Review Article

Gefitinib in the treatment of nonsmall cell lung cancer with activating epidermal growth factor receptor mutation

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Abstract

Lung cancer is still the main cause of cancer-related deaths worldwide, with most patients present with advanced disease and poor long-term prognosis. The aim of lung cancer treatment is to slow down the progression of the disease, to relieve the patients from the lung cancer symptoms and whenever possible, to increase the overall survival. The discovery of small molecule targeting tyrosine kinase of epidermal growth factor receptor opens a new way in the management of advanced nonsmall cell lung cancer (NSCLC). This review will discuss several Phase II and III trials evaluated the clinical efficacy of gefitinib as monotherapy in pretreated patients with advanced NSCLC, as well as both monotherapy and combined with chemotherapy in chemotherapy-naive patients.

Key words: Clinical trials, epidermal growth factor receptor, gefitinib, nonsmall cell lung cancer

INTRODUCTION

Lung cancer is the leading cancer site in males, comprising 17% of the total new cancer cases and 23% of the total cancer deaths.[1] Among females, it was the fourth most commonly diagnosed cancer and the second leading cause of cancer death.[1] Approximately 80-85% of all lung cancers are nonsmall cell lung cancer (NSCLC), which include squamous cell carcinoma, adenocarcinoma, and large-cell carcinoma.[2] The epidermal growth factor receptor (EGFR) is detected by immunohistochemistry on 40-80% of NSCLC.[3]

EGFR (HER-1/ErbB1) is a receptor tyrosine kinase (TK) of the ErbB family, which consists of four closely related receptors: HER-1/ErbB1, HER-2/neu/ErbB2, HER-3/ErbB3, and HER-4/ErbB4.[4] Upon ligand binding and receptor homo- or hetero-dimerization and activation (phosphorylation), activated EGFR signals downstream to the phosphatidylinositol-4,5-bisphosphate 3-kinase/AKT and RAS/RAF/mitogen-activated protein kinases pathways that regulate key cellular processes such as proliferation and apoptosis.[4] In addition, EGFR autocrine pathway plays a crucial role in human cancer, contributing to a number of highly relevant processes in tumor development and progression, including angiogenesis, and metastatic spread.[5]

Accordingly, targeting EGFR has been intensely pursued, with the development of a series of

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promising molecular inhibitors for use in clinical oncology.[6] Targeted cancer therapies focusing on molecular changes specific to cancer may be more effective, and give rise to predictable and more favorable tolerability, than traditional chemotherapy that interferes with all rapidly dividing cells.[7] EGFR-mutant tumors define a unique subset of NSCLC. These tumors display sensitivity to small-molecule EGFR TK inhibitors (TKIs).

In the last decade, two small molecules, orally active, selective, and reversible EGFR-TKIs have been extensively developed in NSCLC: Gefitinib and erlotinib.[8] Gefitinib is the first agent designed with a known molecular target to receive the Food and Drug Administration approval for the treatment of lung cancer, yet its activity is limited to a subgroup of patients with NSCLC.[9]

PRECLINICAL STUDIES

The relative distribution of gefitinib-related material in nude mice bearing subcutaneously human tumor xenografts and in an orthotopic rat lung tumor model was investigated following oral administration (50 mg/kg) of [^{14}C]-gefitinib.[10] Gefitinib was extensively distributed into the tissues of tumor-bearing mice, and unchanged gefitinib was shown to account for most of the tumor radioactivity. The gefitinib tumor concentrations are considerably higher than those reportedly required *in vitro* to achieve complete inhibition of EGFR autophosphorylation in both EGFR-mutant (0.2 umol/L) and wild-type cells (2 umol/L).

MECHANISM OF ACTION

The mechanism of the clinical antitumor action of gefitinib is not fully characterized. Gefitinib is an orally administered low-molecular weight anilinoquinazoline that inhibits the phosphorylation and tyrosine kinase activity of the intracellular ATP-binding domain of EGFR through competitive binding to this site.[11]

PHARMACOKINETICS

Gefitinib is absorbed slowly after oral administration with mean bioavailability of 60%. It is extensively distributed into the tissues and highly protein bound which results in a large volume of distribution of 1400 L and a long half-life of 48 h[12] and is metabolized primarily by CYP3A4, CYP3A5, and CYP1A1, with respective maximum clearance values for metabolism of 0.41, 0.39, and 0.57 mL/min/nmol, respectively.[13]

Findings have suggested that the pharmacokinetics of gefitinib may be involved in its antitumor activity. Nakamura *et al.*[14] measured gefitinib plasma levels on days 3 (D3) and 8 (D8) by high-performance liquid chromatography in 44 patients with advanced NSCLC treated with 250 mg gefitinib daily. They found that high D8/D3 ratio was independently associated with better progression-free survival (PFS) in patients with NSCLC treated with gefitinib.

ADVERSE EFFECT

Gefitinib is regarded as relatively safe agent, with the most reported adverse side effect was being diarrhea and rash.[15] However, considerable number of patients treated with EGFR inhibitors (both EGFR TKIs and monoclonal antibodies group) developed dermatological side effects, most frequently an acneiform eruption but also xerosis, eczema, fissures, telangiectasia, hyperpigmentation, hair changes, and paronychia with pyogenic granuloma.[16]

DRUG INTERACTIONS

Potential drug interactions were common among cancer patients and most often involved medications to treat comorbid conditions.[17] Drug-drug interactions (DDIs) have received increasing attention over the past few decades and several DDIs were reported to be associated with gefitinib.[18] Drugs that induce CYP3A4 activity increase the metabolism of gefitinib, therefore in patients taking drugs such as rifampin or phenytoin, gefitinib dose increase to 500 mg daily can be considered in the absence of severe adverse effects.[19] Drug interactions were also reported in two patients who received both gefitinib and warfarin simultaneously, which caused an enhancement effect of warfarin.[20]

PATIENTS CHARACTERISTIC BENEFITING FROM GEFITINIB

Retrospective analyses of the clinical characteristics of the patients showed that erlotinib and gefitinib were more effective at producing responses in women than men (14% vs. 6%), in patients with adenocarcinoma (14% vs. 4%), and in never-smokers (25% vs. 4%),[21] and high EGFR gene copy number.[22-24] Adenocarcinomas of the bronchioloalveolar subtype and never-smokers patients were previously confirmed by other study that features patient who most likely benefit from gefitinib.[25] Evidence has showed that adenocarcinomas from never-smokers comprise a distinct subset of lung cancers, frequently containing mutations within the TK domain of EGFR that

are associated with gefitinib and erlotinib sensitivity.[26] The term "never-smoker" refer to an individual who has had a lifetime exposure of <100 cigarettes; a "former smoker" has quit smoking for more than 12 months; a "current smoker" is currently smoking or has quit during the past 12 months; and an "ever smoker" (used synonymously with "smoker") is an individual who is either a former or current smoker.[27] Moreover, treatment with the EGFR kinase inhibitor gefitinib causes tumor regression in some patients with NSCLC, more frequently in Japan.[28] Above all, evidence has shown that the factor that determines the sensitivity of gefitinib was EGFR mutation.[29-34] EGFR mutations in exons 19 or 21 are correlated with clinical factors predictive of response to gefitinib and that those with EGFR exon 19 deletion mutations had a longer median survival than patients with EGFR L858R point mutation.[35]

CLINICAL TRIALS

Phase I dose-escalating study investigated the tolerability and toxicity of the gefitinib in 31 Japanese patients with solid tumors.[36] Patients initially received a single oral dose of gefitinib followed by 10-14 days of observation. Oral gefitinib was subsequently administered on 14 consecutive days, every 28 days. Dose escalation was from 50 mg/day to a maximum of 925 mg/day or dose-limiting toxicity (DLT). Most adverse events were mild (grade 1/2); the most frequent were an acne-like rash and gastrointestinal effects. Two of six patients at 700 mg/day had DLT; no further dose escalation occurred. Cmax was reached within 3-7 h and exposure to gefitinib increased with dose. Mean terminal half-life following multiple dosing was 50.1 h (range, 27.8-79.7 h). A partial response (duration 35-361 days) was observed in five of the 23 patients with NSCLC over a range of doses (225-700 mg/day), and seven patients with a range of tumors had disease stabilization (duration 40-127 days). Based on this trial, gefitinib showed a favorable tolerability profile in Japanese patients. The safety profile, pharmacokinetic parameters, and antitumor activity observed in the study are comparable to those observed in patients from the USA and Europe.[36]

Phase II trial was conducted to evaluate the efficacy and safety of gefitinib as first-line therapy for advanced NSCLC with EGFR mutations.[37] Patients with Stage IIIB or IV chemotherapy-naive NSCLC with EGFR mutation were treated with 250 mg gefitinib daily. Twenty (24%) of the 82 patients analyzed had EGFR mutations. Sixteen patients were enrolled and treated with gefitinib. Twelve patients had objective response and response rate was 75% (95% confidence interval [CI], 48-93%). After a median follow-up of 12.7 months (range, 3.1-16.8 months), 10 patients demonstrated disease progression, with median PFS of 8.9 months (95% CI, 6.7-11.1 months). The median overall survival time has not yet been reached. Most of the toxicities were mild. This study showed that gefitinib is very active and well tolerated as first-line therapy for advanced NSCLC with EGFR mutations.

Double-blind, randomized Phase II trial was conducted to assess differences in symptomatic and radiographic response among patients with NSCLC receiving 250-mg and 500-mg daily doses of gefitinib.[38] Of 221 patients enrolled, 216 received gefitinib as randomized. Symptoms of NSCLC improved in 43% (95% CI, 33-53%) of patients receiving 250 mg of gefitinib and in 35% (95% CI, 26-45%) of patients receiving 500 mg. These benefits were observed within 3 weeks in 75% of patients. Partial radiographic responses occurred in 12% (95% CI, 6-20%) of individuals receiving 250 mg of gefitinib and in9% (95% CI, 4-16%) of those receiving 500 mg. Symptoms improved in 96% of patients with partial radiographic responses. The overall survival at 1-year was 25%. There were no significant differences between the 250-mg and 500-mg doses in rates of symptom improvement ($P = 0.26$), radiographic tumor regression ($P = 0.51$), and projected 1-year survival ($P = 0.54$). The 500-mg dose was associated more frequently with transient acne-like rash ($P = 0.04$) and diarrhea ($P = 0.006$). These findings suggest that gefitinib improved disease-related symptoms and induced radiographic tumor regressions in patients with NSCLC persisting after chemotherapy.[38]

The study has evaluated the efficacy and tolerability of two doses of gefitinib in patients with pretreated advanced NSCLC.[39] Two-hundred ten patients with advanced NSCLC who were previously treated with one or two chemotherapy regimens (at least one containing platinum) were randomized to receive either 250-mg or 500-mg oral doses of gefitinib once daily. Efficacy was similar for the 250- and 500-mg/day groups. Objective tumor response rates were 18.4% (95% CI, 11.5-27.3) and 19.0% (95% CI, 12.1-27.9); among evaluable patients, symptom improvement rates were 40.3% (95% CI, 28.5-53.0) and 37.0% (95% CI, 26.0-49.1); median PFS times were 2.7 and 2.8 months; and median overall survival times were 7.6 and 8.0 months, respectively. Symptom improvements were recorded for 69.2% (250 mg/day) and 85.7% (500 mg/day) of patients with a tumor response. The researcher concluded that gefitinib showed clinically meaningful antitumor activity and provided symptom relief as second- and third-line treatment in pretreated advanced NSCLC patients.[39]

Gefitinib in combination with gemcitabine and cisplatin in advanced NSCLC study (INTACT-1) is a Phase III

randomized, double-blind, placebo-controlled, multicenter trial in chemotherapy-naive patients with unresectable Stage III or IV NSCLC to determine whether the addition of gefitinib to standard first-line gemcitabine and cisplatin provides clinical benefit over gemcitabine and cisplatin alone in patients with advanced or metastatic NSCLC.[40] All patients received up to six cycles of chemotherapy (cisplatin 80 mg/m^2 on day 1 and gemcitabine 1,250 mg/m^2 on days 1 and 8 of the 3-week cycle) plus either gefitinib 500 mg/day, gefitinib 250 mg/day, or placebo. There was no difference in efficacy end points between the treatment groups: For the gefitinib 500 mg/day, gefitinib 250 mg/day, and placebo groups, respectively, median survival times were 9.9, 9.9, and 10.9 months (global ordered log-rank [GOLrank] $P = 0.4560$), median times to progression were 5.5, 5.8, and 6.0 months (GOLrank; $P = 0.7633$), and response rates were 49.7%, 50.3%, and 44.8%. Therefore, gefitinib in combination with gemcitabine and cisplatin in chemotherapy-naive patients with advanced NSCLC did not have improved efficacy over gemcitabine and cisplatin alone.[40]

Following INTACT-1 study, INTACT-2, a Phase III, randomized, placebo-controlled, double-blind trial, was conducted to evaluate gefitinib plus paclitaxel and carboplatin in chemotherapy-naive patients with advanced NSCLC.[41] Patients received paclitaxel 225 mg/m^2 and carboplatin area under concentration/time curve of 6 mg/min/mL (day 1 every 3 weeks) plus gefitinib 500 mg/day, gefitinib 250 mg/day, or placebo. After a maximum of six cycles, daily gefitinib or placebo continued until disease progression. There was no difference in overall survival (median, 8.7, 9.8, and 9.9 months for gefitinib 500 mg/day, 250 mg/day, and placebo, respectively; $P = 0.64$), time to progression (TTP), or response rate (RR) between arms. Expected dose-related diarrhea and skin toxicity were observed in gefitinib-treated patients, with no new significant/unexpected safety findings from combination with chemotherapy. Subset analysis of patients with adenocarcinoma who received >90 days chemotherapy demonstrated statistically significant prolonged survival, suggesting a gefitinib maintenance effect. Although the results showed no added benefit in survival, TTP, or RR, compared with standard chemotherapy alone, it confirmed the favorable gefitinib safety profile observed in Phase I and II monotherapy trials.

Placebo-controlled Phase III study investigated the effect on survival of gefitinib as second-line or third-line treatment for patients with locally advanced or metastatic NSCLC.[42] There were 1692 patients who were refractory to or intolerant of their latest chemotherapy regimen were randomly assigned in a ratio of two to one either gefitinib (250 mg/day) or placebo, plus best supportive care. At median follow-up of 7.2 months, median survival did not differ significantly between the groups in the overall population (5.6 months for gefitinib and 5.1 months for placebo; hazard ratio 0·89 [95% CI 0.77-1.02], $P = 0.087$) or among the 812 patients with adenocarcinoma (6.3 months vs. 5.4 months; 0.84 [0.68-1.03], $P = 0.089$). Preplanned subgroup analyses showed significantly longer survival in the gefitinib group than the placebo group for never-smokers ($n = 375$; 0.67 [0.49-0.92], $P = 0.012$; median survival 8.9 vs. 6.1 months) and patients of Asian origin ($n = 342$; 0.66 [0.48-0.91], $P = 0.01$; median survival 9.5 vs. 5.5 months). Gefitinib was well tolerated as in previous studies. This study suggests that treatment with gefitinib was not associated with significant improvement in survival in either coprimary population.[42] There was pronounced heterogeneity in survival outcomes between groups of patients, with some evidence of benefit among never-smokers and patients of Asian origin.

CONCLUSION

The discovery and characterization of EGFR activating mutations and their relationship to sensitivity to gefitinib and erlotinib have provided a basis for transforming NSCLC from a disease treated with conventional combination chemotherapy to one in which subsets of patients with specific EGFR mutations can be effectively treated with targeted therapy.[43] Moreover, among NSCLC patients treated with gefitinib, symptom improvement was complementary to and for most patients, preceded evidence of radiographic regression.[44] This would provide clinically meaningful improvement in symptoms and quality of life for patients with NSCLC.

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Conflicts of interest

There are no conflicts of interest.

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