A 64-year-old woman who has never smoked receives the diagnosis of stage I adenocarcinoma of the lung and undergoes right upper lobectomy. One year later, bone and liver metastases develop. She is treated with carboplatin, paclitaxel, and bevacizumab, but progressive bone metastases are noted after 6 weeks of therapy. An oncologist recommends the initiation of erlotinib therapy.

**The Clinical Problem**

Lung cancer, the leading cause of cancer-related death worldwide, accounted for an estimated 157,300 deaths in the United States in 2010. Approximately 85 to 90% of all cases of lung cancer are non–small-cell lung cancer (NSCLC). Advanced-stage NSCLC is currently considered an incurable disease for which standard chemotherapy provides marginal improvement in overall survival at the expense of substantial morbidity and mortality. Furthermore, less than 30% of patients with metastatic NSCLC have a response to platinum-based chemotherapy, the most commonly used initial treatment in this stage of the disease. Even with the addition of newer agents, such as bevacizumab, to chemotherapy, the median overall survival of patients with metastatic NSCLC remains approximately 1 year, and only 3.5% of patients with metastatic NSCLC survive 5 years after diagnosis.

**Pathophysiology and Effect of Therapy**

The sobering outcomes from studies of current NSCLC therapy have shifted attention to new treatment approaches. The signaling pathway of the epidermal growth factor receptor (EGFR), a cell-surface receptor, is activated in more than half of patients with NSCLC, and this activation can be the result of protein overexpression, increased gene copy number, or genetic mutations. The ERBB receptor family consists of four receptor tyrosine kinases: EGFR (also called ERBB1 or HER1), ERBB2 (also called HER2/neu), ERBB3 (also called HER3), and ERBB4 (also called HER4). All of these except HER3 have tyrosine kinase activity.

Binding of secreted growth factors, such as the epidermal growth factor (EGF) and other EGF-like growth factors, including transforming growth factor α and epiroginulin, induces receptor dimerization, resulting in the phosphorylation of tyrosine residues in the kinase domain. These phosphotyrosines recruit partner proteins that trigger intracellular signaling cascades, chiefly through the mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K) path-
Figure 1. Epidermal Growth Factor Receptor (EGFR) Signaling Pathways. Shown in the left portion of the figure are the four members of the ERBB (or HER) family of receptors. All four members of this family have tyrosine kinase domains in the cytoplasmic portion of the receptor. However, the tyrosine kinase domain of HER3 does not have catalytic activity. The right portion of the figure shows that binding of ligands to the HER family of receptors induces either homodimerization or heterodimerization of the receptors. Dimerization results in phosphorylation of the tyrosine residues of the EGFR kinase domain. The activated receptor may then phosphorylate a wide array of intracellular signaling cascades, such as the RAS–RAF–MEK–ERK and PI3K–AKT pathways, that induce cellular proliferation, angiogenesis, and metastases. EGFR amplification can obviate the requirement for ERK and PI3K–AKT pathways, that induce cellular proliferation, angiogenesis, and metastases. EGFR-specific ligands (e.g., epiregulin and transforming growth factor α) have sought to determine how best to exploit the potential beneficial effects of these agents. (An extensive discussion of the major clinical trials is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.)

In two parallel phase 3 studies, erlotinib and gefitinib were compared with placebo in patients with advanced NSCLC in whom standard chemotherapy had failed. In a National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) trial (BR.21) (ClinicalTrials.gov number, NCT000366477), 731 patients with stage IIIB or IV NSCLC were randomly assigned to receive either erlotinib (at a daily dose of 150 mg) or placebo. In all the patients, who had an Eastern Cooperative Oncology Group (ECOG) performance status ranging from 0 to 3 (Table 1), first-line or second-line chemotherapy had failed. Erlotinib was superior to placebo in analyses of overall survival (6.7 vs. 4.7 months, P=0.001), progression-free survival (2.2 vs. 1.8 months, P<0.001), and quality of life.

Similarly, the Iressa Survival Evaluation in Lung Cancer (ISEL) trial (NCT00242801) was designed to evaluate the effects of gefitinib (at a daily dose of 250 mg), as compared with placebo, on overall survival in patients who had previously been treated with standard chemotherapy. Gefitinib was superior to placebo in terms of the time to treatment failure (3.0 vs. 2.6 months, P<0.001). However, no significant differences were observed in overall survival.

In a subsequent noninferiority trial, gefitinib was compared with docetaxel as second-line therapy in patients with NSCLC. In the Iressa NSCLC Trial Evaluating Response and Survival versus Taxotere (INTEREST) trial (NCT00076388), 1433 patients who had received at least one platinum-based regimen were randomly assigned to receive either gefitinib or docetaxel. Gefitinib therapy resulted in noninferior overall survival, as compared with docetaxel monotherapy (7.6 vs. 8.0 months), with a hazard ratio for death of 1.02 (96% confidence interval [CI], 0.91 to 1.15). Subgroup analyses from the initial clinical trials showed that patients with certain clinical and histologic characteristics (specifically, women, patients of East Asian descent, those with no history of smoking, and those with adenocarcinomas) who received erlotinib or gefitinib had higher rates of response and overall survival.
Furthermore, the presence of specific \( \text{EGFR} \) mutations leading to intrinsic activation of the receptor has been consistently found to be strongly associated with a better therapeutic response.\(^{18-20} \)

These observations have led to clinical trials specifically focusing on the use of \( \text{EGFR} \) tyrosine kinase inhibitors as first-line therapy in responsive subgroups of patients with NSCLC.

In the Iressa Pan-Asia Study (IPASS) (NCT00322452), a phase 3 trial conducted in Asia, patients with advanced adenocarcinoma of the lung who had not undergone previous chemotherapy and who were either lifetime nonsmokers or former smokers with a limited lifetime tobacco exposure were randomly assigned to receive either gefitinib or chemotherapy with carboplatin and paclitaxel.\(^{21} \) The rate of progression-free survival at 1 year was significantly better in the gefitinib group (24.9% vs. 6.7%), with a hazard ratio for progression or death of 0.74 (95% CI, 0.65 to 0.85; \( P<0.001 \)). Although overall survival was similar in the two study groups, there was a suggestion of improvement in quality of life in patients treated with gefitinib.

In two randomized trials conducted in Japan involving 230 and 177 patients, gefitinib was compared with two combinations of platinum and taxane agents as first-line therapy for patients with advanced NSCLC who carried activating \( \text{EGFR} \) mutations. Gefitinib significantly improved the median progression-free survival, as compared with carboplatin and paclitaxel (10.8 vs. 5.4 months; hazard ratio, 0.30; 95% CI, 0.22
Table 1. Eastern Cooperative Oncology Group (ECOG) Performance Status.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Fully active, able to carry on all predisease activities without restriction</td>
</tr>
<tr>
<td>1</td>
<td>Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework or office work)</td>
</tr>
<tr>
<td>2</td>
<td>Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours</td>
</tr>
<tr>
<td>3</td>
<td>Capable of only limited self-care; confined to bed or chair more than 50% of waking hours</td>
</tr>
<tr>
<td>4</td>
<td>Completely disabled and not capable of self-care; totally confined to bed or chair</td>
</tr>
<tr>
<td>5</td>
<td>Dead</td>
</tr>
</tbody>
</table>

CLINICAL USE

Erlotinib received approval from the Food and Drug Administration (FDA) in November 2004 and from the European Medicines Agency in June 2005 as a second- or third-line therapy for patients with locally advanced or metastatic NSCLC. Gefitinib initially received approval by the FDA in 2003. However, on the basis of data from the subsequent ISEL trial, which did not show a survival advantage or an improvement in disease-related symptoms,15 the labeling of gefitinib was modified to limit its use to patients who are currently benefiting or who have previously benefited from gefitinib therapy. In July 2009, the European Medicines Agency granted approval for the use of gefitinib in any line of therapy for patients with NSCLC who carry activating EGFR mutations. The approval of gefitinib is still restricted in the United States, but as of early 2011, the drug is licensed in 66 countries worldwide (www.iressa.com).

Taken together, the available trial data suggest that EGFR tyrosine kinase inhibitors have efficacy that is similar to that of standard chemotherapy as second- or third-line treatment for patients with advanced NSCLC. Among patients receiving first-line therapy, tyrosine kinase inhibitors appear to be inferior to standard chemotherapy overall but superior for selected patients, especially for those with activating EGFR mutations. Although some differences in the trial results for erlotinib and gefitinib have led to differences in regulatory policy, no head-to-head comparison of the two agents has been conducted. Therefore, no definitive conclusions can be drawn regarding substantive differences in the efficacy of these two agents.

The recommended doses are 150 mg for erlotinib and 250 mg for gefitinib, taken orally once daily. Erlotinib has an oral bioavailability of 60% when taken on an empty stomach. Taken with food, erlotinib has a bioavailability of nearly 100%, which potentiates side effects. Therefore, erlotinib should be taken at least 1 hour before or 2 hours after a meal. In contrast, food does not affect the absorption of gefitinib.24,25 The elimination half-life of gefitinib is 48 hours, and its mean bioavailability is 60%.

Erlotinib and gefitinib are metabolized primarily by CYP3A4 and to a lesser extent by CYP3A5 and CYP1A1.24-27 The concurrent use of these agents with CYP3A4 inhibitors or inducers, such as atazanavir, itraconazole, ritonavir, voriconazole, or grapefruit juice, must be monitored carefully, since dose adjustments of the drug may be necessary. Certain CYP3A4 inducers, such as rifampicin, phenytoin, and St. John’s wort, should not be used in combination with erlotinib or gefitinib, since these agents could decrease the bioavailability of the drug. Cigarette smoking induces CYP1A1 and has been correlated with a reduction in erlotinib exposure after a therapeutic dose.28 The solubility of both erlotinib and gefitinib is pH-dependent. Agents that alter gastric pH, such as H₂-receptor antagonists and proton-pump inhibitors, can substantially reduce the plasma levels of EGFR tyrosine kinase inhibitors, and their concomitant use should be avoided.

In keeping with the designs of published phase 3 trials, radiographic assessment of response to erlotinib or gefitinib should occur no more frequently than every 6 to 8 weeks.14,29-31 However, given the potential for substantial side effects, patients should be evaluated by the treating clinician at least monthly initially and then possibly less frequently, depending on the patient’s tolerance of the agent. Daily erlotinib or gefitinib therapy should be continued for as long as the patient’s performance status is adequate and there is no clinical or radiographic progression, since patients with stable disease have been shown to have a clinical benefit. Furthermore, data support the continuation of treatment even...
if a loss of response is documented, since tumor progression is accelerated to a greater degree if the agent is discontinued.\\textsuperscript{32}

A reduction in the dose of erlotinib or an interruption of treatment with either agent should be considered in cases of substantial toxic effects, such as severe rash or debilitating diarrhea.\\textsuperscript{24,25} Although there are no specific recommendations for adjustment of the dose of gefitinib or erlotinib in patients with renal dysfunction, liver function should be monitored periodically during erlotinib or gefitinib therapy, since cases of hepatic failure have been attributed to both agents.\\textsuperscript{33,34} Dose adjustment or treatment interruption should be considered for both agents if the total bilirubin level exceeds three times the upper limit of the normal range or the alanine transaminase levels exceed five times the upper limit of the normal range.\\textsuperscript{24,25}

The length of treatment interruptions must be guided by the patient’s individual response to the treatment break. After an interruption in the administration of erlotinib because of toxic effects, it is recommended that therapy be restarted at a reduced dose. When dose modifications are made, decrements of 50 mg should be instituted with the use of lower-strength tablets.\\textsuperscript{35} If the decision is made to continue gefitinib after a treatment interruption because of toxic effects, the original daily dose of 250 mg should be reinstated, since there are no consensus guidelines for dose reduction and gefitinib is not supplied in lower-strength tablets.\\textsuperscript{25}

In the United States, the costs of a month’s supply of erlotinib (at a daily dose of 150 mg) and gefitinib (at a daily dose of 250 mg) are approximately $4,000 and $1,800, respectively (www.drugstore.com). In countries in which both agents are currently commercially available, erlotinib is approximately 20% more expensive than gefitinib.

### ADVERSE EFFECTS

Erlotinib and gefitinib have similar toxic-effect profiles. However, because the recommended dose of erlotinib is closer to the maximum tolerated dose, it is moderately more toxic than gefitinib. Unlike traditional cytotoxic agents, erlotinib and gefitinib do not typically cause myelosuppression, neuropathy, alopecia, or severe nausea.\\textsuperscript{14,16,36,37} The discontinuation of erlotinib and gefitinib because of toxic effects occurs in 5% and 2% of patients, respectively.\\textsuperscript{14,38} Elderly patients who are treated with erlotinib have clinical outcomes that are similar to those for younger patients but have a higher rate of grade 3 or 4 toxic effects (35% for patients ≥70 years vs. 18% for patients <70 years).\\textsuperscript{39}

In phase 1 studies of both agents, diarrhea was the dose-limiting effect. Diarrhea occurs in up to 55% of patients who are treated with erlotinib, with severe diarrhea occurring in 6% of patients. The incidence of diarrhea in patients receiving gefitinib ranges from 27 to 35%.\\textsuperscript{14,16} In cases of severe diarrhea, therapy should be stopped for up to 14 days until the symptoms have resolved; loperamide may be used to control the diarrhea.

Rash is reported in 75% of patients who are treated with erlotinib\\textsuperscript{24} and in 33% of those treated with gefitinib.\\textsuperscript{25} Among such patients, the onset of rash occurs 7 to 14 days after the initiation of therapy.\\textsuperscript{30} The rash is usually follicular and papulopustular and frequently involves the face, scalp, chest, and back (Fig. 3A and 3B). Various topical and systemic preparations of antibiotics, glucocorticoids, and immunomodulators have been used with some success; moisturizing of the skin is recommended. Acne preparations, such as benzoyl peroxide, must be avoided, since they may exacerbate this common side effect. In patients with rash controlled by topical moisturizers, treatment with erlotinib or gefitinib can continue in an uninterrupted manner. However, in those with severe rash, dose modifications of erlotinib or treatment interruption of either agent may be necessary.\\textsuperscript{35}

Interstitial lung disease is a rare but potentially life-threatening complication of both erlotinib and gefitinib therapy, with an overall incidence of less than 1% in white patients and about 5% in Japanese patients. The risk of this side effect, which usually occurs within the first month of therapy, appears to be increased by previous chemotherapy, previous radiation therapy to the lungs, preexisting parenchymal lung disease, metastatic lung disease, and concomitant pulmonary infection. The onset of unexplained respiratory symptoms should prompt drug interruption while a diagnostic workup is performed. Should interstitial lung disease be confirmed, therapy with EGFR tyrosine kinase inhibitors should be permanently discontinued.\\textsuperscript{24,25}
Areas of Uncertainty

The relatively low response rates achieved with the EGFR tyrosine kinase inhibitors, coupled with their high cost, highlights the need to identify a priori a subgroup of patients who may have a clinical benefit from these agents. The assessment of EGFR mutational status is currently the most reliable predictor of response and of clinical benefit. It remains to be shown whether up-front assessment of the EGFR mutational status for all patients with advanced NSCLC and subsequent treatment with an EGFR tyrosine kinase inhibitor for patients carrying EGFR mutations will result in an overall survival advantage, although this approach has already been adopted by some clinicians.

The skin toxicity of EGFR inhibition has been associated with improved overall and progression-free survival in unselected patients (though not specifically in patients with EGFR mutations). Although the reasons for this association remain unclear, commonly cited hypotheses suggest that the skin toxicity is a surrogate pharmacodynamic indicator of effective EGFR inhibition at the tumor level or that the skin toxicity is a surrogate indicator of an immune-based local inflammatory reaction at the tumor level that provides antitumor activity. Prospective investigation of a correlation between the effects of EGFR inhibition in the skin and tumor tissue is warranted.

Deletions in exon 19 and the L858R point mutation in exon 21, the most common activating EGFR mutations in NSCLC, have both been associated with improved outcomes with erlotinib or gefitinib therapy. However, patients eventually acquire resistance to these EGFR tyrosine kinase inhibitors, with a median time to progression of approximately 12 months. In 50 to 70% of cases, this phenomenon can be explained by the acquisition of a secondary EGFR mutation (most commonly T790M in exon 20) or by the amplification of the MET oncogene, which implies that in 30 to 50% of patients, the mechanisms of resistance are unknown (Fig. 2). Several agents with in vitro activity against EGFR T790M or MET kinases are being evaluated in clinical trials for patients with NSCLC in whom therapy with EGFR tyrosine kinase inhibitors has failed.

Recent data suggest improved progression-...
free survival with erlotinib therapy in combination with other targeted agents. In the ATLAS trial (NCT00257608), patients with advanced NSCLC who had stable or improved disease after treatment with chemotherapy plus the vascular endothelial growth factor inhibitor bevacizumab were randomly assigned to receive maintenance therapy with bevacizumab with or without erlotinib. Progression-free survival was significantly longer in the bevacizumab–erlotinib group (4.8 months) than in the bevacizumab–placebo group (3.7 months; hazard ratio for death or progression, 0.72; 95% CI, 0.59 to 0.88; P = 0.001). The phase 3 BETA Lung Trial (NCT00130728), investigating the benefits of the addition of bevacizumab to erlotinib for second-line therapy of advanced NSCLC, showed a doubling of progression-free survival from combination therapy (3.4 months), as compared with erlotinib monotherapy (1.7 months, P<0.001) but no benefit in terms of overall survival. Further research is warranted to define the role of EGFR tyrosine kinase inhibitors in combination with other targeted agents in patients with NSCLC.

The combined effects of the EGFR tyrosine kinase inhibitors and radiotherapy as primary treatment of NSCLC are currently being investigated. On the basis of the limited data that are currently available, it appears that no substantial additional toxic effects are associated with concomitant therapy with EGFR tyrosine kinase inhibitors during radiotherapy.21,54

**GUIDELINES**

The National Comprehensive Cancer Network (NCCN) recognizes erlotinib as an option for second- and third-line therapy in patients with advanced NSCLC who have an ECOG performance status of 0 to 3. For patients with NSCLC who are known to carry an EGFR mutation, the NCCN suggests erlotinib monotherapy as first-line therapy and even reserves erlotinib as a salvage treatment option in this subgroup among patients with an ECOG performance status of 4. Furthermore, the NCCN recognizes erlotinib as a maintenance agent for patients with stable or responsive disease after first-line platinum-based chemotherapy.55

Although evidence supporting the value of EGFR mutational analysis is growing, no study to date has shown a benefit in overall survival from treatment selection on the basis of mutational status. Therefore, there is no current recommendation for routine mutational analysis in patients with advanced NSCLC. However, if an EGFR mutation is known to exist, therapy with an EGFR tyrosine kinase inhibitor should be instituted.21,55

**RECOMMENDATIONS**

The use of EGFR tyrosine kinase inhibitors should be considered in the case of the patient presented in the vignette, who has progressive metastatic NSCLC despite treatment with a standard chemotherapeutic regimen. We recommend that she begin erlotinib monotherapy at a daily dose of 150 mg. Given the fact that erlotinib has been shown to be beneficial as second-line therapy in unselected patients, treatment without assessment of the EGFR mutational status is acceptable. Special instruction needs to be given regarding the anticipation of and treatment recommendations for rash and diarrhea, the most common adverse effects of erlotinib. Restaging studies should be conducted before the initiation of therapy and 6 to 8 weeks after the initiation to evaluate the patient for response. Single-agent treatment with erlotinib should continue until progression of disease is documented.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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