FRESH FROM THE PIPELINE

Erlotinib hydrochloride

Jonathan Dowell, John D. Minna and Peter Kirkpatrick

Erlotinib

Erlotinib hydrochloride (Tarceva; OSI Pharmaceuticals/Genentech/Roche), a member of a class of targeted anticancer drugs that inhibit the activity of the epidermal growth factor receptor, was approved by the US FDA in November 2004 for the treatment of advanced non-small-cell lung cancer after failure of at least one prior chemotherapy regimen. It is the first such drug to demonstrate an increase in survival in Phase III trials in patients with advanced non-small-cell lung cancer.

Lung cancer has been estimated to be the leading cause of cancer mortality worldwide[1]. The most common form — non-small-cell lung cancer (NSCLC), which accounts for ~75% of cases — is too advanced to be operable in >50% of patients, and standard first-line chemotherapy based on platinum agents only improves survival modestly[2]. Second-line treatment options in patients with advanced NSCLC are limited; docetaxel is the only established choice to be approved by the FDA.

The limited efficacy and lack of specificity of cytotoxic chemotherapy in solid tumours such as NSCLC has provided an impetus to develop therapies that aim to specifically target cancer cells by modulating the aberrant molecular pathways underlying tumour growth and progression, in the hope of achieving greater efficacy with fewer side effects. In particular, protein kinases have emerged as key regulators of all aspects of cancer, and many kinase inhibitors are now being developed. Agents that inhibit the activity of cell membrane receptor tyrosine kinases, such as the epidermal growth factor receptor (EGFR)[3], are among the most advanced in clinical development.

Basis of discovery

EGFR is part of the ERBB family of receptor tyrosine kinases, which has four closely related members: EGFR (ERBB1), HER2 (ERBB2), HER3 (ERBB3) and HER4 (ERBB4). Each member consists of an extracellular ligand-binding domain, a transmembrane domain and an intracellular tyrosine kinase domain[4] (FIG. 1a). Ligand binding to EGFR causes receptor dimerization, either with another EGFR monomer or with another member of the ERBB family. Dimerization activates the tyrosine kinase activity in the intracellular domain, which leads to receptor autophosphorylation and the initiation of signal-transduction cascades involved in cell proliferation and survival[4].

Activation of EGFR has been implicated in processes involved in tumour growth and progression, including cell proliferation, inhibition of apoptosis, metastasis and angiogenesis[3] (FIG. 1a). EGFR is expressed in various solid tumours, including 40–80% of NSCLCs, providing a strong rationale for testing EGFR inhibitors in patients with such tumours[5,6].

Several possible approaches to targeting EGFR have been investigated, including monoclonal antibodies directed against the extracellular ligand-binding domain, such as cetuximab (Erbitux; Imclone Systems/Bristol-Myers Squibb), and small-molecule inhibitors of the intracellular tyrosine kinase domain[3]. A small-molecule EGFR inhibitor, gefitinib (Iressa; AstraZeneca), was approved by the FDA for the third-line treatment of patients with advanced NSCLC in May 2003, and has now been joined by erlotinib.

Drug properties

Erlotinib (previously known as OSI-774 and CP-358774; FIG. 1b) is a small molecule that competes with the binding of ATP to the intracellular tyrosine kinase domain of EGFR, thereby inhibiting receptor autophosphorylation and blocking downstream signal transduction[7–9]. It showed promising anticancer effects in various preclinical cancer models[7,8], prompting its clinical evaluation in a range of cancers, including NSCLC.

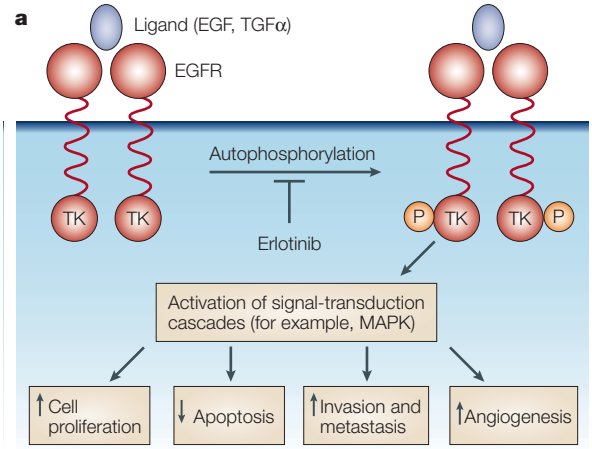
Trial data

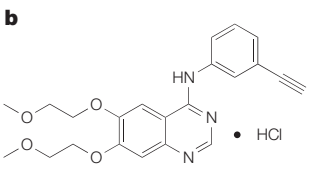
Erlotinib hydrochloride (150 mg orally once daily) was evaluated in a randomized, double blind, placebo-controlled trial involving 731 patients with locally advanced or metastatic NSCLC after failure of at least one chemotherapy regimen[9]. The primary endpoint was survival, which was significantly longer in patients receiving erlotinib hydrochloride: median overall survival in these patients was 6.7 months compared with 4.7 months in patients receiving placebo[9]. Median progression-free survival and tumour response rates in patients receiving erlotinib hydrochloride were 9.9 weeks and 8.9%, respectively, compared with 7.9 weeks and 0.9%, respectively, in patients receiving placebo[9].

Erlotinib hydrochloride has also been evaluated in combination with platinum-based chemotherapy (carboplatin and paclitaxel, or gemcitabine and cisplatin) in two placebo-controlled, randomized trials involving more than 1,000 first-line patients with locally advanced or metastatic NSCLC. No clinical benefit was demonstrated from the addition of erlotinib hydrochloride in these trials[9].

Indications

Erlotinib hydrochloride is indicated for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen[9]. ▶





Erlotinib hydrochloride

N-(3-ethynylphenyl)-6,7-bis (2-methoxyethoxy)-4-quinazolinamine;
$C_{22}H_{23}N_3O_4$•HCl;
M_r = 429.90;
CAS registry number: 183319-69-9

Figure 1 | **EGFR signalling and erlotinib. a** | Simplified illustration of signal transduction through the epidermal growth factor receptor[3,4] (EGFR). Ligand binding leads to receptor dimerization. This results in receptor autophosphorylation, which is inhibited by erlotinib. **b** | Structure of erlotinib hydrochloride. MAPK, mitogen-activated protein kinase; P, phosphate group; TGF, transforming growth factor; TK, tyrosine kinase domain.

NON-SMALL-CELL LUNG CANCER | VIEW FROM THE CLINIC

Analysing clinical issues for targeted therapies for non-small-cell lung cancer this month are John D. Minna, M.D., and Jonathan Dowell, M.D. John Minna is Professor and Director of the Hamon Center for Therapeutic Oncology Research at the University of Texas Southwestern Medical Center. His primary research interest is to determine all of the molecular abnormalities leading to the pathogenesis of lung cancer and to translate this information into new methods for the diagnosis, prevention and treatment of this disease. Jonathan Dowell is Assistant Professor, Department of Internal Medicine at the University of Texas Southwestern Medical Center, and he is also the Chief of Hematology/Oncology at the Dallas VA Medical Center. His primary research interest is in clinical and translational trials in lung cancer.

What are the current key issues in the treatment of non-small-cell lung cancer?

One current key issue in the treatment of NSCLC is that a plateau seems to have been reached with regards to the efficacy of standard chemotherapy. Numerous trials have now demonstrated that platinum-based chemotherapy combinations are the most effective treatment in advanced NSCLC. The drug that is combined with platinum (a taxane, gemcitabine or vinorelbine) seems to affect only the toxicity profile of the regimen, as all have similar efficacy. Attempts to enhance the activity of these regimens by adding a third chemotherapy agent have been uniformly unsuccessful.

Patients vary dramatically in their response to these 'standard' chemotherapies, and another major issue is the development of pharmacogenomic tests based on a molecular assessment of the tumours from individual patients, and also interindividual variations in drug metabolism, to determine which drugs would be best for which patients.

A further key to advancing therapy is the identification of novel molecular targets, such as EGFR, as well as developing drugs that effectively act on these targets, such as erlotinib and gefitinib. In addition, an important current focus is identifying those patients likely to benefit from these therapies. For example, the discovery of somatic mutations in the tyrosine kinase domain of *EGFR* seems to identify a subset of NSCLC patients that are exquisitely sensitive to the EGFR tyrosine kinase inhibitors (TKIs)[10–12]. However, the randomized single-agent trial of erlotinib indicates that there must be patients without EGFR mutations that also derive benefit from drug treatment. Finding molecular correlates of these responses (for example, such as EGFR amplification or gene-expression signatures) will be important for identifying the responding patients prospectively.

What might be the best approach for exploiting targeted therapies in NSCLC? Would earlier treatment, or adjuvant use, be expected to be beneficial? And how much progress is being made with the development of combinations?

For many 'targeted therapies', there is a good preclinical rationale to suggest that they might be more effective in the setting of minimal bulk disease (that is, the adjuvant setting after definitive surgery for early-stage disease). Both of the available EGFR tyrosine kinase inhibitors (gefitinib and erlotinib) are currently being investigated in the adjuvant setting in NSCLC, after the administration of adjuvant chemotherapy. Of course, the ultimate in early treatment is use of the drugs for 'chemoprevention' of the development of lung cancer in high-risk individuals. There is growing evidence that abnormalities of EGFR signalling occur in smoking-damaged lung epithelium as a precursor to cancer, and TKIs as oral agents with little toxicity could have an important role in such prevention.

With regards to combinations of TKIs with other drugs in clinically evident disease, all of the published Phase III trials that have investigated adding a targeted agent to standard chemotherapy for advanced NSCLC have failed to demonstrate a benefit for the combination (including four trials with either gefitinib or erlotinib). Two such trials have yet to be reported — one with bexarotene and one with bevacizumab, and results of these trials are eagerly anticipated. In the case of the EGFR inhibitors, the failure of these drugs to enhance the activity of standard chemotherapy might have been due to the patient population studied. These trials were conducted before the discovery of *EGFR* mutations that are predictive for response to the EGFR TKIs. Given the relatively low incidence of these mutations, the majority of patients included in these trials probably had wild-type *EGFR* in their tumours and would therefore be less likely to benefit from this therapeutic approach. Trials in patients with tumour-acquired *EGFR* mutations are being planned.

With regards to combining targeted agents, some preliminary data are available. Roy Herbst and Alan Sandler at MD Anderson Cancer Center and Vanderbilt University, respectively, conducted a Phase II trial of erlotinib and bevacizumab in advanced NSCLC[13]. The combination was safe and well-tolerated, and enough activity was seen to justify a Phase III comparison with standard chemotherapy in the second-line setting in metastatic disease.

As highlighted above, studies with gefitinib have identified mutations that correlate with drug response. Does the situation seem similar with erlotinib?

William Pao and colleagues from Memorial Sloan-Kettering Cancer Center have found identical mutations in *EGFR* that correlate with response to erlotinib[14]. The same clinical characteristics that are predictive for response to gefitinib also seem to identify those patients most likely to benefit from erlotinib. Women, 'never-smokers', those with adenocarcinoma or bronchoalveolar carcinoma, and patients of East Asian descent are all more likely to respond to treatment with an EGFR TKI, and these clinical features correlate with the presence of an *EGFR* mutation.

Jonathan Dowell and John D. Minna are at the University of Texas Southwestern Medical Center at Dallas, 5323 Harry Hines Boulevard, Dallas, Texas 75390-8593, USA. Peter Kirkpatrick is at Nature Reviews Drug Discovery.
Correspondence to J.D.M. and P.K.
e-mails: john.minna@utsouthwestern.edu; p.kirkpatrick@nature.com

doi:10.1038/nrd1612

1. Parkin, D. M. *et al.* Cancer burden in the year 2000. The global picture. *Eur. J. Cancer* **37**, S4–S66 (2001).
2. Cersosimo, R. J. Lung cancer: a review. *Am. J. Health Syst. Pharm.* **59**, 611–642 (2002).
3. Dancey, J. & Sausville, E. A. Issues and progress with protein kinase inhibitors for the treatment of cancer. *Nature Rev. Drug Discov.* **2**, 296–313 (2003).
4. Yarden, Y. & Sliwkowski, M. X. Untangling the ErbB signalling network. *Nature Rev. Mol. Cell Biol.* **2**, 127–137 (2001).
5. Baselga, J. Why the epidermal growth factor receptor? The rationale for cancer therapy. *The Oncologist* **7** (S4), 2–8 (2002).
6. Salomon, D. S. *et al.* Epidermal growth factor-related peptides and their receptors in human malignancies. *Crit. Rev. Oncol. Hematol.* **19**, 183–232 (1995).
7. Moyer, J. D. *et al.* Induction of apoptosis and cell cycle arrest by CP-358,774, an inhibitor of epidermal growth factor receptor tyrosine kinase. *Cancer Res.* **57**, 4838–4848 (1997).
8. Pollack, V. A. *et al.* Inhibition of epidermal growth factor receptor-associated tyrosine phosphorylation in human carcinomas with CP-358,774: dynamics of receptor inhibition *in situ* and antitumor effects in athymic mice. *J. Pharmacol. Exp. Ther.* **291**, 739–748 (1999).
9. FDA label information [online], <http://www.fda.gov/cder/foi/label/2004/021743lbl.pdf> (2004).
10. Lynch, T. J. *et al.* Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N. Engl J. Med.* **350**, 2129–2139 (2004).
11. Paez, J. G. *et al.* EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science* **304**, 1497–1500 (2004).
12. Shigematsu, H. *et al.* Clinical and biological features of epidermal growth factor receptor mutations in lung cancers. *J. Natl Cancer Inst.* (in the press).
13. Sandler, A. *et al.* Phase I/II trial evaluating the anti-VEGF MAb bevacizumab in combination with erlotinib, a HER1/EGFR-TK inhibitor, for patients with recurrent non-small cell lung cancer. *J. Clin. Oncol.* **22**, 14S (2004).
14. Pao, W. *et al.* EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. *Proc. Natl Acad. Sci USA* **101**, 13306–13311 (2004).