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Tyrosine Kinase Inhibitors and Epidermal Growth Factor Receptor (EGFR) Mutations in Non-Small Cell Lung Cancer:

To Test or Not to Test?

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For several decades, the cornerstone of cancer therapy has been the application of standardized regimens as determined by tumor type and stage. During the last decade we have seen a seismic shift toward personalized medicine, based on the properties of individual tumors. For the most part, personalized medicine depends on identification of oncogene or other specific products required by the tumor cells for sustained growth (“oncogene addiction”), followed by administration of a specific inhibitor to the target.¹² Oncogene addiction is a double-edged sword. It drives tumor cell growth, but its inhibition may result in sustained tumor remissions accompanied by minimal or modest toxicities. Lung cancer has been a prominent target, and the poster child for lung cancer therapy has been targeting addiction to the epidermal growth factor receptor (EGFR) gene product.⁸

The EGFR gene is the prototype of a family of 4 surface receptor tyrosine kinases. Binding of 1 of several ligands to its receptor results in homo- or heterodimerization, initiation of kinase-mediated signaling with resultant downstream effects on many pathways involved with cellular growth and tumor spread. The finding of overexpression of the EGFR gene product in many epithelial cancers resulted in identification of the gene as a likely target. Initially inhibitory monoclonal antibodies were used for this purpose, but they were largely replaced following the development of small molecule reversible tyrosine kinase inhibitors (TKIs), specifically gefitinib (Iressa, AstraZeneca, Wilmington, DE) or erlotinib (Tarceva, Genentech, South San Francisco, CA).⁵ Large trials with TKIs indicated tumor responses, occasionally dramatic and sustained, in specific subsets of non-small cell lung cancer (NSCLC).³ The subsets included adenocarcinoma histology, female sex, East Asian ethnicity, and never smoker status. At first the basis for the responses in specific subsets was unknown. However, in 2004, mutations in the EGFR kinase domain in NSCLC were identified as the major determinant of TKI response, and the mutations were soon found to target the same subsets as those that responded to TKI therapy.⁹ TKI administration, initially used for second- or third-line therapies, gradually came into use as first-line therapy for EGFR mutant tumors.^{6,7}

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However, mutational testing is not available in all centers or in all geographic regions. At a recent Lung Cancer Summit in Taiwan attended largely by Asian physicians involved in lung cancer management, approximately 50% of the audience said that they did not routinely perform EGFR mutational testing (author's personal observations). Reasons included 1) reimbursement or cost issues, 2) unavailability of testing, 3) unavailability of tissue for testing, and 4) lack of necessity for testing. Because mutations and TKI responses largely target identical subsets of NSCLC, arbitrary selection of patients for treatment dependent on their pathologic and demographic characteristics may be an acceptable surrogate for testing. In the current issue of *Medicine*, Wu and colleagues¹³ performed a retrospective analysis of response to gefitinib therapy in NSCLC with or without knowledge of mutational status.

Wu et al¹³ performed a retrospective analysis of 907 eligible Taiwanese NSCLC patients treated with gefitinib. Mutational status was known for slightly more than 50% of the tumors, and 58% of these had activating mutations. As expected, mutational status was the most important determinant of response. However, in cases without known mutational status, selection of the specific subsets mentioned previously was a reasonable surrogate (with the caveat that all study patients were of East Asian ethnicity). This study is important as it confirms, in a large series, that subset selection is a reasonable approach to identify patients for TKI therapy.

The major strengths of the study, other than its size, were that TKI therapy was administered uniformly and patients were followed at a single institution. In addition, mutational testing was performed in a single laboratory. As many NSCLC cases present at advanced stages, diagnostic materials are often limited to small biopsies or cytologic specimens. Some of these specimens may not contain sufficient viable tumor cells for testing, indicating the importance of having alternative means for surrogate selection. However, there are several caveats and other points to consider. The study by Wu et al was a retrospective study, involving first- as well as multiple-line therapies, and all patients were of East Asian ethnicity. As the EGFR mutation rate in NSCLC is sharply lower in non-Asian ethnicities, a much smaller fraction of patients would be selected for therapy in most non-Asian studies. In such populations, using the most efficient method of selection is of greater importance. In several countries TKI administration is only approved as first-line therapy for patients having EGFR mutant tumors. While standards vary widely, reimbursement for TKI therapy may be limited to known mutant cases. In the study by Wu et al, TKI was administered as first-, second-, or third- (or later) line therapy. Obviously, a prospective study using data limited to first- or second-line therapy would have yielded more informative data.

Selection of patients for TKI therapy based on mutational testing is not a guarantee of response. Only about 70%–80% of EGFR mutation-positive tumor cases will have meaningful responses.^{5,6} Patients with mutation-negative adenocarcinomas have superior responses to conventional chemotherapy than to TKI administration,⁶ further indicating the importance of using mutational status to guide therapy selection. Certain mutations, such as insertions in exon 20, secondary mutations (T790M), or increased copy number (amplification) of the MET oncogene are associated with resistance to TKI therapy.⁴ Mutations in the KRAS gene, located downstream of EGFR in its signaling cascade, are

mutually exclusive with EGFR mutations. KRAS mutations are associated with resistance to TKI therapy. Finally, mutations may be present in tumors other than the targeted subsets.⁹ Selection of targeted therapy based entirely on subset identification would miss a substantial number of patients who would potentially benefit from targeted therapy, as well as administer the therapy to some who would respond better to conventional chemotherapy. NSCLC is a highly heterogeneous disease both at the pathologic and mutational levels. Other molecular targets, although less common than EGFR mutations, offer promise of dramatic and sustained responses to targeted therapies. The EML4-ALK fusion oncogene represents one of the newest molecular targets in NSCLC. The fusion results from a small inversion within chromosome 2p, which leads to expression of a chimeric tyrosine kinase, in which the N-terminal half of echinoderm microtubule-associated protein-like 4 (EML4) is fused to the intracellular kinase domain of anaplastic lymphoma kinase (ALK). The potent oncogenic activity of this aberrant molecule can be effectively blocked by small molecular inhibitors that target ALK.¹⁰ Mutations in the BRAF gene, which lies downstream of EGFR and which is required for RAS activation, are much more common in melanomas. Melanomas respond to an oral inhibitor to mutated BRAF,² and there is every likelihood that mutant lung cancers will also respond. Both ALK and BRAF mutations are mutually exclusive of EGFR mutations. In addition, EGFR mutations do appear occasionally in other subsets V that is, male patients, non-adenocarcinoma histologies, and in tobacco-associated cancers.⁹ Thus a full knowledge of the mutational status of activating oncogenes aids in the selection of the optimal targeted therapy and goes beyond TKI therapy.

However, if subset selection has to be used for targeted therapy, one aspect should be considered that has been ignored to date. Several histologic subtypes of adenocarcinomas exist, and some may be associated with specific mutations.¹¹ For instance, EGFR mutant tumors arise from the progenitor cells of the peripheral airways and tend to be peripherally arising adenocarcinomas with noninvasive (lepidic) components. In addition, EGFR mutations are also overrepresented in the papillary and micropapillary subtypes. Mucinous differentiation is associated with KRAS mutations, an absence of EGFR mutations, and absence of response to TKI therapy.¹ ALK translocations are associated with mucinous and signet ring tumors. Thus a potentially important, hitherto unused feature (histologic subtyping of lung adenocarcinomas) may contribute to the subset analysis and selection of targeted therapy.¹¹

At the present time, mutational analysis is the gold standard for selection of targeted therapy in lung cancer, even though it has certain shortcomings. However, the gold standard is not always applicable in all situations or in all parts of the world. Alternative approaches, such as subset selection based on histologic and demographic characteristics, must be explored and utilized on occasion and in special situations. The report by Wu et al¹³ goes a long way toward providing evidence for the validity of such approaches, especially in Asian countries.

Abbreviations

ALK	anaplastic lymphoma kinase
EGFR	epidermal growth factor receptor

NSCLC	non-small cell lung cancer
TKI	tyrosine kinase inhibitor

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