Efficacy of Gefitinib, an Inhibitor of the Epidermal Growth Factor Receptor Tyrosine Kinase, in Symptomatic Patients With Non–Small Cell Lung Cancer: A Randomized Trial

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More persons in the United States die from non–small cell lung cancer (NSCLC) than from breast, colorectal, and prostate cancer combined.1 Each year, more than 60,000 persons develop stages IIIB and IV NSCLC; nearly all go on to die from metastatic spread. In addition, most individuals experience symptoms caused directly by lung cancer. These symptoms are often the first manifestations of the illness and increase in frequency and severity as the disease progresses. Cough, shortness of breath, weight loss, loss of appetite, and chest tightness impair the quality of lives already cut short by NSCLC. For patients with advanced lung cancer, physical well-being and changes in quality of life correlate with survival.2

Context More persons in the United States die from non–small cell lung cancer (NSCLC) than from breast, colorectal, and prostate cancer combined. In preclinical testing, oral gefitinib inhibited the growth of NSCLC tumors that express the epidermal growth factor receptor (EGFR), a mediator of cell signaling, and phase 1 trials have demonstrated that a fraction of patients with NSCLC progressing after chemotherapy experience both a decrease in lung cancer symptoms and radiographic tumor shrinkages with gefitinib.

Objective To assess differences in symptomatic and radiographic response among patients with NSCLC receiving 250-mg and 500-mg daily doses of gefitinib.

Design, Setting, and Patients Double-blind, randomized phase 2 trial conducted from November 2000 to April 2001 in 30 US academic and community oncology centers. Patients (N = 221) had either stage IIIB or IV NSCLC for which they had received at least 2 chemotherapy regimens.

Intervention Daily oral gefitinib, either 500 mg (administered as two 250-mg gefitinib tablets) or 250 mg (administered as one 250-mg gefitinib tablet and 1 matching placebo).

Main Outcome Measures Improvement of NSCLC symptoms (2-point or greater increase in score on the summed lung cancer subscale of the Functional Assessment of Cancer Therapy-Lung [FACT-L] instrument) and tumor regression (≥50% decrease in lesion size on imaging studies).

Results Of 221 patients enrolled, 216 received gefitinib as randomized. Symptoms of NSCLC improved in 43% (95% confidence interval [CI], 33%-53%) of patients receiving 250 mg of gefitinib and in 35% (95% CI, 26%-45%) of patients receiving 500 mg. These benefits were observed within 3 weeks in 75% of patients. Partial radiographic responses occurred in 12% (95% CI, 6%-20%) of individuals receiving 250 mg of gefitinib and in 9% (95% CI, 4%-16%) of those receiving 500 mg. Symptoms improved in 96% of patients with partial radiographic responses. The overall survival at 1 year was 25%. There were no significant differences between the 250-mg and 500-mg doses in rates of symptom improvement (P = .26), radiographic tumor regression (P = .51), and projected 1-year survival (P = .54). The 500-mg dose was associated more frequently with transient acne-like rash (P = .04) and diarrhea (P = .006).

Conclusions Gefitinib, a well-tolerated oral EGFR-tyrosine kinase inhibitor, improved disease-related symptoms and induced radiographic tumor regressions in patients with NSCLC persisting after chemotherapy.

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Many lines of evidence suggest that EGFR has relevance to patients with NSCLC and thus may serve as a potential therapeutic target. Expression of EGFR has been detected by immunohistochemistry testing in from 62% to 93% of resected primary tumors,12 and EGFR mRNA has been found in 100%. The overexpression of EGFR has been variably correlated with clinical outcomes.11,13-15

The oral drug gefitinib (ZD1839, Iressa, AstraZeneca Pharmaceuticals, Wilmington, Del) blocks EGFR tyrosine kinases and prevents epidermal growth factor–induced proliferation in cell culture. It inhibits growth and causes regressions in human tumor xenografts with EGFR overexpression.5 When given to patients with cancer, gefitinib inhibits EGFR activation in skin.16 Phase 1 trials identified diarrhea as dose-limiting at daily oral gefitinib doses of 700 to 1000 mg.17-20 A continuous gefitinib dosing schedule was developed because it was determined to be the best schedule to counter the continuous oncogenic signaling through this receptor, as seen in animal models9 and presumed to occur in persons with cancer. An acne-like rash was also noted. Unlike conventional chemotherapy, gefitinib did not cause myelosuppression, neuropathy, or significant alopecia. In these same phase 1 studies, rapid symptom improvement and radiographic regressions were documented in patients with NSCLC who had previously received chemotherapy.21

In light of preclinical activity in EGFR-expressing tumors, evidence of EGFR expression in NSCLC, and antitumor effects in patients with NSCLC persisting after chemotherapy in the phase 1 trials, we initiated this phase 2 trial of gefitinib. We hypothesized that blocking EGFR tyrosine kinases with gefitinib would lead both to symptomatic benefits and objective regressions in patients with NSCLC. We further tested whether there were important differences in outcomes or adverse effects comparing 250-mg and 500-mg doses of gefitinib using a randomized, double-blind, phase 2 design.

**METHODS**

**Patients**

From November 2000 to April 2001, 221 patients were enrolled at 30 sites in the United States for the second Iressa Dose Evaluation in Advanced Lung Cancer (IDEAL2) trial. Patients were included if they had pathological confirmation of NSCLC; stage IIIB or IV disease extent22; treatment with 2 or more regimens containing cisplatin or carboplatin and docetaxel, given either concurrently or as separate regimens; disease progression or unacceptable toxicity with the last chemotherapy regimen; symptomatic NSCLC as determined by a score of 24 or lower out of 28 using the lung cancer subscale of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality-of-life instrument23,24; measurable or evaluable indicator lesions25; World Health Organization performance status of 0-2; and if they had provided written informed consent. Patients were excluded if they had received chemotherapy or irradiation within 14 days; unresolved toxicity with the last chemotherapy regimen; symptomatic NSCLC as determined by a score of 24 or lower out of 28 using the lung cancer subscale of the Functional Assessment of Cancer Therapy-Lung (FACT-L) quality-of-life instrument23,24; measurable or evaluable indicator lesions25; World Health Organization performance status of 0-2; and if they had provided written informed consent. Patients were excluded if they had received chemotherapy or irradiation within 14 days; unresolved toxicity greater than grade 2 from prior chemotherapy; neutrophil count less than 1.5 x10^9 cells/L, platelet count less than 75 x10^9 cells/L, bilirubin level more than 1.25 times the upper limit of normal, and alanine aminotransferase or aspartate aminotransferase levels more than 2.5 times the upper limit of normal; and creatinine clearance less than 30 mL/min (0.50 mL/s).

Patients were randomized to receive either two 250-mg tablets of gefitinib (500-mg total dose) or one 250-mg gefitinib tablet and 1 matching placebo tablet (250-mg total dose) daily. These dosages were chosen, based on phase 1 study results, to maximize the potential for therapeutic activity with an ample safety margin. Responses had been observed at doses as low as 150 mg in the phase 1 studies.21 Gefitinib and placebo (both supplied by AstraZeneca Pharmaceuticals) were dispensed on day 1 of each 28-day treatment cycle. One blinded dose reduction from 250 to 100 mg or from 500 to 250 mg was permitted.
Symptom Assessments
Symptom assessments were measured using the FACT-L instrument. This instrument was completed pretreatment and then every 28 days. Weekly, patients recorded the presence and severity of 7 symptoms using the lung cancer subscale: shortness of breath, weight loss, clarity of thinking, cough, appetite, chest tightness, and difficulty breathing. Severity was assessed using a 0-4 scale (0-1, most symptomatic; 2-3, less symptomatic; 4, asymptomatic); thus, on the 0 to 28 summed lung cancer subscale score, a score of zero denotes the worst symptoms and 28, none of the 7 symptoms. A 2-point change in the summed score has been proven to correlate with both survival and performance status. Symptom improvement required confirmation of coprimary end point for each dose. For both rates, 100 patients per group yielded a power of 0.90 for a 1-sided .0125 significance-level test that the rate of symptom or radiographic improvement is 5% or less when the true rate is 15%. Secondary end points included overall survival by dose, frequency, and severity of adverse events, and overall quality of life using the FACT-L instrument. Quality of life analyses have been presented and will be reported separately. Kaplan-Meier plots were calculated by dose using an unadjusted log-rank test. Analyses were planned to correlate the symptom improvement and radiographic response rates with each other and with survival. We used logistic regression and χ² tests to explore the coprimary outcomes in relation to disease and demographic factors. The data cutoff date for this analysis was August 1, 2001. Radiographic responses were updated to December 17, 2001, when the trial closed. Survival data were updated May 7, 2002. Statistical analyses were carried out using SAS version 8.1 (SAS Institute Inc, Cary, NC) and StatXact version 4 (Cytel Software Corp, Cambridge, Mass); P < .05 was used to determine statistical significance.

RESULTS
From November 7, 2000, to April 6, 2001, 221 patients were enrolled at 30 sites in the United States (listed at the end of this article). The flow of patients through the trial is illustrated in Figure 1. Five individuals who never received gefitinib were excluded after randomization. Baseline patient characteristics are summarized in Table 1. No significant differences were observed between the treatment groups receiving 250 mg and 500 mg of gefitinib. With their last chemotherapy regimen before starting gefitinib, 170 patients (79%) had disease progression and 38 (18%) had intolerable toxicity, mainly peripheral neuropathy. Overall, 58% of patients had received 3 or more prior chemotherapy regimens. Table 2 shows the severity of 7 lung cancer symptoms at baseline. Pulmonary symptoms were most common. The median number of days receiving gefitinib was 56 and 53 for the 250-mg and 500-mg groups, respectively.
groups receiving 250 mg and 500 mg, respectively. The median number of
groups. Patients completed 84% of lung
cancer subscale assessments while in
the study.

Table 2. Severity of Lung Cancer Symptoms at Baseline*

<table>
<thead>
<tr>
<th>Symptom</th>
<th>No. (%)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Asymptomatic (Score = 4)</td>
</tr>
<tr>
<td>Shortness of breath (n = 216)</td>
<td>20 (9)</td>
</tr>
<tr>
<td>Cough (n = 215)</td>
<td>31 (14)</td>
</tr>
<tr>
<td>Tightness in chest (n = 212)</td>
<td>66 (31)</td>
</tr>
<tr>
<td>Difficulty breathing (n = 213)</td>
<td>22 (10)</td>
</tr>
<tr>
<td>Appetite loss (n = 214)</td>
<td>42 (20)</td>
</tr>
<tr>
<td>Weight loss (n = 216)</td>
<td>97 (45)</td>
</tr>
<tr>
<td>Clear thinking (n = 215)</td>
<td>101 (47)</td>
</tr>
</tbody>
</table>

*Measured using the lung cancer subscale of the FACT-L instrument.23,24

Table 3. Efficacy Results

<table>
<thead>
<tr>
<th>Efficacy Measure</th>
<th>No. (%)</th>
<th>P Value</th>
</tr>
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<tbody>
<tr>
<td>Symptom improvement*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom improvement rate [95% CI]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gefitinib, 250 mg</td>
<td>44 (43) [33-53]</td>
<td></td>
</tr>
<tr>
<td>Gefitinib, 500 mg</td>
<td>40 (35) [26-45]</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>84 (39) [32-45]</td>
<td>.26</td>
</tr>
<tr>
<td>Duration of symptom improvement, median (range), mo†</td>
<td>0 (1+ to 7+)</td>
<td>0 (1+ to 8+)</td>
</tr>
<tr>
<td>Symptom improvement apparent 1 wk</td>
<td>24 (65)</td>
<td>23 (58)</td>
</tr>
<tr>
<td>3 wk</td>
<td>32 (73)</td>
<td>31 (78)</td>
</tr>
<tr>
<td>4 wk</td>
<td>38 (87)</td>
<td>33 (93)</td>
</tr>
<tr>
<td>Symptom improvement rates By sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>23 (38)</td>
<td>15 (24)</td>
</tr>
<tr>
<td>Women</td>
<td>21 (50)</td>
<td>25 (49)</td>
</tr>
<tr>
<td>By histologic cell type</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>34 (49)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>10 (21)</td>
<td>12 (29)</td>
</tr>
<tr>
<td>Radiographic response‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiographic response rate [95% CI]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gefitinib, 250 mg</td>
<td>12 (12) [6-20]</td>
<td></td>
</tr>
<tr>
<td>Gefitinib, 500 mg</td>
<td>10 (9) [4-16]</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>22 (10) [6-14]</td>
<td>.51</td>
</tr>
<tr>
<td>Duration of radiographic response, median (range), mo</td>
<td>7 (3 to 9+)</td>
<td>6 (3 to 8+)</td>
</tr>
<tr>
<td>By sex</td>
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<td></td>
</tr>
<tr>
<td>Men</td>
<td>2 (3)</td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>10 (24)</td>
<td>8 (16)</td>
</tr>
<tr>
<td>By histologic cell type</td>
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<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>10 (14)</td>
<td>9 (12)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (8)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Survival</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival duration, median (range), mo</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>Projected 1-year survival, %</td>
<td>27</td>
<td>24</td>
</tr>
</tbody>
</table>

*Defined as ≥2-point increase in summed score on the lung cancer subscale of the Functional Assessment of Cancer Therapy–Lung instrument.23,24
†Zero indicates that median duration of benefit was not reached.
‡Defined as >50% decrease in tumor size on radiography.

Symptom Improvement

Table 3 lists outcome measures. The symptom improvement rate was 43%
(95% confidence interval [CI], 33%-53%) for patients who received 250 mg
of gefitinib and 35% (95% CI, 26%-45%) for those who received 500 mg
(P = .26). Fifty-five percent of symptom improvements in patients receiving 250
mg and 58% of symptom improvements in patients receiving 500 mg were
apparent after 1 week of treatment. For those patients with symptom improve-
ment, the median durations of benefit were not reached (range, 1+ to 7+
months for patients receiving 250 mg and 1+ to 8+ months for those receiv-
ing 500 mg). For all participants, the best median symptom score improved
25%, from a baseline of 16 (out of 28) to 22 after treatment with gefitinib
(P <.001). For all but 1 study week, the mean change in the summed lung can-
cer subscale score for all patients was 2 or more, the predefined level for signifi-
cant symptom improvement (FIGURE 2). The greatest mean improvement in
summed lung cancer subscale scores (4.8) occurred in the patients with par-
tial radiographic responses. Mean changes were 2.6 for individuals with
stable disease and 1.0 for those with pro-
gression. The change in mean summed
lung cancer subscale scores for pa-
tients with disease progression did not
improve by the prespecified 2-point cut-
defining improvement.

Radiographic Response

The response rate (all partial) was 12%
(95% CI, 6%-20%) for the group receiv-
ing 250 mg of gefitinib and 9% (95% CI,
4%-16%) for the group receiving 500 mg
(P = .51). The P value for the test that the
true rate is greater than 5% was .005 for
the group receiving 250 mg and .06 for
the group receiving 500 mg. The me-
dian duration of radiographic response
was 7 (range, 3 to 9+) months for pa-
tients receiving 250 mg and 6 (range, 3
to 8+) months for patients receiving 500
mg. Symptoms improved in 96% of pa-
tients with partial responses, 73% of
those with no partial response but no
progression (stable disease), and 17%
of those with disease progression (P < .001). Rates of symptom improvement were improved comparing the patients with partial response and those with stable disease (P = .02). Figure 3 displays correlations between symptom improvement and radiographic response.

Symptom improvement and radiographic responses were observed in all patient subgroups. Symptom improvement was more common with adenocarcinoma than with other histologic types (43% vs 30%, P = .06). Response rates were 13% for adenocarcinoma vs 4% for other types (P = .046). The incidence of adenocarcinoma was 79% in women and 58% in men. A multivariable comparison (which included sex, histologic subtype, performance status, age, number of prior regimens, and months from initial diagnosis) demonstrated only female sex to be predictive of response both for symptom improvement (30% vs 31% for women vs men, respectively; P = .006) and radiographic regression (19% vs 3%, P = .001). Eighteen of 22 partial responses (82%) occurred in women.

Partial response rates did not differ significantly whether patients had received 2 (8%), 3 (10%), or 4 or more (15%) prior chemotherapy regimens (P = .38), and rates of symptom improvement were similar based on the number of prior regimens (P = .38). Radiographic response rates did not differ among patients with performance status of 0, 1, or 2 (12%, 9%, and 14%, respectively; P = .53). Rates of symptom improvement also were unaffected by performance status (P = .53).

Survival
The projected median survival was 7 months for patients receiving 250 mg of gefitinib and 6 months for those receiving 500 mg (P = .40). The estimated 1-year survival was 27% for patients receiving 250 mg and 24% for those receiving 500 mg (P = .54). Figure 4 displays the overall survival by dose. Using a landmark analysis to examine the survival of only patients who lived at least 2 months (the time needed to assess radiographic response), median survival differences were observed among partial responders (13 months), patients with no partial response but no progression (ie, stable disease) (9 months), and those with progression (5 months) (P < .001). Also using the landmark method, patients with symptom improvement had a median survival of 13 months vs 5 months for those without symptom benefit (P < .001).

Adverse Effects
Table 4 presents deaths, discontinuations, withdrawals, and gefitinib-related diarrhea and skin toxicities. Skin toxicity, described variably as rash, acne, dry skin, or pruritus, was observed in 62% of patients receiving 250 mg of gefitinib.
mg of gefitinib vs 75% of those receiving 500 mg (P = .04). The rash appeared on the face, neck, and trunk, and commonly faded or improved despite continuing therapy. It occurred during the first treatment cycle in 82% of patients. Although all 22 patients with partial responses had some skin toxicity, 65% of those who did not have a partial response also experienced this adverse effect. Skin toxicity was documented in 86% (72/84) of patients with symptom improvement and in 58% (76/132) of those whose symptoms did not improve (observed difference, 28%; 95% CI, 17%-39%).

Diarrhea was noted in 57% of patients receiving 250 mg of gefitinib and in 75% of those receiving 500 mg (P = .006). No routine prophylactic antidiarrheal medication was given. Only 1 patient receiving 250 mg had diarrhea greater than grade 2 (up to 6 daily bowel movements) compared with 6 patients in the group receiving 500 mg. Two individuals receiving 500 mg withdrew because of diarrhea. In 76% of patients, diarrhea was observed during the first treatment cycle. Symptoms were generally controllable with loperamide taken after each bowel movement. Approximately one third took an antidiarrheal medication. Diarrhea was documented in 82% (69/84) of patients with symptom improvement and in 56% (74/132) whose symptoms did not improve (observed difference, 26%; 95% CI, 14%-38%).

Nineteen percent of patients reported grade 1 or 2 eye toxicities such as redness or itchiness. All were self-limited and in no case led to study withdrawal. Treatment-related vomiting or nausea (grade 1 or 2 only) was observed in 15% and 10% of patients, respectively. There were no cases of investigator-identified interstitial lung disease following gefitinib administration (observed rate, 0%; 95% CI, 0%-1.7%). Pulmonary events (collected as pneumonia, aspiration pneumonia, lung disorder, respiratory distress syndrome) were noted in 13 patients (6 of grade 3 or 4) receiving 250 mg of gefitinib and in 14 patients (8 of grade 3 or 4) receiving 500 mg. None of the pulmonary events were considered drug-related by the investigators. One patient had grade 3 thrombocytopenia and 3 had reversible grade 3 elevations of alanine aminotransferase and aspartate aminotransferase levels that were deemed drug-related. No grade 3 or 4 neutropenia, anemia, or neuropathy occurred.

Only 1 possible treatment-related death was recorded. This patient experienced cavitation of his primary tumor, developed massive hemoptysis, and died on day 11. Only 1 patient receiving 250 mg of gefitinib and 5 patients receiving 500 mg experienced a drug-related adverse event leading to study withdrawal. Dose reductions for toxicity occurred in 1 patient receiving 250 mg and 10 receiving 500 mg. Grade 3 or 4 drug-related adverse events were observed in 7 patients receiving 250 mg and 20 patients receiving 500 mg. Thirty-day all-cause mortality was 3.8% for patients receiving 250 mg and 8.8% for those receiving 500 mg. Sixty-day all-cause mortality was 8.8% for patients receiving 250 mg and 18% for those receiving 500 mg.

**COMMENT**

This trial demonstrated that oral gefitinib given once daily caused rapid symptom improvement and tumor regressions in patients with NSCLC. Until now, only chemotherapy, surgery, and radiotherapy have demonstrated the ability to cause lung tumors to re-
gress. Once these modalities have been exhausted, only supportive care measures remain. Gefitinib, which was designed to achieve its anticancer effects through a different mechanism, can help fill this therapeutic void.

There is no comparable prospective series treating a cohort of symptomatic patients who had received both cisplatin or carboplatin and docetaxel. In a retrospective review of 43 individuals treated with various chemotherapies, the response rate for a third regimen was 2%.³⁶ One study randomized individuals who had received 1 or more chemotherapy regimen(s) to either docetaxel or supportive care alone. The response rate with docetaxel was 6%. Those who did not receive chemotherapy had a median survival of 5 months.³¹ In another “second-line” trial conducted in the United States, radiographic tumor regressions were induced in 7% of patients receiving docetaxel vs 1% of those receiving vinorelbine or ifosfamide.³² The 10% response rate with gefitinib, achieved without myelosuppression or neurotoxicity, and with virtually no hair loss, is provocative in comparison. The results of this trial are consistent with the gefitinib phase 1 experience in patients with NSCLC.²¹ The recent international phase 2 trial (IDEAL1) also compared 250-mg and 500-mg gefitinib doses, but in patients pretreated with 1 or 2 prior chemotherapy regimens who were not required to have symptoms at trial entry. For the 250-mg dose, they reported an 18% radiographic response rate.³³ Similar efficacy has been observed with the EGFR tyrosine kinase inhibitor erlotinib (OSI-774, Tarceva, OSI Pharmaceuticals, Melville, NY).³⁴ In our study, approximately 15% of patients with the “best response” of progression had some symptomatic improvement by study criteria. This likely reflects either a placebo effect or the resolution of adverse effects of the prior chemotherapy regimens.

Adverse effects of gefitinib were generally mild, manageable, noncumulative, and reversible with the cessation of the drug and sometimes even with continued use. Among individuals receiving 250 mg, some degree of skin toxicity occurred in 62% and of diarrhea in 57%. For the 250-mg dose, toxicity caused just 1 patient to stop taking gefitinib and 1 to reduce the dosage. Interstitial lung disease has been associated with use of gefitinib in Japan and reported to occur in 1% to 2% of patients.³³ This is a recognized but uncommon adverse effect of cytotoxic drugs³⁶ and also has been described following treatment with the tyrosine kinase inhibitor imatinib (STI571, Gleevec, Novartis Pharmaceuticals, Basel, Switzerland).³⁵ With no case of interstitial lung disease reported in this trial, the 95% confidence limit for the true incidence of this complication after gefitinib administration ranges from 0% to 1.7%, lower than that observed with many chemotherapeutic agents.³⁶

There were no significant differences in the incidence of symptomatic or radiographic improvement between the 250-mg and 500-mg doses of gefitinib. The incidence and severity of both rash and diarrhea, however, were higher among patients receiving 500 mg. Consistent with the proposed mechanism of action of gefitinib, once plasma levels adequate to block tyrosine kinases such as EGFR have been achieved, additional dose escalations are unlikely to improve response and will increase toxicity. That is likely what we observed in this study. We recommend the 250-mg dose. The IDEAL1 trial reached the same conclusion.³⁵

Can the amount of EGFR protein in tumors predict response to gefitinib? The answer appears to be no. In a combined analysis of tumor EGFR expression levels determined by immunohistochemistry in 157 analyzable specimens submitted from patients enrolled in the IDEAL1 trial and in this study, there were no consistent associations between levels of EGFR expression and radiographic or symptomatic improvements.²⁷ In clinical trials of the EGFR inhibitors cetuximab and erlotinib, response also did not correlate with the degree of EGFR expression measured by immunohistochemistry.³⁴³⁸

Of all clinical characteristics, only female sex and adenocarcinoma histological type showed a correlation with response, both in our study and in the international study.³⁵ Patients in Japan also had higher rates of radiographic re-

<table>
<thead>
<tr>
<th>Table 4. Gefitinib-Related Adverse Effects</th>
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<tbody>
<tr>
<td><strong>Adverse Effect</strong></td>
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<tr>
<td>-------------------</td>
</tr>
<tr>
<td>Possible treatment-related death</td>
</tr>
<tr>
<td>Withdrawal due to drug-related event</td>
</tr>
<tr>
<td>Dose reduction for toxicity</td>
</tr>
<tr>
<td>Any grade 3/4 drug-related event</td>
</tr>
<tr>
<td>Rash, pruritus, dry skin, or acne, grade†</td>
</tr>
<tr>
<td>Any</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>Diarrhea, grade‡</td>
</tr>
<tr>
<td>Any</td>
</tr>
<tr>
<td>1 (increase of &lt;4 stools/d)</td>
</tr>
<tr>
<td>2 (increase of 4–6 stools/d)</td>
</tr>
<tr>
<td>3 (increase of ≥7 stools/d)</td>
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<td>4</td>
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</tbody>
</table>

*This patient died on study day 11 from massive hemoptysis developing from a primary lung lesion that cavitated on therapy. The investigator listed this death as definitely cancer related and possibly related to the study drug.
†Grades listed are the maximum at any time in the trial, and are determined using the Common Toxicity Criteria of the National Cancer Institute.
response than those enrolled from other countries. Investigators from Memorial Sloan-Kettering Cancer Center also have reported that in a multivariable analysis of 140 patients that included 6 people treated as part if this trial, individuals who have never smoked cigarettes and those with any bronchioloalveolar histologic features in their tumor specimens are more likely to respond to gefitinib. Although female sex has been associated with longer survival in patients with advanced NSCLC, it has not been found to be a predictor of radiographic response with chemotherapy.  

No similar controlling mutations of EGFR have been reported in NSCLC. The targeted therapy imatinib inhibits several tyrosine kinases, including those expressed by c-KIT and PDGFR. Imatinib causes dramatic regressions in gastrointestinal stromal tumors regardless of whether the controlling mutations are in the PDGFR or c-KIT genes, because it effectively blocks both tyrosine kinases and the resulting oncogenic signals emanating from either receptor. Similarly, gefitinib may inhibit other tyrosine kinases in addition to EGFR. If this occurred in patients with lung cancer, oncogenic signaling in tumors in the fraction of patients who derive substantial benefit from gefitinib could be driven at least in part by activation of other tyrosine kinases in addition to or instead of EGFR.

Preclinical studies have demonstrated the uncoupling of the effects of EGFR tyrosine kinase inhibition and tumor growth. This observation may be relevant in NSCLC. Since multiple genetic lesions are necessary to initiate lung cancers, many cell-signaling pathways may be aberrant and provide multiple mechanisms to maintain tumors and permit "signaling redundancy." For example, Kirsten-ras mutations, PTEN promoter hypermethylation, PI3-Kα amplification, and p53 mutations are all downstream of EGFR and occur in lung tumors. Any or all of these aberrations may be present in patients whose tumors fail to respond to gefitinib. We may be able to help individuals with gefitinib-resistant tumors by determining which downstream factor works in concert with EGFR and then designing a combination therapy inhibiting both EGFR and the downstream aberration as well. Characterization of the presence or absence of these additional lesions in a given patient’s tumor also could lead to more discriminate use of gefitinib.

The strength of downstream oncogenic signaling can be determined by which member of the HER family dimerizes with EGFR. Identifying the presence of other HER family members in tumors and their degree of dimerization with EGFR may help identify persons with lung cancer more likely to be sensitive to gefitinib. Investigations also have revealed that amino acid substitutions in the ATP binding pocket in regions sequentially distant but conformationally important to the imatinib binding site have been identified in both clinically and laboratory induced mutations of the Abelson tyrosine kinase in chronic myelogenous leukemia. These substitutions confer resistance to imatinib. This mechanism may have relevance to understanding gefitinib resistance and provides yet another direction for research.

The results of this trial proved our study hypothesis. Blocking EGFR tyrosine kinase with gefitinib leads to symptom improvement and radiographic regressions in patients with NSCLC. These findings support the use of gefitinib for the treatment of patients with NSCLC who have received cisplatin or carboplatin and docetaxel, and other agents. The magnitude and duration of benefits, coupled with the safety of gefitinib, justifies its use in patients previously treated with chemotherapy. These results further demonstrate that a therapy that disrupts biological pathways specific for cancer cells can improve the outcome of patients with advanced NSCLC.

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References


