Targeted Therapy for Locally Advanced or Metastatic Non-Small Cell Lung Cancer—Patient Selection Changes the Fate of Gefitinib

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Abstract: Non-small cell lung cancer (NSCLC) presents one of the greatest clinical challenges in oncology. The prevalence of cigarette smoking is the major cause for the high incidence that makes NSCLC the commonest cause of cancer-related death in the western world. Patients frequently present late, with locally advanced or metastatic disease. In this often incurable situation, treatment is delivered with the aim of maximising quality and duration of life. The chosen therapy should, therefore, carry the lowest risk of side-effects in order to maximise clinical benefit. Conventional chemotherapy is typically associated with a long list of possible side effects that may be at best inconvenient, and at worst, dangerous. This group of patients, who may be frail from advanced age, advanced disease stage or additional co-morbidities, would clearly benefit from less toxic but equally effective therapies. Targeted therapeutic agents that inhibit key cell signalling pathways such as the epidermal growth factor receptor (EGFR) have been developed over the last 15 years and have demonstrated proof of principle in clinical trials. The small molecule tyrosine kinase (TK) inhibitors, such as gefitinib, are now established as particularly effective first-line therapy in the subgroup of NSCLC patients whose tumours display EGFR TK mutations that confer sensitivity. Gefitinib has been shown to be non-inferior to docetaxel in second-line therapy, and to have a better side effect profile and more rapid improvement in quality of life than chemotherapy, particularly in patients over 70 years. The publication of landmark studies and consequent changes in licensing have made 2009 the most significant year for gefitinib to date, and we describe the most recent data in the context of relevant translational research.

Keywords: gefitinib, lung cancer, metastatic, advanced, tyrosine kinase inhibitor, epidermal growth factor receptor

Introduction

In 2008, lung cancer represented a sixth of all new cases of cancer and was the commonest cause (30%) of cancer-related mortality in the United States.[1] Non-small cell lung cancer (NSCLC) is more common (85%) than the small cell variant and includes adenocarcinoma, squamous cell carcinoma, and large cell carcinoma subtypes. Cigarette smoking remains the major risk factor for NSCLC and patients may present with persistent cough, shortness of breath, fatigue, loss of appetite, weight loss and haemoptysis. Whilst patients tend to seek medical advice soon after noticing blood-stained sputum, the other symptoms are non-specific and many patients are diagnosed with advanced stage disease through a combination of late presentation and diagnostic difficulty. Patients with early stage NSCLC may be cured with surgery or radiotherapy, but 70% of patients will have locally advanced or metastatic NSCLC at diagnosis. The more advanced-stage tumours may be treated with chemotherapy and radiation, singly, sequentially or in combination. If patients are of inadequate performance status for intensive therapy, treatment will be delivered with palliative intent. Patients may derive significant symptomatic benefit from radiotherapy and from platinum-containing doublet chemotherapy, but the toxicities associated with these, particularly alopecia, should not be underestimated.[2] In 2009, guidelines for the administration of chemotherapy in Stage IV NSCLC were issued by the American Society for Clinical Oncology (ASCO).[3]

With conventional therapy, the outlook for patients with NSCLC is poor (16% overall survival at 5 years in 2003)[1] and the prognosis of patients with NSCLC would be ameliorated considerably by presenting with earlier stage disease. Radiological and molecular screening are popular concepts to increase the rates of early diagnosis and thus reduce mortality from this common cancer[4,5] but are not yet ready for implementation. Whilst cigarette cessation campaigns may be having some success in the United States and Europe, the increasing availability of cigarettes in China and India is thought to portend an explosion of cases. Thus, developing more effective, convenient and less toxic treatments remains a clinical priority.

The ideal characteristics of an anticancer therapeutic include efficacy in the absence of toxicity and good orally bioavailability. To achieve this wide therapeutic window, biological agents targeting proteins that play a key role in critical cell signalling pathways have been developed. Small molecule inhibitors of the epidermal growth factor receptor (EGFR) fulfil the above criteria for a novel agent. Gefitinib (Iressa®, AstraZeneca, UK) has been specifically designed as an inhibitor of cell signalling through the EGFR pathway. In the last year, landmark clinical trials have led to extension of the indications and licensing of gefitinib. The most recent data pertaining to the mechanistic effects, clinical pharmacology, trial data and a perspective on the place of gefitinib in the management of patients with advanced stage NSCLC are discussed in this review.

EGFR Biology and Signalling

As the nomenclature suggests, EGFR detects extracellular growth signals and channels them into epithelial cells, which triggers a network of interacting signalling pathways. Growth factors are effectors of cellular proliferation, differentiation, adhesion, survival and migration and it is therefore evident how deregulation of ligand-receptor interactions can promote the malignant phenotype of a cancer cell. The significance of identifying epidermal growth factor (EGF) was recognised by the Nobel Prize for Medicine.[6] In 1980, the EGF receptor was identified[7] and EGF was noted to induce tyrosine phosphorylation.[8] Homology of the EGFR protein to the oncogenic v-ERB-B transforming protein of avian erythroblastosis virus[9] suggested an important role in cancer cell biology, and the discovery that EGFR is a tyrosine-specific protein kinase[10] provided a mechanism for the putative oncological effects. The *EGFR* gene is located on chromosome 7p12 and encodes a 170 kilodalton (kDa) protein. EGFR is one of 90 tyrosine kinases in the normal cell[11] and is expressed at low levels on all cells, except those of haematopoietic lineage, where it has a role in epithelial development and wound healing. Receptor tyrosine kinases (RTKs) are located in the cell membrane and transmit signals from extracellular growth factors to the cytoplasmic compartments via phosphorylation cascades (Fig. 1). The ERB-B family of receptor tyrosine kinases includes ERB-B1 [EGFR or human epidermal growth factor receptor 1 (HER1)], ERB-B2 (HER2), ERB-B3 (HER3) and ERB-B4 (HER4). The four functional domains of the receptor are highly
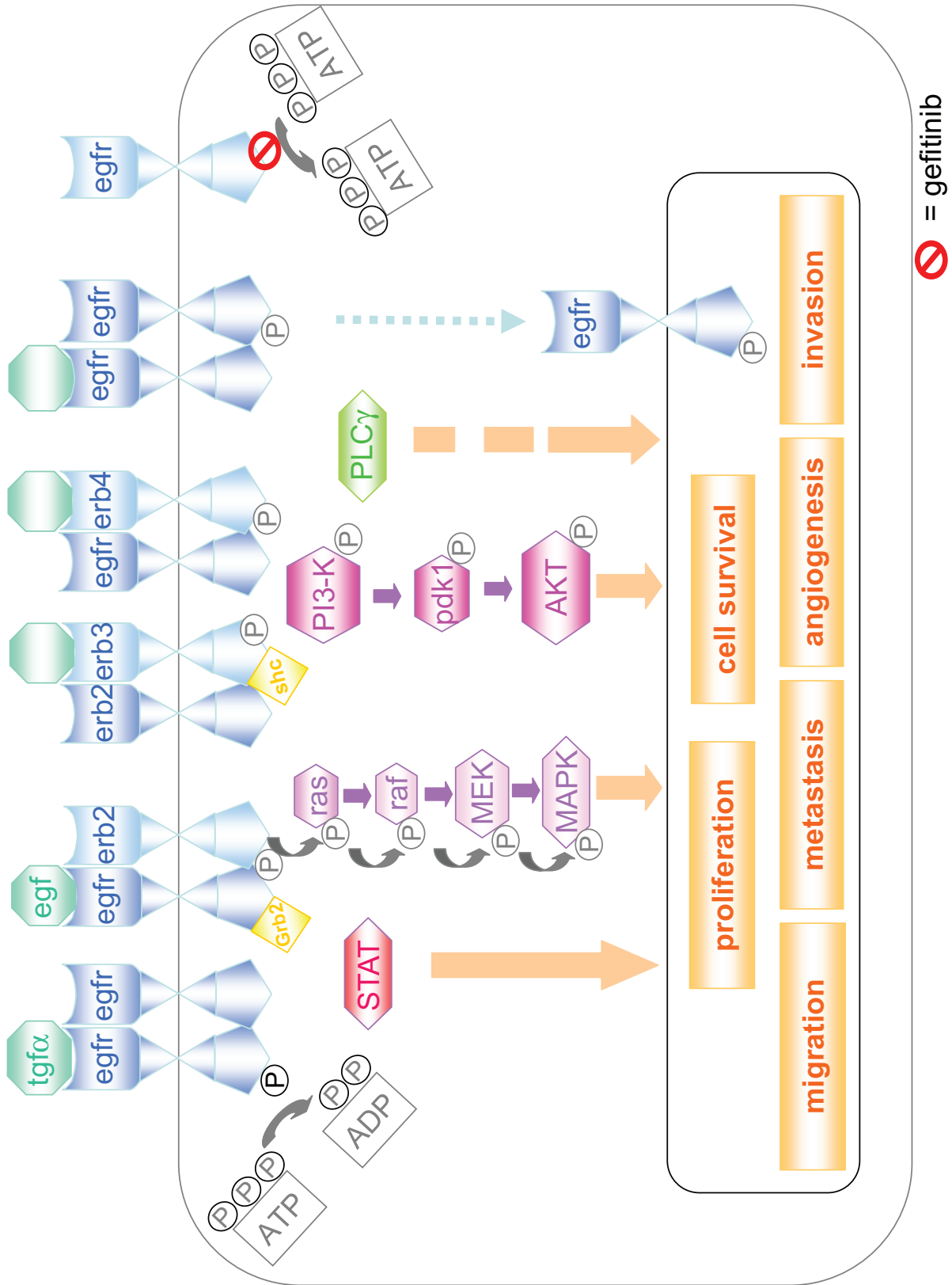
Figure 1. EGFR-related signalling cacades promote the malignant phenotype of the non-small cell cancer cell.

conserved: 1) a cysteine-rich extracellular N-terminal ligand-binding domain, 2) the single α-helix, hydrophobic transmembrane domain, 3) the catalytically active protein kinase domain and 4) the regulatory COOH-terminal domain. The kinase domains of the ERB-B RTKs share homology[12] but differences arise in the extracellular and C-terminal domains. Receptor dimerization induces autophosphorylation of key tyrosine residues in the activation loop of the catalytic domain, which then adopts an open configuration and enables access to ATP thus enhancing the kinase activity.[13] Autophosphorylation of EGFR on these five tyrosine residues permits the binding of adaptor proteins that recruit effector proteins. Downstream signalling pathways are triggered according to which of the five phosphorylation sites are activated. The key signalling pathways include the mitogen-activated protein kinase (MAPK) pathway,[14] the phospholipase C-gamma (PLC-γ) pathway,[15,16] the signal transducer and activator of transcription (STAT) pathways[17] and the phosphoinositide 3-kinase (PI3-K)/AKT pathway.[15,18] Activation of these signalling cascades ultimately leads to nuclear transcription responses that contribute to increased cell proliferation, inhibition of apoptosis, cell migration, invasion, angiogenesis and metastasis.[19]

In cancer, control of cell signalling cascades is impaired and high expression levels of EGFR are believed to contribute to solid tumour progression.[20] EGFR is relatively overexpressed on cancer cells which suggested that tumour cells would be selectively sensitive to EGFR inhibition as compared with normal cells,[21] rendering EGFR a rational therapeutic target. The critical role of EGFR in the pathogenesis of multiple cancers led to the hypothesis that the pharmacological blockade of EGFR activation would have a wider therapeutic window than cytotoxic chemotherapy. Anti-EGF monoclonal antibodies were shown to inhibit growth factor binding[22] and subsequent *in vivo* experiments predicted the clinical success of anti-EGFR antibody therapy.[23–26] To circumvent the limitations of this chimaeric human/murine antibody therapy (hospital attendance for intravenous administration, possible anaphylactic reactions, low tumour bioavailability due to large molecular size), drug development programmes turned to a novel class of anti-EGFR agent, the small molecule tyrosine kinase inhibitor (SMTKI). 'Drugging the kinome',[27] that is to say developing inhibitors of key kinases, has proven to be a rational, feasible and highly successful approach to personalising cancer therapy and the clinical success of EGFR SMTKIs in NSCLC (Fig. 2) has further validated this approach.

Mechanism of Action of Gefitinib

Gefitinib was the first-in-class low molecular weight inhibitor of EGFR, discovered 15 years ago. It is a synthetic 4-anilinoquinazoline and has the molecular formula $C_{22}H_{24}ClFN_4O_3$ and a molecular weight of 447 Da.[28] Gefitinib is an orally bioavailable small
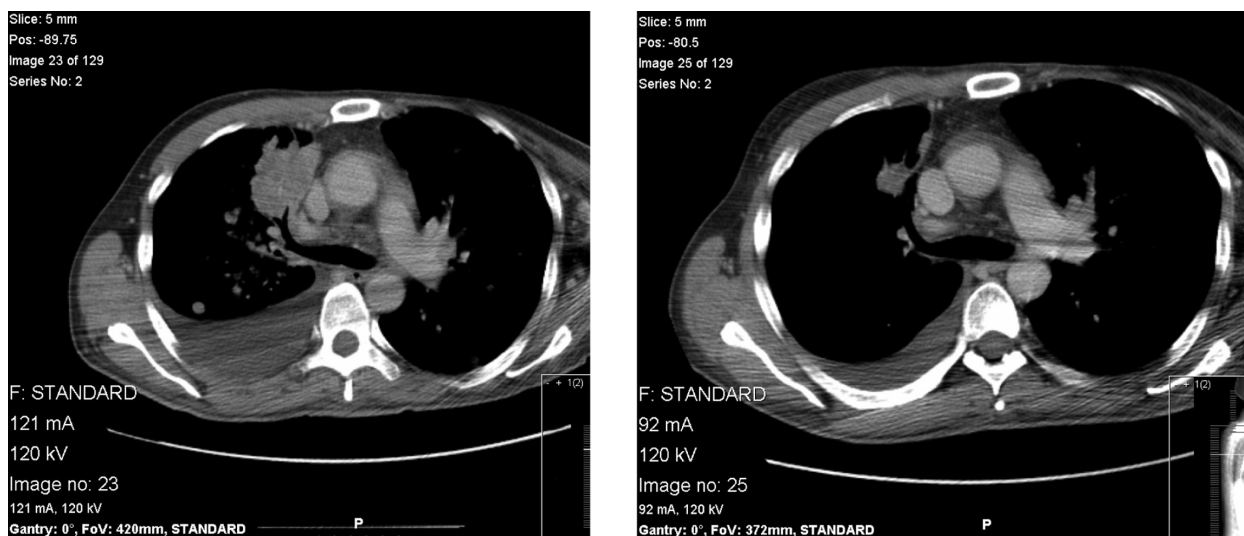
Figure 2. Radiological response in a 45 year-old ex-smoker with non-small cell lung cancer to two months treatment with an EGFR SMTKI.

molecule tyrosine kinase inhibitor of EGFR phosphorylation. Gefitinib inhibits EGFR isolated from the A431 squamous cancer cell line with an IC_{50} of 33 nM and shows 100-fold selectivity over ERB-B2.[28] It is a competitive, and therefore reversible, inhibitor of adenosine triphosphate (ATP) binding on the intracellular tyrosine kinase domain of EGFR[29,30] (Fig. 1). An additional mode of action is the promotion of inactive ligand-bound EGFR homodimers[31] and heterodimers[32] which sequester both ligand and ERB-B receptors. *In vitro*, gefitinib inhibits EGFR autophosphorylation and prevents EGFR-induced activation of p42/p44 MAP kinases, AKT and PLC-gamma1.[33] Consequently, cell migration, production of matrix metalloproteinases, cytoskeleton remodelling and *in vitro* invasion mediated by EGF are also inhibited, suggesting potential anti-metastatic effects.[34,35] The effects of gefitinib are cytostatic, rather than cytotoxic[36] in most cell lines, but promising anti-tumour activity was seen across many human tumour xenografts *in vivo*.[37] Based on the role of EGFR in the relative resistance to conventional therapies[38] some of the earliest preclinical studies successfully tested the hypotheses that gefitinib would be an effective chemo- and radiosensitiser. These promising pre-clinical data rapidly led to clinical trials.

Metabolism and Pharmacological Profile

Gefitinib exhibits linear kinetics over the dosing range up to 700 mg.[39] It is metabolised by CYP3A4, an isoenzyme of cytochrome P450, and CYP2D6. The major metabolite, O-desmethyl gefitinib,[40] does not have activity *in vivo* and is thus unlikely to contribute to drug effect. Inducers of CYP3A4 activity that may decrease levels of gefitinib include phenytoin, carbamazepine, rifampicin, barbiturates and St John's Wort. Patients who have the 'poor CYP2D6 metabolizer' genotype may experience an increase in gefitinib levels, and hence increased toxicity, if a potent CYP3A4 inhibitor such as ketoconazole, posaconazole, voriconazole, protease inhibitors, clarithromycin or telithromycin are administered. An increase in gastric pH by the effects of proton pump inhibitors (omeprazole, lansoprazole) or H2 antagonists (ranitidine) will decrease oral bioavailability. With regard to drug interactions, gefitinib appears to enhance the effects of warfarin, and to potentiate the neutropenic effects of vinorelbine.

90% of gefitinib is bound to protein (albumin and alpha 1-acid glycoprotein). The maximum plasma concentrations achieved from clinically relevant doses range fall between 0.5–1.0 µM, and such plasma levels can also inhibit other RTKs (insulin-like growth factor 1 receptor and platelet-derived growth factor receptor) suggesting there may not be total specificity for EGFR.[41] Patients with moderate to severe hepatic impairment due to cirrhosis have elevated plasma levels of gefitinib, but patients with raised liver enzymes and bilirubin due to liver metastases did not have raised levels.[42] No dose adjustment is advised in patients with impaired renal function if creatinine clearance is above 20 ml/minute, but below this level, there are limited data and caution is advised.[42] There are conflicting data regarding the effect of concomitant cytotoxic chemotherapy on plasma levels,[41] but, like other TKIs, a high-fat meal increases exposure by 30%.[41] The volume of distribution of gefitinib is high at 1400 litres, indicating good tissue penetration, indeed preferential tumour localisation has been reported.[43]

Pharmacokinetic studies associated with phase I trials revealed that, in patients with cancer, peak plasma levels are reached three to seven hours after the daily dose, that steady state levels are reached by seven to ten days[44] and a two to seven fold increase in exposure is seen after 14 days of daily dosing relative to day one. Plasma concentrations above the level required to inhibit the growth of cells *in vitro* (IC_{90}) were achieved by 100 mg gefitinib and maintained for 24 hours, and the terminal half-life of 28 to 85 hours is consistent with once daily dosing.[39]

Clinical Trials
Phase I

In phase I studies, gefitinib was developed to optimum biological dose (OBD); the dose above which no further inhibition of EGFR phosphorylation is seen. OBD is a rational concept unique to molecular targeted therapies as maximum target inhibition can be achieved at a dose below that which causes toxicity. As gefitinib is not a cytotoxic agent, it was maintained that it did not need to be given at the maximum tolerated dose (MTD).[30] A dose range of gefitinib with low toxicity was desirable given the

anticipated chronic use[45] and it was confirmed that gefitinib inhibits EGFR phosphorylation in tumours at the OBD of 250 mg/day,[46] which is approximately a third of the MTD. The results of the phase I trials of gefitinib have been summarised.[47] Two hundred and fifty patients with chemotherapy pre-treated epithelial tumours were recruited to five studies, irrespective of the EGFR status of their tumours, and exposed to daily oral doses of gefitinib between 50 and 1000 mg. Diarrhoea and rash (grades 1 and 2) and hypomagnesaemia were the side effects most frequently reported and the MTD fell between 700 and 1000 mg.[39,46] No complete radiological responses were observed in 221 patients, but many patients remained on treatment for six months or more. Promisingly, partial responses were documented in 10% of pre-treated NSCLC patients.

Efficacy

The linear relationship between dose of gefitinib and exposure led to the exploration of whether 500 mg yields greater clinical efficacy than 250 mg. Two phase II studies [Iressa Dose Evaluation in Advanced Lung Cancer (IDEAL-1 and -2)] showed response rates of unselected NSCLC patients pre-treated with chemotherapy to 250 mg gefitinib of 12 and 17% respectively, one year overall survival between 25–35% and no advantage of 500 mg over 250 mg gefitinib.[48,49] As there was a lower incidence of diarrhoea and rash at the lower dose, 250 mg was chosen for subsequent trials. The IDEAL studies also reported symptomatic improvement in approximately 40% of patients, the same proportion that had benefited from disease control with minimal toxicity at the dose of 250 mg.

Level one evidence from randomised controlled trials evaluating the efficacy of gefitinib in NSCLC is summarised chronologically in Table 1. As platinum-based chemotherapy is the standard of care in the first-line management of advanced NSCLC and gefitinib is a cytostatic and not a cytotoxic, agent, the combination of gefitinib with standard platinum-based chemotherapy regimens was tested in over 4000 unselected chemotherapy-naïve patients with stage III/IV NSCLC in the first phase III trials. Gefitinib dosed at 250 mg and 500 mg was compared to placebo in combination with two standard platinum-based chemotherapy doublets in the two 'Iressa NSCLC Trials Assessing Combination chemoTherapy' trials: gemcitabine

1250 mg/m^2 days 1 and 8 and cisplatin 80 mg/m^2 day 1 (INTACT 1) and paclitaxel 225 mg/m^2 day 1 and carboplatin AUC 6 day 1 (INTACT 2). The combinations were deemed safe and tolerable but addition of the targeted agent did not yield a statistically significant enhancement in response or survival over placebo.[50,51] A possible explanation for the lack of synergy is that gefitinib induces arrest in the pre-mitotic G1 phase of the cell cycle, whereas chemotherapy acts on cycling cells. Indeed comparable trials with an alternative EGFR TKI erlotinib (Tarceva™, Roche/Genentech)[52,53] yielded similar negative results, suggesting a class effect, possibly related to the scheduling.

Having discounted benefit from synchronous administration as a chemosensitizer, the 'Iressa Survival Evaluation in Lung Cancer' (ISEL) trial then compared 250 mg gefitinib to placebo in NSCLC patients with chemotherapy-refractory disease. The targeted agent did achieve statistically significantly prolonged time to disease progression (HR 0.82, 95% CI:0.73–0.92, p = 0.0006) and response rate (8 vs. 1.3%, p < 0.0001). Disappointingly however, these benefits of gefitinib administration did not translate into statistically significant improved overall survival in the total unselected population of patients[54] (Table 1).

A major translational research breakthrough in 2004 has led to successful application of EGFR TKIs in clinical practice in 2009. It had been observed early on that the patients who responded to EGFR TKIs tended to be female non-smokers with the bronchoalveolar subtype of adenocarcinoma. Tumour samples from patients with NSCLC who exhibited a complete response to EGFR TKIs were examined, and mutations in the region of the *EGFR* gene encoding the tyrosine kinase domain were discovered.[55–57] For the first time, an observation had been made that explained the subgroup of responders who had otherwise eclectic clinical characteristics. There are 15 known *EGFR* TK domain mutations and 90% of these are found in exons 18–21, encoding the tyrosine kinase domain of *EGFR*. 90% of these are either small, in-frame deletions in exon 19 that eliminate four amino acids (leucine, arginine, glutamate and alanine, the LREA motif) or point mutations in exon 21 that result in a specific amino acid substitution of leucine by arginine at position 858 (L858R). These mutations in exons 19, 20 and 21 are known as the

Table 1. A chronological summary of the key randomised controlled trials investigating the efficacy of gefitinib 250 mg daily in advanced NSCLC, reflecting the impact of patient selection according to *EGFR* TK mutation status on clinical outcome.

Year	Name of trial	Authors	Patient group	Major findings	Statistics
2009	WTJOG2405	Mitsudomi et al[70]	177 Japanese patients with *EGFR* TK mutations. Chemotherapy-naïve, <75 years. Gefitinib vs. cisplatin/docetaxel	PFS gefitinib superior to chemotherapy in first line setting. No difference in overall survival.	HR PFS 0.49 [95% CI 0.34–0.71, $p < 0.0001$]
2009	IPASS	Mok et al[69]	1200 Asian patients, non- or ex-smokers of <10 pack years for >15 years, adenocarcinoma. First line setting. Gefitinib vs. carboplatin/paclitaxel	If *EGFR* TK mutations detected, gefitinib yielded a significant progression-free survival (PFS) advantage versus chemotherapy. If *EGFR* TK wild type, PFS on gefitinib was inferior to chemotherapy	HR PFS 0.48 [95% CI: 0.36 to 0.43, $p < 0.001$] HR PFS 2.85 [95% CI: 2.05 to 3.98, $p < 0.001$]
2006	ISEL	Thatcher et al[54]	1692 unselected patients, refractory to chemotherapy. Gefitinib plus best supportive care (BSC) vs. BSC.	At median follow-up of 7.2 months, no median survival advantage for gefitinib plus BSC *vs.* BSC in whole population or in adenocarcinoma subgroup (n = 563).	HR 0.89 [95% CI 0.77-1.02, $p = 0.087$] HR 0.84 [95% CI 0.68-1.03, $p = 0.089$]
2008	INTEREST	Kim et al[83]	1466 pre-treated patients (at least one line platinum chemotherapy) Gefitinib vs. docetaxel 75 mg/m² 3-weekly	Gefitinib non-inferior to docetaxel in intention to treat population. Not superior if *EGFR* gene amplification	HR 1.020, [96% CI 0.905–1.150]
2004	INTACT-1	Giaccone et al[50]	1093 chemotherapy-naïve patients Gefitinib (250 or 500 mg) plus gemcitabine/cisplatin vs. gemcitabine/cisplatin plus placebo	No difference in progression-free, median or overall survival if treated with gefitinib plus chemotherapy as compared with placebo plus chemotherapy	Med. survival: 9.9, 9.9, 10.9 mths PFS 5.5, 5.8, 6.0 mths Response rates: 49,7%, 50,3%, 44.8%
2004	INTACT-2	Herbst et al[51]	1037 chemotherapy-naïve patients Gefitinib (250 or 500 mg) or carboplatin/paclitaxel vs. carboplatin/paclitaxel plus placebo	No difference in progression-free, median or overall survival if treated with gefitinib plus chemotherapy as compared with placebo plus chemotherapy	Med survival: 9.8, 8.7, 9.9 months

classical or conventional *EGFR* TK mutations and are rare outside of NSCLC.[55,58–60] The incidence of such mutations in Caucasian patients is 10%–15%[61,62] and is 30%–40% in the Asian population.[63,64]

Certain patients in the ISEL study were also reported according to prospectively planned subgroup analyses. Non-smokers and patients of Asian origin were noted to have significantly longer time to progression and median survival (Table 1), consistent with a likely but unproven higher incidence of *EGFR* TK mutations in patients with these clinical characteristics, but also a lower risk profile for smoking-related morbidities among the non-smokers.[65] Phase II trials of gefitinib in chemotherapy-naïve patients with NSCLC selected by their clinical phenotype or *EGFR* TK mutation status reported a tantalising increase in response rates from approximately 10% in unselected patients with pre-treated NSCLC to 55%–75%.[66,67] The combined analysis of individual patient data from seven Japanese clinical trials that had prospectively evaluated the efficacy of gefitinib in patients with *EGFR* TK mutations confirmed an overall response rate of 76.4% (95% CI 69.5–83.2). The median PFS was 9.7 months (95% CI 8.2–11.1) and median OS was 24.3 months (95% CI 19.8–28.2 months). Interestingly, of the 148 patients, 87 received gefitinib first line and their median PFS was 10.7 months as compared with 6.0 months in patients pre-treated with chemotherapy ($p < 0.001$). There was no significant difference in overall survival however.[68]

The recent publication of the 'Iressa Pan-Asia Study (IPASS) study has prospectively confirmed the enhancement of outcome through appropriate patient selection by demonstrating a statistically significantly enhanced survival benefit of gefitinib in patients with *EGFR* TK mutations[69] (Table 1). In this randomised phase III study, gefitinib was compared with carboplatin/paclitaxel in over 1200 Asian patients with untreated advanced NSCLC and less than 10 pack years smoking history or who ceased smoking more than 15 years ago. The enrolled population was thus enriched for patients likely to respond. In the intention-to treat population, the HR for PFS gefitinib was 0.74. Interestingly, chemotherapy appeared to be more advantageous in the first six months of follow-up but then gefitinib was superior for the remaining 16 months. In patients with classical *EGFR* TK mutations in the IPASS study, the hazard ratio for

progression-free survival was 0.48 (95% CI: 0.36 to 0.43, $p < 0.0001$) for gefitinib vs. chemotherapy as compared with 2.85 (95% CI: 2.05 to 3.98, p) in EGFR wild-type patients.[69] In the WJTOG3405 trial, 177 chemotherapy-naïve patients with a confirmed classical *EGFR* TK mutation were randomised to gefitinib or cisplatin (80 mg/m²) plus docetaxel (60 mg/m²). There was a highly significant PFS advantage for gefitinib (9.2 months, 95% CI 8.0–13.9) versus the chemotherapy doublet (6.3 months, 95% CI 0.336–0.710, log rank $p < 0.0001$).[70]

Gefitinib is a dramatic example of how a therapy that had all but been discarded has proven to be highly effective once targeted to the appropriate patient subgroup. The precedents for this are tamoxifen and trastuzumab (Herceptin®, Roche/Genentech, U.S.A.) where efficacy increases markedly in patients whose tumours express the requisite receptors at clinically significant levels.[71]

The literature surrounding predictive markers of response to EGFR TKIs other than *EGFR* TK mutations has been conflicting. It would be expected that response to gefitinib would relate to levels of expression of the target, but most studies have failed to find an association between EGFR expression levels as measured by immunohistochemistry (IHC).[72–74] A correlation between increased *EGFR* gene copy number and response to gefitinib in advanced NSCLC has been reported.[75] Recently, the ISEL study also identified that high *EGFR* gene copy number (HR 0.61 vs. 1.16) and higher levels of EGFR protein expression (HR 0.77 vs. 1.57) to correlate with improved survival.

Safety

Over 300,000 patients have been treated with gefitinib to date. As the main toxicities of gefitinib are diarrhoea and rash (generally CTC grade 1 and 2 and experienced by 1 in 5 patients) and, unlike chemotherapy it does not cause myelosuppression, gefitinib has a good safety record. Overgrowth and ingrowth of eyelashes have been reported infrequently with EGFR TKIs.[76,77] The pooled dataset of ISEL, INTEREST and IPASS studies (2462 patients) reported 8% grade 3/4 adverse drug reactions (ADRs), but only 3% of patients stopped treatment due to ADRs. The predominant toxicities of diarrhoea and rash are reversible and improve or resolve following discontinuation of

therapy. An interval of up to 14 days is recommended to allow symptoms to resolve then gefitinib should be restarted at 250 mg daily. If the patient cannot tolerate therapy following reinstatement, it should be discontinued, and alternatives considered.

A rare but potentially fatal complication of gefitinib is interstitial lung disease (ILD). The clinical features of shortness of breath, cough and fever may overlap with symptoms of radiation pneumonitis, pneumonia and disease progression and ILD may be difficult to diagnose. Gefitinib is now licensed in 66 countries worldwide, including Japan since 2002 and the United States since 2003. The Japanese post-marketing experience reported a 2% incidence[78] but an expanded access programme in the US found only 0.3% of patients developed this complex condition.[41] ILD is not exclusive to EGFR TKIs however. The INTEREST and ISEL trials reported 1%–1.4% incidence of ILD in the gefitinib arm, and 1%–1.1% incidence in the chemotherapy or placebo arms. In the IPASS study, ILD was diagnosed in 2.6% of the gefitinib-treated patients, and 1.4% of the patients receiving placebo. The risk of developing ILD is greatest in the first four weeks of therapy and both incidence and mortality appear to be associated with smoking, poor performance status (≥ 2), ≥ 65 years old, $\leq 50\%$ normal lung on computerised tomography (CT) scan, <6 months since diagnosis, cardiac co-morbidity, pre-existing ILD and areas of pleural adhesion. Being of Asian origin may also be a risk factor as the incidence of ILD was three times that of the general population in the gefitinib arm, and four-times in the placebo arm in the ISEL trial. The recent WTJOG3405 Japanese Phase III trial reported that 2 of 88 patients in the gefitinib group developed ILD and one patient died.[70]

Patient Preference

Approximately 45% of patients with NSCLC refractory to chemotherapy are reported to achieve stable disease on an EGFR TKI and 30%–40% report improvement in lung-related symptoms after a median of two weeks of therapy with gefitinib.[48,49,79,80] The 'Iressa in Non-small cell lung cancer vs. Vinorelbine Investigation in The Elderly' (INVITE) randomised phase II study evaluated both agents in patients aged over 70 years with advanced NSCLC who were chemotherapy-naïve.[81] Patients were of performance status 0–2 and were randomised to 250 mg gefitinib or 30 mg/m^2 vinorelbine days 1 and 8 on a three-weekly cycle. Efficacy was similar in the two arms (2.7 vs. 2.9 months median progression-free survival), but adverse events were reported more frequently in the chemotherapy arm (41.7% vs. 12.8%). The most surprising aspect of this trial was the greater benefit of chemotherapy, rather than the TKI, in patients with high *EGFR* gene copy number. A lack of benefit of gefitinib when compared with best supportive care was demonstrated in patients of worse performance status (2 or 3) in the 'Iressa in Non-Small cell Trial Evaluating Poor PS Patients' (INSTEP) study.[82] The WTJOG3405 Phase III trial reported the expected pattern of toxicities: myelosuppresssion, alopecia and fatigue in the chemotherapy group and skin toxicity, diarrhoea and liver dysfunction in patients in the gefitinib arm.[70]

Summarising the above data, gefitinib can yield a significant and rapid improvement in quality of life with a better side effect profile than chemotherapy. Patients who are over 70 or who do not wish to receive first-line chemotherapy for fear of side effects or reduced performance status may express a preference for gefitinib, although in Europe, evidence of *EGFR* TK mutations would be required. Other reasons for patients to favor gefitinib would include the oral administration that obviates hospital attendance for intravenous chemotherapy, and the reduced need for venepuncture and inpatient management of chemotherapy-induced toxicities, particularly potentially fatal neutropenic sepsis.

In a randomised phase III of gefitinib versus second-line chemotherapy, the 'Iressa Non-small cell lung cancer Trial Evaluating REsposne and Survival against Taxotere' (INTEREST) trial, the EGFR TKI was confirmed to be non-inferior to docetaxel in over 1400 patients with platinum pre-treated NSCLC (HR for 250 mg gefitinib vs. 75 mg/m^2 docetaxel three-weekly 1.02, 96% CI 0.905–1.15, non-inferiority criterion 1.154).[83] According to the FACT-L QoL scores, patients who had received gefitinib had almost double the rate of improvement of QoL than patients who had received chemotherapy (25.1 vs. 14.7%, OR 1.99, 95% CI 1.42–2.79, p < 0.0001). Gefitinib had a better toxicity profile than docetaxel: adverse events grade 3 or 4 (8.5% vs. 40%) and serious adverse events (3.8% vs. 18.2%). As expected, the lack of myelosuppresion

associated with gefitinib resulted in infrequent grade 3/4 neutropaenia (2.2% vs. 58.2%) and rare febrile neutropaenia (1.2% vs. 10.1%). V-15-32 was a phase III trial conducted in Japan comparing 250 mg gefitinib vs. docetaxel 60 mg/m^2 in a second or third-line setting. This trial failed to demonstrate non-inferiority of gefitinib, yet there was no statistically significant difference in overall survival between the arms.[84] Reasons that gefitinib could not be shown to be non-inferior may include increased cross-over to post-study therapy in the chemotherapy arm confounding the survival data.[65] Again, toxicity scores were lower in the gefitinib arm. A third similar study (ISTANA or 'Iressa as a Second-line Therapy in Advanced Non-small cell lung cancer') randomised Korean patients to gefitinib 250 mg or docetaxel 75 mg/m^2 three-weekly and did, once more, demonstrate a statistically significant increase in progression-free survival in the gefitinib arm (HR 0.73, 90% CI 0.53–1.00) and a difference in response rate favouring gefitinib (28.1% vs. 7.6%, p = 0.0007).[85] The 'Second-line Indication of Gefitinib in Non-small cell lung cancer' (SIGN) study compared 250 mg gefitinib against 75 mg/m^2 docetaxel three-weekly. The trial endpoints were QoL, which was improved in patients receiving gefitinib (33.8% vs. 26%), and symptom relief which was again more marked in the TKI group (36.8 vs. 26%). There were fewer total (51.5% vs. 78.9%) and grade 3/4 (8.8 vs. 25.4%) adverse events on gefitinib and response rates and overall survival were comparable in the two arms (13.2% vs. 13.7% and 7.5 months vs. 7.1 months).[86]

On the basis of the above evidence, gefitinib has now been deemed non-inferior to docetaxel and is a popular choice by patients in the second-line setting, in addition to first-line, given the more attractive side effect profile and better probability of improving QoL more rapidly.

Place in Therapy

The US Food and Drug Administration (FDA) granted fast track approval to gefitinib on May 5, 2003 as monotherapy in patients with locally advanced or metastatic NSCLC where chemotherapy had failed. The basis for approval was the 10.6% response rate of 7 months median duration in the third-line treatment of 139 patients with NSCLC.[48,49] In December 2004, gefitinib did not receive full approval, however, as the

confirmatory trial failed to show a survival advantage over placebo[54] and European licensing was not pursued. A similar trial evaluating an alternative EGFR TKI erlotinib reported a month's advantage in PFS over placebo.[87] Erlotinib became licensed in the second or third line setting in NSCLC and patients receiving gefitinib at that time were crossed over to erlotinib. The lack of inferiority of gefitinib to docetaxel evident in the INTEREST study,[83] and the highly significant prolongation of progression-free survival in selected Asian non-smoking patients with adenocarcinoma of the lung in the IPASS study,[69] have led to a European licence in first-line locally advanced or metastatic NSCLC with classical *EGFR* TK mutations in 2009.

Around 20% of patients who respond to EGFR TKIs do not harbour these classical mutations however.[57] Whether these patients have as yet unidentified mutations, or an alternative mechanism of sensitivity, is unknown. It appears that, for instance, when *EGFR* is not mutated, *EGFR* amplification and high levels of protein expression may correlate with response.[88,89] In addition, not all patients with the classical TK mutations respond. It appears that whilst mutations have been discovered that predict sensitivity to gefitinib in a specific subset of patients with NSCLC, these do not account for all lung cancer patients who might respond to EGFR SMTKI, nor for the majority of clinical responses in other tumour types such as head and neck cancer.[90,91] Determinants of response should, therefore, continue to be sought. *K-ras* mutations predict for a lack of response to anti-EGFR therapies, which is explained by an independent activation of the pro-proliferative MAPK pathway. As *K-ras* mutations are mutually exclusive with *EGFR* TK mutations, they should only be sought in *EGFR* wild-type patients being considered for therapy with EGFR inhibitors.

Despite initial dramatic clinical responses in *EGFR*-mutant NSCLC patients, resistance invariably develops and is generally associated with a second somatic mutation.[92,93] The substitution of methionine for threonine at position 790 (T790M) accounts for 50% of cases of acquired resistance to EGFR SMTKI inhibitors. Amplification of the *MET* gene is another recognised mechanism of acquired resistance to gefitinib.[94,95] There are case reports of response to an alternative EGFR TKI second line, but it is likely that if

performance status allows, patients would cross over to palliative chemotherapy after disease progression.

Future Perspective

Enhancement of the efficacy of gefitinib might be achieved by co-administration of a monoclonal antibody to EGFR, such as cetuximab, with gefitinib. This combination has proven synergistic in the preclinical setting,[96] suggesting either that extracellular and intracellular inhibition of EGFR signalling are not equivalent, that competitive TKI inhibition by the OBD is not sufficient or that an immune response to the antibody, such as antibody-directed cell cytotoxicity (ADCC) is significant.

It is unlikely that EGFR TKIs will be trialled further in combination with chemotherapy without further elucidation of the optimal sequencing of administration. However, as cancer cell molecular biology has been found to underpin the tenets of radiobiology,[97] there is a strong rationale behind using EGFR inhibitors as radiosensitizers.[98] Gefitinib, amongst other EGFR inhibitors, has been shown to successfully enhance radiosensitivity. Radical radiotherapy, that is to say with curative intent, is the standard treatment for patients with early stage NSCLC who are medically or surgically unfit for resection. Concurrent administration of chemotherapy (chemoradiation) may be used in the fittest patients with a 10% survival benefit, but not without toxicity. EGFR signalling is associated with radioresistance. As little as 2 Gray (Gy) of radiation can upregulate EGFR receptor expression,[99] increase release of ligands such as TGFα,[100] inhibit phosphatases[101] and promote translocation of EGFR to the nucleus where it may continue to signal. In theory, gefitinib can counteract these responses, which are thought to contribute to the phenomenon of accelerated repopulation, and gefitinib has been shown to enhance radiation-induced DNA damage by inhibiting repair enzymes downstream of EGFR, such as DNA-PK.[102]

As proof of concept, synergistic inhibition of tumour growth resulted from the combination of gefitinib and radiotherapy in human tumour xenograft models.[103,104] With regard to possible mechanisms, EGFR-TKIs sensitise cancer cells to radiation by anti-proliferative mechanisms and inhibition of DNA repair.[105–107] The effect of gefitinib is greater when radiotherapy is fractionated, suggesting effective inhibition of accelerated repopulation between fractions.[108] Radiation and gefitinib in combination reduce vascular endothelial growth factor (VEGF) levels and tumour vascularity,[109] and a co-operative pro-apoptotic effect has been reported when gefitinib is combined with radiation.[105,110]

Dual inhibition of EGFR with vascular endothelial growth factor receptor 2 (VEGFR-2) by an agent such as vandetanib may supersede targeted inhibition of EGFR alone. It may also be valuable to co-target the PI3-K/AKT pathway with EGFR, either upstream at the ERB-B2 receptor or at PI3-kinase itself. 'Kinase switching', from signalling through EGFR to ERB-B2/ERB-B3 for example, is likely to be a significant escape route for the cancer cell from EGFR inhibition, and broader inhibition with, for example a dual EGFR/ERB-B2 TKI such as lapatinib (lapatinib, Tykerb®, GlaxoSmithkline), or an irreversible pan-ERB-B inhibitor such as canertinib (CI-1033, Pfizer) may prove more effective. Other important molecular targets, where co-targeting may prove synergistic by inhibition of cross-talk, include the insulin-like growth factor 1 receptor (IGF-1R) and mesenchymal epithelial transition receptor (MET).

Conclusion

Gefitinib has recently been described as the 'phoenix rising from the flames'.[111] Until 2009, gefitinib had a lower profile in the therapy of NSCLC than erlotinib which had demonstrated a survival advantage relative to placebo in the BR.21 trial.[87] The IPASS study[69] has demonstrated the benefits of targeting molecular-based therapies to the patient as well as the tumour. In Europe, NSCLC patients with mutations in the *EGFR* TK domain may now receive gefitinib first line. Although the *EGFR* TK mutations create 'addiction' of the NSCLC cancer cell to the EGFR signalling pathway, the correlation between TK mutation status and clinical response is not perfect, and determinants of response in *EGFR* wild-type patients should continue to be sought. *EGFR* gene amplification, the highest levels of EGFR protein overexpression and high levels of ligands such as amphiregulin and epiregulin may be other surrogates for dominant EGFR cell signalling, and thus a more dramatic cellular effect from inhibition of EGFR-related signalling pathways.

In the first line management of NSCLC, gefitinib has asserted superiority to chemotherapy in patients

exhibiting *EGFR* TK mutations. Gefitinib also holds advantages over second-line chemotherapy for unselected NSCLC patients of poor performance status or who are aged over 70 years in particular, in terms of toxicities and improvement in quality of life and symptomatic relief. Irreversible or multi-targeted TKIs may surpass gefitinib in due course, but for the foreseeable future, gefitinib should significantly enhance the quality of life and prolong time to disease progression in patients with advanced or metastatic NSCLC, and is a welcome addition to the current range of therapeutic options

Disclosures

The authors have no conflicts of interest to declare.

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