Erlotinib: Optimizing Therapy with Predictors of Response?

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New drugs developed as anticancer therapy have focused on targeting molecules essential to tumor growth and survival. In particular, protein kinases have emerged as key regulators of all aspects of cancer. Agents that inhibit the activity of cell membrane receptor tyrosine kinases, such as the human epidermal growth factor receptor (HER1/EGFR), have been an attractive target because EGFR is expressed by 30% to 100% of solid tumors (1). Two oral agents targeting EGFR were approved by the Food and Drug Administration (FDA) initially for use in non–small cell lung cancer (NSCLC): gefitinib (Iressa, AstraZeneca, Wilmington, DE) in May 2003 and erlotinib (Tarceva, OSI Pharmaceuticals, Melville, NY) in November 2004. The use of gefitinib was recently limited, however, to those cancer patients who, in the opinion of their treating physician, are currently benefiting or have previously benefited from gefitinib treatment. Erlotinib continues to be investigated in a number of tumor types and was recently approved for the treatment of pancreatic cancer in combination with gemcitabine. Another FDA-approved EGFR-targeting agent is the i.v. administered monoclonal antibody cetuximab (Erbitux, ImClone Systems, Branchburg, NJ), which is directed against the extracellular domain of EGFR and is indicated for treatment of EGFR-expressing metastatic colorectal cancer in patients who are refractory to irinotecan-based therapy. Although multiple monoclonal antibodies targeting EGFR are in development, the article will focus on the FDA-approved oral EGFR tyrosine kinase inhibitors with an emphasis on erlotinib.

Clinical Pharmacology and Clinical Trials

EGFR is a transmembrane receptor that binds to ligand and forms homodimers and heterodimers with other ErbB receptor family members. Erlotinib and gefitinib selectively inhibit EGFR activity by binding to the ATP binding site of the tyrosine kinase domain, preventing activation of the tyrosine kinase portion of the EGFR receptor by blocking phosphorylation. This interrupts downstream signaling, including the mitogen-activated protein kinase and phosphatidylinositol 3-kinase/AKT pathways, thus inhibiting tumor cell proliferation.

In the phase I trial of erlotinib, a significant number of patients had stable disease, including a patient with NSCLC (2). Subsequently, multiple trials showed activity with erlotinib as monotherapy in the treatment of NSCLC; however, in these trials, only a small proportion of patients seemed to benefit from the drug (3–6). The FDA approval of erlotinib for treatment of patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen was based on a randomized double-blind, placebo-controlled phase III trial of 731 patients treated for second-line and third-line advanced NSCLC (6). In this trial, patients receiving 150 mg of erlotinib daily had a response rate of 8.9% with a median survival of 6.7 months, resulting in a 42.5% improvement in median survival compared with patients receiving placebo that had a response rate of <1% and a median survival of 4.7 months. Additionally, 31.2% of patients receiving erlotinib in the study were alive at 1 year versus 21.5% in the placebo arm.

Because of *in vitro* synergy with various chemotherapy agents, the combination of erlotinib with chemotherapy in first-line advanced NSCLC therapy has been evaluated in two large front-line, randomized, placebo-controlled clinical trials (7, 8). The chemotherapy regimens given in these trials were gemcitabine and cisplatin in the TALENT trial involving 1,172 patients (7), or carboplatin and paclitaxel in the TRIBUTE trial involving 1,079 patients (8). There was no clinical benefit in either trial, and currently, concurrent use of erlotinib with chemotherapy in NSCLC is not recommended. Similar to erlotinib, there was no clinical benefit when gefitinib was combined with chemotherapy in either the INTACT-1 or INTACT-2 trials (9, 10). Ongoing trials of erlotinib given after four cycles of platinum-based chemotherapy in patients with NSCLC and exploring different schedules of erlotinib with chemotherapy will clarify the role of erlotinib with chemotherapy in this patient population.

The most recent FDA approval for erlotinib is in combination with gemcitabine for the first-line treatment of patients with locally advanced, inoperable, or metastatic pancreatic cancer. In the phase III trial evaluating the combination, there was a 23% improvement in overall survival with the combination of erlotinib and gemcitabine when compared with gemcitabine alone (hazard ratio, 0.81; $P = 0.028$; ref. 11). The 1-year survival rates were 24% and 17%, respectively. Additionally, there was a significant improvement in progression-free survival in the combination regimen with a hazard ratio of 0.76 ($P = 0.003$). Encouraging data are also emerging in other tumor types, including head and neck cancer and ovarian cancer, with the use of erlotinib in combination with chemotherapy and other targeted therapies.

Predictors of Response and Resistance

Modest response rates were observed from the initial clinical trials of both erlotinib and gefitinib, although some patients showed dramatic responses to both agents. Women, Asians,

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patients with adenocarcinoma, and patients who had never smoked were more likely than other patients to have a response to erlotinib and gefitinib (3, 6, 12, 13). Interestingly, this is the group of patients that most commonly have an EGFR mutation in the tyrosine kinase domain of the *EGFR* gene (12–15). In contrast to the gefitinib trials, however, where mutations in the EGFR tyrosine kinase domain, specifically exons 18 through 21, seem to be associated with responsiveness (16, 17), immunohistochemical analysis of tumor biopsy samples from participants in the trial by Shepherd et al. (6) showed tumor cell expression of EGFR, not mutational status, significantly correlated with the response to erlotinib (12). This was particularly true for patients who had never smoked. Mutations in EGFR did result in higher response rates in this trial compared with patients whose tumors lacked mutations, but the difference was not statistically significant (6). In contrast to the monotherapy data regarding *EGFR* mutations as predictors of response, when erlotinib was combined with chemotherapy in the TRIBUTE trial, *EGFR* mutations were associated with a statistically significant increased response rate but no improvement in survival (18). When gefitinib was combined with chemotherapy in the INTACT trials, *EGFR* mutations did not predict for response (19).

When evaluating EGFR expression status on survival, erlotinib significantly prolonged survival for patients whose tumors were EGFR positive with little effect on those with EGFR-negative tumors, but because of the wide confidence intervals reported, a survival effect in patients with EGFR-negative tumors cannot be excluded (12). Post-marketing studies specifically evaluating response based on EGFR expression status are ongoing in NSCLC. Finally, although responses were higher in patients with EGFR expression, increased number of gene copies, and mutation status, responses were also seen in patients whose tumors lacked these features (6). Further studies need to be conducted to determine if limiting these agents to patients whose tumors have these specific properties prevent some patients from receiving potentially ineffective therapy.

Because *EGFR* mutations may correlate with response, evaluating patients prospectively may allow better patient selection for the use of EGFR tyrosine kinase inhibitors. In September of 2005, the FDA approved a genetic test (EGFR Mutation Assay, Genzyme Corp., Cambridge, MA) for the detection of EGFR mutations in patients with NSCLC (20). To perform the test, cells are microdissected, and DNA is extracted and amplified via PCR followed by bidirectional sequencing of exons 18 to 21 in the tyrosine kinase domain of the EGFR receptor. The mutation analyses are reviewed by a team of 17 surgical pathologists and geneticists who are available for personal consultations.

In addition to mutations in the EGFR tyrosine kinase domain, the development of a rash has been suggested as a possible predictor of response and survival. Although multiple studies with erlotinib have reported a positive correlation between rash and response/survival, the relationship between rash and clinical outcome is less consistent for gefitinib (21). In trials of erlotinib in patients with advanced NSCLC, head and neck squamous cell carcinoma, and advanced ovarian cancer, there was a significant correlation between rash and survival, with rash severity correlating to the median duration of survival (21). Additionally, in the trials of erlotinib combined with chemotherapy in NSCLC, although there was no survival benefit in either trial (9, 10), subanalysis showed a correlation between the development of rash and longer survival (21). Finally, it was recently shown that susceptibility to both rash and pharmacologic effects of EGFR-targeted agents could be linked to polymorphic variations in the *EGFR* gene (22). The relationship between the development of rash and survival is currently being evaluated further, and the results should help guide the use of erlotinib therapy (21).

Although *EGFR* mutations, amplification, and the development of rash have been associated with improved efficacy with the EGFR inhibitors, other molecular etiologies have been explored to predict for resistance. Downstream of EGFR signaling, *KRAS* mutations are the most frequently reported alteration in NSCLC, occurring in ~20% of NSCLC especially in adenocarcinomas and smokers, and are mutually exclusive of EGFR mutations (13). It was recently shown that a lack of activity of the tyrosine kinase inhibitors in NSCLC was associated with *KRAS* mutations (18, 23, 24). Finally, a second mutation (T790M in exon 20 of the tyrosine kinase domain) may contribute to both intrinsic and acquired resistance to tyrosine kinase inhibitors (25, 26).

Adverse Effects

The most common adverse reactions in the pivotal trial of erlotinib for NSCLC were a reversible maculopapular rash and diarrhea (6, 11). Grade 3 and/or 4 rash and diarrhea occurred in 9% and 7%, respectively, of patients treated with erlotinib and resulted in discontinuation of therapy in 1% of patients (6). Dose reductions because of rash occurred in 6% and were caused by diarrhea in 1% (6). The incidence of rash was higher with erlotinib compared with gefitinib in phase II and III studies (21). Data from phase I dose escalation trials indicate that rash is dose dependent, and this may explain the differences in the incidence of rash between erlotinib and gefitinib. Plasma exposure, as measured by area under the plasma concentration-time curve, is ~7.5-fold higher with erlotinib than gefitinib when comparing FDA-approved daily doses of 150 and 250 mg, respectively (21).

Similar to the class of EGFR inhibitors, the development of a rash primarily on the face, neck, and upper torso occurs with erlotinib and is characterized by clusters of monomorphic pustular lesions. Rash onset is usually within 8 days of starting therapy with maximal intensity in the second week. It usually subsides by week 4 in most patients despite continued therapy, although it does persist for longer periods in a few patients. The differences in duration of rash are unclear but may be linked to pharmacogenetic heterogeneity (22). Similarly, the etiology of the rash is unclear, and no clinical trials have specifically evaluated the management of the rash. Various treatments have been evaluated including retinoids, steroids, and antibiotics, but currently, there are no consensus or evidence-based recommendations for management.

Interstitial lung disease occurred in 0.8% patients receiving erlotinib in the pivotal NSCLC trial, similar to the incidence among patients receiving placebo (6). Erlotinib should be discontinued at the development of pulmonary symptoms of dyspnea, cough, or fever. Other adverse effects include transient grade 2 elevations in liver function tests and rare

cases of gastrointestinal bleeding, conjunctivitis, keratitis, and corneal ulceration.

Dose and Administration

Erlotinib is available in a 25, 100, and 150 mg tablet. The daily dose is to be taken at least 1 hour before or 2 hours after ingesting food. An oral dose of 150 mg once daily is given continuously as second-line therapy in patients with NSCLC. For patients with pancreatic cancer, the dose of erlotinib is 100 mg daily in combination with 1,000 mg/m^2 gemcitabine on days 1, 8, and 15 on an every 21-day schedule. The current price for a 30-day supply of the 150 mg erlotinib tablets is approximately US$2,700. Although this represents a significant out-of-pocket expense for patients, no formal pharmacoeconomic studies have been done to compare this cost with any second-line chemotherapy for NSCLC.

Conclusion

Multiple studies have shown activity, albeit low, of the EGFR tyrosine kinase inhibitors in the treatment of NSCLC and other tumors. Since the initial clinical trials, many investigators have investigated factors that would predict for efficacy, including molecular, clinical, and pathologic features. The clinical and pathologic features that predict for response are similar for erlotinib and gefitinib. *EGFR* mutations correlate with responses to both gefitinib and erlotinib, whereas EGFR amplification correlates with response to erlotinib. Finally, the most common adverse event with the EGFR tyrosine kinase inhibitors is a rash, which may be a surrogate for predicting response and possibly survival. Although there is a compelling rationale for the use of these predictors of response to identify patients for treatment with EGFR tyrosine kinase inhibitors, further prospective investigation is required to better define the appropriate patient population for these targeted therapies.

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