Lung Cancer in ‘Never-Smokers’: Molecular Factors Trump Risk Factors

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By Gregory J. Riely, MD, PhD [1]

While they represent a minority of patients with lung cancer, more than 20,000 people in the United States who never smoked cigarettes are diagnosed with lung cancer each year.[1] This makes lung cancer in “never-smokers” one of the 10 most common cancers—more common than ovarian cancer. In this issue of ONCOLOGY, Subramanian and Govindan give an overview of emerging data about lung cancer in never-smokers.[2] The data outlined in this review provide support for the hypothesis that we can define this collection of diseases affecting never-smokers not by the absence of a common risk factor (smoking) but by each tumor’s molecular features.

Molecular Abnormalities

The three most frequently identified, clinically relevant, genetic aberrations seen in never-smokers with lung adenocarcinomas are EGFR mutations, EML4/ALK fusion genes, and KRAS mutations. One of these three molecular abnormalities is found in approximately 70% of never-smokers with lung adenocarcinoma. The discovery of somatic activating mutations in the EGFR gene in patients who had previously responded to erlotinib (Tarceva) or gefitinib (Iressa) was a major breakthrough in lung cancer, which fueled additional research on never-smokers with lung cancer. These mutations (the most common are exon 21 L858R point mutations and exon 19 deletions) occur in a relatively large proportion of never-smokers, ranging from approximately 40%–50% in western populations to 60% in East Asian populations.[3,4]

The EML4/ALK fusion gene is the most recently identified genetic alteration observed in never-smokers with lung cancer.[5] Present in about 3% to 5% of unselected patients with non–small-cell lung cancer (NSCLC) and about 24% of never-smokers with lung adenocarcinomas, the EML4/ALK fusion gene leads to activation of ALK, which causes cellular proliferation that can be blocked by ALK inhibitors in vitro.[6] ALK inhibitors are already in clinical trials for patients with stage IV NSCLC who have a documented EML4/ALK fusion gene. In the phase I trial, the radiographic response rate to PF-02341066 (the first ALK inhibitor tested in this setting) in patients with stage IV NSCLC with an EML4/ALK fusion gene is > 53%. [7] This has led to a randomized phase III trial of PF-02341066 in patients with stage IV non–small-cell lung cancer with EML4/ALK, a trial that began accrual just 2 years after the initial identification of EML4/ALK fusion genes.

While KRAS mutations were initially identified in lung cancer nearly 25 years ago, they were long thought to be present solely in heavy smokers. More recently, as part of an evaluation of a large number of tumors from both smokers and never-smokers, we demonstrated that KRAS mutations occur in approximately 15% of never-smokers with lung adenocarcinoma.[8] Importantly, the KRAS mutations observed in never-smokers are more likely to be transition mutations, not the transversion mutations more commonly observed as a consequence of exposure to the carcinogens in cigarette smoke. The qualitative difference in KRAS mutations observed in never-smokers and former or current smokers suggests that KRAS mutant lung cancer in never-smokers is not simply caused by exposure to secondhand tobacco smoke.

While it is easiest to conceptualize cigarette-smoking history in a dichotomous fashion, there is a continuum of cigarette-smoking exposure, with some patients smoking several packs per day for nearly their entire lives and others who smoked a few cigarettes a day for a year or two. Such
patients have significantly different exposure to the carcinogens in cigarette smoke. When smoking is quantified (eg, by pack-years), it becomes clear that light smokers appear similar to never-smokers, but some heavy smokers share molecular and clinical characteristics with never-smokers. For example, in an analysis of EGFR mutation frequency as a function of pack-years, we observed that the frequency of EGFR mutations was not statistically different from never-smokers until patients had a > 15 pack-year history of cigarette smoking.[3] Even among those with a 51 to 75 pack-year history of cigarette smoking, EGFR mutations were found in 10% of patients. Despite their smoking history, these patients will go on to respond to the EGFR inhibitors erlotinib and gefitinib, emphasizing that what links these patients is not their history of cigarette smoking but the molecular characteristics of the tumors.

Conclusions

The evidence described here and in the accompanying review by Subramanian and Govindan highlight that what defines lung cancer in never-smokers is not the absence of a common risk factor, but a greater frequency of newly identified molecular markers that predict response to therapy. Clear differences in treatment response among never-smokers can be predicted by understanding the molecular basis of the disease. In the Iressa Pan-Asia Study (IPASS), which enrolled never- or light-smoker Asian patients with stage IV lung adenocarcinoma, the response rate of gefitinib in patients without EGFR mutations was 1%. [4] Erlotinib is ineffective in EML4/ALK-driven lung cancer. [6] Erlotinib does not lead to radiographic responses in KRAS mutant lung cancer. [9] If treatment decisions are made solely based on the patient’s risk factors (eg, giving erlotinib or gefitinib because the patient is a never-smoker), there is a risk of choosing an ineffective therapy. By identifying the molecular features of a given patient’s tumor, whether that patient has a history of cigarette smoking or not, we can better understand the tumor and choose the appropriate treatment.

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