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A phase I trial of erlotinib in patients with nonprogressive glioblastoma multiforme postradiation therapy, and recurrent malignant gliomas and meningiomas†

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The objective of this phase I study was to determine the maximal tolerated dose (MTD) of erlotinib in patients with recurrent malignant gliomas (MGs) or recurrent meningiomas on enzyme-inducing antiepileptic drugs (EIAEDs). Dose escalation was by a standard 3 × 3 design. The initial starting dose of erlotinib was 150 mg daily. If no dose-limiting toxicity (DLT) was observed, then dose escalation occurs as follows: 200 mg/day, 275 mg/day, and then increased in 125 mg increments until the MTD was reached. The MTD was defined as the dose where ≤1 of 6 patients experienced a DLT and the dose above had 2 or more DLTs. The MTD was 650 mg/day; the observed DLTs were grade 3 rash in 2 patients at 775 mg/day. Pharmacokinetic analysis showed a significant influence of EIAEDs on the metabolism of erlotinib when compared with our phase II data published separately. Primary toxicities were rash and diarrhea. The MTD of erlotinib in patients receiving EIAEDs is substantially higher than the standard dose of 150 mg. This has important implications for further development of this drug in the treatment of MG as well as the optimal management of patients with other malignancies such as NSCLC who are on enzyme-inducing drugs.

Keywords: erlotinib, glioblastoma, glioma, meningioma, pharmacokinetics

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Malignant gliomas (MGs) are the most common primary brain tumor, with the vast majority in adults being malignant. Despite an aggressive therapeutic approach of surgery, radiation, and chemotherapy, survival remains poor[1] and options are few at recurrence or progression. The identification of growth factors and cell-signaling pathways involved in tumor biology warrants exploration of targeted therapies in this disease. Epidermal growth factor receptor (EGFR) is a tyrosine kinase receptor overexpressed in 40%–60% of MGs and plays an important role in gliomigenesis.[2,3] Preclinical data have shown that blocking EGFR inhibits glioblastoma (GBM) cell proliferation, invasion, and differentiation;[4,5] hence the rationale for targeting this receptor.

Erlotinib targets EGFR and EGFRvIII.[6,7] It is a synthetic quinazolinamine, undergoes significant hepatic metabolism, predominantly via the cytochrome P450 isoenzyme 3A4/3A5 and to a lesser extent by CYP1A2 and the extrahepatic isoform CYP1A1. Peak plasma levels occur 3–4 h after dosing with a bioavailability of approximately 60% after slow absorption; the time to reach steady-state plasma concentration is 7–8 days. Approximately 90% of erlotinib is bound to albumin and alpha-1-acid glycoprotein. The elimination half-life is approximately 36 h. Excretion is predominantly via the feces (83%), with renal elimination of the drug and metabolites accounting for 8% of the administered dose.[8,9]

There is increasing evidence that brain tumor patients receiving chemotherapy or targeted agents on enzyme-inducing antiepileptic drugs (EIAEDs) have lower plasma exposure, resulting from accelerated drug metabolism.[10,11] This drug–drug interaction may results in decreased levels of chemotherapeutic agents administered at conventional doses. Failure to achieve adequate plasma levels of such agents may be one reason for the lack of efficacy in past brain tumor trials. Since erlotinib is a substrate for the cytochrome P450, patients taking EIAEDs are likely to have increased drug metabolism, hence lower plasma levels of erlotinib and its metabolite OSI-420.

The goal of this phase I study was to define the maximum tolerated dose (MTD) and safety profile of erlotinib in patients with recurrent MGs, recurrent meningiomas, or patients with nonprogressive GBM post-RT, who are taking EIAEDs. The hypothesis was that the tolerated dose of erlotinib would be higher than the conventional 150 mg/d. Detailed pharmacokinetic (PK) analyses were performed to fully elucidate the influence of EIAEDs on the PK parameters of erlotinib. A phase II trial was performed in patients who were not on EIAEDs and reported on separately.

Patients and Methods

This protocol was IRB approved at all participating institutions and all patients were required to sign an informed consent prior to enrollment. Patients were $\geq$18 years old and with a life expectancy of $>$8 weeks. Patients must have a Karnofsky performance status of $\geq$60. All patients were required to have a histologically confirmed MG (GBM, anaplastic astrocytoma, anaplastic oligodendroglioma, or anaplastic mixed oligoastrocytoma) or meningioma with unequivocal evidence of tumor progression or recurrence on cranial imaging; patients with GBM post-RT were not allowed to have tumor progression. Patients with low-grade gliomas were eligible if their tumor had undergone malignant transformation confirmed by histologic analysis. Patients having undergone resection of their tumor at recurrence or progression were eligible after they recovered from surgery; evaluable or measurable disease was not required. All patients were required to have pretreatment brain CT or MRI within 14 days of starting therapy and to be on a stable steroid dosage for $\geq$5 days. The same type of brain imaging was required throughout treatment. All patients had to be on EIAEDs (phenytoin, carbamazepine, oxcarbazepine, phenobarbital, and primidone) to be eligible for enrollment.

Patients with radiographic progression of disease within 12 weeks of completion of radiation were required to have clear evidence of disease progression prior to starting erlotinib. If there was a question of radiation changes or necrosis, or for patients treated with interstitial brachytherapy or stereotactic radiosurgery, confirmation of true progressive disease was required, based either on brain imaging (PET, SPECT, MRS or MR perfusion) or tumor-tissue based pathological confirmation. Patients with recurrent MG and meningiomas were limited to 3 prior relapses and 2 prior treatments with chemotherapy or biologic agents. They must have recovered from the toxic effects of these therapies to grade 1 or less and as follows: 4 weeks from prior cytotoxic therapy but 2 weeks from vincristine, 6 weeks from nitrosoureas, 3 weeks from procarbazine administration, 1 week for noncytotoxic agents, for example, *cis*-retinoic acid and 4 weeks for other experimental biologic agents. For the cohort of patients with stable GBM, no prior chemotherapy (including gliadel wafers) was allowed and treatment would begin within 6 weeks of the completion of radiation. All patients were required to have adequate bone marrow function (WBC $\geq$ 3000/μl, ANC $\geq$ 1500/mm^3, platelet count of $\geq$100 000/mm^3, and hemoglobin $\geq$10 mg/dL), adequate liver function (SGOT and bilirubin $<$1.5 times ULN), and adequate renal function (creatinine $<$1.5 mg/dL) within 14 days prior to registration.

Patients with abnormalities of the cornea based on history, congenital abnormality, abnormal slit-lamp examination, or dry-eye syndrome were ineligible. Patients could not have any significant medical illnesses that would compromise their ability to tolerate this therapy. Known HIV-positive patients receiving combination antiretroviral therapy were excluded from the study due to potential drug interactions. Patients with a history of any other cancer (except nonmelanoma skin cancer or carcinoma in situ of the cervix), unless in complete remission and off of all therapy for that disease for $\geq$3 years, were ineligible.

Patients could not be pregnant or breast-feeding. Women of childbearing potential and men agreed to use adequate contraception (hormonal or barrier method of birth control) prior to study entry, for the duration of study participation and then 12 weeks after study completion.

Treatment

Erlotinib was supplied by the National Cancer Institute under the Division of Cancer Treatment and Diagnosis, Cancer Therapy Evaluation Program in a cooperative research and development agreement with Genentech and OSI Pharmaceuticals. The tablets were taken with an 8 ounce glass of water, 1 h before or 2 h after food, in the morning.

The starting dose was a continuous dosing schedule of 150 mg/day for patients in cohort 1. The following doses were to be used for subsequent cohorts: 200 mg/day, 275 mg/day, and then increased in 125 mg increments until the MTD was reached. The MTD was based on dose-limiting toxicity (DLT) observed during the first 28 days of treatment only. DLTs were assessed during the first 28 days of treatment in all patients. Patients completing 28 days of therapy or patients removed for toxicity earlier than 28 days were considered evaluable for toxicity; if patients were removed within 28 days for reasons other than toxicity they were replaced.

A standard 3 + 3 dose escalation scheme was used. Three patients in each dose level were observed for a DLT for 4 weeks from the first day of treatment before additional patients were enrolled at the next dose level. The following dose escalation rules were used: Three patients were studied at the first dose level; if none of the patients experienced a DLT, then the dose was escalated to the next higher level in the 3 subsequent patients. If 1 of the 3 patients experienced a DLT at the current dose, then 3 more patients were accrued to that level. If none of the 3 additional patients suffered a DLT, then the dose was escalated in subsequent patients. If 1 or more of the 3 additional patients experienced a DLT, the MTD was exceeded and 3 more patients were treated at the next lower dose (if only 3 patients were previously treated at that dose). The MTD was the dose at which 0/3 or 1/6 patients experienced a DLT with the next higher dose having at least 2/3 or 2/6 patients encountering DLT. DLT was defined as any of the following events occurring during the first 4-week course of treatment with erlotinib and attributable to the study drug: any grade 3 or 4 thrombocytopenia, grade 4 anemia and neutropenia, any nonhematologic grade 3 or 4 toxicity, or failure to recover from toxicities within 2 weeks of the last dose of erlotinib treatment. Intra-patient dose escalation was not permitted.

Toxicities were graded according to the NCI Common Toxicity Criteria (Version 2.0) scale. If multiple toxicities were seen, the presence of DLT was based on the most severe toxicity experienced.

Pretreatment and Treatment Evaluation

A complete history, neurological examination, brain imaging, and blood work were required within 14 days of starting therapy. Central pathology review was encouraged, but not mandated for confirmation of histology. All patients required a baseline ophthalmologic examination.

A CBC with differential and platelets and a comprehensive metabolic panel were performed every 2 weeks for all patients while on treatment. Patients on warfarin had a PT/INR checked every 1–2 weeks. A physical and neurologic examination occurred every 4 weeks and brain imaging every 8 weeks. Radiographic responses were evaluated at the local institution. Patients had a repeat ophthalmologic examination if they developed ocular symptoms.

PK Evaluation

Sample Collection.

Whole blood (3 mL) was collected in a sodium or lithium heparin-containing tube at the following times: baseline, 1, 2, 4, 6, 8, 12, and 24 h after administration of the first dose in cycle 1. Trough levels were obtained on day 8 and day 1 of cycles 2, 3, and 5. Blood samples were centrifuged within 30 min at 3000 rpm for 15 min to provide the plasma for analyses of erlotinib and OSI-420. Plasma samples were transferred to individually labeled tubes and stored at $\leq -20^{\circ}C$ until analysis.

Analytical Methods.

Concentrations of erlotinib and its *O*-demethylated isomeric metabolites (OSI-420/OSI-413, collectively called OSI-420) in plasma were analyzed using a validated liquid-chromatography mass-spectrometry method with atmospheric pressure chemical ionization in the positive ion mode as previously described.[12] The lower limit of quantitation of erlotinib and OSI-420 was 1 ng/mL. Analytical grade erlotinib and OSI-420 and the internal standard (CP-396,059) were obtained from OSI Pharmaceuticals (Boulder, CO).

PK Analyses

Erlotinib and OSI-420 plasma concentrations were analyzed by noncompartmental methods by J.G.K. The time interval relative to the administration of erlotinib and the actual sample times were used for the determination of the time to peak (t_{max}) and the estimation of the area under the plasma concentration-time curve (AUC_{0-24}) by the linear trapezoidal rule. Peak concentrations (Cp_{max}) were determined by the inspection of each individual's plasma concentration vs time curve. The extent of conversion of erlotinib to OSI-420 (relative metabolic ratio) was determined by dividing the metabolite AUC by the erlotinib AUC.

Statistical Consideration

PK parameters are reported as mean values $\pm$ *SD*. Differences between the EIAED and non-AEIAED

group with respect to the kinetic variables were evaluated using the unpaired 2-tailed "*t*"-test. Two-tailed probability values of $<.05$ were regarded as statistically significant. Relationship between dose and AUC was estimated by the Pearson product–moment correlation coefficient.

Response

Although response was not a study endpoint, it was assessed using the Macdonald criteria[13] to determine treatment continuation.

Results

Between August 15, 2002, and December 3, 2004, 32 patients were recruited onto this study (Table 1). There were 20 men and 12 women with a median age of 45 and Karnofsky performance score of 90. All patients had recurrent MG except 1 with a recurrent atypical meningioma and 1 with a nonprogressive GBM post-RT. Pathology was centrally reviewed in all but 7 patients, one of whom was ineligible. All patients failed prior RT, but one patient with a nonprogressive GBM post-RT started erlotinib after completion of RT. The number of prior chemotherapies ranged from 0 to 3 with a median of 1.5 (Table 1).

Toxicity and Response

Thirty-two patients were treated with erlotinib. The median number of cycles delivered was 2 (range 1–20); 7 patients received four more cycles of therapy. Although not an endpoint, response was assessed in 30 patients with 1 patient having a CR (GBM), 2 SD (1 nonprogressive GBM post-RT and 1 atypical meningioma), and 27 PD.

Table 1. Demographics ($n = 32$)

	Number
Median age	45 (19–76)
Median KPS	90 (60–100)
Men	20
Women	12
Histology	
GBM	21
Anaplastic astrocytoma	8
Anaplastic oligodendroglioma	2
Atypical meningioma	1
Prior treatment	
RT	32
Chemotherapy	
0	3
1	13
2	14
3	2

KPS, Karnofsky performance score.

Table 2. Number of patients per dose level and DLT per dose level

Dose level (mg)	Number of patients treated	Dose limiting toxicity	Toxicity
150	6	1	Rash
200	4[a]	0	
275	3	0	
400	3	0	
525	3	0	
650	6	1	DVT/PE
775	7[a]	2	Rash (2)

[a]One patient in each cohort was replaced because they received inadequate therapy to assess toxicity (1 noncompliance, 1 early PD).

Toxicity is reported for all patients, although 2 patients were deemed ineligible due to having 3 prior chemotherapies and not included in the toxicity analysis for MTD. Ineligible patients were replaced, 1 patient took drug for 10 days without toxicity, and the other had a grade 1 rash and grade 2 granulocytopenia while on the drug for 8 weeks. The DLTs in cycle 1 patients were grade 3 rash in 3 patients (1 at 150 mg/day dose level and 2 at 775 mg/day dose level), and 1 patient had a grade 3 DVT/PE (at the 650 mg/day dose; Table 2). With 2 DLTs (rash) in the 6 patients at the 775 mg/day cohort, the MTD in patients receiving EIAEDs was 650 mg/day. A total of 202 drug-related toxicities were reported in 27 patients while on erlotinib. There were a total of 81 reported toxicities in cycle 1 that were felt to be drug-related by the treating physician; some patients had multiple grades of the same toxicity. The most severe per patient toxicities for each dose level are listed in Table 3. Adverse effects were predictable, mainly rash and diarrhea. There were no treatment-related deaths.

PK Data

The mean ($\pm SD$) PK parameters for erlotinib and OSI-420 are summarized in Table 4. Comparison of the PK parameters at the 150 mg dose level between patients on non-EIAEDs from a parallel phase II trial reported separately (submitted concurrently with phase I) vs EIAEDs (this trial) indicates an effect of EIAEDs on the systemic disposition of erlotinib; we include relevant aspects of the phase II trial PK data for comparison purposes. Mean peak plasma concentrations of erlotinib and its metabolite were 1.5-fold lower and 1.6 higher, respectively, in the EIAED group compared with the non-EIAED group. The difference was only statistically significant ($P = .041$) for the metabolite. Steady-state trough levels for erlotinib and OSI-420 on day 1 of cycles 2 and 3 were both lower for the EIAED. The systemic exposure (AUC_{0-24}) to erlotinib at the 150 mg dose level was significantly ($P = .005$) lower in the EIAED group. There was a trend ($Rs = 0.278$, $P = .008$) in the EIAED for erlotinib AUC values to increase

Table 3. Number and drug related cycle 1 toxicities for each dose level

Dose level (mg/day)	Adverse event	Grade 1 (number of patients)	Grade 2 (number of patients)	Grade 3 (number of patients)
150	ALK PHOS increase	1		
	Anorexia	1		
	Desquamation/rash	1	1	1
	Granulocytopenia	2		
	Hypokalemia	1		
	Hyponatremia	1		
	Evaluated transaminases	1		
	Xerostoma	1		
200	Desquamation/rash	2		
	Diarrhea	1		
	Fatigue		1	
275	Desquamation/rash		1	
	Diarrhea	2		
	Fatigue	1		
	Headache	1		
	Hypophosphatemia		1	
400	Abdominal pain	1		
	Desquamation/rash		2	
	Diarrhea	2		
	Nausea	1		
	Stomatitis	1		
	Urticaria	1		
	Vomiting	1		
	Pruritus		1	
525	Desquamation/rash	3		
	Diarrhea	1		
	Fatigue	2		
	Hypophosphatemia	1		
	Hypertriglyceridemia	1		
650	Increased WBC	1		
	Desquamation/rash	1	2	
	Diarrhea	2		
	Dry skin	1		
	DVT/PE			1
	Hypophosphatemia		1	
	Stomatitis	1		
775	Desquamation/rash	1	2	2
	Diarrhea	3		
	Dizziness	1		
	Elevated transaminases	2		
	Fatigue	1	1	
	Leukopenia	1		
	Nausea	2		
	Pruritus	1		
	Rigors/chills	1		
	Stomatitis	1		
	Thrombocytopenia	1		

in a dose proportional manner over the range 150–775 mg. However, interpatient variability in AUC values was large with a coefficient of variation of 47% at the MTD of 650 mg. In the presence of EIAEDs, the relative extent of conversion of erlotinib to the active metabolite OSI-420 was increased 2.5-fold

Table 4. PK parameters of erlotinib and OSI-420

Group [number of patients]	Dose (mg)	Cp_{max} (ng/mL)		t_{max} (h)		AUC_{0-24}		MR	Erlotinib/OSI-420 trough levels (ng/mL)				
		Erlotinib	OSI-420	Erlotinib	OSI-420	Erlotinib (μg h/mL)	OSI-420 (ng h/mL)		C_1D_2	C_1D_8	C_2D_1	C_3D_1	C_5D_1
Non-EIAEDs [76] (phase II)	150	872 (±399) [76]	68 (±45) [76]	3.0 (±1.91) [76]	3.6 (±3.05) [76]	11.86 (±5.01) [74]	835 (±479) [74]	0.071 (±0.03) [74]	385/25 (±213) (±18) [74]	975/87 (±535) (±76) [61]	1059/100 (±551) (±111) [50]	1050/76 (±518) (±35) [30]	980/85
		(±368) (±38) [12]											
EIAEDs [6]	150	603 (±160) [6]	108 (±53) [6]	2.3 (±1.37) [6]	2.3 (±2.04) [6]	5.33 (±2.04) [5]	941 (±360) [5]	0.18 (±0.08) [5]	92/15 (±75) (±11) [5]	412/63 (±430) (±72) [5]	436/74 (±481) (±76) [4]	—	—
EIAEDs [4]	200	722 (±186) [4]	115 (±44) [4]	2.8 (±2.2) [4]	3 (±2.0) [4]	7.28 (±2.54) [4]	1274 (±487) [4]	0.18 (±0.03) [4]	1651/24 (±103) (±13) [4]	227/48 (±82) (±19) [3]	227/48 (±27) (±28) [3]	105/13 [1]	—
EIAEDs [3]	275	1075 (±308) [3]	122 (±35) [3]	3.3 (±1.2) [3]	4.0 (±2.0) [3]	13.58 (±2.99) [3]	1552 (±366) [3]	0.12 (±0.05) [3]	396/48 (±166) (±7.0) [3]	921/240 (±154) (±59) [2]	688/79 (±117) (±40) [3]	680/58 [1]	—
EIAEDs [2]	400	487 [1]	95 [1]	6 [1]	6 [1]	21.09 [1]	1838 [1]	0.09 [1]	440/29 [1]	634/143 [1]	—	763/59 [1]	745/61 [1]
EIAEDs [2]	525	2327 (±1609) [2]	507 (±508) [2]	3.5 (±3.54) [2]	3.5 (±3.54) [2]	25.94 (±21.6) [2]	5811 (±6445) [2]	0.22 (±0.05) [2]	591/137 (±425) (±156) [2]	1356/283 (±132) (±33) [2]	852/191 (±141) (±72) [2]	945/219 (±16) (±219) [2]	—
EIAEDs [6]	650	1351 (±441) [6]	266 (±75) [6]	2.2 (±0.98) [6]	2.8 (±2.56) [6]	15.77 (±7.43) [5]	2908 (±814) [5]	0.20 (±0.06) [5]	483/86 (±278) (±48) [6]	591/132 (±574) (±123) [5]	591/168 (±566) (±214) [5]	394/104 (±304) (±86) [3]	313/85 [1]
EIAEDs [5]	775	2009 (±1133) [5]	346 (±282) [5]	2.4 (±2.07) [5]	3.0 (±2.00) [5]	18.83 (±11.9) [4]	3572 (±3674) [4]	0.18 (±0.08) [4]	441/53 (±232) (±53) [5]	942/90 (±775) (±58) [5]	—	—	—

Abbreviations: Cp_{max}, peak plasma concentrations; t_{max}, time of Cp_{max}; AUC, area under the curve; PK, pharmacokinetic; EIAEDs, enzyme-inducing anti-epileptic drugs. Values expressed as mean ± *SD*. MR, metabolic ratio (OSI-420 AUC/Erlotinib AUC).

(non-EIAED mean ratio 0.071 vs 0.18 EIAED mean ratio).

Discussion

We completed a phase I trial of erlotinib in patients with recurrent MG, recurrent meningiomas, and nonprogressive GBM post-RT. The MTD of erlotinib in patients on EIAEDs is 650 mg/day; the DLT was grade 3 rash in 2 patients at 775 mg/day. The majority of drug-related adverse events were tolerable (grades I and II). The toxicities seen at our MTD were similar to that seen in other trials using erlotinib at 150 mg/day.

Erlotinib was chosen for a phase I and II (submitted concurrently with phase I) evaluation in this population based on the role of EGFR and EGFRvIII in gliomagenesis and preclinical activity showing that inhibition of these receptors can block key aspects of gliomagenesis.[6,7] In addition to defining the MTD in patients on EIAEDs, we assessed safety and PKs.

This trial confirms the effect of EIAEDs on the metabolism of agents metabolized through the CYP3A4 system. The MTD in patients on EIAEDs is 4.3 times greater than for lung cancer patients treated at 150 mg/day. The trend for neuro-oncologists is to avoid anticonvulsants that induce drug metabolism via the CYP3A4 system to minimize their effects on chemotherapeutic agents. This issue is important for medical oncologists who use agents like erlotinib that interact with EIAEDs and for patients who have brain metastases where undertreatment will occur if this interaction is not considered. The implication is that patients receiving treatment with agents that interact with EIAEDs will be under dosed. These data have important implications for drug interactions with any agent metabolized through the CYP3A4 system, although we have only studied EIAEDs.

In our study, the plasma exposure of erlotinib was significantly reduced in the EIAED patients by about 55% for the AUC_{0-24} following the first dose and 58% based on the day 8 trough levels. However, exposure to the metabolite OSI-420, which has similar activity inhibiting EGFR as erlotinib, was increased by 11% based on the AUC following the first dose. The extent of conversion of erlotinib to OSI-420 was increased by 2.5-fold in the presence of EIAEDs. Our data are comparable to those reported by Prados et al.[14], the interpatient variability and small numbers within each dose level likely account for differences. Given our MTD of 650 mg/day, they did not dose escalate beyond 500 mg/day for patients on EIAEDs so an MTD was not reached; the spectrum of toxicities seen was similar to this trial.

We conclude that the MTD of erlotinib in patients with MGs on EIAEDs is 4.3 times greater than the standard approved dose of 150 mg/day. The toxicities seen at our dose levels are comparable to those reported in at lower doses, mainly rash and diarrhea. The need for higher doses of erlotinib is important for lung cancer patients who are on EIAEDs, as failure to increase the daily dose will lead to suboptimal treatment of their systemic disease.

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