LUNG CANCER IN FOCUS

Current Developments in the Management of Lung Cancer

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Does Plasma-Based Molecular Testing Have a Role in the Routine Care of Lung Cancer?

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H&O What is the gold standard method for detecting genetic mutations in patients with lung cancer?

HW The gold standard for detecting genetic mutations remains the testing of tissue at the time of diagnosis. However, in June 2016, the US Food and Drug Administration (FDA) approved the cobas EGFR Mutation Test v2 from Roche Molecular Diagnostics. This test can detect mutations in the epidermal growth factor receptor gene (*EGFR*) in samples of either blood or tumor. The presence of an exon 19 deletion or L858R mutation determines eligibility for treatment with erlotinib (Tarceva, Genentech/Astellas). By extrapolation, a positive test result also makes a patient eligible to receive either gefitinib (Iressa, AstraZeneca) or afatinib (Gilotrif, Boehringer Ingelheim) as an alternative option for the first-line treatment of *EGFR*-mutated non–small cell lung cancer (NSCLC).

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Since March 2017, the cobas EGFR Mutation Test also has been approved as a companion diagnostic for the second-line use of osimertinib (Tagrisso, AstraZeneca). In this case, the test is used to detect the T790M mutation in *EGFR*. Approval was based on the results of AURA3 (AZD9291 Versus Platinum-Based Doublet-Chemotherapy in Locally Advanced or Metastatic Non-Small Cell Lung Cancer), which was published in the *New England Journal of Medicine* in February 2017. This study looked at second-line osimertinib vs chemotherapy in patients who had received a first-generation EGFR tyrosine kinase inhibitor and whose disease had progressed owing to development of the T790M resistance mutation.

H&O How often are plasma-based tests used in patients with lung cancer?

HW We do not have definitive data on that, but there has been an uptick in the use of these tests. I certainly see this in the San Francisco Bay Area, where I practice, although practice patterns do vary across regions. For most patients, a biopsy is required to confirm an initial diagnosis of cancer, and we use that sample for testing at the time of diagnosis. However, if we do not have enough tissue for some reason, we now have the option of using a plasma-based test that employs next-generation sequencing.

The biggest increase in the use of plasma-based tests is for patients who are known to have an *EGFR* mutation; such mutations occur in approximately 10% to 20% of NSCLCs. Although the initial mutation is found in tissue, the resistance mutation often can be identified with

a plasma test, which allows us to avoid doing another biopsy at the time of disease progression.

In addition to the cobas EGFR Mutation Test, which is approved by the FDA, many practitioners are using assays that are even more sensitive and can find mutations other than the *EGFR* mutations that have been mentioned.

H&O What are the advantages of plasma-based tests over tumor biopsy?

HW The most obvious advantage is that just a blood draw is needed, rather than a procedure, to obtain tissue. Another advantage of plasma-based tests is that the results are available relatively quickly—within a few days or even sooner if an in-house laboratory is available. In contrast, it takes time to schedule a biopsy and several days to have the specimen processed.

Finally, plasma-based testing has the potential to detect mutations that tissue biopsy may miss because of tumor heterogeneity. There are cases in which plasma testing finds a T790M mutation that the tissue testing did not pick up, so the techniques can be somewhat complementary. In a study that we presented at the American Society of Clinical Oncology (ASCO) annual meeting in 2016, we explained that a subset of patients had mutations that were detected only in tissue, and another subset had mutations that were detected only in plasma. For most patients, the results were positive in both assays. Other groups have observed the same phenomenon. For example, in their studies of osimertinib, Geoffrey Oxnard and colleagues detected T790M positivity in the plasma samples of some patients with T790M negativity by tissue testing. In a 2016 study published in the *Journal of Clinical Oncology*, they detected T790M in the plasma of 31% of 58 patients whose tumors were negative for T790M by tissue testing.

At the 2016 ASCO annual meeting, a presentation about the Guardant360 plasma assay (Guardant Health) focused on the detection of driver mutations. Of 362 patients with lung cancer included in the presentation, 120 had actionable mutations on the basis of tumor testing; however, actionable mutations were identified in an additional 51 patients with plasma testing.

H&O What are the limitations of plasma-based tests?

HW The plasma-based assays are not quite as sensitive as the tissue-based tests, although many of them are approaching the same level of sensitivity. At the ASCO annual meeting in 2016, we presented a subanalysis of TIGER-X (Study to Evaluate Safety, Pharmacokinetics, and Efficacy of Rociletinib in Previously Treated Mutant Epidermal Growth Factor Receptor in Non-Small Cell Lung Cancer Patients), in which we were looking for T790M in the tissue, plasma, and urine of patients with NSCLC. We used the BEAMing (beads, emulsification, amplification, and magnetics) method to test plasma. We found that the sensitivity of plasma testing was 81%; it detected 313 of the 387 mutations identified via tissue sampling. Other plasma testing platforms have shown a sensitivity of 80% to 90% for del(19) and the L858R mutation, and a sensitivity of approximately 70% to 80% for T790M. The sensitivity of the cobas EGFR Mutation Test is closer to 50% or 60%. So regardless of the plasma testing method used, plasma testing is not quite as good as tissue testing.

When false negatives occur with plasma testing, a possible explanation is that the tumor is not shedding much DNA. This seems to be more likely in lung cancers that are confined to the thoracic cavity. When false negatives occur with tissue testing, a possible explanation is tumor heterogeneity—T790M clones may be present in the tumor, but not in the area of the tumor that was sampled.

H&O Are there specific genetic alterations that are more likely to be missed with plasma-based testing?

HW Regarding *EGFR*, the sensitivity of plasma-based testing for T790M mutations is not as good as its sensitivity for the initial sensitizing mutations, such as del(19) and L858R. This may be related to the fact that all the tumor cells will have the primary driver mutation, but only a subset may have the resistance mutation. Although most of the data pertain to *EGFR* testing, researchers also are looking at plasma testing for other known driver mutations.

H&O What other relevant mutations is plasma-based testing used to detect?

HW Plasma-based testing is commonly being used to detect mutations in *BRAF* and the *MET* exon 14. It is more difficult to use plasma-based testing for the translocations, such as *EML4-ALK*, but many of the next-generation sequencing platforms can detect those also.

H&O How do you see plasma-based testing being used in the future?

HW We are already using plasma-based testing to detect secondary resistance mutations, and in some cases to detect primary mutations. Someday, we will use it to

monitor patients with driver mutations for the development of resistance. I can also see plasma-based testing being used to select those patients who require adjuvant treatment.

It is possible that this technology will be used for routine cancer screening someday. Aadel Chaudhuri from our group at Stanford presented a poster at the 2017 ASCO meeting. This study looked at patients who had undergone definitive treatment for early-stage cancer with either surgery or radiation. Plasma samples were analyzed for circulating tumor DNA within 4 months after the completion of therapy. Among the 15 patients who had no residual circulating tumor DNA, a relapse occurred in only 1 patient. In contrast, among the 19 patients with residual disease, a relapse occurred in all within 24 months (hazard ratio, 41; $P<.00001$). This finding will require further validation, but it has the potential to change how we consider giving adjuvant therapy and may also lead to changes in cancer screening strategies.

Disclosure

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Suggested Readings

Chaudhuri A, Chabon JJ, Lovejoy AF, et al. Analysis of circulating tumor DNA in localized lung cancer for detection of molecular residual disease and personalization of adjuvant strategies [ASCO abstract 8519]. *J Clin Oncol.* 2017;35(15)(suppl).

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Oxnard GR, Thress KS, Alden RS, et al. Association between plasma genotyping and outcomes of treatment with osimertinib (AZD9291) in advanced non-small-cell lung cancer. *J Clin Oncol.* 2016;34(28):3375-3382.

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