Gefitinib

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Contents

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Abstract

Gefitinib is an orally active selective inhibitor epidermal growth factor receptor (EGFR). The large randomised phase III IPASS study (gefitinib 250 mg, daily vs carboplatin and paclitaxel) showed a beneficial effect on progression-free survival (PFS) and quality of life in selected patient populations under the treatment with gefitinib (HR for TKI 0.74; 95% CI: 0.65–0.85). In the subgroup of patients with EGFR mutation the effect of gefitinib on PFS was notably, PFS HR 0.48; 95% CI: 0.36–0.64, $p < 0.001$) and the objective response rate (RR) was 71.2% with gefitinib versus 47.3% with chemotherapy. However no significant difference of overall survival was found. Based on this study gefitinib was approved for the first-line treatment of the patients with non-small cell lung cancer (NSCLC) with sensitising EGFR mutations (exon 19 deletion or L858R point mutation). Gefitinib is metabolized in the liver. Most of the adverse effects of gefitinib, such as rash, dry skin and diarrhoe, are mild to moderate in severity and are reversible.

Keywords

Non-small cell lung cancer · Epidermal growth factor receptor (EGFR) · EGFR mutation · Tyrosine kinase inhibitor (TKI) · Gefitinib

1 Introduction

Gefitinib (originally coded ZD1839) is an orally bioavailable, competitive, reversible inhibitor of epidermal growth factor receptor's (EGFR) tyrosine kinase domain, which interrupts signaling in target cancer cells with mutated and overactive EGFR. EGFR (HER-1/ErbB1) is a receptor tyrosine kinase of the ErbB family, which also includes Erb2 (HER2), ErbB3 (HER3), and ErbB4 (HER4). EGFR is overexpressed in many human epithelial malignancies including non-small cell lung cancer (NSCLC) (Hirsch et al. 2003). It is linked to multiple signaling pathways involved in tumor growth and angiogenesis such as the Ras/Raf pathway and the PI3K/Akt pathways (Bronte et al. 2014). These pathways ultimately lead to the activation of transcription factors such as Jun, Fos, and Myc, as well as cyclin D1, which stimulate cell growth and mitosis. Uncontrolled cell growth and mitosis lead to cancer. The activating mutations cause ligand-independent activity of receptor tyrosine kinases and occur in 8–15% of patients with NSCLC worldwide (Shigematsu et al. 2005; Pao et al. 2004). These mutations cause structural alterations in the ATP-binding site of the intracellular domain of EGFR as demonstrated by biochemical and crystallographic analyses. Specific missense and deletion mutations in the tyrosine kinase domain of the EGFR genes are most often located in exon 19 as a base pair deletion (delE746_A750; del19) or a substitution of arginine for leucine at position 858 in

exon 21 (L858R). The mutants possess increased affinity for tyrosine kinase inhibitors (TKI) such as gefitinib, erlotinib, afatinib, and osimertinib and lead to clinical response (Arteaga and Engelman 2014). These EGFR mutations are more seen in the patients' subgroup of adenocarcinoma histology, female gender, Asian ethnicity and never-smoking status, stage IV disease at diagnosis, the presence of bone metastases, and the absence of adrenal metastases ($p \leq 0.03$). EGFR mutations occur at about 47.9% Asian patients with adenocarcinoma compared with 15% in Caucasian/European patients (Sholl et al. 2015).

2 Structure and Mechanism of Action

Gefitinib is a low-molecular-weight 4-(3′-chloro-4′-Fluoroanilino)-7-methoxy-6-(3-morpholinopropoxy) quinazoline, $C_{22}H_{24}C1FN_4O_3$, a synthetic anilinoquinazoline compound (Fig. 1).

Gefitinib selectively binds to the adenosine triphosphate (ATP)-binding site of the EGFR tyrosine kinase domain. Thus, the autophosphorylation of the EGFR is inhibited, which results in inhibition of the Ras signal transduction pathway. Gefitinib is a selective inhibitor of the EGFR tyrosine kinase which is also referred to as HER1 or ErbB-1 (Lynch et al. 2004). Thus, the activation of the EGFR tyrosine kinase by the anti-apoptotic Ras signal transduction cascade is inhibited interrupting the uncontrolled cell proliferation leading to induction of apoptosis in cancer cells.

Research on gefitinib-sensitive non-small cell lung cancers has shown that a mutation in the EGFR tyrosine kinase domain is responsible for activating anti-apoptotic pathways (Sordella et al. 2004; Arteaga and Engelman 2014) (Table 1).

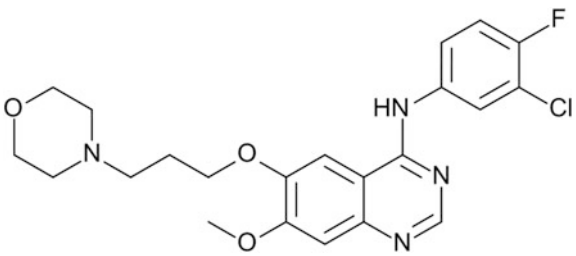

Fig. 1 Structure of gefitinib (*N*-(3-Chloro-4-fluorophenyl)-7-methoxy-6-[3-(morpholin-4-yl)propoxy]chinazolin-4-amin)

Table 1 Efficacy (IC_{50} values) of the EGFR kinase inhibitors gefitinib and afatinib in *EGFR* mutant Ba/F3 cells

EGFR Genotype	Gefitinib (nM)	Afatinib (nM)
L718Q	513	2.76
L844V	154	3.3
ΔE746_A750	43.8	0.52
ΔE746_A750/L718Q	61	2
ΔE746_A750/C797S	12.6	15.7
ΔE746_A750/L844V	24.36	0.66
ΔE746_A750/T790M	>3300	232
ΔE746_A750/T790M/L718Q	>3300	2115
ΔE746_A750/T790M/L844V	>3300	877
ΔE746_A750/T790M/C797S	>3300	678
L858R	49.84	0.51
L858R/L718Q	1117	7.94
L858R/C797S	72.7	185
L858R/L844V	147	1.02
L858R/T790M	>3300	1250
L858R/T790M/L718Q	>3300	1209
L858R/T790M/L844V	>3300	436
L858R/T790M/C797S	>3300	>3300

Modified from Ercan et al. (2015)

3 Pharmacology

Gefitinib is absorbed slowly after oral administration with a mean bioavailability of 60%. Peak plasma levels occur 3–7 h post administration. The mean elimination half-life is 48 h.

The bioavailability of gefitinib is not significantly altered by food intake. In the blood, gefitinib is bound to 90% to serum albumin and alpha 1-acid glycoproteins (independent of drug concentrations). Gefitinib is eliminated by hepatic metabolism, primarily via cytochrome P450 isoenzyme 3A4 (CYP3A4) and much less by CYP3A5 and CYP2D6. Three sites of biotransformation have been identified: metabolism of the N-propoxymorpholino group, demethylation of the methoxy substituent on the quinazoline, and oxidative defluorination of the halogenated phenyl group. Excretion is predominantly via the feces (86%), with renal elimination of drug and metabolites accounting for less than 4% of the administered dose (Campbell et al. 2010). The very high distribution volume of gefitinib (1400 l) indicates that gefitinib is extensively distributed throughout the body in tissues such as liver, kidney, gastrointestinal tract, lung, and in tumors. In nonclinical studies, a single dose of 12,000 mg/m^2 (about 80 times the recommended clinical dose on an mg/m^2 basis) was lethal to rats. Half of this dose did not cause mortality in mice.

4 Clinical Data

4.1 Phase I

In several phase-I studies, the maximum tolerated doses (MTDs) were 800 and 1000 mg/day, respectively (Baselga et al. 2002; Herbst et al. 2002). The antitumor activity was apparent at much lower doses, in particular, in patients with EGFR mutations. The acute toxicity of gefitinib up to 500 mg in clinical studies has been low. Symptoms of overdose include diarrhea and skin rash. The recommended dose of gefitinib is 250 mg per day as a single dose with or without food.

4.2 Phase II/III

The first trials with gefitinib were for unselected populations of patients with advanced NSCLC.

On the basis of encouraging results emerging from phase-II studies (The IDEAL trial), which showed a good activity profile of gefitinib as second/third-line treatment in terms of response rate (RR), a multicentre randomized phase-III trial (ISEL) was conducted comparing the efficacy of this drug versus placebo (Fukuoka et al. 2003). The ISEL study failed to demonstrate an overall survival (the primary endpoint) benefit for gefitinib in an unselected population of predominantly refractory patients with advanced NSCLC (hazard ratio [HR] 0.89; 95% confidence interval [CI] 0.77–1.02; $p = 0.087$; median survival 5.6 vs. 5.1 months). However, gefitinib prolonged median overall survival in never smokers (8.9 vs. 6.1 months; HR = 0.67; 95% CI 0.49–0.92; $p = 0.012$) and the Asian population (9.5 vs. 5.5 months; HR = 0.66; 95% CI 0.48–0.91; $p = 0.01$). The rate of responses was 8% (Thatcher et al. 2005).

In the Phase-III INTEREST (IRESSA NSCLC trial evaluating response and survival against Taxotere) study, gefitinib was compared with docetaxel in the second-line and third-line setting in patients with NSCLC not selected on the basis of clinical or molecular characteristics. The overall survival with gefitinib in unselected patients was not inferior to docetaxel. Median overall survival was 7.6 months in the gefitinib group and 8.0 months in the docetaxel group (HR = 1.020; 96% CI 0.905–1.150). Progression-free survival was similar for gefitinib and docetaxel (593 [90.0%] vs. 544 [82.8%] events; HR 1.04, 95% CI 0.93–1.18; $p = 0.47$; median progression-free survival (PFS) 2.2 vs. 2.7 months). Objective response rates were similar in both treatment groups (9.1% vs. 7.6%; OR 1.22, 95% CI 0.82–1.84; $p = 0.33$). This study reported efficacy in symptom improvement and a better toxicity profile leading to a better quality of life associated with gefitinib treatment (Kim et al. 2008; Douillard et al. 2009).

Further investigations identified that the occurrence of EGFR gene mutations in the kinase domain in specific patient types is strongly associated with response to gefitinib (Lynch et al. 2004).

The first randomized trial to specifically compare gefitinib with chemotherapy in clinically preselected patients with a preplanned subgroup analysis of EGFR-mutated patients was the IPASS (Iressa Pan-Asia Study) trial. The phase-III IPASS trial improved PFS with gefitinib compared with paclitaxel–carboplatin chemotherapy in chemotherapy-naive, never or light smokers with adenocarcinoma histology. The primary outcome of interest was PFS, and the trial was designed to show noninferiority. Participants were not randomly assigned by marker status (presence of EGFR mutation), although the marker analysis was preplanned. The study used the amplification refractory mutation system and EGFR 29-mutation detection testing. Of patients whose tissue was evaluable, almost 60% tested positive for the mutation (primarily exon 21 L858R mutations and exon 19 deletions). In the subset of EGFR mutation-positive patients, PFS was significantly prolonged with gefitinib compared with chemotherapy (HR, 0.74; 95% CI, 0.65–0.85). The study demonstrated the benefit of first-line EGFR TKI over platinum-based combination chemotherapy in patients with EGFR mutation prospectively.

This biomarker translational study of 447 patients with tumor samples available for EGFR mutation analysis confirmed that the benefit is confined to patients with activating mutation (HR for PFS, 0.48; 95% CI, 0.36–0.64), while EGFR mutation-negative patients had a significantly better PFS if treated with chemotherapy (see Fig. 2).

The tumor response rate was significantly higher in patients with activating mutation if they were treated with first-line gefitinib.

Gefitinib showed similar overall survival to chemotherapy with no significant difference in the overall population or in patients with EGFR mutation. However, 64.3% of patients in the chemotherapy arm with activating EGFR mutation received gefitinib as salvage therapy on disease progression post-chemotherapy. This crossover treatment explains the similarity in OS rates between the two treatment arms in the subgroup of patients with activating EGFR mutation (HR, 1.00; 95% CI, 0.76–1.33). Gefitinib improved significantly symptoms related to lung cancer (75.6% vs. 53.9%; OR, 2.70; 95% CI, 1.58–4.62; $p < 0.001$) (Mok et al. 2009; Yang et al. 2008). The IPASS trial was a milestone for the understanding of the activity of gefitinib in patients with EGFR-mutated lung cancer.

The First-SIGNAL [First-Line Single-Agent Iressa Versus Gemcitabine and Cisplatin Trial in Never Smokers with Adenocarcinoma of the Lung] was conducted exclusively in Korea. The study design was similar to that of IPASS, but the primary endpoint was OS. Gefitinib as a first-line therapy did not demonstrate superiority in OS compared with chemotherapy in these clinically selected Korean patients (in never smokers with lung adenocarcinoma at stage IIIb/IV) (HR, 0.932; 95% CI, 0.716–1.213; $p = 0.604$; median OS, 22.3 vs. 22.9 months, respectively). The 1-year PFS rates were 16.7% with gefitinib and 2.8% with chemotherapy (HR, 1.198; 95% CI, 0.944–1.520). Response rates were 55% with gefitinib and 46% with chemotherapy ($p = 0.10$). Only 14% patients had EGFR-mutated lung cancer,

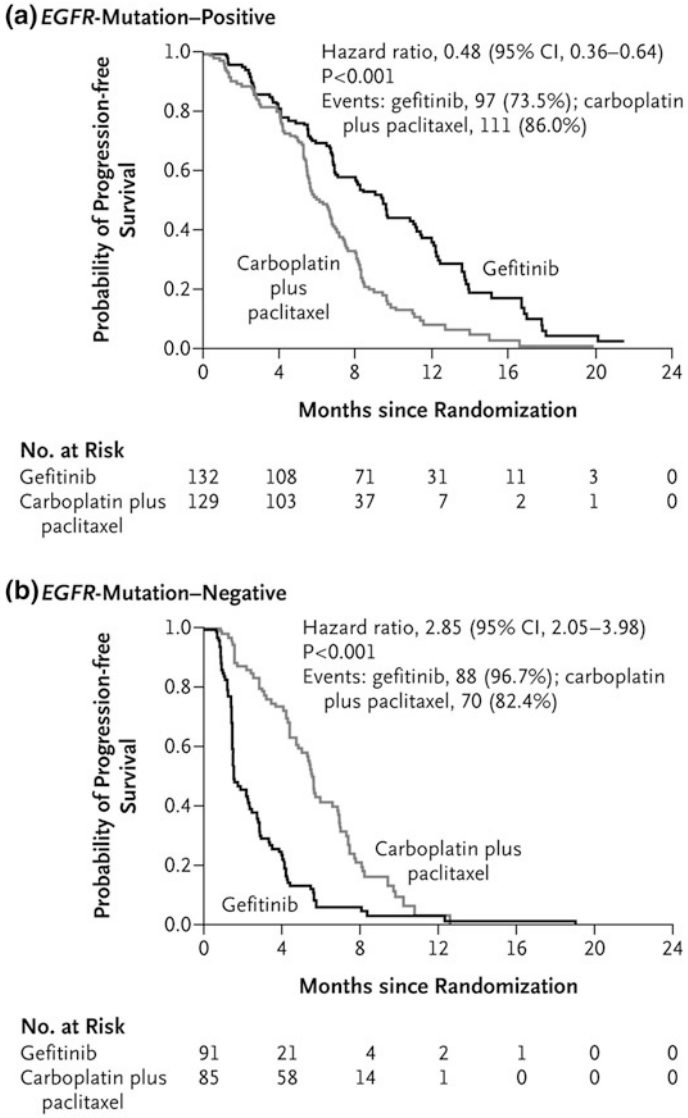

Fig. 2 Progression-free survival curves in EGFR-positive (**a**) and EGFR-negative (**b**) patients (adapted from Mok et al. NEJM 2009)

and the results of the EGFR mutation-positive subgroup for PFS and overall response were limited in number and were in contrast to other trials (Han et al. 2012).

Two randomized Japanese trials, NEJ002 and WJTOG, compared first-line treatment of EGFR-mutated NSCLC with gefitinib versus carboplatin–paclitaxel

and gefitinib versus cisplatin–docetaxel, respectively (Maemondo et al. 2010; Mitsudomi et al. 2010).

The results of the NEJ002 study showed the clear superiority of gefitinib in patients with EGFR-mutated NSCLC with significant improvement in PFS (median PFS 10.8 vs. 5.4 months HR: 0.30, $p < 0.001$) compared with paclitaxel–carboplatin in chemotherapy-naive patients (Maemodo et al. 2010).

The WJTOG3405 phase-III trial supports the IPASS results by showing that Japanese patients with EGFR-mutated NSCLC who received gefitinib had a median progression-free survival time of 9.2 (95% CI, 8.0–13.9) versus 6.3 months (95% CI, 5.8–7.8; HR, 0.489; 95% CI, 0.336–0.710; $p < 0.0001$) for those treated with cisplatin plus docetaxel. The objective response rate was significantly higher among patients receiving gefitinib (62.1%) versus patients receiving chemotherapy (32.2%) (Mitsudomi et al. 2010).

In all these trials, almost all patients who progressed after first-line chemotherapy received gefitinib as second-line treatment. Because of the high crossover rate, the OS was similar in both arms.

A metaanalysis of the IPASS, North-East Japan, West Japan, and first-SIGNAL trials confirms the results of studies comparing chemotherapy and gefitinib in first-line treatment. A higher RR (72% vs. 38% OR: 4.04) and a statistically significant increase in PFS (HR: 0.45) in patients with EGFR-mutated NSCLC treated with gefitinib could be demonstrated (Ku et al. 2011).

In 2009 on the basis of IPASS study, EMA approved gefitinib for the treatment of locally advanced or metastatic NSCLC in all treatment lines limited to patients bearing activating mutations of the EGFR gene (Table 2).

Gefitinib was used as control arm in three phase-IIb or phase-III studies investigating the efficacy of the second- and third-generation EGFR TKIs afatinib (phase-IIb:LUX-LUNG 7), dacomitinib (phase-III: ARCHER), and osimertinib (phase-III:FLAURA) in advanced or metastatic EGFR-mutated NSCLC, respectively (Paz-Ares et al. 2017; Wu et al. 2017; Soria et al. 2018).

Key results are shown in Table 3.

Table 2 First-line treatment of EGFR mutant NSCLC: Gefitinib versus Chemotherapy (CT)

Trial	TKI	Patient group	PFS (month)			OS
			TKI	Chemo	HR (95% CI)	HR (95% CI)
IPASS	Gefitinib	Asian	9.5	6.3	0.48 (0.36–0.64)	0.78 (0.50–1.20)
First signal	Gefitinib	Korean	8.4	6.7	0.61 (0.31–1.22)	0.82 (0.352–1.922)
NEJ002	Gefitinib	Japanese	10.8	5.4	0.322 (0.236–0.438)	0.88 (0.634–1.241)
WJTOG3405	Gefitinib	Japanese	9.6	6.6	0.52 (0.378–0.715)	1.185 (0.767–1.829)

Table 3 First-line treatment of EGFR mutant NSCLC: Gefitinib versus second- or third-generation EGFR TKI

Trial	TKI	Patient group	PFS (month)			OS
			2nd/3rd Gen TKI	Gefitinib	HR (95% CI)	HR (95% CI)
Lux-Lung 7	Afatinib versus Gefitinib	Asian and Non-Asian	11.0	10.9	0.73 (057–0.95) $p = 0.0165$	0.86 (0.86–1.12) $p = 0.2850$
ARCHER	Dacomitinib versus Gefitinib	Asian and Non-Asian	14.7	9.2	0.59 (0.47–0.74) $p < 0.0001$	*
FLAURA	Osimertinib versus Gefitinib or erlotinib	Asian and Caucasian	18.9	10.2	0.46 (0.37–0.57) $p < 0.001$	0.63 (0.45–0.88) $p = 0.007$

*OS at 18 months

4.3 Gefitinib in Combination with Chemotherapy

The concomitant administration of gefitinib and chemotherapy was investigated in a randomized, placebo-controlled trial, The Iressa NSCLC Trial Assessing Combination Treatment (INTACT 2). In this phase-III study, combining gefitinib with paclitaxel and carboplatin in chemotherapy-naive patients with advanced NSCLC did not show a survival benefit for the combination compared to chemotherapy alone (Herbst et al. 2004).

4.4 Resistance to EGFR TKI

The main limitation of the widespread benefits of first- and second-generation EGFR TKIs is the development of acquired resistance in patients with EGFR-mutated NSCLC treated with these drugs. Resistance mutations, e.g., EGFR-T790M, are located at the gatekeeper amino acid residue. This genomic event is present in 60–65% of cases with acquired resistance but recent studies using highly sensitive methods suggest a frequency of up to 35% detection in pretreatment biopsies. T790M abrogates the inhibitor effects of first-generation EGFR TKI by increasing the affinity of the receptor for ATP, leading to disruption of kinase–drug binding and activation of downstream signaling pathways. Other mechanisms of acquired resistance include bypass mechanisms comprising the hepatocyte growth factor receptor (MET), ERBB2, and others. These changes are detected in <15% and can be co-identified with EGFR-T790M in the same tumour sample. Furthermore, cases of tumour transformation to small-cell lung cancer has been seen (for review, see Arteaga and Engelman 2014).

5 Toxicity

The analysis of data from IPASS trial about toxic effects of gefitinib shows a good tolerability profile, with an incidence of adverse events significantly lower compared to chemotherapy (61–13% for chemotherapy vs. gefitinib $p < 0.001$; dose reduction of 35% vs. 16% for gefitinib).

The most frequently reported adverse events (AE) were skin rash (acneiform eruption), diarrhea, and nausea. These were observed within the first month of therapy and generally reversible. Most of the side effects of gefitinib were mild to moderate (grade 1/2). Hepatotoxicity (asymptomatic hypertransaminasemia) occurs rarely and recovered upon discontinuation of therapy. In addition, clinical trials have reported adverse pulmonary events related to gefitinib including interstitial lung disease (ILD) (serious adverse effect in 1% patients worldwide). The incidence is highest in patients of Asian origin, more frequently in Japanese patients (4–6%) than in Caucasian (0.2–0.3%).

Health-related quality of life (QoL) is an important end point for anticancer therapy. Four of the six randomized studies have captured QoL as a secondary end point. Given its lower toxicity profile and higher efficacy, QoL of patients receiving first-line EGFR TKI is better than that of patients receiving first-line chemotherapy. In the IPASS study, improvement in QoL was significantly greater in the gefitinib arm in patients with known activating EGFR mutation, while the opposite was observed in patients with EGFR wild type. A sustained, clinically relevant improvement in global QoL by Functional Assessment of Cancer Therapy-Lung (FACT-L) was observed in 70.2% of EGFR mutation-positive patients treated with gefitinib compared with 44.5% of patients treated with chemotherapy (odds ratio [OR], 3.01; 95% CI, 1.79–5.07; $p < 0.001$).

Compared to the second-generation EGFR TKIs afatinib and dacomitinib with irreversible ATP competition gefitinib has a favorable toxicity profile (Paz-Ares et al. 2017; Wu et al. 2017), while in the FLAURA study osimertinib had also few side effects (see regarding chapters in this book).

6 Drug Interactions

Drugs that induce CYP3A4 activity increase the metabolism of gefitinib. In patients receiving a potent CYP3A4 inducer such as rifampicin or phenytoin, a dose of gefitinib can be increased to 500 mg/day but only in the absence of severe adverse drug reaction (more rash and diarrhea). Patients taking warfarin should have their International Normalized Ratio (INR) monitored. INR elevations and bleeding events have been reported in patients taking both gefitinib and warfarin. Drugs that inhibit CYP3A4 activity (ketoconazole, itraconazole, and others) can lead to higher gefitinib plasma concentrations. H2-receptor antagonists such as ranitidine or cimetidine may reduce plasma concentrations of gefitinib by causing sustained elevations in gastric pH (Shah et al. 2005).

7 Summary and Perspective

For first-line therapy of patients with EGFR-mutated stage IV NSCLC the TKIs erlotinib, gefitinib, afatinib, and osimertinib have been approved. Compared to platinum-containing chemotherapy, PFS, RR, and quality of life are significantly higher in patients treated with EGFR TKIs. Gefitinib was one of the first TKI to be introduced. Gefitinib is effective in terms of PFS and RR in NSCLC patients harboring an EGFR exon 19 deletion or L858R mutation, as seen in the trials mentioned above. The substance has a good toxicity profile. In a direct comparison of gefitinib with afatinib, the side effects were favorable for gefitinib. Comparison with osimertinib showed better efficacy of the latter with regard to PFS, and OS data are awaited and comparable toxicity.

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