Cancer Chemother Pharmacol (2010) 66:53–58
DOI 10.1007/s00280-009-1133-3

ORIGINAL ARTICLE

A phase I dose-escalation and bioavailability study of oral and intravenous formulations of erlotinib (Tarceva®, OSI-774) in patients with advanced solid tumors of epithelial origin

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Received: 22 July 2009 / Accepted: 7 September 2009 / Published online: 3 December 2009

Abstract
Purpose An intravenous (IV) erlotinib formulation has not been characterized in cancer patients but may be useful in those with gastrointestinal abnormalities that impact on the ability to take oral medication. This study sought to determine the maximum tolerated dose (MTD) of erlotinib administered as a single 30-min infusion in patients with advanced solid tumors and absolute bioavailability of erlotinib tablets at matched doses.
Methods This was a two-center, open label, Phase I, dose-escalation and bioavailability study of single dose IV and oral erlotinib.
Results The highest escalated IV erlotinib dose achieved was 100 mg, with only mild adverse events reported. The MTD for IV erlotinib was not reached as a predetermined erlotinib plasma concentration cap of 4 μg/mL was exceeded in 3/6 patients. No dose-limiting toxicity was observed. Median bioavailability of erlotinib tablets was 76%.
Conclusions A 100 mg single IV dose of erlotinib, given as a 30-min infusion, was well tolerated with only minor adverse events and the high level of bioavailability of oral erlotinib was confirmed.

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Keywords Erlotinib · Intravenous · Bioavailability · Dose escalation

Introduction

Erlotinib (Tarceva®, OSI Pharmaceuticals, Melville, NY; Roche, Basel, Switzerland; Genentech, South San Francisco, CA, USA) is an orally active, potent selective inhibitor of the epidermal growth factor receptor (EGFR) tyrosine kinase [1]. It is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of at least one prior chemotherapy regimen, and in combination with gemcitabine for the treatment of patients with local advanced, unresectable, or metastatic pancreatic cancer.

The absolute bioavailability of oral erlotinib was previously determined in a randomized crossover study in healthy subjects [2]. This study compared the plasma $AUC_{0-\infty}$ of a single oral 150 mg erlotinib tablet with a single 25 mg erlotinib IV infusion given over 30 min. The IV dose of 25 mg was selected as the lowest dose that would provide the quantifiable erlotinib plasma concentrations necessary for this assessment. The results indicated that the terminal phase differed significantly between the two formulations, with a mean terminal half-life of 21.3 h following the oral dose and 13.1 h following IV administration, a difference attributed to faster clearance of erlotinib at the IV 25 mg dose compared with the oral 150 mg dose. Calculation of erlotinib bioavailability using noncompartmental methods resulted in a value of 106% (95% CI 99–114%). Data analysis using a two-compartment nonlinear model with a nonlinear elimination process provided what is considered a more accurate estimate of bioavailability of 59% (95% CI 55, 63%).

Intravenous administration of erlotinib has previously not been characterized in cancer patients. Here we present findings concerning single 30-min IV infusion of erlotinib in patients with advanced solid tumors of epithelial origin. Characterization of an IV formulation may be of clinical value for patients with gastrointestinal abnormalities, including inability to take oral medication, requirement for IV alimentation, active peptic ulcer, or prior surgical procedures affecting absorption. The objectives of the study were to determine the maximum tolerated dose (MTD) and recommended dose of erlotinib administered as a single 30-min infusion in patients; to determine the safety, tolerability, dose-limiting toxicities (DLT), and pharmacokinetic profile in this patient population; and to determine the absolute oral bioavailability of erlotinib tablets at matched doses.

Patients and methods

This was a two-center, open label, Phase I, dose escalation and bioavailability trial of single dose IV and oral erlotinib in patients with advanced solid tumors, conducted at the Christie and Royal Marsden Hospitals in the UK.

Patient eligibility

The study population comprised adult patients with advanced and/or metastatic solid tumors of epithelial origin either refractory to previous therapy, or not deemed candidates for further cytotoxic chemotherapy. It was considered appropriate to permit enrollment to a broad patient population and not restrict to the approved indication for single agent erlotinib of patients with previously treated NSCLC. Patients must have had a minimum of 21 days from last chemotherapy, and recovered from treatment-related toxicities. Patients had an ECOG PS ≤ 2, a predicted life expectancy of at least 12 weeks, and adequate hematopoietic, hepatic, and renal function. An entry criterion of patients refraining from smoking for 25 days (14 days prestudy and 11 days on study) was imposed to reduce the inter-patient variability of erlotinib pharmacokinetics given the known impact of smoking on erlotinib plasma clearance [3].

Research ethics committees of the participating centers approved the study before patient accrual, in accordance with regulatory and institutional guidelines. The study was conducted using good clinical practices and all patients provided written informed consent.

Study design and treatment

The dose-escalation schema utilized cohorts of at least three patients each, in which each patient received a single IV infusion of erlotinib (formulated in 6% [w/v] 6% aqueous Captisol® [CyDex Pharmaceuticals, Lenexa, KS] at a concentration of 10 mg/mL) over 30 min on day 1 followed by a matched single oral dose of erlotinib (supplied as 25 mg tablets) on day 8 for calculation of absolute oral bioavailability. Upon completion of each dose level cohort, the investigators and sponsor reviewed observed toxicities and erlotinib plasma levels to determine if dose escalation to the next cohort was appropriate. Dose cohorts were filled sequentially and doses were escalated in 25 mg increments when all patients at a given dose level completed a single IV infusion of erlotinib with acceptable tolerability in the first 7 days following treatment. The starting dose was 25 mg.

The MTD of the IV formulation was defined as the dose at which two of six patients experienced a DLT by day 7. The recommended IV dose of erlotinib was defined as one dose level below the MTD. A DLT was a toxicity considered related to study drug, occurring within the first 7 days of treatment and defined as either: a Common Terminology Criteria for Averse Events v3.0 (CTC) grade 3 or 4 toxicity (excluding alopecia or unpremedicated or inadequately treated nausea, vomiting, or diarrhea); or a CTC grade 3 AST and/or ALT for $\geq$7 days or CTC grade 4 AST and/or ALT. In addition, the occurrence of any CTC grade 3 or 4 toxicity had to also represent at least a 2-grade increase from baseline to be considered a DLT.

In the event an MTD was not established, an escalation cap was imposed of either a dose level of 200 mg or if two of three patients in a cohort had an observed erlotinib C_{max} of $\geq$4 μg/mL, whichever occurred first. The mean C_{max} following a 25 mg IV infusion in healthy adult subjects was 0.545 μg/mL. Assuming dose linearity, the mean C_{max} at 200 mg would be 4.36 μg/mL, which is below the 5.6 μg/mL plasma concentrations observed following a single oral 1,000 mg dose in humans and also below the C_{max} observed for the lowest IV dose (7 mg/kg) tested in dogs, approximately 5 μg/mL. The no observed adverse effect level (NOAEL) dose by this route was not established in dogs but was <7 mg/kg. Furthermore, if the pharmacokinetics of erlotinib were similar between the IV and oral routes when administered at similar doses, 200 mg given intravenously should be equivalent to a 338 mg dose administered orally (based on 59% absolute oral bioavailability).

The recommended IV dose of erlotinib was the dose level below the MTD. When the recommended dose of IV erlotinib was determined, 6–10 patients evaluable for PK were to be treated at this dose level to further evaluate the safety profile and pharmacokinetic profile.

At the investigators' discretion, patients could receive standard-dose (150 mg PO QD) oral erlotinib treatment after day 11.

Pharmacokinetic analyses

Pharmacokinetic samples were taken on days 1–3 and days 8–11 and plasma concentrations of erlotinib and its active metabolite, OSI-420, were determined using a previously reported validated LC/MS/MS (liquid chromatography with triple quadrupole tandem MS detection) assay [4]. Noncompartmental methods were used to calculate pharmacokinetic parameters: $AUC_{0-\infty}$, C_{max}, T_{max}, CL (IV only), V_{ss} (IV only), and oral bioavailability for each patient. Absolute oral bioavailability of erlotinib tablets was calculated as the ratio of erlotinib $AUC_{0-\infty}$ following a single IV dose on day 1 with that from the matched single oral dose on day 8. For $AUC_{0-\infty}$ values to be reportable there had to be sufficient data obtained in the terminal elimination phase such that less than 20% of the value was extrapolated.

Descriptive statistics (*N*, median, min, max, and geometric mean where appropriate) were calculated for pharmacokinetic parameters. Deviations from dose linearity of C_{max} and $AUC_{0-\infty}$ were tested using analyses of variance with trend tests.

Results

Patient characteristics

Between May and December 2005, 10 male and six female patients with advanced and/or metastatic tumors of epithelial origin were enrolled, (Table 1). All 16 patients had received prior chemotherapy; 50% received two or more prior regimens. Half of the patients had prior radiotherapy, 15 patients underwent prior disease-related surgery, and two patients received prior hormonal therapy, immunotherapy, or cytostatic therapy. Patients with a broad variety of tumor histologies were enrolled, with the most common tumor type being esophageal ($n = 4$).

Patients received at least 1 erlotinib dose in the following dose cohorts: 25 mg ($n = 3$), 50 mg ($n = 4$), 75 mg ($n = 3$), and 100 mg ($n = 6$). All 16 patients received the single IV erlotinib dose; however, only 15 patients completed the study, as one patient in the 50 mg cohort with a history of DVT discontinued on day 8 before starting the oral erlotinib dose due to an unrelated adverse event of DVT (see Fig. 1).

Toxicity

Table 2 presents an overall summary of safety during the 11-day pharmacokinetic phase of the study, which included the IV (days 1–7) and oral (days 8–11) dosing stages. Neither the single IV nor oral dose of erlotinib resulted in any notable toxicity, as evidenced by the absence of any grade 3/4 adverse events, treatment-related > grade 1 severity, serious adverse events, dose-limiting toxicities, or notable changes in laboratory values.

During the IV portion of the study, nine patients experienced adverse events, the most frequent being diarrhea (3 patients, 19%), vomiting, and anemia (2 patients each, 13%). Two patients experienced IV grade 1 erlotinib-related adverse events (injection site reaction and pruritus). During the oral portion of the study, eight patients experienced

Table 1 Patient demographics and disease characteristics

Characteristics	All cohorts ($N = 16$)
	n (%)
Gender	
Female	6 (38%)
Male	10 (63%)
Race	
White	15 (94%)
Other	1 (6%)
Age (years)	
Median	54
Min–max	24–74
18–39	2 (13%)
40–64	10 (63%)
≥65	4 (25%)
Prior chemotherapy regimens	
1	8 (50%)
2	3 (19%)
3	2 (13%)
4	3 (19%)

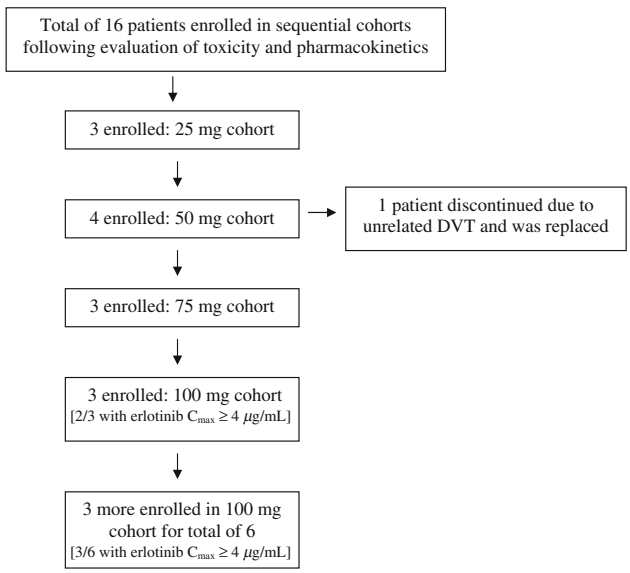

Fig. 1 CONSORT diagram

Table 2 Overall summary of safety—pharmacokinetic phase

	All cohorts IV $N = 16$ *n* (%)	All cohorts oral $N = 15$ *n* (%)
Patients with at least 1 AE	9 (56)	8 (53)
Patients with at least 1 treatment-related AE	2 (13)	3 (20)
AEs regardless of causality by worst severity		
Grade 1	6 (38)	4 (27)
Grade 2	3 (19)	4 (27)
Grade ≥3	0 (0)	0 (0)
Treatment-related AEs by worst severity		
Grade 1	2 (13)	3 (20)
Grade 2	0 (0)	0 (0)
Grade ≥ 3	0 (0)	0 (0)
Patients with at least one SAE	0 (0)	0 (0)
Patients with at least one treatment-related SAE	0 (0)	0 (0)
Patients who discontinued study due to AE	1 (6)	0 (0)
Patients who died on treatment or within 30 days	1 (6)	1 (7)
Patients who died due to a treatment-related AE	0 (0)	0 (0)

adverse events, with diarrhea and arthralgia (2 patients each, 13%) occurring most frequently. Three patients experienced grade 1 erlotinib-related adverse events during the oral phase, including one patient with dermatitis acneform, one with dry skin and pruritus, and one with diarrhea.

Determination of MTD and recommended IV dose

The protocol mandated that IV dose escalation would stop if two of three patients had an observed erlotinib C_{max} ≥4 μg/mL even if an MTD had not been reached. This capped C_{max} value was achieved at the 100 mg dose level, which was expanded to six patients. Three of the six patients had an observed erlotinib $C_{max} > 4$ μg/mL, therefore the study was closed and an MTD for IV erlotinib was not established.

Because no MTD was established, it was not possible to formally determine a recommended IV single dose of erlotinib. The 100 mg IV dose level, however, was well tolerated with only mild adverse events reported for the six patients at that level.

Pharmacokinetics

Pharmacokinetic data were collected and analyzed for 16 patients during the IV and oral portions of the study (Table 3). Of these, oral bioavailability of the erlotinib tablets could not be assessed for four patients. In two patients (both in the 25 mg cohort), the IV administration was interrupted by problems with the infusion pumps. Another patient did not have bioavailability calculated because there was >20% extrapolation in the $AUC_{0-\infty}$ following IV administration, and the final patient had only IV PK data as a result of study discontinuation prior to the administration of the day 8 oral dose.

Figure 2 illustrates median erlotinib plasma concentration versus time plots for the different dose cohorts using planned blood collection times**.** Median erlotinib plasma concentration versus time plots for the 100 mg IV and oral dose are shown in Fig. 3. Following the IV administration, median plasma C_{max} and $AUC_{0-\infty}$ of erlotinib increased with dose and did not significantly deviate from dose linearity, $P = 0.9144$ and $P = 0.1761$, respectively. The median plasma C_{max} and $AUC_{0-\infty}$ also increased with dose following oral administration and did not significantly deviate from dose linearity, $P = 0.9054$ and $P = 0.5053$, respectively. The median oral bioavailability of the erlotinib tablets was 76% (min–max of 47–131%) and appeared to be independent of dose.

OSI-420 plasma vs time profiles (not shown) were consistent with observations in previous studies. OSI-420 plasma concentrations tracked with parent concentrations over time and the median ratio of $AUC_{0-\infty}$ of OSI-420 to erlotinib across all doses was 6.2 and 7.3% following IV and oral administration, respectively, and appeared independent of dose.

Discussion

A maximum tolerated single IV dose of erlotinib was not determined in this study due to the cessation of dose escalation

Table 3 Non compartmental pharmacokinetics of erlotinib following IV and oral dosing

Parameter		IV				Oral			
		25 mg	50 mg	75 mg	100 mg	25 mg	50 mg	75 mg	100 mg
C_{max} (μg/mL)	*N*	1	4	3	6	3	3	3	6
	Median	0.683	1.32	1.56	4.07	0.252	0.473	0.542	1.25
	Min–max		0.848–10.7	1.03–2.11	1.69–6.67	0.251–0.376	0.262–0.834	0.346–0.936	0.341–3.46
	Geometric mean		1.99	1.50	3.75	0.288	0.469	0.560	1.16
T_{max} (h)	*N*	–	–	–	–	3	3	3	6
	Median	–	–	–	–	4.2	4	4	3.07
	Min–max	–	–	–	–	1.03–7.00	3.98–4.00	2.02–7.05	1.00–7.08
$AUC_{0-\infty}$ (μg h/mL)	*N*	1	4	2	6	3	3	3	6
	Median	2.97	8.62	13.2	32.0	3.10	3.20	11.5	29.9
	Min–max		4.85–24.4	11.3–15.0	13.9–48.0	2.61–8.71	3.15–16.0	7.04–14.8	7.30–45.4
Clearance (L/h)	*N*	1	4	3	6	–	–	–	–
	Median	8.41	7.13	6.64	3.12	–	–	–	–
	Min–max		2.05–10.3	5.00–6.64	2.08–7.21	–	–	–	–
Terminal half-life (h)	*N*	1	4	3	6	3	3	3	6
	Median	5.06	7.07	6.19	12.4	5.47	6.03	7.75	14.4
	Min–max		2.75–15.2	5.30–22.9	9.61–18.4	3.34–21.8	2.94–11.3	5.60–21.1	7.48–18.7
Volume of distribution (L)	*N*	1	4	3	6	–	–	–	–
	Median	56.0	43.1	67.0	60.7	–	–	–	–
	Min–max		20.7–117	40.7–203	30.1–95.0	–	–	–	–
Bioavailability (%)	N	–	–	–	–	1	3	3	6
	Median	–	–	–	–	104	65.6	113	89.9
	Min–max	–	–	–	–	–	64.3–65.9	47.0–131	52.6–111

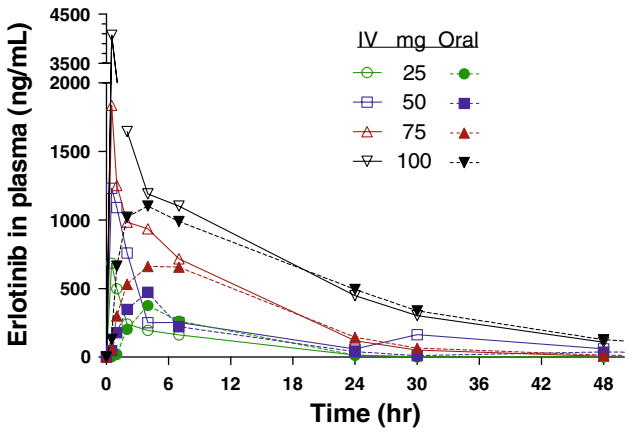

Fig. 2 Median erlotinib plasma concentrations versus time

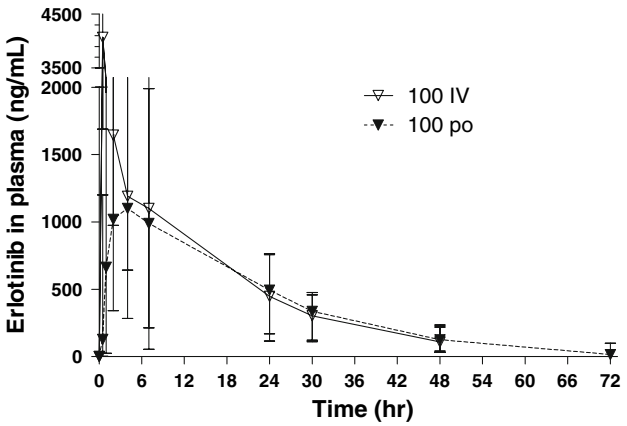

Fig. 3 Median (range) erlotinib plasma concentrations versus time (100 mg dose)

when patient's erlotinib plasma concentrations reached/exceeded a predetermined cap of ≥4 μg/mL. This cap was established as a conservative precaution based on observations from a repeat dose erlotinib toxicology study in dogs where a bolus IV administration of erlotinib at 15 mg/kg resulted in ataxia, tremors, salivation, transient decreased activity, and papillary dilation. In this dog study, apparent toxicity was observed following IV administration at exposures that were below those tolerated by dogs given oral erlotinib. This observation remains unexplained, and so to be conservative in humans, this cap was imposed. Human exposure to IV erlotinib prior to this trial was limited to 25 mg in healthy subjects and therefore did not provide a basis to set an exposure limit for this trial. Although a slower infusion did reduce the observed toxicity in dogs, the half-life in dogs is much shorter than in humans

(~2 vs. 24 h). So it was feasible to significantly impact the exposure in dogs by changing from IV bolus to 30 min infusion. To achieve similar effects in humans would require continuous infusion at a very slow rate or highly diluted solution for many hours.

The erlotinib maximum plasma concentrations in this preclinical study were in the 5–7 μg/mL range. When the dose was given as a 30-min infusion, the effects were reduced. The reasons for these effects are unknown and have not been observed in any other preclinical study, or in humans at plasma concentrations far in excess of these values (following oral erlotinib). Prior to the current Phase 1 study, the only tolerability data for IV erlotinib in humans was from the 25 mg single dose administered to healthy adult subjects [2]. The highest IV dose administered in the current study (100 mg) was well tolerated with only mild adverse events reported for the six patients at that level.

The pharmacokinetics of erlotinib and its active metabolite, OSI-420, showed high interpatient variability (plasma clearance IV CV 54.2%, and apparent oral clearance CV 66.9%) that is consistent with previous PK studies. Combined with the small numbers of patients exposed, this complicates data interpretation but some observations may still be made. For both routes of administration, erlotinib C_{max} and $AUC_{0-\infty}$ values did not deviate from dose proportionality. However, there are differences in the erlotinib terminal half-life at escalating doses over the dose range for the both routes of administration. Median half-lives for each dose level following IV administration ranged from 5 to 12 h with increasing dose and 5 to 14 h following oral doses. This supports the conclusion drawn in the healthy subject bioavailability study that this is a dose effect and not related to route of administration.

While statistically erlotinib C_{max} and $AUC_{0-\infty}$ values did not significantly deviate from dose proportionality, the erlotinib plasma concentrations observed at the 100 mg dose, both IV and oral, were about twofold higher than those observed at the 75 mg dose. These preliminary findings of IV dose proportionality require validation in a larger study given the high interpatient variability and small sample size. An earlier study, Hidalgo et al. [5] reported dose proportional changes in C_{max} and AUC across the dose range 25–200 mg of oral erlotinib.

Finally, this study confirmed the high level of oral absorption of erlotinib in cancer patients, median of 76%, consistent with the findings from the study in healthy subjects (59%).

Conclusions

A 100 mg single IV dose of erlotinib, given as a 30-min infusion, was well tolerated with only minor adverse events in this study of advanced cancer patients with solid tumors. The high bioavailability of oral erlotinib was confirmed when matched IV and oral doses were administered in this patient population.

Acknowledgments Authors Shaw, Reid and Judson gratefully acknowledge the support of the National Institute for Health Research, London, UK.

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