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Gefitinib

Christine R. Culy and *Diana Faulds*

Adis International Limited, Auckland, New Zealand

Contents

Abstract

▲ Gefitinib (ZD1839) is an orally active selective inhibitor of epidermal growth factor receptor tyrosine kinase, an enzyme that regulates intracellular signalling pathways implicated in the proliferation and survival of cancer cells.

▲ In human non-small cell lung cancer (NSCLC) cell lines and xenografts, gefitinib dose-dependently inhibited cellular proliferation and tumour growth, and potentiated the cytotoxic effects of chemotherapy and/or radiation.

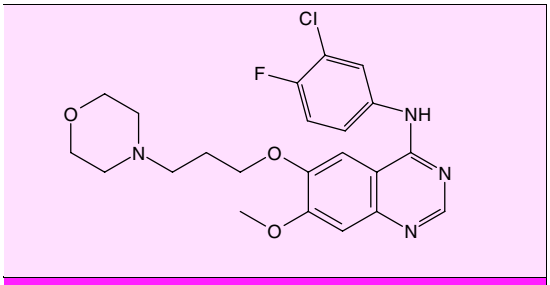
▲ Gefitinib is orally bioavailable and is cleared via the cytochrome P450 3A4 pathway. In patients receiving gefitinib (50 to 700 mg/day) in phase I trials, steady-state plasma concentration was reached in 7 to 10 days.

▲ In patients with advanced NSCLC who had failed one or two prior chemotherapies, gefitinib 250 or 500mg once daily induced an objective response in ≈19% of patients in a double-blind trial (n = 210).

▲ In another double-blind trial including 216 patients with NSCLC who had failed two or more prior chemotherapies, gefitinib 250 or 500mg once daily induced an objective response in 11.8 and 8.8% of patients, respectively; ≈40% showed an improvement in disease-related symptoms.

▲ Gefitinib was generally well tolerated and the most common adverse events were mild skin rashes and diarrhoea.

Features and properties of gefitinib (ZD1839)	
Indication	
Monotherapy treatment in patients with inoperable or recurrent non-small cell lung cancer	
Mechanism of action	
Epidermal growth factor receptor tyrosine kinase inhibitor	
Dosage and administration	
Recommended dosage	250mg once daily
Route of administration	Oral
Pharmacokinetic profile following a single oral dose of 50mg in patients with solid tumours (n = 8)	
Peak plasma concentration (mean)	43 μg/L
Time to peak plasma concentration (median)	3h
Terminal half-life (mean)	34h
Adverse events	
Most frequent	Mild rash and diarrhoea



Chemical structure of gefitinib (ZD1839) [4-(3-chloro-4-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy) quinazoline]

Lung cancer remains the most frequently diagnosed cancer worldwide and is the leading cause of cancer mortality in developed countries including the US, UK and Japan.[1,2] Non-small cell lung cancer (NSCLC) is the most common form of lung cancer, accounting for up to 75% of all cases.[1] Patients with resectable NSCLC tumours have the greatest chance of surviving their disease; however, over 50% of patients with NSCLC present with unresectable locally advanced or metastatic disease (stage IIIB/IV) and prognosis in these patients is poor.[1]

Chemotherapy plays a major role in patients with inoperable NSCLC. A number of agents are now available for use in NSCLC (e.g. vinorelbine, paclitaxel, docetaxel, gemcitabine, vinblastine, mitomycin, irinotecan, topotecan) and these are usually used in combination with platinum agents (carboplatin, cisplatin).[3] While currently available regimens have little or no effect on overall survival, chemotherapy can palliate disease-related symptoms and may provide a small short-term survival benefit. Compared with best supportive care, platinum-based combination therapy significantly improved 1-year survival by 10% (from 5 to 15%), with an increased median survival of 6 weeks in one large meta-analysis.[4] Second-line treatment options in patients with advanced NSCLC are very limited and docetaxel is the only agent to show any survival benefit in these patients.[5,6]

Over the last few decades, research into the biological mechanisms of tumour growth have yielded several novel molecular targets for drug therapy, one of which is the epidermal growth factor receptor (EGFR). EGFR is a member of the erbB family of cell surface receptors which have an intracellular tyrosine kinase domain.[7] The EGFR is a monomeric receptor which can be activated by a variety of ligands including epidermal growth factor (EGF), transforming growth factor-α (TGFα), amphiregulin and betacellulin. Ligand binding causes the EGFR to dimerise, activating tyrosine kinase activity in the intracellular domain and resulting in autophosphorylation of both intracellular domains.[8] This initiates a cascade of intracellular signalling events which have been implicated in the proliferation of cancer cells and other growth- and survival-promoting processes (see figure 1).

EGFR is expressed or overexpressed in a wide range of solid tumours, including 40 to 80% of NSCLCs.[9] In addition, several studies indicate that a high level of EGFR expression is associated with advanced disease, development of a metastatic phenotype and poor prognosis.[9]

Gefitinib[1] (ZD1839) is a low molecular weight, synthetic anilinoquinazoline [4-(3-chloro-4-fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy) quinazoline][8] which selectively inhibits the tyrosine kinase activity of EGFR. This agent is under investigation in a number of cancer types; however, this review will focus on its potential as monotherapy treatment in NSCLC.

1. Pharmacodynamic Properties

Gefitinib inhibits the activity of EGFR by competing with adenosine triphosphate for its binding site on the intracellular tyrosine kinase domain of the receptor.[10] This inhibits autophosphorylation of EGFR and blocks downstream signalling (see figure 1).

- Gefitinib inhibited isolated EGFR-tyrosine ki-

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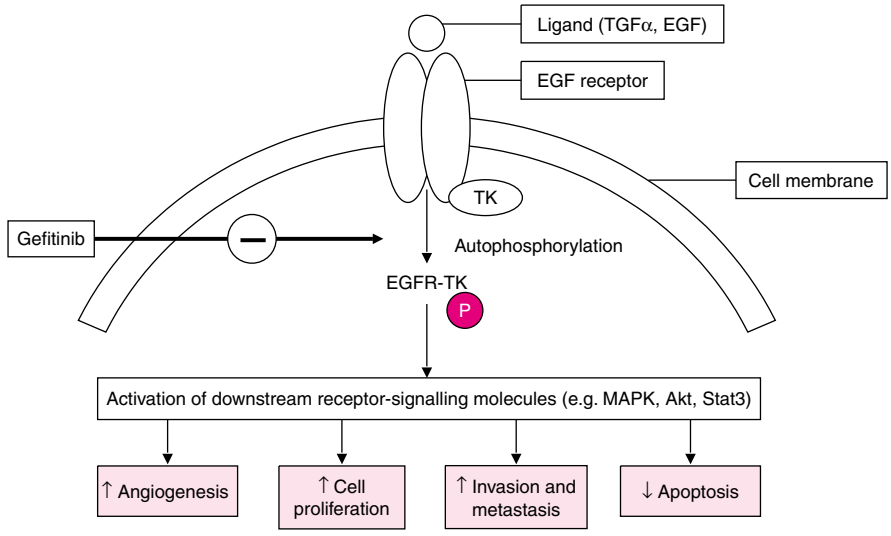

Fig. 1. Simplified schematic illustration of the epidermal growth factor (EGF) receptor signal transduction cascade and the site of action of gefitinib; **TGF**α = transforming growth factor-α; **TK** = tyrosine kinase; **MAPK** = mitogen-activated protein kinase.[11,12]

nase extracted from A431 squamous cell carcinoma (SCC) cells with a 50% inhibitory concentration (IC_{50}) of 23 nmol/L.[13] Gefitinib also inhibited autophosphorylation of EGFR in a number of tumour cell lines in culture including KB oral squamous, A549 lung, DU145 prostate and HT29 colorectal (IC_{100} of 0.16 to 0.8 μmol/L).[14]

• In contrast, gefitinib exhibits weak activity against other tyrosine kinases such as erbB2, KDR, and c-flt, or serine/threonine kinases including protein kinase C, MEK-1 and ERK-2; IC_{50} values are at least 100-fold higher for these kinases than for EGFR tyrosine kinase.[11]

Effects on Downstream Signal Transduction

• In *ex vivo* A431 tumour xenograft samples,[15] gefitinib induced a dose- and time-related inhibition of c-fos mRNA (measured by reverse transcriptase-polymerase chain reaction). Inhibition of c-fos mRNA was greatest 6 hours after dosing and normal levels were not restored until approximately 36 hours. Treatment with gefitinib 50 and 200 mg/kg reduced transcription of c-fos mRNA to 6 and 0.4% of control, respectively.

• Gefitinib also inhibited mitogen-activated protein kinase (MAPK) activity in human A431 and DiFi cancer cell lines (which overexpress EGFR) at growth-inhibitory concentrations.[16] Furthermore, in skin biopsies from patients with NSCLC who received gefitinib in a phase I trial, MAPK expression was markedly reduced compared with pretreatment biopsies;[17] this reduction correlated with a decreased number of proliferating cells (indicated by reduced Ki67 staining and an increase in $p27^{Kip1}$ staining).

• In another study in head and neck SCC lines, gefitinib delayed cell-cycle progression by disrupting regulation of cyclin-dependent kinase 2.[18] Gefitinib (concentrations not reported) induced a complete G1 arrest after 72 hours (as determined by bivariate bromodeoxyuridine/DNA cell cycle kinetic analysis) which was associated with a dose- and time-dependent upregulation of the cyclin-dependent kinase inhibitor $p27^{Kip1}$. The upregulation of $p27^{Kip1}$ coincided with a dose-

dependent reduction in cyclin-dependent kinase 2 activity.

• Gefitinib also inhibits the antiapoptotic Akt/nerve factor (NF)-κB pathway.[19] In NSCLC PC-9 cells, treatment with gefitinib (1 to 100 nmol/L) dose-dependently inhibited tumour necrosis factor-α (TNFα)-induced Akt and I-κB phosphorylation. In addition, gefitinib (10 to 100 nmol/L) significantly inhibited NF-κB transcription activity and NF-κB oligonucleotide binding (as assessed by electromobilty shift assay and a dual-luciferase reporter assay using a specific NF-κB oligonucleotide and plasmid). In contrast, these effects were not observed in NSCLC PC-14 cells, which have demonstrated resistance to gefitinib.[19]

• In another investigation, gefitinib inhibited p21-activated kinase 1 activity (which is required for cell directional motility and survival) in head and neck and breast cancer cell lines.[20] Furthermore, EGFR-induced formation of motile cytoskeleton structures and *in vitro* invasiveness in these cells were completely inhibited by gefitinib (quantitative data not reported).

• Gefitinib 0.5 μmol/L almost completely inhibited EGF-induced production of angiogenic factors vascular endothelial growth factor (VEGF) and interleukin (IL)-8 in A431 and KB3-1 cell lines.[21] In other EGFR-expressing cancer cell lines which were treated for 5 days with differing concentrations of gefitinib,[22] endogenous production of VEGF, TGFα and basic fibroblast growth factor were reduced in a concentration-dependent manner: gefitinib IC_{50} values for the decrease in production of angiogenic factors were similar to those required for inhibition of cell growth.

• Gefitinib also showed antiangiogenic effects *in vivo*.[21,22] In mice with established GEO tumour xenografts that were administered with gefitinib (1.25 to 5 mg/day by intraperitoneal injection for 5 days over 2 weeks), tumour-induced vascularisation (quantified by immunhistochemistry using an anti-factor VIII related-antigen monoclonal antibody) was reduced.[22] Administration of gefitinib (concentration not reported) also blocked EGF-induced neovascularisation of the cornea in mice.[21]

Antitumour Effects of Gefitinib in Non-Small Cell Lung Cancer

In Vitro Studies

• In NSCLC cell lines with high (H226-squamous), moderate (A549-adeno, H157-squamous) and low (H322-adeno) EGFR expression, gefitinib showed dose-related growth inhibition over the range of 0.1 to 10 μmol/L (as determined by flow cytometry in MMT cell viability assays).[23,24] IC_{50} values were similar to those obtained in the very high EGFR-expressing human A431 SCC cell line (0.1 μmol/L).

• This study also evaluated the antiproliferative effects of gefitinib in combination with radiation or other chemotherapeutic agents.[23] According to the combination-index isobologram (CI) equation, synergistic to additive interactions (CI ranging from 0.51 to 1.1) were noted between gefitinib and radiation in all cell lines. In the H226 cell line, combinations of gefitinib with vinorelbine or paclitaxel were synergistic (CI <0.5) whereas additive to antagonistic effects were observed with cisplatin and gefitinib (CI 1 to 1.5).[23,24]

• Gefitinib has also shown antiproliferative effects in cisplatin- and docetaxel-resistant NSCLC cell lines. In PC-9 cells, IC_{50} values in normal and cisplatin-resistant cell lines were equivalent (0.02 μmol/L). PC-14 cells were relatively resistant to gefitinib (IC_{50} = 20 μmol/L); similar IC_{50} values were obtained for cisplatin-resistant (25 μmol/L) and docetaxel-resistant (23 μmol/L) PC-14 cell lines.[25]

• Gefitinib was also shown to increase apoptosis in PC-9 cells[26] and other cell lines[27] when administered at high concentrations. In PC-9 cell cultures,[26] apoptotic cell death (assessed by terminal deoxynucleotide transferase-mediated dUTP nick-end labelling [TUNEL] staining and fluorescence-activated cell sorter analysis) was observed at gefitinib doses > 100 nmol/L; however, concentrations of 3 to 30 nmol/L had no effect.

In Vivo Studies

• In mice with well-established NSCLC tumour xenografts,[28] gefitinib (50 to 200 mg/kg/day) induced dose-related tumour growth inhibition over 2 weeks of treatment. At the maximum tolerated dose (MTD; 150 mg/day), gefitinib produced 70 to 80% growth inhibition of A549 and SK-LC-16 NSCLC tumours and 50 to 55% growth inhibition of LX-1 lung cancer tumours (the latter of which had low EGFR-expression).[28]

• Gefitinib also potentiated the inhibitory effects of several chemotherapy agents on the growth of A549 and LX-1 xenografts,[28] with some combinations resulting in tumour regression (see figure 2). Combination treatment with gefitinib and paclitaxel or docetaxel was particularly effective and several mice became tumour-free; however, tumour regrowth occurred following discontinuation of treatment. In contrast, gefitinib did not improve the activity of gemcitabine.[28]

• In this study,[28] the combination of gefitinib with other chemotherapeutic agents required a ≥2-fold reduction in the gefitinib single-agent MTD dose (150 mg/kg) for optimum tolerance.[28]

• Gefitinib was also shown to enhance radiation sensitivity of NSCLC tumour xenografts in mice.[29] In established A549 or SL-LC-16 tumours (0.4 to 0.6cm diameter), MTDs of fractionated radiotherapy (40 Gy/day for 5 days over 2 weeks) and gefitinib (150 mg/kg) could be administered without significant toxicity. Marked tumour regression (50 to 99%) was observed compared with controls.

• Gefitinib (40 mg/kg by subcutaneous injection) was also shown to increase apoptosis in PC-9 xenografts in mice (as assessed using TUNEL staining and fluorescence-activated cell sorter analysis) in another analysis.[26]

2. Pharmacokinetic Properties

Absorption and Distribution

• Studies in rats and dogs indicated that the oral bioavailability of gefitinib was approximately 50%,

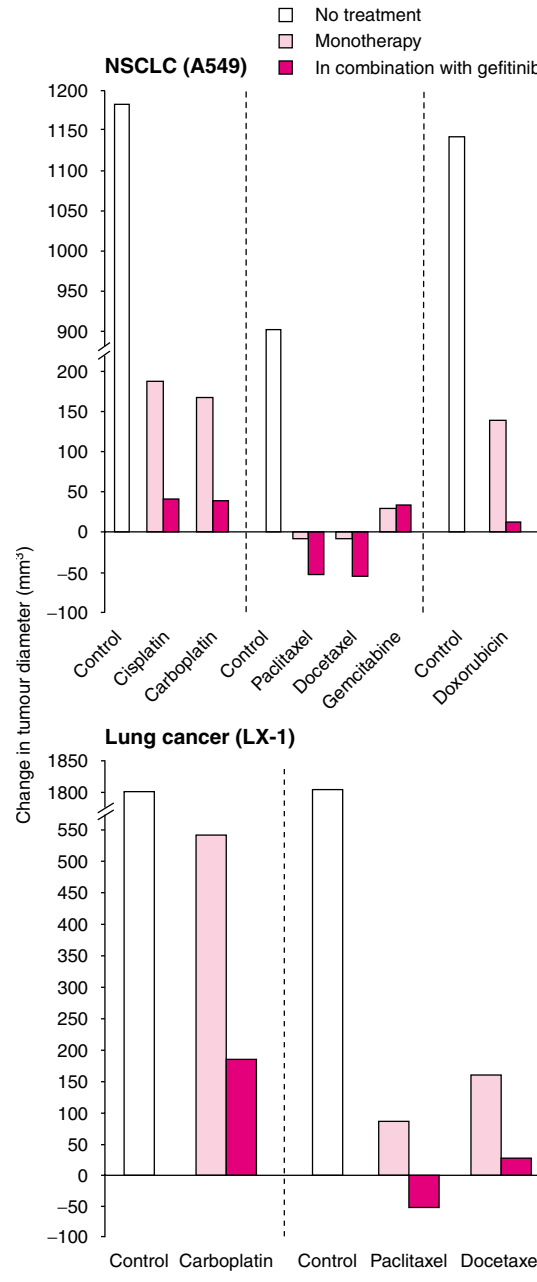

Fig. 2. The antitumour effects of various chemotherapy agents administered alone or in combination with gefitinib (50 or 75 mg/kg) against A549 non-small cell lung cancer (NSCLC) and LX-1 lung cancer tumour xenografts in nude mice (two to three experiments of three to four mice per group; measurements were made 2 to 3 days after dose or at the nadir for a regressing tumour).[28]

with the drug extensively distributed throughout body tissues and organs.[8]

• Maximum plasma concentrations (C_{max}) typically occurred within 3 to 7 hours (t_{max}) following single oral doses of up to 500mg in healthy volunteers,[30,31] and up to 700mg in patients with solid tumours.[32]

• C_{max} and area under the plasma concentration-time curve (AUC) showed a dose-related increase in patients with solid tumours receiving gefitinib 50 to 700mg once daily for 2 weeks (n = 64; 7 to 9 patients per dose group): mean C_{max} ranged from 106 to 2146 μg/L and mean AUC_{24h} ranged from 1670 to 36 077 μg • h/L. Steady-state gefitinib plasma concentrations were achieved by day 7 to 10 for all doses.[32]

• Similar results were found in Japanese patients with solid tumours (n = 31) who received a similar gefitinib administration schedule (50 to 700 mg/day for 2 weeks; 4 to 6 patients per dose group) in another investigation:[33] mean C_{max} ranged from 74 to 1251 μg/L and mean AUC_{24h} ranged from 1236 to 23 356 μg • h/L.

• Consistent with the terminal half life ($t_{½}$; see below), systemic exposure to gefitinib increased with repeated administration. In patients with solid tumours, the mean C_{max} of gefitinib 50mg following a single oral dose (43 μg/L) was more than doubled after 2 weeks of daily treatment (106 μg/L).[32] The AUC was also increased 3-fold from 563 μg • h/L (single dose) to 1670 μg • h/L (multiple dose administration); t_{max} remained the same.

• Food does not have a clinically significant effect on the bioavailability of gefitinib. In a crossover study including 18 healthy volunteers,[30] the mean C_{max} of a single oral dose of gefitinib 50mg was reduced (by 34%) when administered in fed versus fasting conditions; no significant change in any other pharmacokinetic parameter was observed.[30]

• In a second crossover study investigating the effects of food in 25 healthy volunteers receiving a more therapeutically relevant gefitinib dose (250mg),[31] both mean C_{max} and AUC were increased (by 34 and 37%) under fed conditions, but the changes were not considered to be clinically significant.

Metabolism and Elimination

• The mean terminal $t_{½}$ of gefitinib was 34 hours in European patients with solid tumours receiving a single oral dose of 50mg; there was no evidence that $t_{½}$ changed with repeated administration.[32] In patients receiving 50 to 700mg once daily for 2 weeks, the mean $t_{½}$ ranged from 37 to 65 hours (mean of 48 hours across all dose levels).[32] Similar results were obtained in Japanese patients in another investigation.[33]

• Urinary recovery of unchanged gefitinib in healthy volunteers was <0.5% at doses of 1 to 75mg, indicating that renal excretion is not a major route of elimination.[30]

• Gefitinib is metabolised in the liver via the cytochrome P450 (CYP) 3A4 enzyme system. In two crossover studies in healthy volunteers,[34] the C_{max} of gefitinib (500mg) was reduced by 65% when administered in the presence of rifampicin (rifampin) [a potent CYP3A4 inducer; n = 18] and was increased by 32% when administered in the presence of itraconazole (a potent CYP3A4 inhibitor; n = 24); AUC values showed a corresponding decrease of 83% with rifampicin and an increase of 58% with itraconazole.

• No dosage adjustment of gefitinib appears necessary in patients with moderately impaired hepatic function.[35] In 34 patients with solid tumours who received treatment with gefitinib 250mg once daily for 28 days, the mean steady-state AUC values in patients with normal (n = 18) versus moderately impaired hepatic function due to liver metastases (n = 16) were 8.8 versus 9.5 μg • h/L; corresponding C_{max} and steady-state plasma clearance values were 458 versus 517 μg/L and 28.7 versus 26.7 L/h, respectively.

3. Therapeutic Trials

The efficacy of monotherapy treatment with gefitinib has been investigated in patients with NSCLC. The primary clinical endpoint was tu-

mour response; however, due to the preliminary nature of most reports, information on response criteria was not always provided. According to the World Health Organisation criteria,[36] a complete response is defined as the disappearance of all detectable malignant disease for ≥4 weeks, a partial response is a ≥50% decrease in tumour size for ≥4 weeks, stable disease is no change in lesions (±25%), and progressive disease is a ≥25% increase in one or more measurable lesions; an objective response includes complete and partial responses.

Phase I Trials

The antitumour effects of oral gefitinib have been reported in four phase I dose-escalation trials including patients with NSCLC or other solid tumours who received intermittent treatment (14 days of therapy followed by 14 days of observation)[32,33] or continuous treatment (28 days).[37] The majority of patients had heavily pretreated and/or refractory tumours; only results from patients with NSCLC are presented here.

- In the only fully-published investigation,[32] 64 patients with solid tumours received intermittent treatment with gefitinib (50 to 700 mg/day; 7 to 10 patients per dosage level). Of the 16 patients with NSCLC, four (25%) had a partial response within 2 to 12 weeks of treatment (300, 400, 525 and 700mg dose) which lasted for approximately 2 to 26+ months; three additional patients with NSCLC had stable disease.

- In another study conducted in Japan (n = 31; 23 with NSCLC)[33] which investigated a similar intermittent gefitinib administration schedule (50 to 700 mg/day; 4 to 6 patients per dosage group), five patients with NSCLC (22%) showed a confirmed partial response. These responses were observed at doses of 225 (1 patient), 400 (1 patient), 525 (2 patients) and 700mg (1 patient) and persisted for 4, 6+, 1, 3+ and 2+ months, respectively.

- Two other phase I trials (combined total of 127 patients; 50 with NSCLC)[37] investigated a continuous administration schedule of gefitinib (150 to 1000 mg/day; 14 patients per dosage level). At the time of follow-up, a total of 193 28-day cycles had been completed (median of two per patient, range one to eight). Among those with NSCLC, one patient had a confirmed partial response (150mg dose, lasting for 9+ months) and two had a reduction in measurable disease.[37]

Phase II Trials

Two double-blind, randomised phase II trials (IDEAL-1 and IDEAL-2) have evaluated the antitumour activity of oral gefitinib in patients with metastatic or locally advanced NSCLC. Patients in IDEAL-1 had failed one or two previous chemotherapy regimens (at least one of which was platinum-based)[38] whereas patients in IDEAL-2 had failed two or more chemotherapy regimens containing platinum and docetaxel.[39] Both studies investigated gefitinib dosages of 250 and 500 mg/day, given continuously until disease progression or unacceptable toxicity.

In addition to tumour response, both trials evaluated disease-related symptoms and quality of life according to the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire and its seven-item disease-specific Lung Cancer Subscale (LCS).[40,41] An improvement in disease-related symptoms and quality of life was prospectively defined as a ≥2-point increase in LCS and ≥6-point improvement in the FACT-L, respectively, lasting for ≥4 weeks. Symptom improvement was a primary endpoint in IDEAL-2 (but not IDEAL-1). All evaluated patients were symptomatic at baseline (LCS ≤24); median LCS scores (which range from 0 [worst] to 28 [best]) ranged from 16 to 18 and median FACT-L scores (which range from 0 [worst] to 316 [best]) were ≈85 in both studies.

Results of these studies are available in abstract/poster form only.[38-41]

- IDEAL-1 included 210 patients who had failed to respond to one (56%) or two (44%) prior chemotherapies.[38] In the 250 and 500 mg/day dosage groups, the percentage of patients achieving an objective response (18.4 *vs* 19%) or with stable dis-

ease (36 *vs* 32.4%) was similar, as was median progression-free (2.7 *vs* 2.8 months) and overall survival (7.8 *vs* 8.1 months). Overall, objective response rates were similar in patients receiving gefitinib as second- or third-line treatment (17.9 and 19.8%, respectively).[38]

• In the 140 patients in IDEAL-1 who were evaluated for symptom response (i.e. those with LCS ≤24),[41] 40% receiving gefitinib 250mg and 37% receiving gefitinib 500mg showed an improvement (median time to symptom improvement was 8 days). Compared with patients who showed no improvement, patients who improved had a longer progression-free survival (4.2 *vs* 2.0 months) and longer overall survival (median not reached *vs* 6.7 months). Symptom improvement was correlated with tumour response (see figure 3).[41]

• Patients in IDEAL-1 who were evaluated for symptom response (n = 140) also showed an improvement in quality of life. An improvement in FACT-L was observed in 23.9 and 21.9% of patients receiving gefitinib 250 and 500 mg/day, respectively (median time to improvement of 29 days).[41]

• Similar results were obtained in IDEAL-2. Patients in this study (n = 216) had received two (41%), three (33%) or four or more (25%) prior chemotherapy regimens containing platinum and docetaxel.[39] In patients receiving gefitinib 250 and 500 mg/day, 11.8 and 8.8% showed an objective response which persisted for 3 to 7+ months and 31 and 27% had stable disease. Median survival was 6.1 and 6.0 months in the 250 and 500mg groups, respectively.[39]

• Symptom improvement was a primary endpoint in IDEAL-2[40] and all patients were symptomatic at study entry. In patients receiving 250 and 500 mg/day, an improvement was observed in 43 and 35%, respectively. Symptom response was rapid (median time to improvement of 9 to 10 days) and lasted 1 to 7+ months. In addition, patients who showed a response had a longer survival duration than those who did not show a response (8.1 *vs* 3.7 months). As observed in IDEAL-1, symptom improvement was correlated with tumour response (see figure 3).[40]

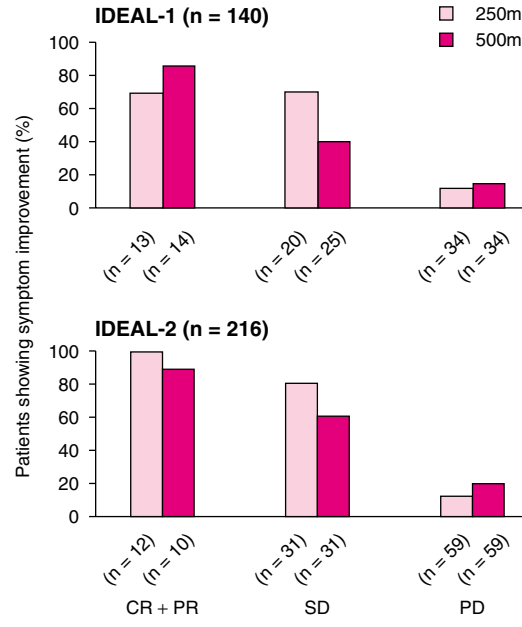

Fig. 3. Symptom improvement according to response in patients with pretreated metastatic or locally advanced non-small cell lung cancer who received oral gefitinib 250 or 500mg once daily in two double-blind, randomised phase II trials (IDEAL-1[41] and IDEAL-2[40]). Symptom improvement was defined as ≥2-point increase in the Lung Cancer Subscale lasting for ≥4 weeks. **CR** = complete response; **PD** = progressive disease; **PR** = partial response; **SD** = stable disease.

• Patients in IDEAL-2 also showed an improvement in quality of life:[40] 34.3 and 22.8% of patients receiving gefitinib 250 and 500 mg/day, respectively, showed an improvement in FACT-L scores and the median time to improvement was 30 and 29 days, respectively.

4. Tolerability

Gefitinib was generally well tolerated in phase I[32,33,37] and II[38,39] clinical trials in patients with NSCLC or other solid tumour types. Adverse events were usually mild and transient and the most commonly occurring events were grade 1/2 skin changes (rash, acne, dry skin, pruritus) and

grade 1/2 gastrointestinal effects (diarrhoea, vomiting, nausea); a low incidence (<9%) of drug-related grade 3/4 adverse events was reported in patients receiving gefitinib 250 mg/day. In all studies, adverse events were graded according to Common Toxicity Criteria and treatment was continued until disease progression or unacceptable adverse events occurred.

• Adverse events occurring in two dose-escalation studies conducted in Europe (n = 64)[32] and Japan (n = 31)[33] in patients receiving intermittent gefitinib treatment (50 to 700 mg/day; 14 consecutive days of treatment every 28 days) are outlined in figure 4. In both these studies, 700 mg/day was considered the MTD because of the occurrence of drug-related grade 3/4 adverse events (including diarrhoea, elevated hepatic transaminases, vomiting, abdominal pain); this dosage is well above that shown to have antitumour efficacy (see section 3).

• Skin reactions (rash/acne) occurred in approximately 50% of patients in both trials.[32,33] This event was grade 1/2 in all but one patient receiving 525 mg/day in the European study. Symptoms usually appeared by day 10 to 14 of treatment and resolved or decreased in intensity during the off-treatment period or upon treatment withdrawal.[32] Skin reactions were generally more common in patients receiving higher doses: 77 to 100% of patients in the 525 and 700mg dose groups experienced this event in both studies.[32,33]

• Diarrhoea was another frequent event, occurring in 53% of patients in the European study.[32] This was grade 1/2 in all patients except those receiving gefitinib 700 mg/day: three of nine patients in the European study[32] and one of six patients in the

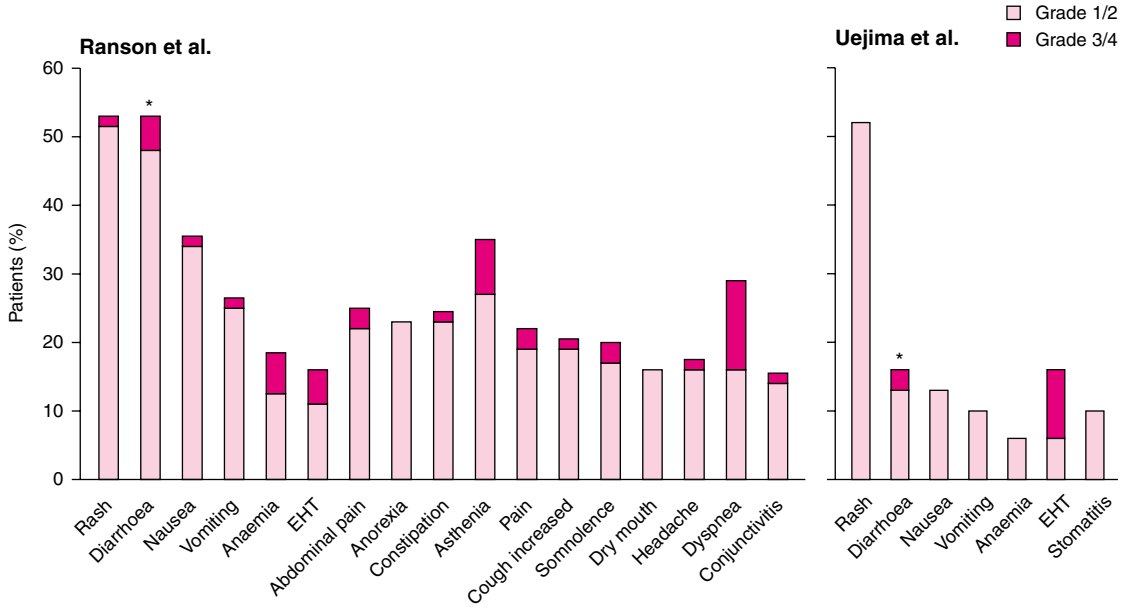

Fig. 4. Adverse events reported in two dose-escalation studies in patients with a range of solid tumour types receiving intermittent oral gefitinib treatment over the dosage range of 50 to 700 mg/day (14 days of therapy followed by 14 days of observation). The first study (Ranson et al.)[32] included 64 patients (n = 7 to 10 per dosage group) who received a total of 154 treatment cycles (range 1 to 14 per patient, median of 2); the second study (Uejima et al.)[33] included 31 Japanese patients (n = 4 to 6 per dosage group) who received a total of 62 treatment cycles (range 1 to 9 per patient). Results of the second study were presented in a poster.[33] Adverse events were graded according to Common Toxicity Criteria; **EHT** = elevated hepatic transminases; * indicates that grade 3/4 toxicities only occurred in patients receiving gefitinib 700 mg/day.

Japanese study[33] experienced grade 3/4 diarrhoea at this dosage level.

• Other grade 3/4 events occurring in the European study were generally isolated reports, inconsistently observed and usually associated with the patient's tumour type and location. Grade 3/4 events occurring in ≥2 patients included dyspnoea (n = 8; only observed in patients with NSCLC or ovarian cancer with ascites), asthenia (n = 5), anaemia (n = 4), increased hepatic transaminases (n = 3), abdominal pain (n = 2), pain (n = 2) and somnolence (n = 2). Not all events were clearly drug-related.[32]

• Similar tolerability findings were reported in two ongoing phase I studies (n = 127) evaluating the tolerability of continuous gefitinib administration (150 to 1000 mg/day).[37] A total of 193 28-day cycles (median of 2 per patient; range 1 to 8) have been completed to date and the most frequent adverse events were grade 1 to 2 skin changes (58% of patients), diarrhoea (44%), nausea (25%) and vomiting (22%). At the time of reporting, the MTD had not yet been reached and the 800 mg/day dosage is under evaluation.

• In two phase II trials (IDEAL-1[38] and IDEAL-2[39]) including 210 and 216 patients with NSCLC who were followed for up to 8 months, grade 3/4 drug-related adverse events occurred in 8.7 and 6.9% of those receiving gefitinib 250 mg/day and 30.2 and 17.5% of those receiving 500 mg/day. As observed in phase I studies, the most commonly occurring drug-related events were grade 1/2 skin reactions and diarrhoea (quantitative data not reported).[38,39]

5. Dosage and Administration

• Gefitinib has recently been approved in Japan for use in patients with inoperable or recurrent NSCLC at a dosage of 250mg once daily.[42,43] This dosage was found to have equivalent efficacy to 500 mg/day and caused fewer grade 3/4 adverse events in two phase II trials.[38,39]

• Phase I clinical data suggest that dosages of up to 700 mg/day are generally well tolerated in patients with NSCLC or other tumour types.[32,33]

• Results of one pharmacokinetic analysis[35] suggest that dosage adjustment is not necessary in patients with mild to moderate hepatic impairment (see section 2).

• Drugs which affect the CYP3A4 enzyme system may influence the metabolism of gefitinib.[34]

6. Gefitinib: Current Status

Gefitinib has recently been approved in Japan for the monotherapy treatment of recurrent or inoperable NSCLC and is currently under regulatory review in several countries including the US, Switzerland and Australia.[43] In addition, several clinical trials evaluating the efficacy of gefitinib in combination with other chemotherapy and/or radiotherapy regimens in patients with NSCLC have been reported,[44-46] and early encouraging results have been obtained in patients with head and neck cancer.[46]

The recommended dosage of gefitinib for monotherapy treatment in patients with NSCLC is 250mg once daily.[42] In two randomised, double-blind trials, 250 mg/day showed equivalent efficacy to 500 mg/day and was associated with a lower frequency of grade 3/4 drug-related adverse events. These results from the IDEAL trials show that monotherapy treatment with gefitinib is an effective treatment option in patients with NSCLC who have previously received platinum-based treatment.

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Correspondence: *Christine R. Culy*, Adis International Limited, 41 Centorian Drive Private Bag 65901, Miarangi Bay, Auckland 10, New Zealand.
E-mail: demail10@adis.co.nz