Advanced EGFR Mutation-Positive Non–Small-Cell Lung Cancer: Case Report, Literature Review, and Treatment Recommendations

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Introduction

Lung cancer is the leading cause of cancer mortality worldwide. In the United States, lung cancer accounted for an estimated 159,480 deaths in 2013, which is more than breast, colon, prostate, and pancreatic cancer deaths combined. Although smoking is the leading risk factor for lung cancer, 15% to 20% of lung cancers occur in never smokers. Up to 90% of all lung cancers are classified as non–small-cell lung cancer (NSCLC), and the majority present with advanced or metastatic (stage IV) disease.

Conventional treatment for advanced NSCLC has consisted of chemotherapy. However, despite proven benefits in an appropriately selected population (good performance status), the impact of traditional chemotherapy on progression-free survival (PFS) and overall survival (OS) remains small. Currently, the 1-year survival rate for a patient with stage IV NSCLC is, at best, around 50% (25% 2-year survival).3

Our improved understanding of cell signaling pathways that control cellular proliferation, differentiation, and survival combined with our increased ability to screen for specific mutations that drive malignant transformation and oncogenic behavior, has altered our treatment of advanced NSCLC. We can now provide a more individualized approach associated with improved progression-free survival and quality of life.
Case Report
A 38-year-old white woman with a history of “allergies” presented to her primary care physician for an annual checkup and revealed complaints of persistent sinus congestion, cough, and mild progressive dyspnea. Computed tomography (CT) of the chest revealed a large right upper lobe pulmonary mass (7.0 cm at its greatest diameter) with bilateral pulmonary metastases and right hilar, prevascular, pretracheal, and subcarinal lymphadenopathy. CT-guided biopsy of the primary mass revealed a poorly differentiated non–small-cell carcinoma, consistent with an adenocarcinoma (cytokeratin 7 and thyroid transcription factor 1 positive).

The patient had never smoked cigarettes or had no history of prior exposure to second-hand smoking. She had no notable occupational or travel exposures. Other than her recent dyspnea and allergic symptoms, she was active and functional with a good appetite and energy level, and also stable weight. She had a good performance status (Eastern Cooperative Oncology Group 1), and her physical examination was normal except for mild bilateral pulmonary rhonchi.

The patient was started on traditional chemotherapy consisting of a platinum-based doublet. After 6 cycles of therapy, she experienced partial radiographic and clinical response; however, 5 months after chemotherapy discontinuation, she developed disease progression and worsening of her symptomatology, particularly severe cough, sinus congestion, and dyspnea. She was referred to our institute, where mutational analysis was performed that revealed the presence of an exon 19 deletion in the EGFR gene. The patient was started on oral erlotinib (150 mg, on an empty stomach) for recurrent, advanced-stage EGFR exon 19 mutation-positive lung adenocarcinoma.

A comparison of CT images of the chest at baseline or initiation (prior to erlotinib) and 3 months following the initiation of erlotinib revealed a clear radiographic response with almost complete resolution of the large, primary right upper lobe mass and a 50% to 75% reduction in size in the nearly 50 bilateral metastatic nodules originally present.

Nine months following the initiation of erlotinib, one of the patient’s small pulmonary nodules increased. Subsequent radiographic evaluation during the next 2 months displayed clear radiological progression, including the presence of new brain metastasis. Clinically, the patient worsened; despite enrollment in 2 other clinical trials, she ultimately died due to disease progression 27 months following her original diagnosis.

Discussion
EGFR is a 1186 amino acid transmembranes receptor protein that consists of an extracellular region with a ligand-binding domain and an intracellular region with tyrosine kinase and regulatory domains linked by a transmembrane domain. This protein is expressed on epithelial, mesenchymal, and neurogenic tissues. Several ligands bind to the receptor, inducing homologous and/or heterologous dimerization and subsequent autophosphorylation of the intracellular domain, leading to a cascade of signal transduction and resulting in cell proliferation and survival, the inhibition of apoptosis, and the activation of angiogenesis. Downregulation occurs through several different mechanisms.

In 1993, researchers found that EGFR was overexpressed in lung cancer tissue when compared with adjacent normal tissue. Subsequent studies testing EGFR inhibitors in NSCLC revealed a specific subset of patients who frequently experienced the best or strongest clinical response. Consequently, a clear and defined phenotype emerged of East Asian, female nonsmokers with adenocarcinoma that later was confirmed to be a surrogate for the presence of underlying somatic mutations within the EGFR gene.

A study by Pao and Miller has shown that mutations in the EGFR gene occur more often in women (37.5%) than in men (15.0%), in never-smokers (50.8%) than in former/current smokers (9.0%), and in patients of East Asian origin (29.1%) than in patients from the United States (9.5%). The two most common are a deletion in exon 19 and an L858R point mutation in exon 21. Both of these mutations affect protein structure near the adenosine triphosphate cleft of the tyrosine kinase domain of EGFR, rendering the protein kinase extremely sensitive to inhibition with drugs like gefitinib and erlotinib.

Gefitinib and erlotinib are orally administered, reversible, and highly specific small-molecule tyrosine kinase inhibitors (TKIs) that competitively block adenosine triphosphate binding to the tyrosine kinase domain of EGFR. Gefitinib was the first to receive conditional approval (later withdrawn) by the US Food and Drug Administration (FDA) after showing response rates of 9% to 12% in unselected patients with previously treated or recurrent NSCLC. In 2007, erlotinib gained permanent FDA approval for a similar indication based on the results of the National Cancer Institute of Canada’s BR.21 phase III trial. In both cases, the predictive phenotype previously described was apparent. Thus, with the recognition of a potentially sensitive population and an oncogenic target in NSCLC and the availability of highly specific drug inhibitors against it, trials testing for the activity of the drugs and the predictive value of the recognized phenotype and later genotype were conducted.

The first randomized phase III study (IRESSA Pan-Asia Study [IPASS]) that selected patients based on phenotype (East Asians, light or never-smokers, lung adenocarcinomas) was conducted by Mok et al. In this trial, in which single-agent gefitinib was comp...
pared with paclitaxel plus carboplatin in patients with advanced NSCLC who were naive to chemotherapy, a significantly improved 12-month PFS rate was found in the gefitinib-treated population (PFS rates of 25% vs 7%). In addition, a subgroup analysis revealed significantly longer PFS rates with gefitinib in patients who harbored an activating (exons 19 or 21) EGFR mutation. By contrast, patients without EGFR mutations (wild-type EGFR gene) experienced significantly shorter PFS rates when treated with gefitinib when compared with chemotherapy. As the first study following this design, IPASS was also informative because of two other findings: (1) the incidence of EGFR mutations in the overall (phenotypically selected) population was almost 60% (approximately 65% for women and 50% for men), and (2), ironically, the OS rates for both populations were statistically similar.

A second study conducted in South Korea (First SIGNAL) was similarly designed for an untreated population of patients with lung adenocarcinoma enriched for the presence of EGFR mutations. However, only about one-half of the patients underwent genetic testing, with the incidence of EGFR mutations among them close to 50%. Similar to that shown for the IPASS trial, a better PFS rate was seen in patients with EGFR mutations treated with gefitinib, whereas the wild-type patients had better PFS rates with chemotherapy. The differences here were not statistically significant but likely due to the small subpopulation analyzed. In addition, OS rates did not differ between treatment arms.

These 2 trials allow us to conclude that it should be the presence of the activating EGFR mutation (tumor genotype), not the patient phenotype (Asian, never-smoker, female, adenocarcinoma), that should drive the decision to treat a patient with advanced NSCLC naive to chemotherapy with an EGFR TKI.

In 3 subsequent randomized phase III trials (WJTOG3405, NEJ002, and OPTIMAL) that compared treatment with EGFR TKIs to platinum-based doublet chemotherapy in patients with advanced-stage NSCLC naive to chemotherapy who were selected based on genotype rather than phenotype, a significantly improved PFS rate was again demonstrated in association with EGFR TKI treatment compared with chemotherapy. However, given that the patient populations involved in these studies consisted of nearly all East Asian patients, translation of these results to other ethnic populations remained in question. Consequently, Rosell et al enrolled European patients from Spain, Italy, and France in a phase III trial (EURTAC) that compared erlotinib with cisplatin plus docetaxel or gemcitabine in the treatment of advanced EGFR mutation-positive NSCLC. A significantly prolonged PFS rate was seen with EGFR inhibition compared with traditional chemotherapy, leading to the expansion of the FDA approval of erlotinib to include chemotherapy-naive patients or those with previously untreated advanced NSCLC as long as they carried an EGFR-activating mutation (deletion in exon 19 and an L858R point mutation in exon 21).

Within 2 weeks of initiating therapy with erlotinib, our patient experienced rapid and significant improvement of her symptoms; in addition, her cough, congestion, and dyspnea eventually resolved. Furthermore, despite the development of a (mild) skin rash and (minimal) diarrhea, typically described with EGFR TKI therapy, she also experienced a major improvement in her quality of life. The Figure depicts comparative CT imaging of her pre- and (3 months) post-erlotinib chest.

Although EGFR TKIs have shown excellent activity in patients with NSCLC selected based on the presence

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Figure. — Radiographic response to EGFR TKI therapy (erlotinib) in a patient with advanced EGFR mutation-positive (exon 19 deletion) NSCLC (adenocarcinoma). (A) Baseline chest CT is shown, prior to erlotinib. (B) Chest CT of the same patient 3 months after starting erlotinib (posttherapy). CT = computed tomography, EGFR = epidermal growth factor receptor, TKI = tyrosine kinase inhibitor.
Patient Population to Be Tested

Treatment Recommendations

Because of consistent data shown across all populations studied and described in the different randomized phase III trials previously analyzed (Table 17-22,26-30), our recommendation, which is backed with strong scientific support, is that patients with advanced or recurrent NSCLC known to carry an activating mutation in the EGFR gene (exons 19 and 21), such as the one presented in our case, should be treated with an EGFR TKI at the earliest possible point in time. In the United States, erlotinib is currently the drug of choice and the only EGFR TKI available, although afatinib, due to its recent FDA approval, would also be a reasonable option and will soon be available.

We are mindful that this recommendation is yet to be generally accepted and/or practically applicable and that a number of questions still need to be answered. Who should be tested? When should the mutation test be performed? Should chemotherapy be withheld (or delayed) until the mutation test result is available? Should the mutation test be performed (or delayed) until the mutation test result is available? Should the mutation test be performed (or delayed) until the mutation test result is available?

Table — Selected Phase III Randomized Trials of EGFR TKIs vs Platinum Doublet Chemotherapy in Untreated or Chemotherapy-Naive Patients Selected/Enriched for or With Advanced EGFR Mutation-Positive NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Location</th>
<th>Inclusion Criteria</th>
<th>Intervention</th>
<th>Primary Endpoint</th>
<th>Selected Results</th>
<th>Comments</th>
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<tr>
<td>Phenotypic Selection</td>
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<tr>
<td>Mok et al\textsuperscript{17}</td>
<td>1,217</td>
<td>East Asia</td>
<td>Adenocarcinoma only Never-smokers/Light smokers Previously untreated (chemotherapy-naive) No activating EGFR mutation required</td>
<td>Gefitinib vs carboplatin + paclitaxel</td>
<td>PFS</td>
<td>mPFS = 5.7 (95% CI, 8.0–13.9) vs 5.8 mos (5.8–7.8); HR = 0.74 (95% CI, 0.65–0.85; P &lt; .0001) OS = 18.6 vs 17.3 mos; HR = 0.91 (95% CI, 0.76–1.10)</td>
<td>Subgroup analysis led way to further focused studies ORR gefitinib = 43% ORR chemotherapy = 32.2% (P &lt; .001) HR mutation-positive = 0.48 (95% CI, 0.36–0.64; P &lt; .0001)</td>
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<tr>
<td>Han et al\textsuperscript{18}</td>
<td>313</td>
<td>South Korea</td>
<td>Adenocarcinoma only Never-smokers Previously untreated (chemotherapy-naive) No activating EGFR mutation required</td>
<td>Gefitinib vs cisplatin + gemcitabine</td>
<td>OS</td>
<td>mPFS = 5.8 (95% CI, 4.1–6.5) vs 6.4 mos (95% CI, 5.8–7.0); HR = 1.198 (95% CI, 0.944–1.52; P = .133) OS = 23.3 vs 22.9 mos; HR = 0.832 (95% CI, 0.716–1.213; P = .684)</td>
<td>Subgroup analysis led way to further focused studies ORR gefitinib = 55.4% ORR chemotherapy = 46.0% (P = .101) HR mutation-positive = 0.544 (95% CI, 0.269–1.1; P &lt; .086)</td>
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<td>Genotypic Selection: Gefitinib</td>
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<tr>
<td>Mitsudomi et al\textsuperscript{19}</td>
<td>172</td>
<td>Japan</td>
<td>All histologies (adenocarcinoma 97%) Any smoking status Previously untreated (chemotherapy-naive) Activating EGFR mutation required (exon 19 deletion, L858R point mutation)</td>
<td>Gefitinib vs cisplatin + docetaxel</td>
<td>PFS</td>
<td>mPFS = 9.2 (95% CI, 8.0–13.9) vs 6.3 mos (5.8–7.8); HR = 0.489 (95% CI, 0.336–0.710; P &lt; .0001) OS = 30.9 mos (95% CI, 24.1–upper level CI not assessible) vs NR (95% CI, 15.0–upper level CI not assessible); HR = 1.638 (95% CI, 0.75–3.58)</td>
<td>ORR gefitinib = 62.1% ORR chemotherapy = 32.2% (P &lt; .0001)</td>
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<tr>
<td>Study</td>
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<td>EGFR Mutation</td>
<td>Comparator</td>
<td>Outcomes</td>
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<td>Maemondo et al&lt;sup&gt;20&lt;/sup&gt;</td>
<td>Japan</td>
<td>228</td>
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<td>Inoue et al&lt;sup&gt;26&lt;/sup&gt;</td>
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| Meta-Analysis | | 1,021 | Meta-analysis | | | | | | | | Genotypic Selection: Erlotinib

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<td>PFS</td>
<td>mPFS = 13.1 (95% CI, 10.58–16.53) vs 4.6 mos (4.21–5.42 mos); HR = 0.16 (95% CI, 0.10–0.26; P &lt; .0001)</td>
<td>No OS available</td>
<td>Erlotinib vs gemcitabine + carboplatin: ORR erlotinib = 83% ORR chemotherapy = 36% (P &lt; .0001)</td>
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CI = confidence interval, EGFR = epidermal growth factor receptor, HR = hazard ratio, mPFS = median progression-free survival, NR = not reached, ORR = overall response rate, OS = overall survival, ORR = overall response rate, RR = relative risk, TKI = tyrosine kinase inhibitor.
Timing of Mutation Test
The recommendation on when to test is a somewhat more practical one. The role of EGFR TKIs in the curative setting, both in EGFR-mutant and wild-type tumors, remains controversial.\textsuperscript{31,32} Thus, we believe (and it is our practice) that the test should be performed only in patients with advanced or recurrent (incurable) disease. Practically speaking, testing a patient following curative lung cancer surgery provides no advantage because the test can always be performed later, upon recurrence, from the archived surgical tissue, if necessary.

Withholding or Delaying Chemotherapy
Regarding the decision to withhold or delay systemic chemotherapy until mutation analysis results are available, we believe that this decision should be based on the patient’s clinical presentation on a case-by-case basis. Patients with good performance status, devoid of tumor symptomatology, or with “low burden” of disease may be amenable to waiting. In the opposite scenario, starting chemotherapy would be the appropriate step to take.

Stopping Chemotherapy and Switching to a TKI When Test Results Return Positive
Data are not conclusive to definitively answer whether chemotherapy should be stopped and treatment switched to a TKI in a patient whose mutation test returns positive. However, 3 different approaches can be reasonably considered. (1) The absence of overall survival benefit for EGFR TKIs in untreated patients and the proven benefit of these drugs (eg, erlotinib)\textsuperscript{16} in the second- and third-line settings suggest that TKI treatment could be reserved for after first-line chemotherapy. (2) Based on the subset analysis on EGFR mutation-positive patients from the SATURN trial,\textsuperscript{36} the use of erlotinib is supported as switch maintenance (after 4 cycles of platinum-doublet chemotherapy) in this population due to the observed OS benefit (HR = 0.48; 95% CI, 0.14–1.62). (3) The approach we most often pursue is discontinuation of chemotherapy (particularly if it was only recently started) in favor of single-agent erlotinib therapy.

Although OS rates mirror those of standard chemotherapy in all of the trials described, we believe this observation can be misleading if interpreted as a lack of survival benefit and outside the context of the implicit crossover design included in all trials (76% to 95% crossover\textsuperscript{22,29}). Rather, we believe that the survival equivalence speaks of the high activity and benefit of the EGFR TKIs by their ability when used in those patients failing chemotherapy (crossover treatment) to “rescue” them from failure and to re-establish their survival benefit. Furthermore, safety and quality of life advantages for EGFR TKIs cannot be ignored, as demonstrated by the IPASS and First-SIGNAL trials, among others, with this approach preventing patients from being exposed to adverse events of chemotherapy.

A major challenge remains for those patients due to the development of acquired resistance to gefitinib and erlotinib (first-generation EGFR TKIs), which is the rule rather than the exception, and the inevitable development of recurrent or progressive disease (EGFR TKI median PFS range: 8–13 months).\textsuperscript{27} Further studies have looked into newer EGFR TKIs (second-generation EGFR TKIs, afatinib)\textsuperscript{34} as well as other novel approaches. The LUX-Lung 3 and 6 trials\textsuperscript{28,29} have reported the efficacy of afatinib, an irreversible, dual EGFR, HER-2 TKI. These trials have also shown superiority in terms of PFS to traditional platinum-doublet chemotherapy in patients with EGFR mutation-positive lung adenocarcinomas. However, an additional advantage was the activity shown against tumors with genetically derived resistance to gefitinib/erlotinib (EGFR exon 20 T790M mutations).\textsuperscript{33} Furthermore, animal models have shown promising results when combining EGFR TKIs with MET TKIs in an effort to suppress alternative resistance mechanisms,\textsuperscript{35} with these findings leading to positive initial results and to definitive clinical trials, which are currently ongoing.\textsuperscript{36}

Conclusions
With our continually improving understanding of the pathways that control cellular proliferation, differentiation, apoptosis, and survival (hallmarks of cancer),\textsuperscript{37} and our increasing ability to rapidly screen for specific mutations that prove responsible for malignant transformation (driver mutations) and oncogenic behavior, the treatment paradigm of advanced non–small-cell lung cancer (NSCLC) is gradually shifting from the traditional platinum-doublet\textsuperscript{38} of “one-size-fits-all” chemotherapy\textsuperscript{39} to a more individualized or personalized therapy in which targeted and/or biologic (small molecules or monoclonal antibodies) cancer therapies have jumped to the forefront of our therapeutic armamentarium and clinical research.

In the span of 10 years, the observation of increased epidermal growth factor receptor (EGFR) expression in tumor tissues has led to the development and approval of specific drugs by the US Food and Drug Administration. In the subsequent 10 years, a specific genotype was elicited that predicted activity and benefit to EGFR tyrosine kinase inhibitors, and EGFR inhibition was shown to be superior to standard chemotherapy when given as first-line treatment to patients with advanced NSCLC carrying exon 19 and 21 EGFR mutations.

Although a patient’s phenotypic characteristics may influence the frequency with which the genotypic abnormality is identified, it is the latter that drives the natural course of the disease and the decision of whether to use an EGFR tyrosine kinase inhibitor or not.
References