients in Stratum A of our study who received 140 dasatinib and 150 mg erlotinib, respectively, the $C_{\max}$ and AUC_{0-24h} values of dasatinib on day 28 of cycle 1 were 284 and 110 % higher than those values obtained following administration of 140 mg/day dasatinib alone on day 5 in three patients treated on a separate phase I trial (CA180-002, data on file). Therefore, increased dasatinib exposure when concomitantly administered with erlotinib appears to be due to erlotinib's inhibition of CYP3A.

The solubility of dasatinib is pH-dependent and its absorption may be limited by co-administration of gastric pH modifiers [12]. This factor is of relevance to CNS tumor patients who are frequently on H2-blockers or proton-pump inhibitors. We attempted to limit the impact of gastric pH modifiers on dasatinib absorption by administering a single dose of ranitidine (150 mg) at least 4 h after dasatinib administration to all patients.

We observed minimal anti-tumor activity most likely due to the phase I design, the degree of patient pre-treatment, including prior bevacizumab therapy in over 50 %, and overall low dasatinib exposures. Limited anti-tumor was also recently reported for dasatinib and erlotinib among NSCLC patients [13]. Potential strategies to increase the anti-tumor activity of this regimen in future CNS tumor studies may include twice daily dasatinib dosing and enrollment of an enriched patient population that is predicted to benefit from SFK and EGFR inhibitors. In addition, evaluation of less heavily pretreated patients and those who have not progressed on bevacizumab may increase anti-tumor benefit. Finally, efforts to minimize the impact of co-administered gastric pH modifiers on dasatinib exposure is particularly relevant for malignant glioma patients.

Conclusion

We report the first clinical trial incorporating a combination regimen targeting EGFR and SFK among malignant glioma patients. In addition to establishing the MTD, we confirm that targeting EGFR and SFK can be safely performed among malignant glioma patients. Although combination regimens against interactive mediators of aberrantly activated cell signaling pathways represent an appealing therapeutic approach for many complex cancers including malignant glioma, careful evaluation of pharmacokinetic interactions and pharmacodynamic assessment of target inhibition, as well as the identification of an enriched patient subset with increased likelihood of response, will likely be required to increase the success of this approach.

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Fig. 1. Dose-normalized individual dasatinib C_{max} (a) and AUC_{0-24h} (b) following oral administration of dasatinib once per day without erlotinib in week 1 of cycle 1 and with erlotinib on day 28 of cycle 1 (*stratum A*: 150 mg erlotinib once per day without EIAEDs. **b** 450 mg erlotinib once per day with EIAEDs)

Table 1

Patient characteristics (% unless otherwise indicated)

Characteristic	Stratum A—not on EIAED	Stratum B—on EIAED	All
Number of patients	24 (51)	23 (49)	47
Median age (years)	56.7	49.1	51.2
Range	27.6–74.0	22.3–69.6	22.3–74.0
Gender			
Male	15 (63)	15 (65)	30 (64)
Female	9 (37)	8 (35)	17 (36)
Histology			
GBM	20 (83)	16 (70)	36 (77)
GS	–	1 (4)	1 (2)
AA	3 (13)	6 (26)	9 (19)
APXA	1 (4)	–	1 (2)
KPS			
90–100	11 (46)	13 (57)	24 (51)
80	10 (42)	4 (17)	14 (30)
70	3 (13)	6 (26)	9 (19)
Median time from original diagnosis to enrollment (weeks)	71.4	100.0	78.3
Range	42.0–376.0	20.0–411.4	20.0–411.4
Surgery prior to enrollment			
GTR	2 (8)	1 (4)	3 (6)
STR	–	1 (4)	1 (2)
Biopsy	–	–	–
None	22 (92)	21 (91)	43 (91)
Number prior progressions			
1	7 (29)	10 (43)	17 (36)
2	6 (25)	9 (39)	15 (32)
3	11 (46)	4 (17)	15 (32)
Prior bevacizumab			
Yes	15 (63)	12 (52)	27 (57)
No	7 (29)	10 (43)	17 (36)
Prior VEGFR2 TKI	2 (8)	1 (4)	3 (6)

AA anaplastic astrocytoma, APXA anaplastic pleomorphic xanthroastrocytoma, EIAED enzyme-inducing anti-epileptic drugs, GBM glioblastoma, GTR gross total resection, GS gliosarcoma, KPS Karnofsky performance status, STR subtotal resection, TKI tyrosine kinase inhibitor, VEGFR2 vascular endothelial growth factor receptor-2

Table 2

Dose-limiting toxicities by stratum and dose level

Stratum*	Dose level	# Patients treated	# Cycles administered	DLT	
				Type	Grade # Patients
A	1	6	6	Fatigue	4
A	2	6	10	Diarrhea	3 1
A	3	6	8	Diarrhea	3 1
A	4	6	10	Rash**	3 1
A	4			Acute renal failure***	3 1
A	4			Diarrhea**	3 1
B	1	6	15	None	
B	2	6	16	None	
B	3	5	11	None	
B	4	6	12	Fatigue	3 1
B	4			Thrombocytopenia	3 1

* A patients not on CYP3A enzyme-inducing anti-epileptics (EIAEDs: phenytoin, phenobarbital, carbamazepine, oxcarbazepine, primidone), B patients on EIAEDs

** All occurred in same patient

Table 3

Number of patients with treatment-related toxicity

Toxicity	Grade 2		Grade 3		Grade 4	
	A	B	A	B	A	B
Stratum *						
Anemia		1 (4) **				
Anorexia		1 (4)				
Creatinine increase			1 (4)			
Diarrhea	2 (8)	5 (22)	3 (13)	2 (9)		
Dyspnea	3 (13)		1 (4)			
Fatigue	4 (17)	7 (30)	3 (13)	2 (9)	1 (4)	
Infection	1 (4)	1 (4)				
Mucositis	2 (8)	2 (9)				
Nausea	3 (13)	4 (17)				
Neutropenia				1 (4)		
Rash	11 (46)	12 (52)	2 (8)	2 (9)		
Thrombocytopenia				1 (4)		
Transaminase elevation				1 (4)		

* Stratum: A includes patients not on CYP3A-enzyme inducing anti-epileptic drugs (EIAEDs); B includes patients on EIAEDs

** Numbers in parentheses indicate percentage of treated patients

Table 4

The ratio of dasatinib pharmacokinetic parameters following oral administration of dasatinib in week 1 of cycle 1 without erlotinib versus those on day 28 of cycle 1 with erlotinib

	Stratum A				Stratum B			
	T_{max}	C_{max}	AUC _{0-24h}	$t_{1/2}$	T_{max}	C_{max}	AUC _{0-24h}	$t_{1/2}$
N	6	6	6	6	5	5	4	4
Mean ratio	0.85	1.85	1.67	0.76	0.74	4.21	2.57	1.28
CV%	58	112	70	47	48	58	40	44

AUC_{0-24h} steady-state area under the concentration versus time curve from time 0 to 24 h, ng h/mL; C_{max} maximum steady-state concentration, ng/mL; T_{max} time to reach maximum concentration, hour; $t_{1/2}$ terminal elimination half-life, hour Stratum A: 150 mg erlotinib once per day without EIAEDs; B: 450 mg erlotinib once per day with EIAEDs