Epidermal growth factor receptor tyrosine kinase inhibitors: similar but different?

Yuri Rukazenkov, Georgina Speake, Gayle Marshall, Judith Anderton, Barry R. Davies, Robert W. Wilkinson, D. Mark Hickinson and Alan Swaisland

Two small-molecule epidermal growth factor receptor tyrosine kinase inhibitors, gefitinib and erlotinib, have been approved for the treatment of non-small-cell lung cancer. Here, we compare the pharmacology and pharmacokinetics of these agents, and reflect on how these properties may affect important clinical questions including the clinical efficacy, optimum dose, and whether there is a relationship between skin rash and clinical outcome for each of these agents. Gefitinib and erlotinib have similar mechanisms of action and pharmacological profiles; however, different molecular structures confer pharmacokinetic differences that may have important clinical implications. Although gefitinib 250 mg/day produces lower mean plasma concentrations and area under the plasma concentration versus time curve compared with erlotinib 150 mg/day, published data suggest that gefitinib significantly accumulates in tumour tissue. This difference may partly explain why it seems possible to achieve maximum clinical efficacy with gefitinib at doses significantly lower than its maximum tolerated dose and, hence, use of an optimal biological dose approach with this agent. We hypothesize that gefitinib is used and is effective at a dose below the maximum tolerated dose as it accumulates in tumour tissue, thus providing the concentration needed at its target to achieve effective epidermal growth factor receptor inhibition in the tumour while causing less skin toxicity than erlotinib; therefore, skin rash is not a useful predictive factor for efficacy with gefitinib. *Anti-Cancer Drugs* 20:856–866 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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AstraZeneca, Alderley Park, Macclesfield, Cheshire, UK

Correspondence to Dr Yuri Rukazenkov, AstraZeneca, Alderley Park, Macclesfield, Cheshire SK10 4TG, UK
Tel: +44 1625 582828; fax: +44 1625 514900;
e-mail: Yuri.Rukazenkov@astrazeneca.com

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Introduction

Epidermal growth factor receptor (EGFR) is a transmembrane receptor belonging to a family of four related proteins: EGFR (HER1), HER2, HER3 and HER4 [1]. Ligand binding to the extracellular portion of EGFR, HER3 or HER4 triggers the formation of functionally active heterodimers that result in receptor autophosphorylation and transphosphorylation through their intrinsic tyrosine kinase activity [2,3]. This receptor stimulation triggers intracellular pathways that, when misregulated, can result in tumourigenesis by abnormal cell proliferation, invasion, metastasis and inhibition of apoptosis [2]. EGFR and its ligands are commonly overexpressed in a number of epithelial tumour types and, as such, the EGFR is an attractive target for antitumour therapies [1].

The first EGFR small-molecule tyrosine kinase inhibitor (EGFR-TKI) to gain marketing approval was gefitinib (IRESSA, AstraZeneca, Macclesfield, Cheshire, UK). Currently, two small-molecule EGFR-TKIs, gefitinib and erlotinib (Tarceva, OSI Pharmaceuticals, New York, USA), have been approved for the treatment of non-small-cell lung cancer (NSCLC). Erlotinib is also approved for the treatment of pancreatic cancer in combination with gemcitabine. These molecules compete reversibly with ATP to bind to the intracellular catalytic domain of EGFR tyrosine kinase, thus inhibiting EGFR autophosphorylation and downstream signalling. Gefitinib and erlotinib were each compared with placebo in randomized, double-blind phase III studies in patients with pre-treated NSCLC [4,5]. Although both studies recruited patients who were considered ineligible for further chemotherapy, the gefitinib study required patients to be refractory to or intolerant of their latest chemotherapy regimen, but refractoriness was not an inclusion criteria for the erlotinib study; therefore, the gefitinib study recruited more patients who did not respond to the previous line of therapy. In the IRESSA Survival Evaluation in Lung cancer (ISEL) study, gefitinib 250 mg/day was associated with some improvement in survival, but this did not reach statistical significance in either the overall population or the subgroup of patients with adenocarcinoma [5]. In the BR.21 study, erlotinib 150 mg/day significantly improved survival compared with placebo [4]. The different outcomes of the BR.21 and ISEL studies have been

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widely debated and, despite the fact that the study patient populations differed, there is a misperception that it was because of a suboptimal dose of gefitinib [2,6,7]. More recently, two major phase III studies on NSCLC with gefitinib reported positive results using the same standard dose of gefitinib (250 mg/day), proving its equivalent efficacy with respect to overall survival versus docetaxel in pre-treated advanced NSCLC [8] and superior efficacy with respect to progression-free survival (PFS) versus doublet chemotherapy in highly selected chemo-naive patients [9]. Here, we review the pharmacology and pharmacokinetics of gefitinib and erlotinib and their clinical implications.

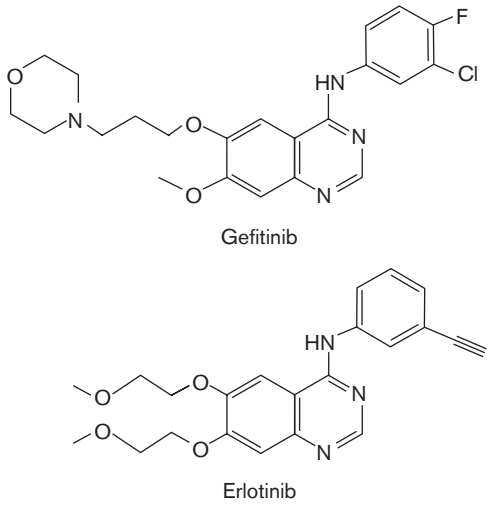
Structure of gefitinib and erlotinib

Both the marketed drugs erlotinib and gefitinib are based on the 4-anilino-quinazoline kinase pharmacophore. The structural differences between the two molecules lie in the aniline substituents, where erlotinib has an acetylene group and gefitinib a chlorine and fluorine, and in the quinazoline substituents where the major difference is the weakly basic side chain of gefitinib (Fig. 1). Crystallography studies suggest that both drugs bind EGFR in a similar manner at the ATP-binding pocket, with the aniline head group fitting into the selectivity pocket of EGFR [10,11]. The differences in the side chains of gefitinib and erlotinib may result in differing phamacokinetic profiles, as discussed later.

Pharmacology of gefitinib and erlotinib

Gefitinib and erlotinib have been shown to possess almost identical activities across a range of in-vitro and xenograft assays, suggesting that they have a similar pharmacological profile [12]. When examined in the same experiment, in-vitro enzyme analysis has shown that gefitinib and erlotinib have comparable K_i values against wild-type (1.79 and 3.86 nmol/l, respectively) and L858R mutant EGFR (1.22 and 4.76 nmol/l, respectively) and no significant differences in activity were found across an enzyme panel of more than 200 isolated targets (predominantly kinases) [12]. If any differential enzyme target inhibition by gefitinib and erlotinib exists, it did not translate into any significant difference in antitumour activity in cell lines or in a human tumour xenograft model. Gefitinib and erlotinib showed a high correlation in growth inhibitory activity across a panel of 34 NSCLC cell lines (Pearson's $r = 0.975$), including three cell lines harbouring activating EGFR mutations (Fig. 2) [12]. Similar activities were observed in other panels of cell lines, including head and neck [13,14] cancer. An assessment of pharmacodynamic biomarkers showed that gefitinib and erlotinib had a comparable dose response on: EGFR inhibition as shown by inhibition of pEGFR; cell proliferation measured by inhibition of BrdU uptake; and apoptosis (annexin V labelling) (Fig. 3) [12]. In-vivo studies using LoVo xenografts growing in nude mice found no significant difference between gefitinib and erlotinib in tumour growth inhibition (56 and 54%, respectively) when both drugs were dosed once daily at comparable levels based on tolerance [percentage body weight loss: $-2.2\% \pm 1.1$ (standard error) and $-1.5\% \pm 1.9$, compared with body weight of animal on day of selection to study, for gefitinib and erlotinib, respectively] (Fig. 4a) [12]. Analysis of LoVo tumour xenografts from treated animals indicated consistent pharmacokinetic/pharmacodynamic relationships for gefitinib and erlotinib with direct correlations between tumour levels of compound and inhibition of pEGFR pharmacodynamic activity (Fig. 4b). Overall, these direct comparisons of gefitinib and erlotinib under identical experimental conditions suggest that these two compounds have very similar pharmacological activities.

Fig. 1



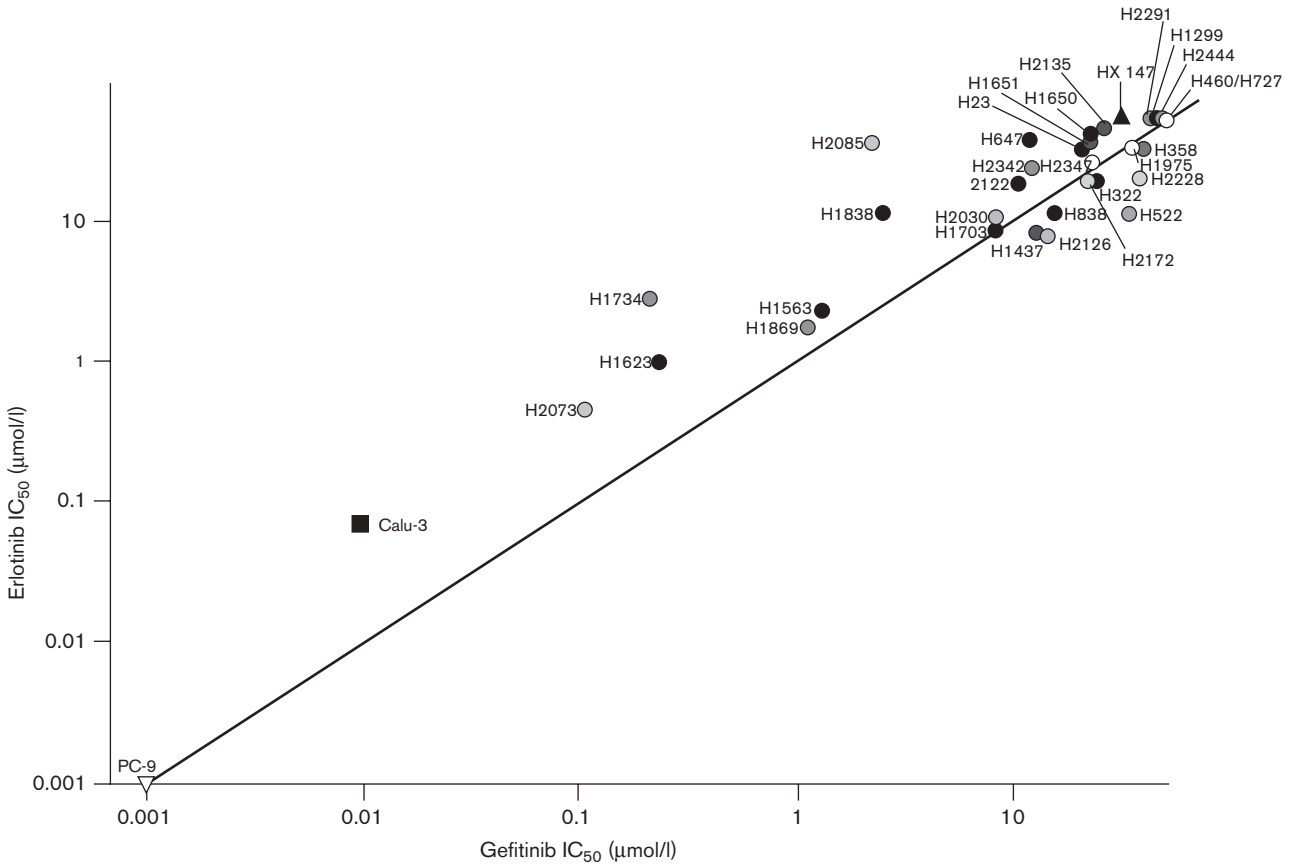
Structural comparison of gefitinib and erlotinib.

These results are consistent with those of earlier studies that determined the in-vitro and in-vivo potency of either gefitinib [15] or erlotinib [13,16]. However, as both drugs are competitive inhibitors of EGFR tyrosine kinase, their inhibition effect depends on the ATP concentration in the assay, which makes cross-comparisons between different publications difficult to interpret.

Pharmacokinetics of gefitinib and erlotinib

The key pharmacokinetic parameters for both gefitinib and erlotinib in humans are summarized in Table 1. In humans, orally administered gefitinib is absorbed fairly slowly, with maximum plasma concentrations generally occurring 5–7 h after the dose. The extent of absorption is high and the absolute bioavailability from the 250-mg tablet is approximately 60% in healthy volunteers and

Fig. 2



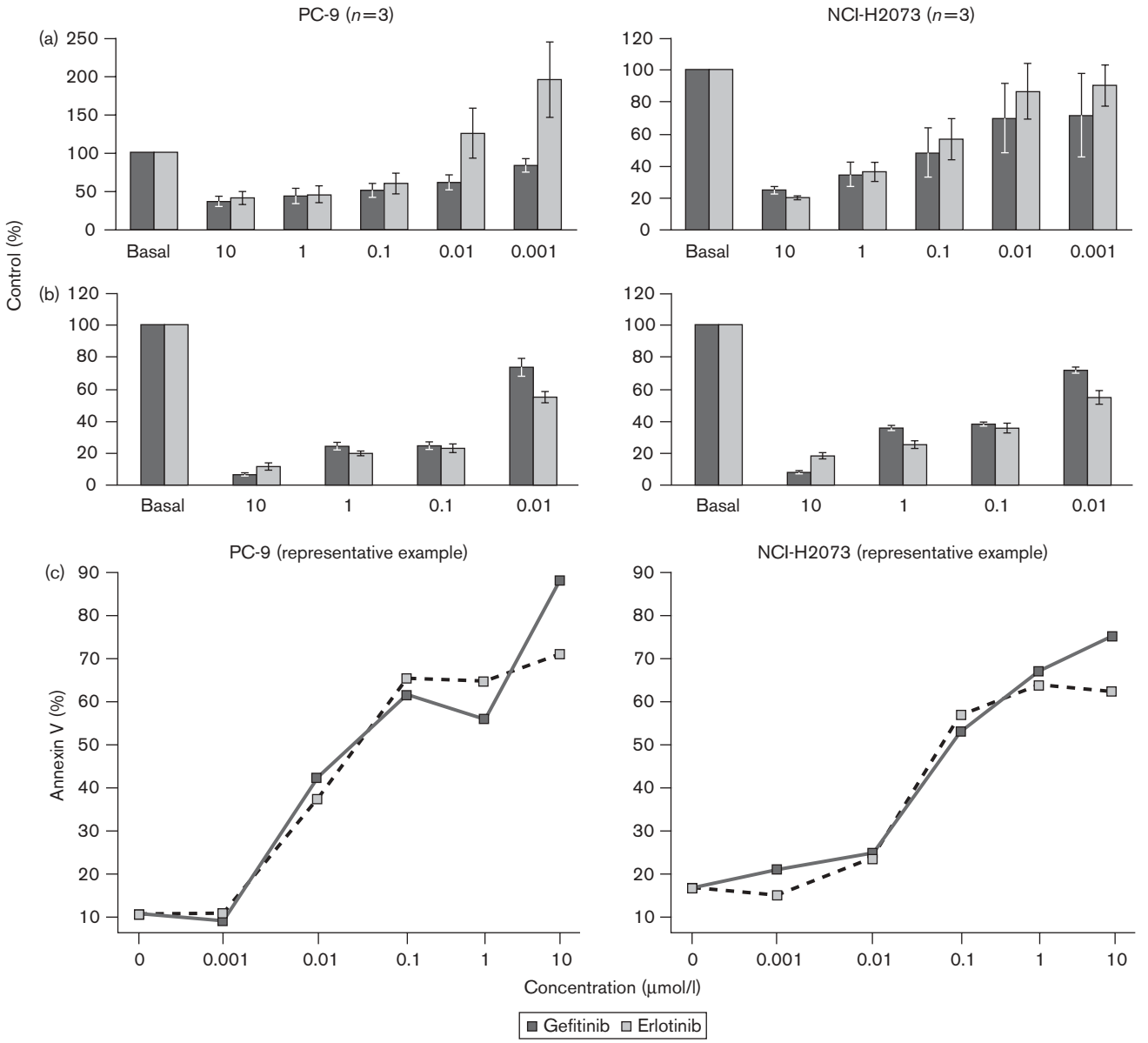
Activities of erlotinib and gefitinib across a panel of non-small-cell lung cancer (NSCLC) cell lines. NSCLC cell lines were seeded at 2500 cells/well in 96-well plates [12]. The cells were allowed to settle for 4 h before treatment with a range of concentrations of gefitinib and erlotinib (0–50 μmol/l). After incubation for 96 h, viable cell number was assessed using an MTS endpoint [using the CellTiter 96 AQ_{ueous} One Solution Cell Proliferation Assay (Promega, Madison, Wisconsin, USA; #G1111) as per the manufacturer's instructions]. The IC_{50} for gefitinib and erlotinib were calculated using Origin software (Northampton, Massachusetts, USA). All are NCI cell lines with the exception of PC-9, Calu-3, and HX147.

cancer patients [17]. Erlotinib absorption is more rapid (t_{max} 2–4 h) [21], but the absolute bioavailability is similar [18]. Administration of gefitinib with food results in a small (35%) increase in bioavailability that is not considered clinically relevant [17]. In contrast, food leads to a doubling of the area under the plasma concentration versus time curve (AUC) for erlotinib after a single dose [19], leading to the recommendation to take the erlotinib tablet 1 h before or 2 h after a meal [37].

Gefitinib has a high systemic clearance (about 40% hepatic blood flow) but, because of the high volume of distribution (1400 l in cancer patients), plasma concentrations are maintained over a relatively long period resulting in a terminal half-life of about 2 days in cancer patients [17]. Erlotinib has a somewhat different profile, with a lower systemic clearance (4.4 l/h calculated from Frohna *et al.* [18]) and a much lower volume of distribution than gefitinib, variously quoted values as 136 l [21], 233 l [22,23] and 131 l [24], though the comparability between the value for gefitinib derived after intravenous administration and that for erlotinib after oral administration is questionable. The lower distribution and clearance for erlotinib combine to produce a half-life of 36 h [22], although shorter half-lives have been reported, mainly in studies in healthy volunteers [18,31,19,34].

Gefitinib and erlotinib are cleared mainly by metabolism and subsequent biliary excretion [30,29]; urinary clearance is minimal. In-vitro studies have shown that gefitinib is mainly metabolized by CYP3A4 with minor contributions from CYP2D6 and CYP3A5 [27]. Subsequent reports suggest that gefitinib may be metabolized by the predominantly extra-hepatic CYP1A1, although the quantitative contribution to gefitinib metabolism is unknown [28]. CYP2D6 is responsible for the formation of *O*-desmethyl gefitinib and this metabolite is absent in individuals expressing the CYP2D6 'poor metabolizer' genotype [38]. Erlotinib is also

Fig. 3

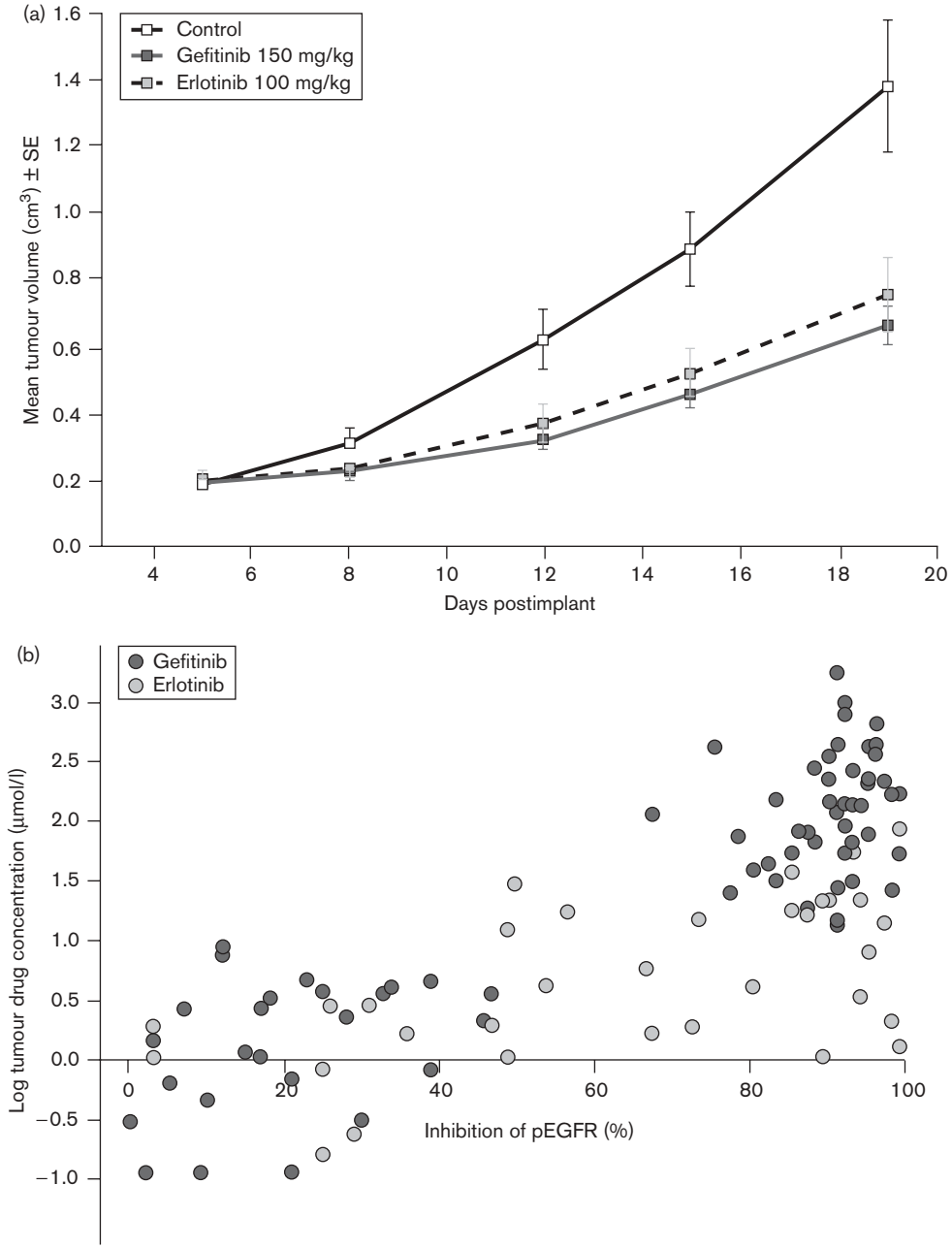


Effects of gefitinib and erlotinib on (a) epidermal growth factor receptor (EGFR) activity as shown by inhibition of pEGFR, (b) cell proliferation as shown by BrdU uptake and (c) apoptosis as shown by annexin V labelling [12]. PC-9 (expresses mutated EGFR delE746-A750) and NCI-H2073 (expresses wild-type EGFR) NSCLC cell lines seeded at 2500 cells/well were incubated with 0–50 μmol/l of gefitinib or erlotinib for 96 h. Pharmacodynamic biomarkers associated with EGFR activity, proliferation and cell cycle progression were analysed according to the manufacturer's instructions: EGFR DuoSet ELISA kit from R&D Systems (Minneapolis, Minnesota, USA; #PYC1095–5); BrdU ELISA kit from Roche (Basel, Switzerland; #11647229001); Annexin V-PE (phycoerythrin) from BD Biosciences Pharmingen (San Diego, California, USA; #556421).

metabolized predominantly by CYP3A4, with contributions from CYP1A2 and the extra-hepatic CYP1A; CYP2D6 is not involved [28]. Simulations using SimCYP [34] indicted that 70% of erlotinib clearance is by CYP3A4 and 30% by CYP1A2.

An in-vitro study also showed that gefitinib weakly inhibits CYP2D6 [32]. A clinical study using metoprolol as a probe substrate for this isozyme suggested little potential for interactions with drugs dependent on CYP2D6-mediated metabolism for their clearance [32]. Drug–drug interaction studies in healthy volunteers showed that gefitinib plasma concentrations are increased by approximately 80% in the presence of itraconazole, a potent CYP3A4 inhibitor. This increase may be clinically relevant, as adverse experiences are related to dose and exposure. The combination of a single dose of gefitinib with rifampicin, a potent CYP3A4 inducer, resulted in an

Fig. 4



(a) Activity of gefitinib and erlotinib against the LoVo xenograft model [12]. Female nude mice were implanted subcutaneously with 1×10^7 LoVo cells per mouse. Tumours were grown for 5 days before animals were selected and randomized into groups. Animals were gavage dosed with gefitinib (150 mg/kg) or erlotinib (100 mg/kg) for 14 doses and tumour volume was measured twice weekly using callipers.
(b) Pharmacodynamic comparison of gefitinib and erlotinib in LoVo xenografts. Log tumour drug concentrations are plotted against the percentage inhibition of phosphorylated epidermal growth factor receptor (pEGFR), determined by ELISA (Biosource, Paisley, UK; #KMR9081) according to the manufacturer's instructions.

average 83% reduction in the plasma AUC [32]. Thus, comedication with other CYP3A4 inducers (e.g. phenytoin, carbamazepine, barbiturates, or St John's Wort) may potentially reduce efficacy. Similar properties have been observed for erlotinib, where an 86% reduction in AUC was produced by the CYP3A4 inhibitor ketoconazole [34] and a 67% decrease in AUC resulted from treatment with rifampicin [33]. Erlotinib pharmacokinetics have been shown to be affected by smoking [31] and this has been linked with the involvement of CYP1A1 and CYP1A2 in erlotinib clearance. Studies in healthy volunteers suggested that much of the loss in erlotinib exposure in

Table 1 Key pharmacokinetic parameters of gefitinib and erlotinib in humans

	Gefitinib at 250 mg/day	Erlotinib at 150 mg/day
Bioavailability	59% [17]	60% [18]
	No clinically significant effect of food [17]	Food increases bioavailability by up to 100% [19]
Volume of distribution at steady state, mean	1400 l in cancer patients [20]	131–233 l [21–24]
AUC_{ss}	5.0–5.7 μg h/ml[a] [25]	15.2 (10.4–22.1) μg h/ml [26]
Metabolism	No significant active metabolites [20]	Two active metabolites (5% of total) [26]
	Primarily by CYP3A4 [27]	Primarily by CYP3A4 and, to a lesser extent, by CYP1A2 [28]
Elimination		
route	Through faeces, <4% urine [29]	>90% through faeces, 9% urine [30]
$t_{1/2}\beta$ Effect of smoking	41 h (mean) [20]	36 h (median) [22]
	Appears to be no effect (AstraZeneca, Data on File 2009)	Increases clearance [31]
Drug interactions	CYP3A4 inducer/inhibitor reduces/increases exposure [32]	CYP3A4 inducer/inhibitor reduces/increases exposure [33,34]
	Limited potential to inhibit CYP2D6 [32]	
MTD	800–1000 mg/day [35,36]	150 mg/day [21]

AUC_{ss}, area under the curve at steady state; MTD, maximum tolerated dose; $t_{1/2}\beta$, terminal elimination half-life.
[a]At doses of 225 and 300 mg/day.

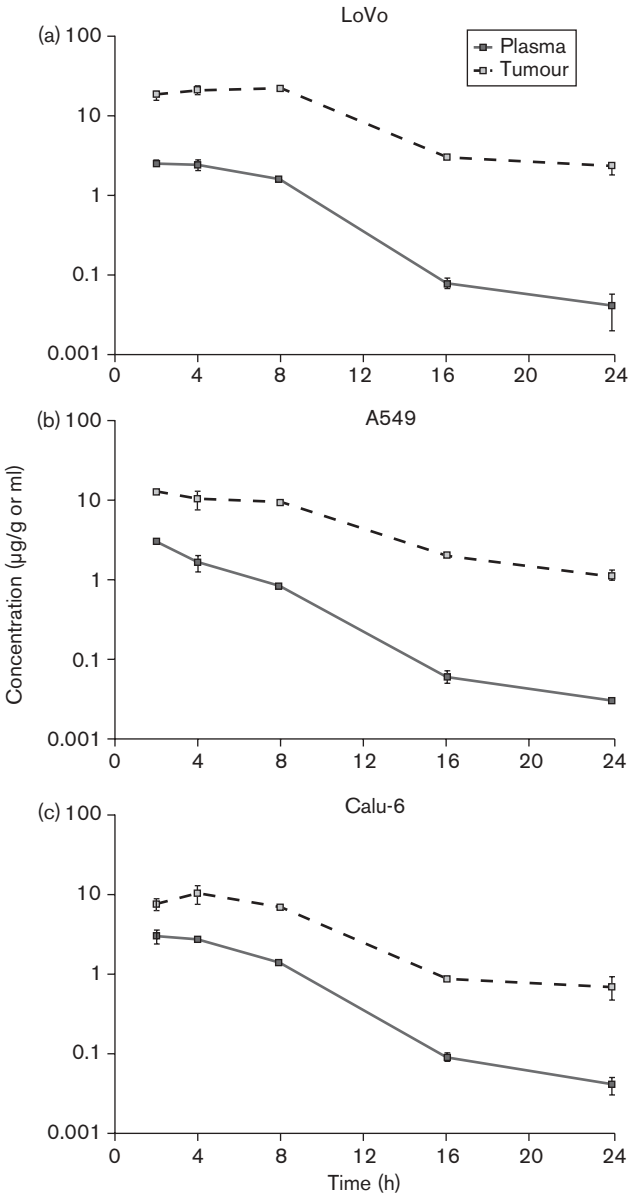
smokers could be restored by giving a 300-mg dose. This observation is consistent with the finding that 300 mg was the maximum tolerated dose (MTD) in patients who continue to smoke during therapy [39]. The effect of smoking on the pharmacokinetics of gefitinib has not been prospectively studied; however, a comparison between patients who admitted smoking and those who claimed to be nonsmokers did not show different steady state trough plasma concentrations in two phase II studies on NSCLC (AstraZeneca, Data on File 2009).

The high distribution volume of gefitinib implies significant passage of the drug out of the circulation and into the tissues. This was evident in distribution studies in rats [29]. Furthermore, studies in nude mice bearing subcutaneous human tumour xenografts (LoVo, A549 and Calu-6) and in an orthotopic rat lung tumour model (NCI-H460) showed extensive uptake of gefitinib, particularly into the tumour (tumour to plasma ratio 4.3-fold to 12.4-fold) (Fig. 5) and into skin [40]. The relevance of these observations to humans was shown in two clinical studies where gefitinib concentrations in homogenates of breast [40] and non-small-cell lung [41] tumour tissue biopsies were measured. On average, concentrations were 42-fold higher in breast tumour and 60-fold higher in NSCLC tumour than in coincident plasma samples. In contrast, but consistent with the lower distribution volume, erlotinib did not show marked tumour penetration in preclinical studies, achieving a tumour/plasma ratio of only 0.4 in a mouse HN5 xenograft study [13]. This observation is consistent with the tumour/plasma ratio observed in a small clinical study where the concentration of erlotinib in human lung or larynx tumours was about 63% of the corresponding plasma concentration [42]. These differences between gefitinib and erlotinib highlight the difficulty of drawing comparisons between the two agents based solely on plasma concentration measurements. Nevertheless, plasma concentration data are more readily obtained and, for gefitinib, have been used to relate drug exposure in patients to relevant preclinical indices of pharmacological activity. Wolf *et al.* [43] reported from phase I studies in cancer patients that concentrations would generally be maintained above the IC_{90} for inhibition of growth of KB cells at doses of gefitinib above 100 mg/day. In pharmacodynamic studies in the skin of cancer patients participating in phase I trials, gefitinib inhibited EGFR activation and affected downstream receptor-dependent processes, such as decreasing MAPK activation and keratinocyte proliferation, increasing the expression of p27KIP1 and maturation markers and increasing apoptosis, at all dose levels, before reaching dose-limiting toxicities [44]. Evidence of decreased activation of EGFR and downstream effects, including reduction in p-ERK and p-Akt and upregulation of p27, have also been observed in the skin of patients with head and neck cancer treated with erlotinib [45]. In the phase II studies in patients with NSCLC taking gefitinib 250 mg/day, steady-state minimum (trough) plasma concentrations of gefitinib averaged 261 ng/ml (range 44–1199) (AstraZeneca, Data on File 2009). Taking into account the 91% plasma protein binding of gefitinib [29], these values equate to free concentrations ranging from 9.7 to 332.2 nmol/l. Thus, despite the data indicating much higher levels of gefitinib in tumour than in plasma, the steady-state trough free plasma concentrations still exceed the in-vitro IC_{50} for inhibition of EGFR phosphorylation in A431 cells (33 nmol/l [15]) in the majority (86%) of patients.

Dose selection for gefitinib and erlotinib

The approved recommended doses of gefitinib and erlotinib are 250 and 150 mg/day, respectively. Although erlotinib is dosed at its MTD, the recommended dose of gefitinib is only about one-third of its reported MTD.

Fig. 5



Concentration of gefitinib in plasma and tumour xenografts after four daily oral doses (50 mg/kg) of gefitinib to female nude mice bearing (a) LoVo, (b) A549 or (c) Calu-5 tumour xenografts. Mean concentration obtained from three animals; bars, ± SE. Reproduced with permission from the American Association for Cancer Research, McKillop *et al.* [40]; permission conveyed through Copyright Clearance Center Inc.

Dose selection for gefitinib was based on the optimum biological dose approach with the aim of achieving maximum inhibition of the EGFR target at a dose level below the MTD [43]. On the basis of the results of preclinical studies and subsequent phase I trials, in which patients with a range of solid tumours received up to 1000 mg/day of gefitinib [35,36,46,25], two doses of gefitinib (250 and 500 mg/day) were selected for phase II evaluation in patients with advanced pre-treated NSCLC. At these doses, gefitinib concentrations were expected to be sufficient to achieve effective inhibition of EGFR. The MTD was 800 and 1000 mg/day in the two phase I studies that used once-daily oral dosing, and the predominant dose-limiting toxicities were diarrhoea and rash [35,36]. In the two dose-randomized phase II studies, IRESSA Dose Evaluation in Advanced Lung cancer (IDEAL) 1 and IDEAL 2, there were no differences between the two doses in efficacy as measured by objective response rate (12 vs. 9% in IDEAL 1 and 18 vs. 19% in IDEAL 2 at 250 and 500 mg/day, respectively), disease control rate (42 vs. 36% in IDEAL 1 and 54 vs. 51% in IDEAL 2, respectively), PFS (1.9 vs. 2.0 months in IDEAL 1 and 2.7 vs. 2.8 months in IDEAL 2, respectively), and overall survival (6.5 vs. 5.9 months in IDEAL 1 and 7.6 vs. 8.0 months in IDEAL 2, respectively) [47,48]. However, the lower 250-mg/day dose was associated with better tolerability, with lower incidences of dose reductions and withdrawals because of toxicity and of grade 3/4 drug-related adverse events, suggesting that these adverse effects were dose-dependent and exposure-dependent [47,48]. Therefore, 250 mg/day was selected as the optimal biological dose. A similar approach of selecting the optimal biological dose was used for the targeted agent imatinib (Gleevec or Glivec; Novartis, East Hanover, New Jersey, USA) [49]. In this case, doses of up to 1000 mg/day of imatinib tested in phase I studies failed to reach the MTD defined by nonhaematological toxicity. Doses of 400 and 600 mg/day were selected for phase II evaluation and provided a level of drug exposure above that at which apoptosis was observed in preclinical models. Therefore, for chronic myeloid leukaemia, the recommended doses of imatinib are 400 mg/day for chronic phase and 600 mg/day for all other stages/phases.

In the case of erlotinib, the recommended dose of 150 mg/day meets the classical definition of MTD [21]. Dose-limiting toxicities at doses of erlotinib exceeding 150 mg/day were diarrhoea and skin rash [21], indicating that these are the most common adverse effects of the EGFR-TKIs class.

Clinical efficacy of gefitinib and erlotinib

Both gefitinib and erlotinib have been studied in several phase III trials in patients with NSCLC. In the placebo-controlled ISEL study of gefitinib plus best supportive care in patients with pre-treated advanced NSCLC, a statistically significant improvement in overall survival was not found in the overall population [$n = 1692$, hazard ratio (HR): 0.89, 95% confidence interval (CI): 0.77–1.02, $P = 0.087$] or the subgroup of patients with adenocarcinoma ($n = 812$, HR: 0.84, 95% CI: 0.68–1.03, $P = 0.089$) [5]. In contrast, in the placebo-controlled BR.21 study of erlotinib in previously treated advanced NSCLC, erlotinib was associated with a statistically significant

improvement in survival in the overall population ($n = 731$, HR: 0.70, 95% CI: 0.58–0.85, $P < 0.001$) [4]. The objective response rates in both studies were similar: 8.0% versus 1.3 and 8.9% versus 0.9% in the ISEL and BR.21 studies, respectively. A likely explanation for the lack of significant survival benefit in the overall population of the ISEL study is that the study included more patients with refractory disease than in the BR.21 study; 38.4% had progressive disease as their best response to their most recent chemotherapy in the ISEL study compared with 20.8% of patients who had progressive disease as their best response to prior chemotherapy in the BR.21 study [4,5].

More recently, a major global phase III study has shown noninferiority of gefitinib compared with docetaxel, a standard of care for pre-treated NSCLC, in terms of overall survival ($n = 1433$, HR: 1.020, 96% CI: 0.905–1.150), with a more favourable tolerability profile and improved quality of life in previously treated advanced NSCLC [8]. The results of ongoing phase III studies comparing erlotinib with chemotherapy in patients with pre-treated advanced NSCLC are awaited.

In chemotherapy-naive patients with advanced NSCLC, neither gefitinib nor erlotinib has been shown to provide a survival benefit when added to standard combination chemotherapy [50–53].

Recently, superior PFS for gefitinib compared with carboplatin/paclitaxel ($n = 1217$, HR: 0.74, 95% CI: 0.65–0.87, $P < 0.0001$) has been shown in chemotherapy-naive, never or light exsmokers in Asia whose tumours have adenocarcinoma histology [9]. However, the treatment effect was not constant over time with Kaplan–Meier curves for PFS crossing over after 6 months. The biomarker-based analysis showed that gefitinib was significantly superior to doublet chemotherapy in patients with EGFR mutation-positive tumours, whereas standard chemotherapy showed a statistically significant advantage over gefitinib in EGFR mutation-negative tumours.

There have been numerous attempts to identify patients who are most likely to benefit from EGFR-TKIs using different EGFR biomarkers. The use of EGFR protein expression in the tumour measured by immunohistochemistry has produced conflicting data [50,53–57] suggesting that EGFR overexpression by itself might not be sufficient and/or indicative of active EGFR pathway involvement in tumour cell signalling. The use of EGFR gene copy number in the tumour measured by fluorescence in-situ hybridisation has also generated conflicting data; compared with placebo it seemed to predict the efficacy of EGFR-TKIs [56,57], but was not predictive when gefitinib was compared versus the active comparator docetaxel [8] or vinorelbine [58]. Thus, the interpretation of these biomarker data are complicated by different comparators (placebo or active comparator) used in the different trials as well as by a significant overlap between biomarkers, especially between increased gene copy number and somatic activating mutations of the EGFR gene. As mentioned earlier, recently reported data from the IPASS study showed that an EGFR mutation test can identify patients with tumours harbouring activating EGFR mutations who are likely to benefit significantly more from gefitinib treatment than from a standard multiagent chemotherapy regimen [9].

Does rash predict for response to gefitinib and erlotinib?

An acneiform-like skin rash is commonly observed in patients with solid tumours treated with EGFR-TKIs and is related to EGFR inhibition in the skin [59]. Several studies have suggested that the rash is associated with response to EGFR-TKIs; however, not every patient who develops rash subsequently responds to treatment and *vice versa*, therefore how useful is rash as a surrogate marker of efficacy?

Analyses from several phase II and III studies with erlotinib have found associations between improved survival and occurrence and severity of rash in patients with advanced NSCLC [60]. In the BR.21 study, 81% of the 444 erlotinib-treated patients developed rash: 30% grade 1, 41% grade 2, 9% grade 3 and 1% grade 4 [60]. Overall survival correlated with rash severity with HRs of 0.29 (95% CI: 0.22–0.38, $P < 0.001$) for $\geq$ grade 2 versus no rash and 0.41 (95% CI: 0.31–0.55, $P < 0.001$) for grade 1 versus no rash. Median overall survival was 11.1, 7.1 and 3.3 months for patients with $\geq$ grade 2, grade 1 and no rash, respectively. However, overall survival was also longer in the 18% of placebo-treated patients who developed rash (HR: 0.67, 95% CI: 0.46–0.98, $P = 0.039$), although this improvement did not correlate with severity of rash (median survival 7.4, 8.2, and 4.7 months in patients with $\geq$ grade 2, grade 1 and no rash, respectively). The overall objective response rate was 9%: 1% among the erlotinib-treated patients who did not develop rash compared with 10% of those who developed grade 1 rash and 13% of those who developed $\geq$ grade 2 rash. On the basis of such results, it has been suggested that physicians and patients should view the development of rash as a desirable outcome, perhaps as a sign of erlotinib-induced biological effect [60]. A pilot study has shown that dose escalation to tolerable rash to 200–350 mg/day of erlotinib was feasible [61], but it has been reported that the interim results do not suggest a higher response rate in patients undergoing dose escalation [26]. Dose intensity may not explain the lack of skin toxicity in all cases; for example, a lack of susceptibility to develop rash may reflect an immune-compromised status and could be associated with a worse prognosis [59].

There is less evidence to support the use of rash as a surrogate marker of EGFR inhibition and clinical benefit with gefitinib. Although some studies have shown such a link [62–64], these often have not used the correct statistical methods for analyzing such data. Analyses need to be adjusted for the fact that both adverse effects and efficacy are measured after randomization and are correlated with the confounding factor of time on treatment, using techniques such as landmark analysis. Without the correct methods, an apparent correlation between any adverse effect and efficacy is likely to be observed on any treatment, including placebo (as observed in the study by Wacker *et al.* [60]), but this may be simply because of the confounding. In the ISEL study, although the overall objective response rate with gefitinib (8%) was similar to that of erlotinib in BR.21, the incidence of rash was approximately half of that associated with erlotinib: 37% (2% grade 3 or 4) with gefitinib and 10% with placebo (1% grade 3 or 4) [5]. A retrospective analysis of objective response by incidence of early onset of skin toxicity (defined as rash, acne, pruritus, or dry skin within 28 days) in the IDEAL 2 study found that there was no statistically significant difference in the objective response rate between those with or without early onset skin toxicity at either dose [65]. At 250 mg/day, 67 and 25% of those patients who ultimately responded did not have skin toxicity by day 14 and 28, respectively. Examining rash specifically, across both IDEAL 1 and IDEAL 2 studies, 29% (9 of 31) of responders given 250 mg/day did not experience any rash during treatment [65]. Overall, phase I and IDEAL data showed that increasing doses of gefitinib increased the incidence of rash, but not the response rate [65]. Interestingly, the standard 150-mg/day dose of erlotinib produces a three-fold higher exposure compared with 250 mg/day of gefitinib, as measured by AUC, and has been reported to be associated with high rate of rash (81% in BR.21 study [60]). These data suggest that the incidence of rash can be related to EGFR-TKI exposure in the systemic circulation rather than directly with efficacy outcomes. We hypothesize that as gefitinib accumulates in tumour tissue and is used at a dose below the MTD, it causes less skin toxicity than erlotinib while still providing the concentration needed at its target to achieve effective EGFR inhibition in the tumour. Although rash may be a surrogate marker of exposure and may be linked with efficacy for erlotinib, the pharmacokinetic differences between gefitinib and erlotinib mean that it is not a useful predictive factor for efficacy with gefitinib.

Conclusion

Both gefitinib and erlotinib are small-molecule EGFR-TKIs with similar mechanisms of action and pharmacological profiles. Both agents have proven their clinical utility in phase III randomized studies. However, structural differences confer pharmacokinetic differences that may have important clinical implications. Although gefitinib 250 mg/day produces lower mean plasma concentrations and AUC compared with erlotinib 150 mg/day, published data suggest that gefitinib accumulates significantly in tumour tissue. This difference may at least partly explain why it seems possible to achieve maximum clinical efficacy with gefitinib at doses significantly lower than its MTD and, hence, use of an optimal biological dose approach with this agent

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