Cancer Chemother Pharmacol (2008) 62:387–392
DOI 10.1007/s00280-007-0616-3

ORIGINAL ARTICLE

The plasma and cerebrospinal fluid pharmacokinetics of erlotinib and its active metabolite (OSI-420) after intravenous administration of erlotinib in non-human primates

Holly J. Meany · Elizabeth Fox · Cynthia McCully · Chris Tucker · Frank M. Balis

Received: 12 July 2007 / Accepted: 19 September 2007 / Published online: 12 October 2007

Abstract
Purpose Erlotinib hydrochloride is a small molecule inhibitor of epidermal growth factor receptor (EGFR). EGFR is over-expressed in primary brain tumors and solid tumors that metastasize to the central nervous system. We evaluated the plasma and cerebrospinal fluid (CSF) pharmacokinetics of erlotinib and its active metabolite OSI-420 after an intravenous (IV) dose in a non-human primate model.
Methods Erlotinib was administered as a 1 h IV infusion to four adult rhesus monkeys. Serial blood and CSF samples were drawn over 48 h and erlotinib and OSI-420 were quantified with an HPLC/tandem mass spectroscopic assay. Pharmacokinetic parameters were estimated using non-compartmental and compartmental methods. CSF penetration was calculated from the AUC_{CSF}:AUC_{plasma}.
Results Erlotinib disappearance from plasma after a short IV infusion was biexponential with a mean terminal half-life of 5.2 h and a mean clearance of 128 ml/min per m^2. OSI-420 exposure (AUC) in plasma was 30% (range 12–59%) of erlotinib, and OSI-420 clearance was more than 5-fold higher than erlotinib. Erlotinib and OSI-420 were detectable in CSF. The CSF penetration (AUC_{CSF}:AUC_{plasma}) of erlotinib and OSI-420 was <5% relative to total plasma concentration, but CSF drug exposure was ~30% of plasma free drug exposure, which was calculated from published plasma protein binding values. The IV administration of erlotinib was well tolerated.
Conclusions Erlotinib and its active metabolite OSI-420 are measurable in CSF after an IV dose. The drug exposure (AUC) in the CSF is limited relative to total plasma concentrations but is substantial relative the free drug exposure in plasma.

Keywords Erlotinib · Pharmacokinetics · Cerebrospinal fluid · Non-human primate

Introduction

Erlotinib hydrochloride (OSI-774, Tarceva®) is an orally bioavailable small molecule that selectively and reversibly inhibits the tyrosine kinase activity of epidermal growth factor receptor (EGFR). Erlotinib inhibits EGFR autophosphorylation and thereby blocks multiple intracellular signaling pathways that promote cellular proliferation, resistance to apoptosis, tumor invasion and angiogenesis [5, 10, 15, 17, 21, 22, 24].

EGFR is over-expressed in a number of human cancers, including malignant gliomas and cancers that metastasize to the central nervous system, such as melanoma, breast cancer, and non-small cell lung cancer [6]. EGFR is therefore a potential therapeutic target in central nervous system tumors and responses to erlotinib have been observed in early phase clinical trials in patients with glioblastoma multiforme, especially those tumors expressing high levels of EGFR [2, 7, 8, 18–20, 22, 23].

E. Fox · C. McCully · F. M. Balis
Pediatric Oncology Branch, National Cancer Institute,
10 Center Drive, Bldg. 10 CRC, Bethesda, MD 20892, USA

H. J. Meany (✉)
Children's National Medical Center, Washington, DC, USA
e-mail: hmeany@cnmc.org

C. Tucker
OSI Pharmaceuticals, Boulder, CO, USA

In humans, erlotinib is eliminated by extensive CYP450-mediated metabolism to several inactive metabolites, as well as the active, *O*-demethylated metabolites, OSI-420 and OSI-413 [11]. OSI-420 and OSI-413 are indistinguishable in the pharmacokinetic assay and will be referred to as OSI-420 in this paper. After a low intravenous dose of 25 mg in healthy volunteers, the clearance of erlotinib is 75 ml/min and the terminal half-life is 13 h [4], and after a standard oral dose in cancer patients, the apparent clearance is 100 ml/min and the half-life is 24 h. Protein binding of erlotinib in human plasma is 92–95% [9].

In order to characterize the central nervous system pharmacology of erlotinib, we evaluated the plasma and cerebrospinal fluid (CSF) pharmacokinetics of erlotinib and OSI-420 after an intravenous dose of erlotinib in our non-human primate model, which is predictive of CSF pharmacokinetics of a variety of anticancer drugs in humans [14] and representative of drug concentration in the extracellular fluid of the brain [3].

Materials and methods

Drug

Erlotinib hydrochloride (Tarceva®, *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine, monohydrochloride; molecular weight 429.90 g/mole) was supplied by OSI Pharmaceuticals Inc. (Uniondale, NY) as a 10 mg/ml solution in Captisol (sulfobutylether-β-cyclodextrin, CyDex Inc., Lenexa, KS). A target erlotinib dose of 10 mg/kg, mean 10.1 mg/kg and range 8.4–11.1 mg/kg, was diluted in sterile water with 5% dextrose to 60 ml total volume and administered as a 1 h continuous intravenous (IV) infusion. The erlotinib dose was capped at 150 mg, accounting for the lower weight based dose administered to one animal.

Animals

Four adult male rhesus monkeys (*Macaca mulatta*), weighing 8.23–16.4 kg, were used for this study. The animals were group housed in accordance with the Guide for the Care and Use of Laboratory Animals and fed NIH Open Formula Extruded Non-Human Primate Diet twice daily. The experimental protocol was reviewed and approved by the National Cancer Institute's Animal Care and Use Committee. Animals received erlotinib as an IV infusion through a jugular venous port ($n = 2$ animals) or brachial vein ($n = 2$) and blood samples were drawn from a saphenous venous catheter on the side contralateral to drug administration. CSF samples were obtained from a temporary lumbar catheter ($n = 1$) or an indwelling Pudenz silicon catheter attached to a subcutaneously implanted Ommaya reservoir ($n = 3$). The reservoir was pumped four times prior to and after each CSF sample to ensure adequate mixing within the ventricle.

Experiments

One ml blood samples were collected in heparinized tubes prior to the start of the erlotinib infusion, 30 min into the infusion, at the end of the 60 min infusion and then 5, 15, and 30 min and 1, 2, 4, 6, 8, 10, 24, and 48 h after the completion of the infusion. The plasma was separated by centrifugation and stored at −70°C. CSF samples in 0.3 ml aliquots were collected prior to the start of the erlotinib infusion, 30 min into the infusion at the end of the 60 min infusion and then 15 min, 1, 2, 4, 6, 8, 10, 24, and 48 h after the completion of the infusion. CSF samples were immediately stored at −70°C. The first animal (9S6) to receive erlotinib did not have a ventricular reservoir in order to assess the safety and tolerability of intravenous drug administration before giving the drug to animals with indwelling Ommaya reservoirs. Therefore, CSF samples in this animal were obtained though a temporary lumbar catheter. The other three animals had an implanted Ommaya reservoir from which CSF was sampled.

Sample analysis

Plasma and CSF concentrations of erlotinib and OSI-420/413 were measured with a previously described isocratic, reverse-phase high-pressure liquid chromatography/tandem mass spectroscopy assay [4]. The lower limit of quantification for the parent drug and metabolites was 1 ng/ml and within-day and between-day values for precision and accuracy were <20% [25].

Pharmacokinetic analysis

The plasma and CSF pharmacokinetics of erlotinib and OSI-420 were analyzed by non-compartmental and compartmental methods. The area under the concentration curve (AUC_{0-last}) was calculated with the linear trapezoidal method and extrapolated to infinity ($AUC_{0-\infty}$) using the terminal rate constant derived from the slope of the natural log-transformed concentrations and times on the terminal elimination phase of the decay curve. Terminal half-life was calculated by dividing 0.693 by the terminal rate constant. Steady state concentration (C_{ss}) was estimated from the $AUC_{0-\infty}$, which is equal to the $AUC_{0-24\,h}$ at steady state, divided by the standard dosing interval (24 h). Erlotinib clearance was calculated by dividing the dose administered by the $AUC_{0-\infty}$. Volume of distribution at steady state and mean residence time were determined from the erlotinib area under the moment curve and $AUC_{0-\infty}$ with

correction for the duration of drug infusion. CSF penetration of erlotinib and OSI-420, expressed as a percent, was calculated from the AUC_{CSF}:AUC_{plasma} ratio. For erlotinib, the $AUC_{0-\infty}$ in the CSF and plasma were used to calculate the CSF penetration. For OSI-420, the AUCs in CSF and plasma to the last measured time point in CSF were used to determine the CSF penetration, because the limited number of measurable CSF concentrations on the decay portion of the curve did not allow for calculation of the terminal rate constant and half-life of OSI-420 in the CSF. Published values for protein binding were used to calculate the AUCs of free erlotinib and OSI-420 in plasma [9].

A three compartment model (a central and peripheral compartment for erlotinib and a single compartment for OSI-420) with first order exchange rate constants between the erlotinib central and peripheral compartments, first order conversion of erlotinib to OSI-420 and first order elimination of OSI-420 was fit using MLAB (Civilized software, Bethesda, MD) to the mean time-concentration data from two animals (G4 and 15398) that were similar in weight, received a similar dose of erlotinib and had complete sample sets which included data 48 h following drug administration. The purpose of the model was to explore the relative plasma clearance rates for the parent drug and metabolite after an intravenous dose. Model parameters included the volume of the central compartment for erlotinib (V_E), the elimination rate constant for conversion of erlotinib to OSI-420 (k_m), the inter-compartmental exchange rate constants for erlotinib (k_{cp} and k_{pc}), the volume of the OSI-420 compartment (V_M) and the elimination rate constant for OSI-420 (k_{me}). The model predicted clearance of erlotinib was derived from $V_E k_m$ and the clearance of OSI-420 was derived from $V_M k_{me}$.

Results

Table 1 lists the plasma pharmacokinetic parameters for erlotinib and OSI-420, and Fig. 1a shows the mean plasma concentration time profiles for the parent drug and its active metabolite. The plasma disappearance of erlotinib after the short IV infusion was bi-exponential, and the terminal portions of the erlotinib and OSI-420 curves were parallel. Plasma erlotinib concentration at the end of the 1 h infusion ranged from 3,310 to 6,150 ng/ml ($n = 3$). The mean (±SD) erlotinib C_{ss} was 1,040 ± 316 ng/ml, and the mean (±SD) terminal half-life was 5.17 ± 1.48 h. The $AUC_{0-\infty}$ ranged 18,708–35,663 ng h/ml, and the mean (±SD) clearance was 128 ± 22 ml/min per m^2, the mean (±SD) Vd_{ss} was 2.87 ± 0.65 l/kg and the mean (±SD) MRT was 7.06 ± 2.27 h.

OSI-420, the active erlotinib metabolite, achieved a mean peak plasma concentration of 755 ± 331 ng/ml, which occurred within 6–17 min of the end of the infusion

Table 1 Non-compartmental plasma pharmacokinetic parameters for erlotinib and OSI-420

Animal	Erlotinib							OSI-420			
	AUC_{0-last} (ng h/ml)	$AUC_{0-\infty}$ (ng h/ml)	EOI (ng/ml)	C_{ss} (ng/ml)	Half-life (h)	Clearance (ml/min per m^2)	Vd_{ss} (l/kg)	MRT (h)	AUC_{0-last} (ng h/ml)	$AUC_{0-\infty}$ (ng h/ml)	C_{max} (ng/ml)	Half-life (h)
9S6	35,500	35,700	5,850	1,490	6.72	98.1	2.86	9.71	17,900	20,200	1,250	7.71
G4	18,700	18,700	3,310	779	5.71	151	3.69	8.18	4,470	4,900	569	7.70
15398	20,600	20,600	6,150	857	5.05	124	2.85	5.29	2,420	2,450	586	4.05
RQ3561	24,700	24,800	5,920	1,030	3.21	138	2.09	5.06	4,580	4,750	613	5.21
Mean (±SD)	24,800 (±7,500)	24,900 (±7,600)	5,310 (±1,340)	1,040 (±320)	5.17 (±1.48)	128 (±22)	2.87 (±0.65)	7.06 (±2.27)	7,340 (±7,120)	8,080 (±8,170)	755 (±331)	6.17 (±1.83)

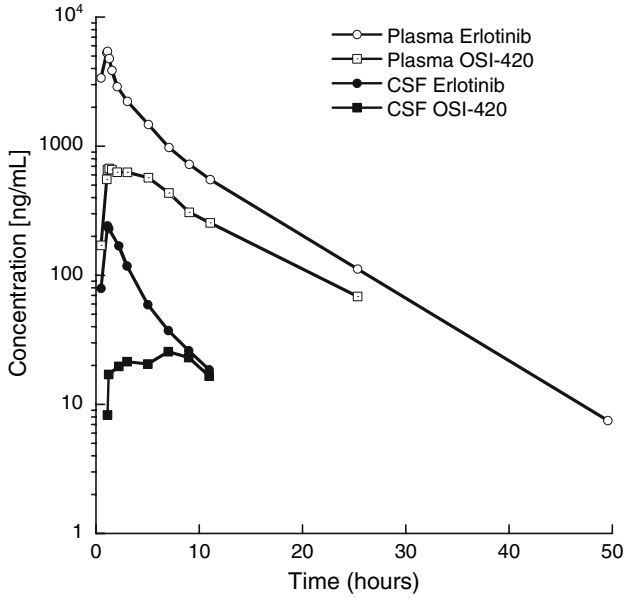

Fig. 1 Mean ($n = 4$) concentrations of erlotinib (*circles*) and OSI-420 (*squares*) in plasma (*open symbols*) and CSF (*closed symbols*)

in three animals and 4 h after the end of infusion in the fourth animal. The $AUC_{0-\infty}$ of OSI-420 was variable and ranged from 2,450 to 20,200 ng h/ml with a mean (±SD) of 8,080 ± 8,170 ng h/ml. The ratio of the OSI-420 to erlotinib $AUC_{0-\infty}$ (on a molar basis) ranged from 0.12 to 0.59 (mean ± SD, 0.30 ± 0.21). The mean (±SD) terminal half-life of OSI-420 was 6.17 ± 1.83 h.

A 3-compartment pharmacokinetic model was fit to the mean plasma erlotinib and OSI-420 concentrations from animals G4 and 15398. The volume of the central compartment for erlotinib was 0.83 l/kg and the volume of distribution for OSI-420 was 1.8 l/kg. The elimination rate constants for erlotinib (the rate of conversion of erlotinib to OSI-420) and OSI-420 were 0.58 and 1.6 h^{-1}, respectively, and the model predicted clearances of erlotinib and OSI-420 were 160 and 945 ml/min per m^2, respectively. The R^2 value for the model fit was 0.99 in both animals.

Erlotinib and OSI-420 were quantifiable in the CSF after IV administration. CSF pharmacokinetic parameters for erlotinib and its metabolite are presented in Table 2, and the mean CSF concentration profiles are shown in Fig. 1. Peak erlotinib concentrations occurred at the end of the infusion ($n = 1$) or with the first CSF sample after completion of the infusion ($n = 3$) and were detectable for 10 h after the end of the drug infusion. The peak concentration ranged from 136 to 402 ng/ml and mean (±SD) CSF half-life was 3.62 ± 0.64 h. The $AUC_{0-\infty}$ of erlotinib ranged from 485 to 1,574 ng h/ml, and the mean CSF penetration of erlotinib (from the ratio AUC_{CSF}:AUC_{plasma}) was 3.7 ± 0.8%.

OSI-420 was detectable in CSF samples that were drawn from a temporary lumbar catheter from the end of the erlotinib infusion through hour 20 in animal 9S6. This animal also had the highest plasma concentrations of erlotinib and OSI-420. In the remaining three animals, OSI-420 levels were detectable in CSF until 2 ($n = 2$) or 4 ($n = 1$) h after the end of the infusion. The mean peak CSF concentration was 23 ± 17 ng/ml measured 1 ($n = 3$) or 3 ($n = 1$) h after the end of the infusion. The mean CSF half-life of OSI-420 was 5.6 ± 2.0 h. The $AUC_{0-\infty}$ ranged 74–466 ng h/ml (mean ± SD, 188 ± 186 ng h/ml). The ratio of the CSF AUCs of OSI-420 to erlotinib (on a molar basis) ranged from 0.12 to 0.31 (mean 0.18). The AUC_{CSF}:AUC_{plasma} ratio for OSI-420 was 2.6 ± 1.2%.

IV administration of erlotinib was well tolerated in the four animals. During the first experiment, IV fluids were administered prior to and following drug infusion and a single dose of ondansetron was administered ~5 h post-infusion for nausea. There were no other complications in this animal and subsequent animals did not require an antiemetic.

Discussion

The CSF penetration of erlotinib and its active metabolite OSI-420 was <5% relative to total (protein bound + free) plasma drug exposure (AUC). However, the protein binding

Table 2 Non-compartmental cerebrospinal fluid pharmacokinetic parameters for erlotinib and OSI-420

Animal	Erlotininb				OSI-420			
	AUC_{0-last} (ng h/ml)	$AUC_{0-\infty}$ (ng h/ml)	C_{max} (ng/ml)	Half-life (h)	AUC_{CSF}: AUC_{plasma} (%)	AUC_{0-last} (ng h/ml)	C_{max} (ng/ml)	AUC_{CSF}: AUC_{plasma} (%)[a]
9S6	1,370	1,570	402	4.34	4.4	298	48.1	2.8%
G4	428	485	136	3.80	2.6	17.7	10.4	1.3%
15398	701	769	233	3.51	3.7	33.2	16.5	3.1%
RQ3561	902	976	232	2.81	3.9	47.1	17.2	2.1%
Mean (±SD)	851 (±398)	951 (±462)	251 (±111)	3.62 (±0.64)	3.7 (±0.77)	98.9 (±132.9)	23.1 (±17.0)	2.3% (±0.8)

[a] Calculations based on the AUC to the last measured time point in CSF

of erlotinib is 92–95% in humans [9] and cynomolgus monkeys, and 91% of OSI-420 is protein bound in human plasma. CSF is relatively protein free and is considered to be an ultrafiltrate of plasma [12]. Therefore, drug exposure and penetration of a drug into CSF should also be compared to free drug concentration in plasma. When corrected for the degree of plasma protein binding, the CSF penetration ranges from 46 to 73% for erlotinib and is 26% for OSI-420. For drugs like erlotinib that exert their pharmacologic effect through receptor binding, free drug concentration at the effect site is the primary determinant of the intensity of a drug's effect. The plasma drug exposure (AUC) of erlotinib measured in adults following administration of a standard 150 mg single oral dose is comparable to the AUC obtained with this model, that of the metabolite OSI-420 was 5-fold less in humans [4]. CSF penetration is measured as a percentage of systemic exposure; therefore, we would expect a similar CSF erlotinib concentration to be obtained with oral administration in humans. Therefore, despite the relatively low penetration of erlotinib and OSI-420 relative to total plasma concentration, the concentrations achieved in the CSF when viewed relative to free plasma concentrations may support the early encouraging clinical results with this agent in patients with CNS tumors. Erlotinib and OSI-420 are equipotent, and the combined concentrations of erlotinib + OSI-420 achieved in the CSF exceeded the IC_{50} (7.9 ng/ml or 20 nM) for the EGFR tyrosine kinase inhibition in intact tumor cells [15].

The CSF pharmacokinetics of erlotinib and OSI-420 after oral erlotinib were recently reported in a single 8-year-old patient who had a primary thalamic brain. CSF samples were obtained from a ventriculoperitoneal shunt that was externalized because of *Streptococcus viridans* meningitis [1]. The CSF penetration of erlotinib (7%) and OSI-420 (9%) was higher in this patient than in our model, but this may be explained by the effect of meningeal inflammation, which is known to enhance the CSF penetration of non-lipophilic anti-infective drugs [13, 16].

The clearance of erlotinib in the non-human primate (130 ml/min per m^2) was higher than the true clearance reported in humans (40 ml/min per m^2) who received a lower IV dose [4]. In addition, the OSI-420 to erlotinib $AUC_{0-\infty}$ ratio of 30% in non-human primates is greater than the 5% ratio reported in humans (21), indicating that the conversion of erlotinib to OSI-420 is more rapid in the primates. Our pharmacokinetic data predicts that the clearance of OSI-420 is more than 5-fold higher than that of erlotinib, and this accounts for the lower plasma concentrations of the active metabolite compared to the parent drug. OSI-420 concentrations were also lower in CSF than erlotinib and the penetration was slightly less.

In summary, erlotinib and its active metabolite OSI-420 are measurable in CSF after an IV dose. The drug exposure in the CSF is limited relative to total plasma concentrations but is substantial relative the free drug exposure in plasma. The ratio of active metabolite to parent drug in the non-human primates was greater than previously reported in humans and probably reflects interspecies differences in the rate of conversion of erlotinib to OSI-420.

References

1. Broniscer A, Panetta JC, O'Shaughnessy M, Fraga C, Bai F, Krasin MJ, Gajjar A, Stewart CF (2007) Plasma and cerebrospinal fluid pharmacokinetics of erlotinib and its active metabolite OSI-420. Clin Cancer Res 13:1511–1515
2. Cloughesy T, Yung A, Vrendenberg J, Aldape K, Eberhard D, Prados M, Vandenberg S, Klencke B, Mischel P (2005) Phase II study of erlotinib in recurrent GBM: molecular predictors of outcome. Am Soc Clin Oncol Ann Meeting Proc 23:Abst #1507
3. Fox E, Bungay PM, Bacher J, McCully CL, Dedrick RL, Balis FM (2002) Zidovudine concentration in brain extracellular fluid measured by microdialysis: steady-state and transient results in rhesus monkey. J Pharmacol Exp Ther 301:1003–1011
4. Frohna P, Lu J, Eppler S, Hamilton M, Wolf J, Rakhit A, Ling J, Kenkare-Mitra SR, Lum BL (2006) Evaluation of the absolute oral bioavailability and bioequivalence of erlotinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in a randomized, crossover study in healthy subjects. J Clin Pharmacol 46:282–290
5. Grunwald V, Hidalgo M (2003) Development of the epidermal growth factor receptor inhibitor OSI-774. Semin Oncol 30:23–31
6. Gullick WJ (1991) Prevalence of aberrant expression of the epidermal growth factor receptor in human cancers. Br Med Bull 47:87–98
7. Haas-Kogan DA, Prados MD, Tihan T, Eberhard DA, Jelluma N, Arvold ND, Baumber R, Lamborn KR, Kapadia A, Malec M, Berger MS, Stokoe D (2005) Epidermal growth factor receptor, protein kinase B/Akt, and glioma response to erlotinib. J Natl Cancer Inst 97:880–887
8. Halatsch ME, Schmidt U, Behnke-Mursch J, Unterberg A, Wirtz CR (2006) Epidermal growth factor receptor inhibition for the treatment of glioblastoma multiforme and other malignant brain tumours. Cancer Treat Rev 32:74–89
9. Hidalgo M, Bloedow D (2003) Pharmacokinetics and pharmacodynamics: maximizing the clinical potential of Erlotinib (Tarceva). Semin Oncol 30:25–33
10. Huether A, Hopfner M, Sutter AP, Schuppan D, Scherubl H (2005) Erlotinib induces cell cycle arrest and apoptosis in hepatocellular cancer cells and enhances chemosensitivity towards cytostatics. J Hepatol 43:661–669
11. Ling J, Johnson KA, Miao Z, Rakhit A, Pantze MP, Hamilton M, Lum BL, Prakash C (2006) Metabolism and excretion of erlotinib, a small molecule inhibitor of epidermal growth factor receptor tyrosine kinase, in healthy male volunteers. Drug Metab Dispos 34:420–426
12. Loscher W (1979) A comparative study of the protein binding of anticonvulsant drugs in serum of dog and man. J Pharmacol Exp Ther 208:429–435
13. Lutsar I, McCracken GH Jr, Friedland IR (1998) Antibiotic pharmacodynamics in cerebrospinal fluid. Clin Infect Dis 27:1117–1127, quiz 1128–1119
14. McCully CL, Balis FM, Bacher J, Phillips J, Poplack DG (1990) A rhesus monkey model for continuous infusion of drugs into cerebrospinal fluid. Lab Anim Sci 40:520–525

15. Moyer JD, Barbacci EG, Iwata KK, Arnold L, Boman B, Cunningham A, DiOrio C, Doty J, Morin MJ, Moyer MP, Neveu M, Pollack VA, Pustilnik LR, Reynolds MM, Sloan D, Theleman A, Miller P (1997) Induction of apoptosis and cell cycle arrest by CP-358,774, an inhibitor of epidermal growth factor receptor tyrosine kinase. Cancer Res 57:4838–4848
16. Nau R, Sorgel F, Prange HW (1998) Pharmacokinetic optimisation of the treatment of bacterial central nervous system infections. Clin Pharmacokinet 35:223–246
17. Normanno N, De Luca A, Bianco C, Strizzi L, Mancino M, Maiello MR, Carotenuto A, De Feo G, Caponigro F, Salomon DS (2006) Epidermal growth factor receptor (EGFR) signaling in cancer. Gene 366:2–16
18. Prados MD, Lamborn KR, Chang S, Burton E, Butowski N, Malec M, Kapadia A, Rabbitt J, Page MS, Fedoroff A, Xie D, Kelley SK (2006) Phase 1 study of erlotinib HCl alone and combined with temozolomide in patients with stable or recurrent malignant glioma. Neurooncology 8:67–78
19. Rao RD, James CD (2004) Altered molecular pathways in gliomas: an overview of clinically relevant issues. Semin Oncol 31:595–604
20. Razier J, Abrey L, Wen P, Cloushesy T (2004) A phase II trial of erlotinib (OSI-774) in patients (pts) with recurrent malignant gliomas (MG) not on EIAEDs. Am Soc Clin Oncol Ann Meeting Proc 22:Abst #1502
21. Sutter AP, Hopfner M, Huether A, Maaser K, Scherubl H (2006) Targeting the epidermal growth factor receptor by erlotinib (Tarceva) for the treatment of esophageal cancer. Int J Cancer 118:1814–1822
22. Tang PA, Tsao MS, Moore MJ (2006) A review of erlotinib and its clinical use. Expert Opin Pharmacother 7:177–193
23. Vogelbaum MA, Peereboom D, Stevens G, Barnett G, Brewer C (2004) Phase II trial of the EGFR tyrosine kinase inhibitor erlotinib for single agent therapy of recurrent Glioblastoma Multiforme: interim results. Am Soc Clin Oncol Ann Meeting Proc 22:Abst #1558
24. Woodburn JR (1999) The epidermal growth factor receptor and its inhibition in cancer therapy. Pharmacol Ther 82:241–250
25. Zhao M, He P, Rudek MA, Hidalgo M, Baker SD (2003) Specific method for determination of OSI-774 and its metabolite OSI-420 in human plasma by using liquid chromatography-tandem mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci 793:413–420