INTRODUCTION

Lung cancer is the leading cause of death from cancer in the U.S. It was estimated that 172,570 new cases would be diagnosed and approximately 163,510 patients would die as a result of this disease in 2005. Non–small-cell lung cancer (NSCLC) accounts for 80% to 85% of all lung malignancies; 40% to 50% of patients present with stage IV (metastatic) disease.

Erlotinib (CP-358 774; OSI-774/R1415; Tarceva®, OSI/Genentech), is an oral, human epidermal growth factor receptor type 1/epidermal growth factor receptor (HER1/EGFR) tyrosine kinase inhibitor, similar to gefitinib (Iressa®, AstraZeneca). It has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of NSCLC. Overexpression and dysregulation of HER1/EGFR have been associated with increased tumor growth, proliferation, angiogenesis, metastasis, and inhibition of apoptosis. Erlotinib’s binding to HER1/EGFR and its inhibition of HER1/EGFR–associated tyrosine kinase interfere with cell communication, preventing excessive cell proliferation. Overexpression of HER1/EGFR occurs in approximately 70% to 80% of NSCLC patients and has been associated with resistance to chemotherapy and with a poor prognosis.

Erlotinib, manufactured by OSI Pharmaceuticals, is distributed and marketed by Genentech, Inc. It received a priority approval under the Pilot 1 Program for Continuous Marketing Applications on November 18, 2004.

MECHANISM OF ACTION

Although erlotinib’s mechanism of action is not fully understood, it is thought to reversibly bind to the adenosine triphosphate (ATP) binding site of the tyrosine kinase domain associated with HER1/EGFR, located on the surface of normal and cancer cells. This binding inhibits the phosphorylation of the tyrosine kinase, interfering with cell communication, signal transduction, and, ultimately, cellular growth.

PHARMACOKINETICS AND PHARMACODYNAMICS

The bioavailability of erlotinib is approximately 60% on an empty stomach and approaches 100% when it is taken with food. Peak plasma concentrations are reached four hours after dosing. Protein binding to albumin and alpha-1 acid glycoprotein is between 92% and 95%, with an apparent volume of distribution of 232 liters.

The drug is metabolized primarily by the cytochrome P450 (CYP) 3A4 isoenzyme and, to a lesser extent, by CYP1A2 and CYP1A1. After administration of a 100-mg dose, 83% of the dose is recovered in the feces and 8% in urine. The elimination half-life after a single dose is 36.2 hours; steady-state plasma concentrations are achieved within seven to eight days of therapy. The patient’s age, weight, and sex do not appear to affect clearance of the drug; however, there is a 24% higher rate of clearance in smokers.

No data are available regarding the effect of hepatic or renal failure on the pharmacokinetics of erlotinib.

INDICATION

Erlotinib is indicated for patients with metastatic or locally advanced NSCLC who have not responded to at least one chemotherapeutic regimen. On the basis of results from two phase 3 clinical trials (TRIBUTE and TALENT), it is not recommended for use in combination with platinum-based chemotherapy as the first-line treatment of NSCLC.

In these randomized, placebo-controlled trials, the addition of erlotinib to carboplatin (Paraplatin®, Bristol-Myers Squibb) and paclitaxel (Taxol®, Bristol-Myers Squibb) or gemcitabine (Genzmar®, Eli Lilly) and cisplatin regimens in previously untreated patients did not provide additional benefit in survival, time to progression, or response rate compared with the platinum-based regimens alone.

Trials are ongoing for the treatment of other cancers, including those of the pancreas, kidney, bladder, mouth and throat, esophagus, colon and rectum, head and neck, breast, brain, prostate, cervix, ovary, and liver, as well as neurofibrosarcoma and advanced solid tumors.

CLINICAL EFFICACY

Non–Small-Cell Lung Cancer

The FDA’s approval of erlotinib was based on results from a pivotal phase 3 trial of 731 patients with stage IIIIB/IV NSCLC (Eastern Cooperative Oncology Group performance status 0 to 3). These patients had received one or two previous chemotherapeutic regimens, and they were not eligible for further chemotherapy (93% had received prior platinum-based agents, 37% prior taxanes, and 49% had received two prior regimens).

The patients were randomly assigned, in a 2:1 ratio, to receive erlotinib 150 mg or placebo daily; 488 received erlotinib, and 243 received placebo. Survival, based on the intent-to-treat analysis, was the primary endpoint; progression-free survival, response, toxicity, and quality of life were secondary endpoints.

Statistically significant results were reported for prolongation of survival (6.7 months with erlotinib and 4.7 months with placebo). The hazard ratio (HR) was statistically significant results were reported for prolongation of survival (6.7 months with erlotinib and 4.7 months with placebo). The hazard ratio (HR) was
0.70, with a 95% confidence interval (CI) of 0.58–0.85 (P < .001). Progression-free survival was 2.2 months with erlotinib and 1.8 months with placebo (HR = 0.61, 95% CI, 0.51–0.74; P < .001).

Overall responses with erlotinib were 8.9% and 0.9% with placebo (95% CI, 6.6–12%; P < .001).13,14 Quality-of-life endpoints, as measured by median time to symptomatic deterioration for erlotinib versus placebo, were as follows:

- cough, 4.9 months versus 3.7 months (P = .04)
- dyspnea, 4.7 months versus 2.9 months (P = .03)
- pain, 2.8 months versus 1.9 months (P = .04)

The most frequently reported adverse drug events (ADEs) were rash and diarrhea. A total of 19% of the erlotinib patients required dose reductions. Five percent of the erlotinib patients and 2% of the placebo patients discontinued therapy because of ADEs.

No cases of interstitial lung disease were reported.15 One-year survival rates were 31.2% with erlotinib and 21.5% with placebo.7

Subset analyses were performed to evaluate the significance of various pretreatment characteristics. On the basis of univariate analyses, the response to therapy correlated significantly with female sex (P = .007), a history of never smoked (P < .001), Asian ancestry (P = .02), histological features of adenocarcinoma (P < .001), and polysomy or amplification of EGFR (P = .03).13 Similar survival rates were reported for all subsets except HER1/EGFR tumor status and smoking status.13,15 Although the HER1/EGFR-tumor status was known for only 325 of the 731 patients, the HER1/EGFR status and smoking status.13,15 Although the HER1/EGFR-tumor status was known for only 325 of the 731 patients, the HER1/EGFR status was known for only 325 of the 731 patients, the HER1/EGFR status and smoking status.13,15 Although the HER1/EGFR status was known for only 325 of the 731 patients, the HER1/EGFR status was known for only 325 of the 731 patients, the HER1/EGFR status was known for only 325 of the 731 patients.

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According to univariate and multivariate analyses, the interaction between EGFR status and erlotinib treatment was not significant (P = .199 and P = .127, respectively).15 The subgroup of patients who had never smoked (HR = 0.42, 95% CI, 0.28–0.64; P < .001) also demonstrated improved survival rates compared with patients who had ever smoked (HR = 0.87, 95% CI, 0.71–1.05; P = .14).16 In one analysis, patients who had never smoked and who were HER1/EGFR-positive demonstrated the largest survival benefit (HR = 0.28; P = .0007); however, data for HER1/EGFR–negative patients who had never smoked were not reported for comparison.15 These data suggest that a history of smoking may be more predictive of length of survival than EGFR status.13,14 Additional trials are necessary to clarify and confirm these results.

Numerous trials are ongoing in the NSCLC patient population. Various erlotinib regimens are being evaluated, including single-agent, first-line treatment12 and combination therapies with bevacizumab (Avastin®), Genentech,13 paclitaxel and carboplatin, and radiation.12

Pancreatic Cancer19–22

A Supplemental New Drug Application was filed with the FDA in April 2005 for the first-line treatment of advanced pancreatic cancer with the combination of erlotinib and gemcitabine.19 Results of a phase 3 trial comparing gemcitabine with or without erlotinib are available in abstract form.20,21 A total of 569 patients with metastatic pancreatic adenocarcinoma were randomly assigned to receive gemcitabine 1,000 mg/m² IV weekly with daily doses of oral erlotinib 100 mg or placebo. The erlotinib doses were increased to 150 mg/day in 48 patients.

Results showed statically significant increases in overall survival and a reduced risk of death (HR = 0.81; 95% CI, 0.67–0.97; P = .025) and progression-free survival in the erlotinib group (HR = 0.76, P = .003). Median survival increased from 5.9 months in the placebo arm to 6.4 months in the erlotinib group. No difference in tumor response was detected between the groups (9% with erlotinib vs. 8% with placebo).22 However, the erlotinib arm experienced increased incidence of grade 1 and 2 rash, diarrhea, and hematological toxicity.20,21

Interstitial lung disease was reported in 2.1% of the erlotinib-treated patients, compared with 0.4% of placebo patients.19 The incidence of grade 3 and 4 toxicities was similar in both groups.

No significant difference in survival was detected with regard to HER1/EGFR status.22 More studies are needed to determine which patients would most benefit from this treatment regimen.

ADVERSE EFFECTS

The most common ADEs reported in patients receiving erlotinib were rash and diarrhea. Grade 3 and 4 rash occurred in 9% of patients, and grade 3 or 4 diarrhea was reported in 6%. As a result, 1% of patients discontinued therapy.

Table 1 presents the ADEs that occurred in 10% or more of patients receiving erlotinib.2 A potential correlation has been shown with the occurrence of rash and appropriate levels of dosing and, in some cases, prolonged survival. Research is ongoing to determine whether this can be used as a marker of efficacy.6,23

PRECAUTIONS

The following events have been reported with erlotinib use and warrant caution:

- Rare cases of interstitial lung disease (0.6%), including fatalities, occurred between five days and nine months (median, 47 days) after the initiation of therapy. Most cases were also associated with other confounding factors.7
- Asymptomatic elevations in liver function enzymes were observed. Patients may require a dosage adjustment or may have to discontinue therapy if ADEs are severe. Caution should be used in patients with hepatic insufficiency.7
- Increases in International Normalized Ratios (INRs), along with rare instances of bleeding, were reported. Abnormalities have occurred in patients who took concomitant anticoagulant therapy and in patients who did not.7

DRUG INTERACTIONS

Erlotinib is metabolized primarily in the liver by the CYP3A4 enzyme. Co-administration with any CYP3A4 inhibitor (e.g., ketoconazole, ciprofloxacin, metronidazole, clarithromycin, or fluconazole) would consequently increase erlotinib serum levels. Increases of two thirds in the area under the curve (AUC) continued on page 571
Adverse Drug Events Associated with Erlotinib Therapy
in a Randomized, Controlled, Phase 3 Clinical Trial

<table>
<thead>
<tr>
<th>Incidence</th>
<th>Adverse Effect: NCI–CTC Grades 1–4 (Erlotinib/Placebo %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 50%</td>
<td>Rash (75/17), diarrhea (54/18), anorexia (52/38), fatigue (52/45)</td>
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<tr>
<td>26%–50%</td>
<td>Dyspnea (41/35), cough (33/29), nausea (33/24)</td>
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<td>Infection (24/15), vomiting (23/19), stomatitis (17/3)</td>
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<td>keratoconjunctivitis sicca (12/3), abdominal pain (11/7)</td>
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</tbody>
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NCI–CTC = National Cancer Institute Common Toxicity Criteria.
Adapted from package insert for erlotinib (Tarceva®).7

have been reported with concurrent ketoconazole administration.7,24 Conversely, coadministration with a CYP3A4 inducer (e.g., carbamazepine, dexamethasone, phenytoin, rifampin, nafcillin) would probably decrease the serum concentration of erlotinib.

A three-fold increase in clearance and a two-thirds decrease in the AUC has occurred with concurrent rifampin administration.7,24 Because erlotinib is highly protein-bound, caution should be used when it is administered with other protein-bound drugs.5

DOSAGE AND ADMINISTRATION

Erlotinib is available as an oral, film-coated tablet in 25-, 100-, and 150-mg strengths. The recommended dose is 150 mg daily, taken on an empty stomach to ensure consistent absorption. After treatment is initiated, it should be continued until there is either evidence of disease progression or until ADEs become intolerable.7

Dosage reductions, necessitated by ADEs or concomitant administration of a CYP3A4 inhibitor, should be accomplished in 50-mg increments. If interstitial lung disease or other progressive pulmonary symptoms are observed, erlotinib therapy should be discontinued.7

According to studies of overdoses, single doses up to 1,000 mg and 1,600 mg, respectively, have been tolerated in both healthy subjects and patients with cancer. In another trial, healthy subjects did not tolerate twice-daily doses of 200 mg because of high rates of ADEs.7

SAFETY

No data are available on the use of this agent in children. Erlotinib is classified as a Pregnancy Category D medication. Women of childbearing age should be advised to take birth control precautions while receiving erlotinib and for two weeks after terminating treatment. No data are available on the drug’s excretion into breast milk.7

MONITORING REQUIREMENTS

Liver function tests should be ordered periodically to look for asymptomatic increases in liver enzyme levels. In addition, prothrombin time or INR should be monitored routinely in patients receiving concurrent anticoagulant therapy.7

It has been suggested that rash might have a correlation with appropriate dosing levels and, in some cases, prolonged survival.5,23 In a subanalysis of a phase 2 trial, rash occurred in all seven patients experiencing an objective response, 21 of 22 (95%) who had stable disease, and in 15 of 28 (54%) who had progressive disease. Prolonged survival also correlated with the severity of rash. The median survival time was 8.5 months for patients experiencing a grade 1 rash and 19.6 months for those with a grade 2 or 3 rash, compared with 1.5 months for those without rash (P < .001).6

In an analysis of three single-agent phase 2 trials of erlotinib, the incidence of rash was 75% in patients with refractory NSCLC, 79% in those with head and neck cancer, and 82% in those with ovarian cancer. In all three trials, patients with rash showed statistically significant increased survival time compared with patients without rash, although there was no correlation between the incidence or severity of rash and the level of HER1/EGFR measured before therapy.25

In an analysis of 23 clinical trials in which rash was evaluated as a surrogate marker of the drug’s efficacy, 19 trials showed a positive correlation or trend. The mechanism is not clear, but it is believed that the rash is caused by the inhibition of HER1/EGFR in the skin. Two trials are ongoing to evaluate the development of rash as a marker in determining dosage.23

COST

Erlotinib is available in bottles containing 30 tablets. The average wholesale price per tablet is $27 for 25 mg, $74.29 for 100 mg, and $84.42 for 150 mg.26 Although reimbursement is currently unavailable through Medicare Part B,27 the cost of this drug is covered under the Medicare Replacement Drug Demonstration project, which will remain in effect until December 31, 2005, when Medicare Part D becomes effective.28

Specific insurance reimbursement information is available through Genentech’s Single Point of Contact.27 For qualified uninsured or underinsured patients, a program is available through Genentech’s Access to Care Foundation.29

ALTERNATIVE THERAPIES

Combination chemotherapy is the first-line treatment (i.e., a taxane/platinum combination) for patients with NSCLC who are not candidates for surgery.3 Erlotinib is being marketed as second-line or third-line drug therapy.7 Table 2 (see page 572) compares the treatment regimens and costs of other approved second-line and third-line therapies.30–32

CONCLUSION

Erlotinib offers the advantages of oral administration and less toxicity compared with traditional chemotherapy. It is the first targeted therapy approved for the treatment of NSCLC with documented improvement in survival. It is also less costly than standard second-line chemotherapy for NSCLC.

Additional issues being studied include potential markers of efficacy, such as rash, and whether patient selection can be enhanced based on a potential correlation of magnitude of EGFR expression with sensitivity to erlotinib.6,23,33

Table 1

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NCI–CTC = National Cancer Institute Common Toxicity Criteria.
**Table 2: Comparison of Erlotinib and Alternative Second-Line and Third-Line Therapies for Non-Small-Cell Lung Cancer**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Place in Therapy</th>
<th>Route of Administration</th>
<th>Recommended Dosage</th>
<th>Cost (AWP) for 21 Days*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erlotinib (Tarceva&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Second- and third-line</td>
<td>Oral</td>
<td>150 mg once daily</td>
<td>$1,772.75</td>
</tr>
<tr>
<td>Docetaxel (Taxotere&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Second-line</td>
<td>IV infusion</td>
<td>75 mg/m² on day one of each 21-day cycle</td>
<td>$2,607.68</td>
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<tr>
<td>Pemetrexed (Alimta&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Second-line</td>
<td>IV infusion</td>
<td>500 mg/m² on day one of each 21-day cycle</td>
<td>$4,875.00</td>
</tr>
<tr>
<td>Gefitinib (Iressa&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Third-line</td>
<td>Oral</td>
<td>250 mg once daily</td>
<td>$1,429.58</td>
</tr>
</tbody>
</table>

AWP = average wholesale price; IV = intravenous; mg = milligram.

* Doses based on a patient with a body surface area of 1.73 m².


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**REFERENCES**

19. Moore MJ, Goldstein D, Hamm J, et al. Erlotinib improves survival when added...
continued from page 572


