Small molecule epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors in non-small cell lung cancer

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Despite recent developments in the diagnosis and conventional treatment of non small cell lung cancer (NSCLC), the prognosis remains unsatisfactory, with 5-year survival rates of approximately 15% for all stages. To date, chemotherapy represents the standard treatment for advanced-non small lung cancer, but efficacy of currently available cytotoxic drugs is modest. Median survival does not exceed 8–10 months. New treatment strategies are needed and considerable hope has been placed in therapeutics that specifically target the molecular mechanisms of tumour growth. One molecular target of particular relevance to lung cancer pathogenesis is the epidermal growth factor receptor (EGFR), a cell membrane receptor tyrosine kinase. Several inhibitors of EGFR fuctonal activation have been developed. Among these, erlotinib (Tarceva) and gefitinib (Iressa) are two orally bioavailable, small molecule EGFR inhibitors of the tyrosine kinase enzymatic activity which prevent EGFR autophosphorylation and activation. In monotherapy, gefitinib and erlotinib have determined a 10–20% response rate and a 30–50% symptom improvement in previously treated, chemotherapy refractory, advanced NSCLC patients. Furthermore, a randomized, placebo controlled, multicenter phase III study has shown a two months improvement in median survival with erlotinib in the second or third line treatment of metastatic NSCLC patients. We will summarize the clinical evidence on the anticancer activity of small molecule EGFR inhibitors.

Key words: non-small cell lung cancer, growth factor receptors, EGFR, small molecule tyrosine kinase inhibitors

introduction

Growth factors are locally secreted hormones that are involved in regulating proliferation, differentiation and survival of normal cells. These proteins activate specific cell membrane receptors on target cells. The uncontrolled production of these specific cell growth promoting molecules, and the abnormal, enhanced expression on their cell membrane of specific growth factor receptors, are one of major mechanism by which cancer cells acquire autonomous and dysregulated proliferation [1].

The epidermal growth factor (EGF) belongs to a family of related peptides (EGF-like growth factors), which includes transforming growth factor α (TGFA), amphiregulin, heparin binding-EGF (HB-EGF), epipligulin, heregulins, neuregulins (1–4), and betacellulin (BTC) [2]. EGF-like growth factors bind to and activate one or more closely related receptors: the EGF receptor (EGFR) (or ErbB1/HER1), ErbB-2/Neu/HER2, ErbB-3/HER3 and ErbB-4/HER4 [2]. They share the same structure: an extracellular domain that interacts with a specific ligand, a short transmembrane domain, and a tyrosine kinase domain within the cell, which is the activator of downstream intracellular signaling. Each receptor has a certain degree of homology with the others, but they differ in terms of ligand binding and tyrosine kinase activity. After ligand binding to a single chain EGFR, active couples of receptors (receptor dimers) are formed. These proteins can signal within the cell by activating through an intrinsic tyrosine kinase activity the autophosphorylation of the same growth factor receptor. This event triggers a series of intracellular pathways which brings to the nucleus the molecular signals for activating specific gene transcription and for cell cycle progression, leading to cancer cell proliferation, induction of angiogenesis and metastasis formation. The signalling pathway involves activation of ras, raf and mitogen-activated protein kinase (MAPK), which determine the activation of several nuclear proteins that regulate cell cycle progression from G1 to S phase. EGFR activation in cancer cells can be due to: 1, EGFR overexpression; 2, increased production of ligands, such as TGFA and amphiregulin; 3, EGFR gene amplification and EGFR gene mutations.

EGFR inhibitors in NSCLC

According to Mendelsohn’s hypothesis, formulated in the early ’80s, the pharmacologic blockade of EGFR activation may be
able to inhibit cancer cell proliferation, and cancer cells may be selectively sensitive to EGFR inhibition as compared to normal cells [3]. Two types of anti-EGFR targeting agents have reached advanced clinical development: monoclonal antibodies (Mabs) and small molecule inhibitors of the EGFR tyrosine kinase enzymatic activity [4–6]. MAbs against the extracellular domain of the EGFR block ligand binding and receptor activation. Small molecule epidermal growth factor receptor (EGFR) tyrosine-kinase inhibitors (TKIs) compete with ATP for binding to the intracellular catalytic domain of the EGFR tyrosine kinase and, thus, prevent EGFR autophosphorylation and downstream signaling.

Erlotinib (Tarceva®, OSI-774; Genentech, South San Francisco, CA, USA) and Gefitinib (Iressa®, ZD1839; Astra Zeneca, Macclesfield, United Kingdom), two orally available, reversible and selective EGFR-TKIs, are the most advanced EGFR-targeted drugs in NSCLC treatment and will be discussed in detail in this review.

gefitinib

It is a low molecular weight (447 mol.wt), synthetic anilino-quinazoline derivative. Phase I trials have determined gefitinib doses of 250 or 500 mg as continuous once-daily, oral schedule [5–6]. Gefitinib monotherapy was well tolerated. The most frequently reported adverse events were diarrhea and acne-like skin rash. The activity of gefitinib in NSCLC has been tested in two phase II trials [7–8]. Both were designed as randomized phase II trials, and patients were randomly assigned to receive in a double-blind fashion two doses of gefitinib (250 mg/die or 500 mg/die), in monotherapy. The IDEAL-1 study enrolled 210 patients, which were not selected based on EGFR expression, in Europe, Australia, South Africa and Japan [7]. Patients were eligible after failure of one or two previous chemotherapy regimens (with at least one of those containing platinum). Major end-point of this study was the objective response rate. The lower dose of gefitinib produced objective responses in 18.4% and the higher dose determined response in 19.0% of the patients. Stable disease was obtained in 36% and 32% patients, respectively. Symptom improvements were recorded in 40.3% and 37% patients; median progression-free survival times were 2.7 and 2.8 months; and median overall survival times were 7.6 and 8.0 months, respectively. Therefore, gefitinib at 250 mg dose was equally active as compared to the 500 mg dose. However, the tolerability profile was significant better with the 250 mg daily dose. Importantly, median time to improvement was very rapid, only 8 days from the start of treatment. The IDEAL-2 study had a similar design, but was conducted in the United States and was reserved to patients who had received at least 2 previous chemotherapy regimens [8]. Main outcome measures were the improvement of symptoms and the objective response rate. Symptoms of NSCLC improved in 43% of patients receiving 250 mg of gefitinib and in 35% of patients receiving 500 mg. Objective responses were documented in 12% and 9% of patients receiving the lower and the higher dose, respectively. Based on the results of these two trials, gefitinib has been approved by the Food and Drug Administration (FDA) in May 2003 as single agent treatment of patients with locally advanced or metastatic NSCLC after failure of both platinum-based and docetaxel chemotherapies [9].

The role of Gefitinib in combination with chemotherapy has been also assessed in advanced NSCLC. Two large (1093 and 1037 patients in each trial, respectively), randomized, multicenter, double-blind, three-arm, placebo controlled, phase III 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-IV NSCLC patients were conducted [10–11]. No patient selection based on EGFR expression in cancer cells was done. Despite the promising preclinical results, no significant differences were observed in the outcome of patients treated with chemotherapy alone or with the addition of gefitinib in both of these two parallel studies.

Thatcher et al., have recently reported the results of a phase III trial named ISEL which has been designed to compare gefitinib with best supportive care in patients with advanced NSCLC who had received one or two prior chemotherapy regimens [12]. In 1692 patients (the ISEL is the largest study conducted in the refractory advanced NSCLC population) a difference between gefitinib and placebo was reported, although this did not reach a statistical significance in the overall or adenocarcinoma histology population. Pre-planned sub group analyses suggested survival benefits in patients of Oriental, Asian origin and in patients who never smoked. Specifically, at a median follow-up of 7 months, median survival was 5.6 vs. 5.1 months (HR 0.89; 95% CI:0.78–1.03; P = 0.11) in the overall population, and 6.3 vs. 5.4 months in patients with adenocarcinoma histology (HR 0.83; 95% CI:0.67–1.02; P = 0.07) for gefitinib and placebo respectively. As stated before, pre-planned subgroup analyses indicated statistically different survival outcomes in smokers vs never smokers and in patients of Oriental vs non-Oriental origin. In patients of Oriental origin, gefitinib–treated patients survived longer than placebo-treated patients (HR 0.66; 95% CI:0.48–0.91; P = 0.01, median survival 9.5 vs. 5.5 months, respectively). A similar results was seen in never smokers, where gefitinib–treated patients survived longer than placebo-treated patients (HR 0.67, 95% CI: 0.49–0.91, P = 0.01, median survival 8.9 vs. 6.1 months, respectively). Statistically significant improvements in response rate were observed for gefitinib compared with placebo.

erlotinib

It is a low molecular weight, orally bioavailable, quinazoline derivative which selectively and reversibly inhibits the tyrosine kinase activity of EGFR. Phase I studies in patients with advanced solid tumors have shown a tolerability profile similar to Gefitinib. The recomended dose for continuous treatment was 150 mg/day. In a phase II study by Perez Soler et al. [13], erlotinib was administered to 57 patients with EGFR-expressing NSCLC tumors, previously treated with platinum-based chemotherapy. Objective responses were reported in 12.3% of patients. In this trial, exploratory analyses were conducted to investigate any potential relationship between skin toxicity and clinical outcomes. Interestingly, rash was documented in all
seven patients who experienced an objective response and in 21 (95%) of 22 patients who had disease stabilization. Rash was included in the multivariate analysis along with the other factors, it was the most significant predictor of survival, with hazard ratios of 0.13 for grade 1 and 0.05 for grade 2/3, respectively (P < 0.0001 for each factor). The final results of the BR.21 study, a phase III, multicenter, randomized, placebo-controlled trial undertaken to determine whether erlotinib prolonged survival in NSCLC patients after one or two regimens of chemotherapy have been recently presented [14]. This phase III trial enrolled 731 patients, who were randomized to receive either erlotinib or placebo in a 2:1 ratio. Overall response rate to experimental drug was 8.9%. Median OAS was 6.7 months for erlotinib versus 4.7 months in the placebo group (P = 0.001). The PFS was 2.2 months for erlotinib and 1.8 months for placebo (P < 0.001). This has been the first randomised trial to demonstrate that an EGFR TKI is able to prolong survival after chemotherapy for NSCLC. It has been shown that objective response is more frequent in women (14% vs. 6%, P = 0.0065), in patients with adenocarcinoma compared to other histotypes (14% vs. 4%, P < 0.0001), in patients without history of smoke (25% vs. 4%, P < 0.0001). In consideration of the BR.21 study results, erlotinib has been approved by the FDA in November 2004 for the treatment of chemotherapy-resistant advanced NSCLC patients. The results of two large multicenter phase III studies of first line carboplatin-paclitaxel (TRIBUTE study) or cisplatin-gemcitabine (TALENT study) with or without erlotinib in stage IIIB-IV NSCLC patients have been recently reported [15]. Both studies, similarly to the INTACT studies with gefitinib, have failed to show any difference in overall survival between the standard and the erlotinib-containing treatment.

**conclusions**

Small molecule EGFR-TKIs, such as gefitinib and erlotinib, have shown promising clinical activity as monotherapy in a small subset of chemotherapy refractory NSCLC patients. Furthermore, erlotinib has been shown to significantly improve survival in an unselected population of patients following the failure of one or two chemotherapy regimens. A series of relevant issues, such as the appropriate selection of potentially responsive patients, with the identification of clinical and biological predictive factors of response to therapy, the valuable combination with cytotoxic treatments and/or with other molecularly targeted agents, are all important areas of clinical and translational research in NSCLC [16]. Some of these topics will be discussed in detail in the review articles by Cappuzzo et al. and by Tortora et al. in the same issue of the journal.

**references**