The role of EGFR inhibitors in nonsmall cell lung cancer

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Purpose of review

The epidermal growth factor receptor is a cell membrane receptor that plays a key role in cancer development and progression. Ligand-activated epidermal growth factor receptor-dependent signaling is involved in cell proliferation, apoptosis, angiogenesis, invasion, and metastasis. Targeting the epidermal growth factor receptor represents a promising molecular approach in cancer treatment. Several antiepidermal growth factor receptor agents are in clinical development. This review focuses on the available clinical data on epidermal growth factor receptor-targeting drugs in the treatment of nonsmall cell lung cancer.

Recent findings

Three drugs are currently in phase 2 and phase 3 development as single agents or in combination with other anticancer therapies in nonsmall cell lung cancer patients: cetuximab (Erbitux), a chimeric human–mouse monoclonal IgG1 antibody that blocks ligand binding and functional epidermal growth factor receptor activation; and erlotinib (Tarceva) and gefitinib (Iressa), two orally bioavailable, small-molecule epidermal growth factor receptor inhibitors of tyrosine kinase enzymatic activity that prevent epidermal growth factor receptor autophosphorylation and activation. Single-agent gefitinib treatment has determined a 10 to 20% response rate and a 30 to 50% symptom improvement in previously treated, chemotherapy-refractory advanced nonsmall cell lung cancer patients. Gefitinib has been the first epidermal growth factor receptor-targeting agent to be registered as an anticancer drug in several countries, including Japan, Australia, and the United States, for the third-line treatment of chemoresistant nonsmall cell lung cancer patients.

Summary

Antiepidermal growth factor receptor has shown promising antitumor activity in nonsmall cell lung cancer patients with a mild toxicity profile. However, a series of important clinical issues such as selection of potentially responsive patients and optimal combination with conventional anticancer treatments needs to be addressed to use these drugs better in lung cancer.

Keywords

nonsmall cell lung cancer, autocrine cancer cell growth, growth factor receptors, signal transduction, monoclonal antibodies, small-molecule tyrosine kinase inhibitors

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Abbreviations

EGF	epidermal growth factor
EGFR	epidermal growth factor receptor
ILD	interstitial lung disease
MAb	monoclonal antibody
NSCLC	nonsmall cell lung cancer
TKI	tyrosine kinase inhibitor

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Introduction

Epidermal growth factor (EGF) belongs to a family of related peptides (EGF-like growth factors) that includes transforming growth factor-α, amphiregulin, heparin-binding EGF, epiregulin, heregulins, neuregulins (1, 2, 3, and 4), and betacellulin [1]. EGF-like growth factors bind to and activate one or more closely related receptors: the EGF receptor (EGFR, or ErbB-1/HER1), ErbB-2/neu/HER2, ErbB-3/HER3, and ErbB-4/HER4 [1,2]. The EGFR is a 170-kDa transmembrane glycoprotein that consists of an extracellular domain, a short transmembrane domain, and an intracellular region containing tyrosine kinase activity. The other three family members have a similar structure with a high degree of homology in the tyrosine kinase domain. The extracellular domains confer different specificity and selectivity to different EGF-like growth factors and are less conserved among the four receptors. No ligand is known for ErbB-2. Receptors exist as inactive monomers [1,2]. Ligand binding causes homodimerization or heterodimerization between the EGFR and another member of the EGFR family, and subsequent autophosphorylation of the intracellular domains, which initiates a cascade of intracellular signals that directly or indirectly control cell proliferation, angiogenesis, invasion, and metastasis [2,3].

Activation of the transforming growth factor-α–EGFR autocrine growth pathway is a common mechanism for autonomous nonsmall cell lung cancer (NSCLC) growth [4]. This is generally the result of EGFR overexpression without gene amplification and/or the result of increased

concentration of ligands, such as transforming growth factor-α and amphiregulin [4]. EGFR gene amplification is observed only in approximately 10% of NSCLCs [5]. Enhanced EGFR expression is observed in 40 to 80% of NSCLC patients [5,6]. This is accompanied by the expression of one or more other EGFR family members and of different ligands with a high degree of heterogeneity in both positivity and the levels of expression of these proteins [6]. Although some reports have suggested a correlation between EGFR overexpression and worse survival [7], there is no definitive evidence of a prognostic role of EGFR family members in NSCLC [4–6].

Epidermal growth factor receptor as a target for cancer therapy

Two types of anti-EGFR-targeting agents have reached advanced clinical development: monoclonal antibodies (MAbs) and small-molecule inhibitors of EGFR tyrosine kinase enzymatic activity (Table 1) [8,9••,10••]. MAbs against the extracellular domain of the EGFR block ligand binding and receptor activation. Tyrosine kinase inhibitors (TKIs) prevent the autophosphorylation of the EGFR intracellular tyrosine kinase domain. These molecules are generally competitors of ATP for binding to the intracellular catalytic domain. Although MAbs are highly specific for EGFR binding, TKIs may be less selective and may block other members of the EGFR family. In fact, based on the mechanism of action, small-molecule EGFR TKIs can be distinguished as reversible or irreversible TKIs and as selective for the EGFR or active also against other members of the family (Table 1).

Although the mechanism of action and the biologic effects of MAbs and small-molecule TKIs have differences, such as route of administration and biodistribution, induction of EGFR downregulation, potential activation of immune functions that could be clinically relevant [11•,12•], the antitumor effects of EGFR inhibition in human cancer models are (1) inhibition of cancer cell proliferation with G0–G1 cell cycle arrest and, in some cases, induction of apoptosis; (2) antiangiogenesis through inhibition of angiogenic growth factor production; (3) inhibition of invasion and metastasis; and (4) potentiation of antitumor activity of cytotoxic drugs and of radiotherapy [8,9••,10••].

Clinical studies with epidermal growth factor receptor inhibitors in nonsmall cell lung cancer

Cetuximab (Erbitux), a chimeric human–mouse anti-EGFR MAb, and erlotinib (Tarcev) and gefitinib (Iressa), two orally available, reversible, and selective EGFR-TKIs, are the most advanced EGFR-targeted drugs in NSCLC treatment and are discussed in detail in this review.

Gefitinib

Gefitinib is a low-molecular weight (447 Da), synthetic anilinoquinazoline derivative. Gefitinib is an orally active, selective, and reversible inhibitor of EGFR tyrosine kinase [13–15]. The initial five phase 1 trials of gefitinib monotherapy that were conducted in approximately 250 heavily pretreated advanced cancer patients have shown in 99 NSCLC patients a promising antitumor activity, with partial responses lasting from 1 to 16 months in eight patients and regression of nonmeasurable but evaluable disease in two patients [16••,17••,18,19]. In addition, approximately one third of patients have had long-lasting stable disease for 3 months or more. Interestingly, in those patients with tumor response and disease stabilization, a significant improvement in quality of life and disease-related symptoms as measured by the Lung Cancer Subscale of the Functional Assessment of Cancer Therapy questionnaires was observed [20•]. Gefitinib monotherapy was well tolerated. The most frequently reported adverse events were diarrhea and acnelike skin rash. These side effects were reversible. Grade 3 diarrhea was dose limiting at the 700- to 1000-mg dose level. Based on these results, two large phase 2 trials of gefitinib monotherapy in advanced NSCLC pa-

Table 1. Antiepidermal growth factor receptor agents in clinical development

Drug	Biochemical characteristics	Target selectivity	Clinical development in NSCLC
Cetuximab (Erbitux)	Human–mouse chimeric MAb	Selective for EGFR	Phase III
EMD 72000	Humanized MAb	Selective for EGFR	Phase I
ABX-EGF	Fully human MAb	Selective for EGFR	Phase I
hR3	Humanized MAb	Selective for EGFR	Phase I
Gefitinib (Iressa)	Reversible TKI	Selective for EGFR	Phase III; as of November 2003, registered in 10 countries worldwide, including the United States, as third-line therapy in NSCLC
Erlotinib (Tarceva)	Reversible TKI	Selective for EGFR	Phase III
CI-1033	Irreversible TKI	Pan-ErbB inhibitor	Phase I
PKI-166	Reversible TKI	EGFR/ErbB-2 dual inhibitor	Phase I
GW2016	Reversible TKI	EGFR/ErbB-2 dual inhibitor	Phase I
EKB-569	Irreversible TKI	EGFR/ErbB-2 dual inhibitor	Phase I

EGFR, epidermal growth factor receptor; MAb, monoclonal antibody; NSCLC, nonsmall cell lung cancer; TKI, tyrosine kinase inhibitor.

tients that have failed one or more chemotherapy lines have been conducted. In a multicenter, European and Japanese randomized, phase 2 trial of gefitinib as second- or third-line single-agent therapy (IDEAL 1, or Iressa Dose Evaluation in Advanced Lung Cancer), 210 advanced NSCLC patients who were not selected based on EGFR expression received either 250 mg or 500 mg oral daily treatment [21••]. An overall response rate of 18.4% and 19% was observed in the 250-mg and 500-mg gefitinib groups respectively. Stable disease was obtained in 36% and 32% patients respectively. Symptom improvement rates were 40.3% and 37%, median progression-free survival times were 2.7 months and 2.8 months, and median overall survival times were 7.6 months and 8.0 months respectively. Gefitinib at the 250-mg daily dose was equally active compared with 500 mg. However, the tolerability was significantly better with the 250-mg daily dose. A parallel phase 2, randomized study was conducted in the United States (IDEAL 2) in 216 unselected, symptomatic, advanced NSCLC patients who were resistant to at least two previous chemotherapy regimens, one containing a platinum derivative and one containing docetaxel [22••]. NSCLC symptoms, as measured by a 2-point or greater increase in the Functional Assessment of Cancer Therapy–Lung Cancer Subscale score, improved in 43% of patients receiving 250 mg gefitinib and in 35% of patients receiving 500 mg. These effects were rapidly occurring in most patients (*ie*, within 3 weeks in 75% of responding patients). Partial responses were detected in 12% and in 9% of patients treated with gefitinib 250 mg and 500 mg respectively. Symptoms improved in 96% of patients with partial responses. One-year overall survival was 25%. Also in this study, the higher dose of gefitinib was associated with worse side effects, such as acnelike skin rash and diarrhea. On the basis of these clinical trials, gefitinib has been licensed for platinum and docetaxel chemorefractory advanced NSCLC patients as third-line treatment in 10 countries, including Japan, Australia, and the United States [23]. Therefore, gefitinib represents the first approved anti-EGFR-targeting drug. Single-agent gefitinib antitumor activity has also been confirmed by a large, international, extended access program that has been conducted with gefitinib 250 mg in advanced NSCLC patients who progressed after standard chemotherapy and/or radiation therapy [24,25]. In these series, objective responses have been observed in 10 to 15% of patients. Moreover, gefitinib clinical activity has been reported in NSCLC elderly and/or poor performance status patients as well [26•,27–29]. Gefitinib monotherapy has also shown anticancer activity against brain metastasis in advanced NSCLC patients [30•,31•]. Emerging clinical data support the hypothesis that gefitinib may be significantly more active in certain NSCLC histotypes such as in adenocarcinomas and in bronchioloalveolar carcinomas and in women with no smoking history [32•–34•]. The role of gefitinib in combination with chemotherapy has also been assessed in advanced NSCLC. A pilot study has shown that treatment with gefitinib (250 mg or 500 mg daily dose) in combination with carboplatin–paclitaxel appeared feasible and well tolerated in previously untreated patients with advanced stage IIIB to IV NSCLC [35]. Pharmacokinetic data demonstrated that coadministration of gefitinib does not affect the clearance of either carboplatin or paclitaxel. Of 24 patients, five had partial responses (median duration of response, 5 months) and 11 patients obtained disease stabilization. The median survival for the 24 patients was 8 months. One-year and 2-year survival rates were 39% and 22% respectively. The combination of another platinum-based chemotherapy regimen (cisplatin–gemcitabine) with oral gefitinib (250-mg or 500-mg daily dose) was evaluated in 18 advanced NSCLC patients as first-line treatment (Giaccone *et al.*, Abstract presented at the AACR-NCI-EORTC International Conference in Molecular Targets and Cancer Therapeutics, 2001). The combination was tolerable, with no increase in chemotherapy-related toxicity and no interference with the pharmacokinetics of these drugs. The combination of gefitinib with docetaxel as second-line treatment is also under evaluation in advanced NSCLC patients [36,37]. Preliminary results of these studies suggest that both 250- and 500-mg daily doses can be combined with standard-dose docetaxel (75 mg/m^2 every 3 weeks). Two large (1093 and 1037 patients in each trial respectively), randomized, multicenter, double-blind, three-arm, placebo-controlled phase 3 trials of gefitinib (250 mg or 500 mg daily) in combination with cytotoxic agents (cisplatin–gemcitabine, Iressa Non-Small-Cell-Lung Cancer Trial Assessing Combination Treatment [INTACT 1] trial, or carboplatin–paclitaxel INTACT 2 trial) as first-line treatment in stages IIIB to IV NSCLC patients were conducted [38•,39•]. No patient selection based on EGFR expression in cancer cells was done. No difference in overall survival, as the primary end point of these two parallel studies, has been reported. Different explanations for the lack of efficacy of gefitinib plus standard doublet cytotoxic therapy have been proposed [40,41••]. Chemotherapy and gefitinib could target the same cancer cell population and, therefore, response to chemotherapy masks the response to the EGFR inhibitor. Chemotherapy may directly or indirectly affect EGFR function and/or expression, and thus may reduce or abrogate the antitumor activity of gefitinib. It seems more conceivable that because of the high molecular and clonal heterogeneity of NSCLC cells, only a subset of EGFR-positive NSCLC patients have tumors that are significantly dependent on the EGFR pathway and who, therefore, could obtain a clinical benefit by an anti-EGFR drug [41••]. Interstitial lung disease (ILD) was first reported in Japanese advanced NSCLC patients receiving gefitinib and in those who were pretreated with chemotherapy and/or radiotherapy [42•]. ILD has been observed in 291 of 17,500 Japanese patients (1.7%)

treated with gefitinib [42•]. However, ILD has been observed in only 0.3% of 56,000 NSCLC patients who received gefitinib in the United States, Europe, and Australia as part of an expanded access program [43•]. No differences in any type of pulmonary adverse events have been observed in the double-blind, placebo-controlled, randomized INTACT 1 and 2 trials (0.9% in the placebo group compared with 1.1% in the 250-mg/day and the 500-mg/day gefitinib groups) [38•,39•]. Notably, ILD has been observed in NSCLC patients receiving standard cytotoxic treatments (1 to 5% incidence with chemotherapy or with radiotherapy) [43•]. A series of phase 3 trials is currently evaluating the role of gefitinib as adjuvant treatment in radically resected NSCLC patients, the possibility of using gefitinib as maintenance therapy after first-line chemotherapy in advanced NSCLC patients, and the antitumor activity of gefitinib compared with docetaxel in the second-line treatment of advanced disease.

Erlotinib

Erlotinib is a low-molecular weight, orally bioavailable, quinazoline derivative that selectively and reversibly inhibits the tyrosine kinase activity of EGFR [44]. Phase 1 studies in patients with advanced solid tumors have shown a tolerability profile similar to gefitinib. Major toxicities were acnelike skin rash and diarrhea, which was the dose-limiting toxicity at 200 mg daily. The recommended dose for continuous treatment was 150 mg/day [44]. Erlotinib is currently in phase 2 to phase 3 development in advanced NSCLC. Preliminary evidence of antitumor activity of erlotinib in patients with advanced NSCLC who failed a platinum-based therapy was recently reported [45]. In this phase 2 study, a complete response was observed in 1 of 57 patients, and partial responses were obtained in six patients. Stable disease was detected in an additional 17 patients. The median survival for these patients was 259 days, with a 1-year survival of 48%. A retrospective analysis of acnelike rash occurrence in this phase 2 study has suggested that rash severity (grade 2 or more) compared with no skin lesions is predictive of increased survival (no rash, 1.5 months median survival; grade 1 toxicity, 8.5 months median survival; grade 2 to 3 toxicity, 19.6 months median survival) [46••]. Based on these observations and on the hypothesis that skin rash may be a surrogate for clinical activity, a trial has recently been initiated in chemotherapy refractory advanced NSCLC patients to evaluate the feasibility of erlotinib dose escalation to induce tolerable rash without other toxicities. Interestingly, no correlation between the degree of skin toxicity and outcome has been observed so far with gefitinib clinical trials. A series of phase 2 and phase 3 studies of erlotinib as a single agent or in combination with various chemotherapy regimens is ongoing in NSCLC [47]. In this respect, erlotinib treatment as a single agent is also under evaluation in the second- or third-line treatment of advanced NSCLC patients in two randomized phase 3 clinical trials in comparison with docetaxel or with best supportive care respectively. Similar to the INTACT trials, two large (approximately 1000 patients in each study), multicenter, randomized, phase III studies of first-line carboplatin–paclitaxel or cisplatin–gemcitabine with erlotinib in stage IIIB to IV NSCLC patients have been performed (47). On October 1, 2003, a press release from the industries (Genentech, San Francisco, CA; Roche, Basel, Switzerland; and OSI Pharmaceuticals, Boulder, CO) that are producing erlotinib stated that both studies, similar to the INTACT studies with gefitinib, failed to show any difference in overall survival between the standard and the erlotinib treatment.

Cetuximab

Cetuximab is a chimeric human–mouse IgG1 anti-EGFR-blocking MAb. It was the first anti-EGFR-targeted agent to start clinical evaluation in cancer patients [48]. In the phase 1 studies the most frequent cetuximab-related adverse events were skin toxicities, fever and chills, asthenia, transient transaminase elevations, and nausea [49]. Skin toxicities were reversible flushing, acnelike rashes, and folliculitis. The maximum tolerated dose was not reached. Cetuximab had nonlinear pharmacokinetics. Based on the doses for complete saturation of antibody clearance, the recommended loading dose and the subsequent weekly maintenance doses for phase 2 studies were 400 mg/m^2 and 250 mg/m^2 respectively. The combination of cetuximab with various two-drug chemotherapy regimens has been evaluated as first-line treatment in EGFR-positive advanced NSCLC patients. In a phase 1/2 trial of cetuximab plus carboplatin–gemcitabine chemotherapy, 10 partial responses (28.6%) and 11 stable diseases (60%) in 35 patients were observed [50]. The median time to progression and the median overall survival were 165 days and 310 days respectively. The combination of carboplatin–paclitaxel plus cetuximab was evaluated in 31 patients as first-line treatment in EGFR-positive advanced NSCLC [51]. Partial responses were observed in nine patients (29%) and disease stabilization was obtained in the other 11 patients (35.5%), with a median time to progression of 4.5 months and a median overall survival of 15.7 months. A phase 2 trial of cetuximab in combination with docetaxel as second-line treatment in chemotherapy refractory/resistant EGFR-positive advanced NSCLC has recently been reported [52]. One complete response and 11 partial responses (overall response rate, 22.2%) were observed in the 54 treated patients. The other 18 patients (33.3%) had stable disease. The median overall survival was 7.5 months. The initial results of a randomized, phase 2 study (LUCAS, or Lung Cancer Cetuximab Combination Study) comparing as first-line therapy cisplatin–vinorelbine with the same combination plus cetuximab in EGFR-positive stage IIIB to IV NSCLC patients have been presented. A higher response rate with

no increase in chemotherapy toxicity was observed in the chemotherapy plus cetuximab group compared with the chemotherapy-alone group: one complete response and 15 partial responses out of 30 treated patients (53.3% response rate) versus 10 partial responses in 31 treated patients (32.2% response rate) [54••]. However, complete data from this study and phase 3 trials are necessary to define whether cetuximab significantly improves the activity and the efficacy of standard chemotherapy in NSCLC.

Conclusion

Both anti-EGFR MAbs and small-molecule TKIs have shown an excellent toxicity profile with mild and reversible side effects in NSCLC patients. However, a series of clinically important issues on the use of EGFR-targeted therapies in NSCLC is emerging [54••]. First, the importance of the measurement of the levels of expression of EGFR within the tumor to select cancer patients for treatment with these drugs is not yet clear. Although EGFR expression is found in most NSCLCs, responses are observed only in a subgroup of patients. There is no evidence of a relation between EGFR overexpression and likelihood to respond to anti-EGFR drugs. Moreover, it seems that adenocarcinomas and bronchioloalveolar carcinomas are more sensitive than squamous cell carcinomas. Furthermore, it could be necessary for the response to EGFR inhibitors the expression of the other three EGFR-related receptors and of the EGFR ligands such as transforming growth factor-α and amphiregulin. Finally, the intracellular signal transduction pathways that act downstream to EGFR could influence the response to anti-EGFR agents. In this respect, cancer cells may escape from growth inhibition by using alternative growth pathways or by constitutive activation of downstream signaling effectors [54••]. In summary, the implementation of translational, research-oriented clinical trials with EGFR inhibitors in NSCLC is needed to establish fully their role in NSCLC management. The major aims of these studies should be the identification of clinically relevant molecular markers of potential sensitivity or resistance to therapy, and the identification of pharmacologic and mechanistic interactions of anti-EGFR agents and chemotherapy or radiotherapy for the more appropriate integration of these drugs with conventional treatment.

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