Review

Targeting the Epidermal Growth Factor Receptor in Non-Small Cell Lung Cancer

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Abstract

Fifteen \% or fewer of patients with non-small cell lung cancer (NSCLC) survive 5 years. The current standard of care for patients with locally advanced or metastatic NSCLC is systemic chemotherapy with a two-drug combination regimen that includes a platinum agent. Although systemic chemotherapy reduces the rate of death attributable to lung cancer, disease progression is inevitable and dose-limiting toxicities restrict their use. New molecularly targeted therapies aim to inhibit specific pathways and key molecules implicated in tumor growth and progression while sparing normal cells. Several therapies, which target signal transduction pathways involved in angiogenesis, metastasis, and apoptosis, are in clinical development to treat lung cancer. Among these targeted therapies are the oral, small-molecule epidermal growth factor receptor-tyrosine kinase (EGFR-TK) inhibitors gefitinib and erlotinib. Both therapies have been validated preclinically as new treatment approaches for NSCLC and have shown single-agent activity against advanced, chemorefractory NSCLC in clinical trials. This article focuses on the biology of the EGFR-TK signal transduction pathway, its role in the proliferation of solid tumors, and the rationale for the clinical development of EGFR-TK inhibitors. We also review clinical trials with EGFR-TK inhibitors in NSCLC and future directions of investigation with these targeted agents.

Introduction

The TK\textsuperscript{3} activity of the EGFR has received considerable attention as a target for cancer therapy (1, 2). In recent clinical trials, selective and orally active EGFR-TK inhibitors gefitinib [IRESSA (ZD1839); AstraZeneca] and erlotinib [Tarceva (OSI-774); OSI and Genentech] produced objective tumor responses and symptom improvement in some patients with NSCLC who had previously received chemotherapy (3–5). This was the first class of oral targeted therapies to produce such responses in advanced NSCLC. Although chemotherapy can result in life-threatening toxicities, the EGFR-TK inhibitors have far better safety profiles in patients with advanced NSCLC.

Lung cancer is the leading cause of cancer death in both men and women in the United States and throughout the world (6, 7). The 5-year survival rate for lung cancer patients remains very poor with 15\% or less surviving 5 years (6). Nonetheless, this is improved compared with the 5\% 5-year survival rate in the United States in the 1960s and the 5\% rate still seen in many parts of the world. The major reasons for the poor survival rate for lung cancer are the lack of effective screening and early diagnosis procedures, the propensity for early metastasis, and the inability of systemic therapies to cure patients with widely metastatic disease. This is not to conclude that there have been no advances in lung cancer therapy. Systemic chemotherapy produces a 26–32\% reduction in the hazard rate of death for patients with advanced stage II/IV NSCLC that includes adenocarcinomas, squamous carcinomas, and large cell carcinomas (8–10). Chemotherapy also reduces lung cancer-related symptoms and improves quality of life in patients with advanced NSCLC (8–11).

The current standard of care for patients with locally advanced or metastatic NSCLC is systemic chemotherapy with a two-drug combination regimen that includes a platinum agent (8). Such two-drug combinations, developed in the 1990s, were shown to be more effective than the best supportive care or treatment with a single chemotherapy agent. These two-drug combinations were also shown to be as effective as, but less toxic than, combinations of three or more chemotherapy drugs. The efficacy is similar for several of these two-drug combinations. Trials of the SWOG and the ECOG compared five different two-drug combinations in previously untreated patients with advanced NSCLC and found that they had similar efficacy in terms of tumor response rates and overall survival (Table 1; Refs. 12 and 13). Other large randomized trials from the United States and Europe have also shown the equivalence of a number of two-drug combination regimens, and superiority compared with single-agent chemotherapy regardless of whether the single agent is an older agent such as cisplatin or a newer agent such as paclitaxel, docetaxel, or gemcitabine (14–18).

The development of NSCLC disease progression on chemotherapy, mAb, monoclonal antibody; IDEAL, IRESSA dose evaluation in advanced lung cancer; LCS, Lung Cancer Subscale; FACT-L, Functional Assessment of Cancer Therapy—Lung; INTACT, IRESSA NSCLC trial assessing combination therapy.
other therapy is inevitable, because these regimens do not result in cure. Until recently, there were no Food and Drug Administration approved agents for use in the second-line setting. Docetaxel was approved on the basis of randomized trials in patients whose disease had progressed on platinum-based chemotherapy (19, 20). The objective response rates of docetaxel were only 5–10% associated with a modest survival improvement. No agent produced tumor response in more than 5% of patients in the third-line treatment setting.

The cytotoxic mechanism of action of chemotherapy agents imposes inherent limitations on their use. These agents nonspecifically kill normal proliferating cells and, as a result, are frequently associated with dose-limiting toxicities. Many of these effects, such as nausea, vomiting, and hair loss, are troubling to the patient but are not life threatening. Perhaps the most troubling effect is fatigue. Other frequent toxicities may be disabling even if not life threatening. Among these would be the neuropathy associated with paclitaxel and the severe fluid retention or effusion associated with docetaxel. All of the cytotoxic chemotherapy agents produce hematological toxicities that are often life threatening and occasionally fatal. The careful observation of sequential blood counts and the i.v. infusions of biological response modifiers, and vaccines (24–26). Among these various approaches are small-molecule inhibitors of tumor cell TKs. Gefitinib and imatinib have been validated clinically as new treatment approaches for malignancies (3–5, 23). Furthermore, the EGFR-TK inhibitors gefitinib and erlotinib have shown single-agent activity against advanced, chemorefractory NSCLC in clinical trials described below (3–5, 27).

**EGFR-TK: A Molecular Target in NSCLC**

**EGFR-TK Biology and Signaling in Solid Tumors.**

The EGFR is a cell surface receptor encoded by the *HER1* (HER type 1) or ErbB1 gene (1). EGFR belongs to a family of receptor TKs that includes *HER2/neu* (ErbB2), *HER3* (ErbB3), and *HER4* (ErbB4). EGFR and TGF-α are the two predominant ligands for EGFR (28, 29). The binding of these ligands to the extracellular domain of EGFR results in dimerization of the receptor monomer with another EGFR molecule or another member of the HER family (Fig. 1). Dimerization produces structural changes in the intracellular portion of the receptor that activate the TK domain. The enzymatic activity of EGFR-TK transfers phosphate moieties from ATP to specific tyrosine residues in the cytoplasmic tail of the EGFR protein. These phosphotyrosine residues then act as docking sites for various downstream effectors (Fig. 2). Some of these effectors are adapter molecules, such as growth factor receptor-bound protein 2 (Grb2) and Src homology collagen protein (Shc), which serve as platforms to assemble the downstream signaling elements necessary for activating cellular proliferation (30). Other molecules are enzymes that are activated on EGFR-TK-dependent phosphorylation, including src of sevenless (SOS), PI3K, and Grb 2-associated binder-1 (Gab-1). Multiple major signal transduction pathways are initiated by EGFR autophosphorylation, including the Ras-MAPK signaling cascade, Src, and the signal transducers and activators of transcription (STAT) pathways, which are widely used by growth signals to induce gene tran-

**Table 1 Overview of efficacy results from large comparative trials of first-line chemotherapy regimens for advanced NSCLC**

<table>
<thead>
<tr>
<th>Trial end point</th>
<th>SWOG 9509</th>
<th>ECOG 1594</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response, %</td>
<td>25–28</td>
<td>17–22</td>
</tr>
<tr>
<td>Median survival, mo</td>
<td>8.1–8.6</td>
<td>7.4–8.1</td>
</tr>
<tr>
<td>Time to tumor progression, mo</td>
<td>4</td>
<td>3.1–4.2</td>
</tr>
<tr>
<td>1-year survival, %</td>
<td>36–38</td>
<td>31–36</td>
</tr>
</tbody>
</table>

*See Refs. 12, 13.*

agents that were recently approved by the Food and Drug Administration include trastuzumab, a mAb targeting the HER2/neu receptor protein in breast cancer; imatinib (Gleevec (STI571): Novartis), a small molecule receptor TK inhibitor targeting Bcr/abl in chronic myelogenous leukemia and c-Kit in gastrointestinal stromal tumors, (22, 23); and gefitinib, an orally active EGFR-TK inhibitor used as monotherapy in the treatment of patients with advanced or metastatic NSCLC who have failed to respond to platinum-based and docetaxel chemotherapies. Depending on the specific molecule targeted and the mechanism of inhibition, these agents may offer novel clinical benefits compared with outcomes with cytotoxic chemotherapy, or at least the minimum comparable benefits with reduced general toxicity and improved convenience.
scription and promote diverse cell responses. The particular dimer combinations that form at the cell surface after ligand binding determine which signaling molecules will be recruited to the surface (29–33).

Ligand binding is the most extensively studied mechanism of EGFR-TK activation, but a variety of other cellular mechanisms are now known to influence EGFR-TK activity in tumor cells. For example, some mutations in the EGFR gene result in expression of EGFR proteins with constitutively activated TK activity, the most well-known being the EGFRvIII mutation. Defective inactivation mechanisms (e.g., phosphatases, and receptor endocytosis and degradation) may also result in sustained signaling. Heterologous receptors and signal transduction pathways, including interactions or dimerization with other ErbB receptor types, have been shown to cross-activate EGFR-TK.

Cellular proliferation as a result of EGFR-TK activation may occur via several signal transduction pathways; however, proliferation signals are strongly mediated by the MAPK pathway. After recruitment of adapter molecules on the activated EGFR complex, stepwise activation of Ras, Raf, MAP/Erk kinase (MEK1), and extracellular regulated kinase (Erk) proteins leads to increased activity of transcription factors, such as Elk1 and c-fos, key molecules that prime the cell for proliferation and activate cell cycle progression (29). Activated EGFR has been shown to induce the expression of cyclin D, which is crucial in cell cycle progression and is commonly increased in solid tumors.

Activated EGFR-TK also influences the malignant progression of solid tumors. TGF-α and EGF induce angiogenesis by up-regulating the expression of vascular endothelial growth factor (VEGF) in tumor cells. Increased microvessel density has been found in tumors that express activated EGFR-TK (34). In addition, EGFR-TK interacts with components of the integrin pathway involved in cell–cell adhesion, which is crucial for tumor cell invasion of adjacent tissues (29, 35, 36). EGFR-TK also promotes invasiveness through the up-regulation or activation of matrix metalloproteinases and stimulates tumor cell motility that further contributes to metastasis (37–39).

EGFR-TK activation indirectly inhibits apoptosis in tumor cells, promoting tumor cell survival and resistance to cytotoxic therapies. This activity is mediated by PI3K, which activates Akt, an important signaling molecule in antiapoptotic pathways involving the transcription factor nuclear factor κB. Akt also regulates activity of the Ras-MAPK pathway, which is important for cellular proliferation (29). Interaction with signals from heterologous pathways, including those activated by stress inducers, neurotransmitters, hormones, and lymphokines, adds additional complexity to the EGFR-TK signaling network (31). These pathways involve G-protein-coupled receptors, which can transactivate EGFR. Cross-talk between EGFR and other receptors allows for EGFR-TK signals to activate other pathways.

Increased expression of EGFR and its signaling pathways has been associated with a high percentage of tumors in the lung, breast, head and neck, colon, prostate, esophagus, and cervix (1, 2). These elevated levels of EGFR may be the result of transcripational or posttranscriptional alterations or genomic mutation (34). Differences in the methodologies used and in the criteria for determining EGFR expression levels make it difficult to compare study results (2, 40). Various methods of meas-
uring EGFR levels in tumor tissues include immunohistochemistry (Fig. 3), immunoassays, and assessment of RNA levels. Although some studies have shown a correlation between high expression of EGFR and decreased survival times, most studies of NSCLC patients have failed to show that EGFR expression is independently prognostic of survival (2, 34). The prognostic value of EGFR expression is increased when analyzed in conjunction with its dimeric partners, such as HER2/neu/ErbB2, or with ligands, such as TGF-$\alpha$ or EGF (41–43). High levels of EGFR in tumors result in an increase in EGFR ligand-binding sites and higher levels of the TK enzyme, as well as an increase in initiation sites for signal transduction inside the tumor cell. These findings indicate that there is an important role for aberrant EGFR signaling in the development and progression of various human tumors. In addition, they provide a strong rationale for EGFR-TK as a target molecule for the development of new cancer therapies.

**EGFR-TK Inhibitors.** Different approaches to inhibiting EGFR have resulted in a number of EGFR-targeted agents in clinical development including small-molecule EGFR-TK inhibitors, mAbs, vaccines, immunotoxins, and recombinant ligand–toxin fusion proteins (1, 44).

Small-molecule EGFR-TK inhibitors act by blocking the ATP binding site of the EGFR-TK enzyme inside tumor cells (Fig. 4). On the basis of this mechanism of action, EGFR-TK inhibitors have the potential to inhibit all mechanisms of EGFR-TK activation, including constitutively activating mutations and receptor cross-talk. EGFR-TK inhibitors were designed to selectively inhibit EGFR-TK relative to other kinase enzymes present in normal tissues (28). Gefitinib, erlotinib, and CI-1033 (Pfizer) are among the EGFR-TK inhibitors in clinical development (Table 2; Refs. 1 and 45–48). Both gefitinib and erlotinib selectively and reversibly inhibit EGFR-TK, whereas CI-1033 is an irreversible pan-ErbB family inhibitor. The small-molecule EGFR-TK inhibitors also inhibit signals induced by EGFR heterodimerization with other members of the ErbB family. Compared with anti-EGFR mAbs such as cetuximab [Erbitux (C225); ImClone], EGFR-TK inhibitors offer the advantages of oral bioavailability and once-daily treatment.

The targeted agent cetuximab, [Erbitux (C225); ImClone], is a chimeric mAb directed against the extracellular, ligand-binding domain of EGFR that competes with ligand for receptor binding (1, 49, 50). Cetuximab was not studied as a single agent in NSCLC but is currently being evaluated in combination with carboplatin/paclitaxel and cisplatin/gemcitabine in untreated patients with stage IV NSCLC, and with docetaxel in patients with chemotherapy-refractory tumors. ABX-EGF (Abgenix) is another anti-EGFR mAb in Phase I clinical trials. mAbs can also be coupled with various toxic agents such as bacterial toxins or...
radioactive particles, which may be used as delivery devices. The binding of the mAbs to the extracellular domain of EGFR triggers endocytosis of the receptor-immunotoxin complex to the cytoplasm, in which the various toxins act to inhibit protein synthesis and induce apoptosis (51). In another approach for targeting toxins to EGFR-expressing tumor cells, chimeric molecules are created by fusing portions of the genes for ligands (EGF, TGF-α) with a toxin gene. One example of such a toxin-fusion protein, DAB389-EGF, is in Phase II clinical trials for NSCLC (24).

Both EGFR-TK inhibitors and anti-EGFR antibodies are effective in preclinical models for inhibiting the growth of a variety of human tumor cell lines, including lung, colorectal, breast, and prostate, suggesting their potential for broad applicability for solid tumor types (1). Preclinical studies also showed that EGFR inhibition results in synergy with chemotherapy agents or radiation therapy in cell lines that are sensitive to EGFR inhibitors (52). For example, in cell viability assays, gefitinib treatment was synergistic with the cytotoxic chemotherapy agents, vinorelbine and paclitaxel, and had additive effects with cisplatin (52). Similarly, gefitinib in combination with radiation has shown growth-inhibitory effects ranging from synergistic to additive in gefitinib-sensitive cell lines (52). Lung tumor xenografts have also been inhibited by gefitinib alone or in combination with chemotherapy agents (53). Gefitinib, erlotinib, and cetuximab have all been shown to potentiate the antitumor effects of most cytotoxic agents, including platinum-based chemotherapy agents in preclinical models with cell lines sensitive to EGFR inhibition. Gefitinib also showed activity against NSCLC xenografts in combination with taxanes, doxorubicin, and antifolates (45, 52–54).

Pharmacodynamic studies indicate that EGFR-TK inhibitors and anti-EGFR antibodies block cell cycle progression in the G1 phase by up-regulating p27Kip1, a cell cycle inhibitor, and down-regulating c-fos, a transcriptional activator that is prominent in EGFR-mediated signaling (45, 52–55). Elevated levels of p27Kip1 block cell cycle progression in the G1 phase of growth. This sustains the hypophosphorylated state of the retinoblastoma (RB) gene product, which is necessary to keep cells from progressing in the cell cycle (37, 56).

The inhibition of tumor growth seen with EGFR-TK inhibition is also accompanied by decreases in vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), and TGF-α, all potent inducers of tumor angiogenesis (57). Thus, inhibitors of EGFR/EGFR-TK may also inhibit tumor growth by interfering with angiogenesis (58, 59). These observations suggest that by inhibiting EGFR-TK, gefitinib and erlotinib treatment alters expression levels of key molecules in tumor cells that are important for stimulating proliferation, cell cycle progression, tumor angiogenesis, metastasis, and inhibition of apoptosis.

**Clinical Trials of EGFR-TK Inhibitors in NSCLC**

**Phase I Trials.** Several anti-EGFR agents have been tested alone or in combination with other agents in Phase I trials that included patients with NSCLC. Phase I trials of gefitinib followed two escalating dose schedules: (a) once-daily gefitinib given continuously for 28 days; or (b) intermittent gefitinib, with 14 days on and 14 days off treatment (60–62). In the intermittent-dosing trials, doses ranged from 50 to 925 mg/day. In the continuous-dosing trials, doses ranged from 150 to 1000 mg/day. Tumor EGFR status

![Fig. 4 The mechanism of action of EGFR-TK inhibitors in blocking signal transduction through EGFR-TK.](image-url)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Mechanism of action in vitro</th>
<th>Clinical status</th>
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</thead>
<tbody>
<tr>
<td>ZD1839 (gefitinib)</td>
<td>EGFR-TK inhibitor HER1 (KB&lt;sub&gt;b,c&lt;/sub&gt;; CG&lt;sub&gt;b&lt;/sub&gt;) HER2 (KB&lt;sub&gt;c&lt;/sub&gt;; CG&lt;sub&gt;b&lt;/sub&gt;)</td>
<td>Phase III (Approved)</td>
</tr>
<tr>
<td>OSI-774 (erlotinib)</td>
<td>EGFR-TK inhibitor HER1 (2–20 nM; ≤100 nM) HER2 (0.2 μM; &lt;3 μM)</td>
<td>Phase III</td>
</tr>
<tr>
<td>CI-1033 (none)</td>
<td>EGFR-TK/HER2 inhibitor HER1 (1.7 nM; 7.4 nM) HER2 (5 nM; N/A)</td>
<td>Phase I</td>
</tr>
<tr>
<td>C225 (cetuximab)</td>
<td>Anti-EGFR antibody</td>
<td>Phase II/III</td>
</tr>
<tr>
<td>ABX-EGF (none)</td>
<td>Anti-EGFR antibody</td>
<td>Phase II</td>
</tr>
<tr>
<td>EGF-P64K (none)</td>
<td>Vaccine</td>
<td>Phase II/III</td>
</tr>
<tr>
<td>DAB389-EGF (none)</td>
<td>Immuno toxin</td>
<td>Phase II</td>
</tr>
</tbody>
</table>

*See Refs. 45–48.

*<sup>a</sup> KB, kinase/binding inhibition; CG, cell growth inhibition; N/A, not available.

*<sup>b</sup> KB varies based on the source of purified HER1/2.

*<sup>c</sup> CG varies based on cell line tested.
was not an eligibility requirement in these trials. Patients were selected based on having tumor types that were all known to express EGFR at a high rate, including NSCLC and colorectal, prostate, head and neck, ovarian, breast, renal, and pancreatic cancers.

In total, 252 patients were recruited for Phase I trials of gefitinib (60–62). Almost all of the patients had received prior treatment with radiotherapy and/or chemotherapy, and many had received multiple prior chemotherapy regimens. Of the patients enrolled, 100 had advanced, previously treated NSCLC. The most common adverse events were diarrhea, acneiform rash, nausea, asthenia, and vomiting. The majority of adverse events were grade 1 or 2 and transient; grades 3 and 4 events were rare (62). Dose-limiting toxicities including reversible diarrhea and rash occurred at daily doses of 700 to 800 mg. Pharmacokinetics were consistent with once-daily dosing (60, 62).

Histopathological studies of pretreatment and posttreatment skin biopsy specimens from Phase I trials showed that treatment with gefitinib suppressed EGFR phosphorylation, inhibited MAPK activity, reduced the proliferation index as judged by staining for Ki67 (a nuclear proliferation-associated antigen), and increased both the apoptotic index and the expression of p27


The mAb cetuximab, which is administered i.v., was in-
gefitinib as second-line versus third-line treatment (17.9% versus 19.8%; Ref. 3). Adenocarcinoma, which characteristically expresses less EGFR than does squamous cell carcinoma, was identified as one of the prognostic factors associated with objective response (3.5 times more likely to respond to treatment than other tumor histologies; Ref. 3). The overall symptom improvement rate, as measured by the LCS, was 40 and 37%, respectively, and improvement occurred rapidly with a median time to improvement of 8 days (3). Among responders, 78% exhibited symptom improvement based on the LCS and 53% reported a quality-of-life improvement as measured by FACT-L (67).

The most frequent adverse events were generally mild and included rash, pruritus, and dry skin. Table 4 (3) lists the most frequent adverse events reported in the IDEAL-1. Grades 3 and 4 adverse events that occurred at a frequency of ≥5% were seen only in patients dosed at 500 mg/day and included rash (7%) and diarrhea (8%). Of the 216 patients enrolled in IDEAL-2, 41, 33, and 25% of patients had received two, three, or four or more previous chemotherapy regimens, respectively (4). Similar response rates were achieved across subpopulations by number of prior regimens in this trial (Fig. 5; Ref. 4). The lack of a response rate decrement in patients with increased therapies is different from that with standard therapy.

The tumor response rates for the 250 mg/day and 500 mg/day groups were 11.8 and 8.8%, respectively, and the median duration of tumor response ranged from 3 to ≥7 months (4). In addition, disease stabilization occurred in 31% of patients in the 250 mg/day group and in 27% of patients in the 500 mg/day group (4). As in the IDEAL-1 trial, the response rate for patients with adenocarcinoma in IDEAL-2 was significantly higher than for other tumor histologies (13 versus 4%; P < 0.05; Ref. 4) Symptom response rates for the 250 mg/day and 500 mg/day groups in IDEAL-2 were 43 and 35%, respectively (4). The median duration of symptom response ranged from 1 month to ≥7.4 months. Symptomatic responses also occurred early in this study; 60% of symptom responders did so within 2 weeks of treatment. The median survival for both groups was ~6 months. Improvement in quality of life, as measured by FACT-L, was observed in 86% of patients who showed an objective tumor response and in 52% of patients with stable disease (68).

In summary, IDEAL-1 and IDEAL-2 were large randomized Phase II trials of gefitinib that demonstrated antitumor and symptom responses in a meaningful proportion of advanced, chemotherapy-refractory NSCLC patients. The response rates were considerably higher than those previously reported with chemotherapy, placebo, or best supportive care. In addition, gefitinib was shown to have a good tolerability and safety profile, with reversible skin rash and diarrhea as the most frequent adverse events.

Erlotinib was evaluated in a smaller, single-dose Phase II trial in 56 chemotherapy-refractory NSCLC patients who had disease progression or relapse after at least one prior platinum-based chemotherapy regimen (27). Tumors were required to express EGFR by immunohistochemistry. The objective response rate was 12.3%, with stable disease in 26.3% of patients and a median survival of 37 weeks. Tumor response was not associated with EGFR expression level. Treatment with erlotinib was generally well tolerated. The most common adverse event was acneiform rash, which occurred in 78% of patients. The similarity in skin toxicities between the anti-EGFR agents suggests that this effect may be typical with this class of drug (27). Patients with a severe rash had a superior survival compared with those without rash. A Phase III trial comparing erlotinib with placebo in patients with advanced chemotherapy-refractory NSCLC has been completed by the National Cancer Institute of Canada.

**EGFR-TK Inhibitors in Previously Untreated NSCLC**

**Phase I Trials.** The fact that gefitinib and erlotinib produced objective responses in second- and third-line mono-

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Results from Phase II studies of patients with NSCLC treated with gefitinib&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial end point</td>
<td>IDEAL-1</td>
</tr>
<tr>
<td></td>
<td>250 mg/day</td>
</tr>
<tr>
<td></td>
<td>(n = 103)</td>
</tr>
<tr>
<td>Objective tumor response, %</td>
<td>18.4</td>
</tr>
<tr>
<td>Symptom improvement, %</td>
<td>40.3</td>
</tr>
<tr>
<td>Disease control, %</td>
<td>54.4</td>
</tr>
<tr>
<td>Overall survival, mo</td>
<td>7.6</td>
</tr>
</tbody>
</table>

<sup>a</sup> See Refs. 3, 4.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Most frequent drug-related adverse events IDEAL-1&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IDEAL-1</td>
</tr>
<tr>
<td></td>
<td>250 mg/day</td>
</tr>
<tr>
<td></td>
<td>(n = 103)</td>
</tr>
<tr>
<td>Rash, %</td>
<td>47</td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea, %</td>
<td>40</td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td>0</td>
</tr>
<tr>
<td>Pruritus, %</td>
<td>30</td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td>0</td>
</tr>
<tr>
<td>Dry skin, %</td>
<td>27</td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td>0</td>
</tr>
<tr>
<td>Nausea, %</td>
<td>12</td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td>1</td>
</tr>
</tbody>
</table>

<sup>a</sup> See Ref. 3.
therapy settings, led to Phase I feasibility trials combining gefitinib or erlotinib with first-line chemotherapy regimens in previously untreated advanced NSCLC patients. The combination of gefitinib and carboplatin/paclitaxel yielded an overall response in 25% of patients and stable disease in 33% (5). With gefitinib/cisplatin/gemcitabine combination, tumor response or stable disease was observed in all of the patients with NSCLC (four of eight partial response and four of eight stable disease). In both of these pilot trials, gefitinib treatment did not increase the overall toxicity of chemotherapy (5).

Erlotinib was evaluated in three small Phase I trials in combination with several different chemotherapy regimens including gemcitabine/cisplatin, paclitaxel/carboplatin, and docetaxel in patients with a variety of advanced solid tumors (64). Overall, tumor responses and stable disease were seen in some patients in each of these Phase I trials. In trials with gemcitabine/cisplatin and paclitaxel/carboplatin, dose-limiting toxicities of neutropenia and diarrhea were seen with 100-mg/day erlotinib (69–71). Dose-limiting neutropenia was also observed with 75-mg/day erlotinib in combination with docetaxel (69–71). In each study, dose reductions or amendments in dosing schedules were required to reduce dose-limiting toxicities. Combination therapy was better tolerated with these modifications.

Phase III Trials. Gefitinib was investigated with two-drug chemotherapy regimens in two large randomized double-blind placebo-controlled Phase III trials, each enrolling more than 1000 previously untreated, advanced NSCLC patients (72, 73). These studies were termed INTACT-1 and INTACT-2. The chemotherapy regimens were cisplatin/gemcitabine in INTACT-1 and carboplatin/paclitaxel in INTACT-2 (72, 73). Patients received a maximum of six cycles of chemotherapy and either 250 mg or 500 mg/day gefitinib. After chemotherapy, patients continued on gefitinib alone or placebo until disease progression. There was no significant differences in response rates, time to progression, or survival between the gefitinib arm and the placebo arm of either trial (72, 73). The reasons for the negative results in these trials are unclear.

It is also possible that antagonistic effects could occur between chemotherapy and gefitinib in tumors that are resistant to gefitinib. Some investigators have suggested that the efficacy of gefitinib in combination with chemotherapy regimens may be dependent on the schedule or sequence of administration, a hypothesis that requires further investigation. For example, tumor responsiveness to gefitinib may be altered by phenotypic or genotypic changes that occur during or immediately after chemotherapy. Two randomized studies of erlotinib in combination with chemotherapy are completed in patients with previously untreated, advanced NSCLC. In “TRIBUTE,” ~1050 patients were treated with 150 mg/day erlotinib and six cycles of gemcitabine/cisplatin. In “TALENT,” ~1024 patients were treated with 150 mg/day erlotinib and six cycles of paclitaxel/carboplatin. Initial results suggest that like the INTACT, erlotinib plus chemotherapy did not significantly improve survival in either trial.

It is possible that only a fraction of patients are likely to respond to EGFR inhibitors. Therefore, a means to select patients who are most likely to respond to treatment with EGFR inhibitors is needed. Whereas expression of EGFR alone does not seem to predict response to gefitinib, other molecules may predict clinical benefits (75). This illustrates how the model for EGFR inhibitors is different from the trastuzumab model. In the trastuzumab model, clinical benefit is directly linked to the level of HER2 expression (22). Future studies will explore novel ways to select patients with potential for clinical benefit.

Future Directions

EGFR expression and TK activity is found in the majority of NSCLC patients across all disease stages as well as in patient with other common solid tumors (1, 2). Agents that inhibit EGFR have demonstrated clear antitumor activity in the important population of patients with advanced, metastatic NSCLC who have received prior chemotherapy. However, these agents may also have applicability for lung cancer at earlier stages, or in other solid tumor types.

One area of active research focuses on developing assays to determine which patients and tumor types are most likely to respond favorably to EGFR-TK inhibitors. Preclinical studies have shown that the level of EGFR expressed by a given tumor cell line is not in itself a determinant of antitumor response (74). Such predictive assays need to focus on the level of activation of EGFR-TK and downstream signaling molecules. The activation status of EGFR-TK and other cell signaling molecules in tumors may be analyzed by immunohistochemistry or proteomics before and after treatment with EGFR-TK inhibitors. In addition, the genetic profiles of NSCLC tissues may be analyzed by gene microarray technologies. These translational approaches are needed to gain insight into which genetic markers might be prognostic of clinical benefit with EGFR-TK inhibition, indicative of EGFR-TK inhibition activity, or predictive of tumor responses once treatment has been initiated. In trials with tamoxifen, it has been shown that there was a considerable reduction in the proliferation index as assessed with Ki67 from the
time of initial biopsy to surgery in response to anti-estrogen treatment (75–77).

On the basis of the mechanism of EGFR-TK inhibition, it may be possible to draw a parallel between the potential of targeted agents in lung cancer and hormone therapies, such as tamoxifen, in breast cancer. First approved for advanced breast cancer, tamoxifen was later approved as adjuvant therapy and for risk reduction in breast cancer in high-risk premenopausal and postmenopausal women. Today, tamoxifen is widely used in breast cancer therapy at various stages of disease (78). In the adjuvant setting for hormone receptor-positive breast cancer, initial results of an intergroup study (SWOG 8814) have indicated that delaying tamoxifen until after chemotherapy had an estimated 18% advantage for disease-free survival when compared with concurrent adjuvant use of tamoxifen and chemotherapy (79). These results suggest that tamoxifen may antagonize chemotherapy regimens, and support a practice of starting tamoxifen after adjuvant chemotherapy is completed (79). This finding provides support for a parallel interpretation of the INTACT trial results in advanced NSCLC. Although no benefits to concurrent use of gefitinib with chemotherapy regimens were found in these trials, the potential benefit of sequential treatment of EGFR-TK inhibitors after completion of chemotherapy regimens is currently under investigation for advanced NSCLC.

To assess the role of gefitinib as adjuvant therapy, the National Cancer Institute of Canada will assess gefitinib in patients who have completed surgical resection for stage I, II, or IIIA NSCLC. Patients are randomized to receive 250 mg/day of gefitinib or placebo after resection. Overall survival is the primary end point of the trial. Secondary end points will include disease-free survival, quality of life, and predictive value of EGFR expression as a marker of prognostic significance. Patients are stratified by disease stage, prior radiation therapy, gender, and squamous versus nonsquamous histology. Accrual of 1050 patients is necessary to discern a significant improvement of 33% in 5-year survival. Another Phase III trial, SWOG S0023, is investigating chemoradiation with consolidated docetaxel followed by a randomization to gefitinib or placebo for inoperable stage IIIA/B NSCLC. A study to investigate erlotinib in combination with radiation therapy and chemotherapy in patients with stage III NSCLC is also ongoing.

Increased expression of EGFR can occur very early, even in precancerous lesions. On the basis of this rationale, a pilot trial is currently evaluating gefitinib in the chemoprevention of lung tumors. The Specialized Programs of Research Excellence (SPORE) Phase III multicenter trial in former/current smokers with a history of cancer will compare the effects of gefitinib and placebo on changes in molecular markers of malignant progression in bronchial tissue (80–82). A Neoadjuvant Phase III trial, currently underway at M.D. Anderson Cancer Center, is exploring the use of erlotinib in patients in a preoperative setting. The design of this trial provides pre- and posttreatment tissue samples for analysis of the EGFR and a host of downstream markers (i.e., phospho-EGFR, phospho-AKT, and so forth; Fig. 6). These trials include extensive analysis of biopsy specimens to determine the molecular changes that underlie malignant transformation and that could serve as biomarkers of tumor progression. In addition to the use of gefitinib in advanced NSCLC, alone or in combination with other therapies, EGFR-TK inhibition may offer a new strategy for affecting lung cancer at earlier stages by preventing or reducing precancerous disease with fewer patients developing cancer.

Conclusions

Novel targeted therapies, such as EGFR mAb and EGFR-TK inhibitors, provide useful palliation in the treatment of advanced NSCLC and provide an innovative strategy for chemoprevention strategies. A major unanswered question is how to optimally select patients for therapy, because the majority of lung cancer patients do not respond to therapy and have no survival or symptom benefit. Identification of those patients who are most likely to respond to EGFR-TK inhibitor treatment is likely to be feasible and will advance the potential to determine the survival effects of these agents in optimal populations. In addition, assessment of the potential for EGFR-TK inhibitors to delay recurrence or provide chemoprevention of solid tumors will occur in the next few years.

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References

1. Mendelsohn, J. Blockade of receptors for growth factors: an antican-
cer therapy—the fourth annual Joseph H Burchenal American Associ-
2. Hirosch, F. R., Varella-Garcia, M., Bunn, P. A., Jr., Di Maria, M. V.,
Veve, R., Bremms, R. M., Baron, A. E., Zeng, C., and Franklin, W. A.
Epidermal growth factor receptor in non-small cell lung carcinomas:


Targeting the Epidermal Growth Factor Receptor in Non-Small Cell Lung Cancer

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