EGFR Mutations and Sensitivity to Gefitinib

TO THE EDITOR: The important study by Dr. Lynch and colleagues (May 20 issue) suggests that specific mutations in the epidermal growth factor receptor (EGFR) characterize a subgroup of non–small-cell lung cancers that may be highly responsive to gefitinib therapy. Do these mutations predict a greater sensitivity to chemotherapy as well? The overall objective response rate to first-line combination chemotherapy for metastatic non–small-cell lung cancer is about 20 percent. Only tumors from a small cohort of patients who had a response to gefitinib were studied for the specific mutations, but all patients except one had also received prior chemotherapy. Although the authors describe Patient 6 as “representative” of the cohort, the percentage of other patients who previously had a response to chemotherapy is not reported. If the rate of response to first-line chemotherapy was high for the other patients in the cohort who had a response to gefitinib, the specific mutations may be predictive of either chemotherapy or gefitinib sensitivity, thus identifying a distinct subgroup of patients with non–small-cell lung cancer.

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TO THE EDITOR: Lynch et al. elegantly demonstrate the presence of gain-of-function mutations of EGFR in patients with non–small-cell lung cancer who had a response to gefitinib. However, the authors do not mention whether there were correlations between mutational findings and the results of immunohistochemical studies or fluorescence in situ hybridization (FISH), the most commonly used techniques for detecting EGFR. In fact, we observed that responsive cases had heterogeneous results of FISH.
analysis, but showed cytoplasm-restricted expression of EGFR on immunohistochemical evaluation; conversely, unresponsive cases were negative or displayed a cell-membrane staining pattern (unpublished data). In a similar fashion, gastrointestinal stromal tumor is characterized by activating c-kit mutations, but the gene product, the transmembrane tyrosine kinase KIT, is aberrantly expressed in the cytoplasm, whereas other KIT-positive tumors without c-kit mutations show KIT immunoreactivity on cell membranes. Successful results with the use of EGFR and KIT inhibitors are primarily related to gene mutations involving exons encoding for juxtamembrane protein domains, possibly leading to cytoplasmic internalization of mutated tyrosine kinase. If this theory is confirmed, one can expect therapeutic benefits from the use of antibodies against EGFR rather than small molecules in lung cancer expressing nonmutated EGFR at the membrane level.

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In response to Rossi et al., we note that previous studies have shown no correlation between responsiveness to gefitinib and levels of EGFR expression, as measured by immunohistochemical analysis. In the cases we studied, we did not detect amplification of either wild-type or mutant EGFR alleles. As noted above, EGFR amplification (measured by FISH) is common in glioblastomas but does not appear to be correlated with gefitinib responsiveness. Again, we cannot comment on unpublished data relating to cellular expression patterns of EGFR, but we note that EGFR mutations are within the kinase domain, not the juxtamembrane domain. We agree that the effectiveness of antibodies directed against EGFR needs to be evaluated in mutation-negative cases.

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