Biomarker Assays for Lung Ca Making Progress

BY SUSAN LONDON

CORONADO, CALIF. — A variety of lung cancer–associated biomarkers are being tested in assays that may improve diagnosis and treatment of this disease, according to three studies reported at a joint conference of the American Association for Cancer Research and the International Association for the Study of Lung Cancer.

Blood-Based Biomarker Profile

A blood-based biomarker profile discriminates well between patients who have early-stage lung cancer and those individuals who are cancer free but at high risk, reported Dr. Gina Lee, a pulmonary and critical care physician at the University of California, Los Angeles.

She and her colleagues hypothesized that molecular changes in the developing tumor environment would be reflected in changes in levels of inflammatory, angiogenic, and tumorigenic proteins that can be detected in peripheral blood.

They used a bead-based multiplex immunoassay to assess levels of 40 biomarkers in serum samples from 90 patients who had lung cancer of any stage and from 56 cancer-free controls who were at high risk because of lengthy former smoking status and older age.

Levels of 21 biomarkers differed significantly between the 28 patients with stage I lung cancer and the cancer-free controls.

In a logistic regression model that focused on selected biomarkers, participants were more likely to have stage I cancer if they had higher levels of interleukin 2 (odds ratio, 51.4), interleukin 3 (OR, 11.0), and macrophage-derived chemokine (OR, 10.9).

"Our results suggest that we can find tumor-associated biomarkers that are differentially expressed in stage I vs. at-risk controls," Dr. Lee said. "However, we are also interested in the clinical scenario where individuals present to clinicians with a lung nodule seen on chest x-ray or a CT scan of indeterminate significance."

Therefore, she and her colleagues will evaluate the 40 biomarkers in pre- and postresection serum samples from patients in the ACOSOG (American College of Surgeons Oncology Group) Z4031 trial. Roughly one-fifth of patients undergoing resection for lung nodules in that trial were found to have benign lung disease.

High-Throughput Protein Assay

A protein signature identified by a high-throughput assay correctly classifies the large majority of patients with and without lung cancer, reported Dr. Rachel Ostroff, clinical research director at SomaLogic Inc., a diagnostic development company in Boulder, Colo.

The SOMAmer technology used in the study relies on aptamers (oligonucleotides that bind to specific proteins with high affinity) to measure 825 proteins in serum simultaneously with subpicomolar sensitivity, she explained.

The investigators analyzed more than 1,300 serum samples from patients with stage I-III non–small cell lung cancer (20%) and two control groups: individuals with benign calcified pulmonary nodules (40%) and long-term smokers with no evidence of cancer (40%). They were divided into training and verification sets.

Analyses identified a signature of 12 proteins that were differentially expressed between the groups with and without lung cancer, including cell adhesion molecules, cytokines, angiogenesis markers, and tyrosine kinases, among others.

The signature had an area under the curve of 0.91 in the training set and 0.90 in the verification set, Dr. Ostroff reported. In the training set, sensitivity was 91% for cancer of all stages (90% for stage I) and specificity was 84%. In the verification set, sensitivity was 89% for cancer of all stages (87% for stage I) and specificity was 84%.

The signature has also been tested in breast, prostate, and other cancers. "Certainly, some of the markers are also differentially expressed in those cancers, as you would expect," Dr. Ostroff said. "But … when you combine all of those 12 markers together, it is much more specific for lung cancer than those others."

Tumor MicroRNA Analysis

A trio of tumor microRNAs predict de novo resistance to first-line chemotherapy among patients with small cell lung cancer, reported Dr. Glenn J. Weiss, a pulmonary oncologist with Scottsdale (Ariz.) Healthcare and the Translational Genomics Research Institute (TGen) in Phoenix.

"Small cell lung cancer patients have not had key breakthroughs for improved therapy in years, in part, because a one-size-fits-all approach for treatment is the current standard," he commented in an interview.

In the study, which was funded in part by the TGen Foundation, he and his colleagues extracted RNA from formalin-fixed, paraffin-embedded tumor specimens obtained from 34 patients with small cell lung cancer before they started chemotherapy, which was a platinum-based regimen in most cases.

Study results, reported in a poster, showed that of 21 evaluable patients, 4 (19%) had chemoresistance (defined as progression despite chemotherapy).

MicroRNA array analyses identified 16 microRNA biomarkers as possible predictors of progression.

Polymerase chain reaction analyses validated that three of them—miR-92a-2*, miR-147, and miR-574-5p—were indeed associated with progression, Dr. Weiss said.

The investigators are currently assessing how the identified microRNAs may reduce a tumor's sensitivity to chemotherapy, according to Dr. Weiss.

"If we can independently validate our findings in other tumor sample sets collected from small cell lung cancer patients, we can begin to explore [by] using these microRNAs to design better clinical trials and perhaps find new therapies that help patients at higher risk for resistance to current standard chemotherapy treatment," he concluded. ■

Disclosures: *Dr. Lee reported that she had no conflicts of interest related to the study. Dr. Ostroff's employer is the manufacturer of the study assay. Dr. Weiss has filed patents for the use of microRNAs as theranostics, and has received funding from the Sylvia-Chase Foundation, the American Cancer Society, the IBIS Foundation of Arizona, the TGen Foundation, and Scottsdale Healthcare to conduct this work.*