Biomarker Assays for Lung Cancer Fill Pipeline

BY SUSAN LONDON

CORONADO, CALIF. — A variety of lung cancer–associated biomarkers are being tested in assays that may improve diagnosis and treatment, 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 (*P* less than .05 for each). For distinguishing between these groups, this panel had an area under a receiver operating characteristic curve of 0.92.

In a logistic regression model focusing 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). For distinguishing between patients with stage I lung cancer and at-risk controls, a panel consisting of these three biomarkers had an area under the curve of 0.93, a sensitivity of 97%, and a specificity of 77%.

"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."

Dr. Lee reported that she had no conflicts of interest related to the study.

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%). Analyses identified a signature of 12 proteins that were differentially expressed between the groups with and without lung cancer.

In the training set, the signature's 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%.

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.

In the investigation, 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 patients (19%) had chemoresistance (defined as progression despite receiving chemotherapy).

MicroRNA array analyses identified 16 microRNA biomarkers as possible predictors of progression. Polymerase chain reaction analyses validated that three of them were indeed associated with progression, according to Dr. Weiss, who has filed patents to use them as "theranostics." ■

Childhood Cancer Survivors Warrant Monitoring as Adults

BY SHERRY BOSCHERT

One in every 640 young adults in the United States survived cancer as a child, and approximately two-thirds of them have at least one chronic health problem.

Better cancer treatments in recent decades increased pediatric cancer survivor rates from below 50% to today's average of 80%, and as a result there is more focus on the long-term medical needs of survivors. Depending on their disease and the treatment they received, these patients are at higher risk for secondary cancers, cardiovascular and lung diseases, learning disabilities and memory difficulties, vision and hearing problems, or infertility.

Long-term follow-up programs for childhood cancer survivors have proliferated in the past 5 years, but too often these patients aren't recognized or adequately cared for, Dr. Anna T. Meadows said in an interview.

"There aren't enough primary care doctors who want to undertake follow-up of pediatric cancer survivors," said Dr. Meadows, director of the Cancer Survivorship Project and the Living Well After Childhood Cancer program at the Children's Hospital of Philadelphia. "People are not really thinking that the kids grow up, when the average age of our survivors is now in the 40s."

Dr. Meadows and her associates reviewed reports of subsequent neoplasms in 14,358 participants in the National Cancer Institute's Childhood Cancer Survivor Study. They estimated 30-year cumulative incidences of 9% for second malignant neoplasms and 7% for nonmelanoma skin cancers (J. Clin. Oncol. 2009;27:2356-62).

Although only 13% of the cohort were survivors of Hodgkin's lymphoma, these patients accounted for 34% of the second malignant neoplasms, mainly because of an increased risk for breast cancer; among 157 second breast cancers, 60% were Hodgkin's survivors. The largest proportions of nonmelanoma skin cancers occurred in survivors of Hodgkin's lymphoma (38%), leukemia (32%), and CNS tumors (9%).

A separate systematic review by Dr. Tara Henderson, which is slated to be published in the April issue of the Annals of Internal Medicine, found a 12%-21% risk for breast cancer in female survivors of Hodgkin's lymphoma who were treated with radiation.

"It's the same incidence as in women who have a BRCA mutation, so it's very high risk," said Dr. Henderson, a pediatric oncologist and director of the Childhood Cancer Survivors Center at the University of Chicago, in an interview.

'There aren't enough primary care doctors who want to undertake follow-up of pediatric cancer survivors.'

DR. MEADOWS

Like breast cancers in the general population, breast cancer in childhood cancer survivors is curable if diagnosed early, Dr. Henderson noted, so she recommends earlier screening for breast cancer in Hodgkin's lymphoma patients—starting mammography and MRI screening 8 years after treatment or at age 25 years, whichever comes last.

Radiation therapy also commonly increases later risk for skin cancers, sarcomas, and thyroid cancer. "We just have to make clinicians aware that the risk is there," she said.

Dr. Paul Nathan agreed. If "an adult shows up in your practice for a particular problem who has had cancer as a child, you need to pay close attention," he said in an interview. "Lumps or bumps that you may otherwise think are fairly innocent in a 20- or 30-year-old may not be" innocuous in cancer survivors, said Dr. Nathan, a hematologist/oncologist at the Hospital for Sick Children, Toronto.

He recommends that physicians consult guidelines for long-term follow-up of childhood cancer survivors, which are updated every 2 years by the Children's Oncology Group and are available at www.survivorshipguidelines.org. If you know the type of cancer and/or the treatment in the patient's past, the guidelines can tell you what health risks the patient might face and how best to provide follow-up care and screening, Dr. Nathan said.

It's not uncommon, however, for adult patients to know little about their childhood cancer diagnosis or treatment. A grant from the Agency for Healthcare Research and Quality is helping Dr. Karen J. Wasilewski-Masker and her associates at Children's Healthcare of Atlanta to develop SurvivorLink, a computerized network. In what may be the first project of its kind in the country, SurvivorLink would give primary care physicians, surgeons, and other specialists throughout Georgia access to medical summaries and information on any patient seen in her institution's Childhood Cancer Survivorship Program, she said in an interview.

Not only do survivors need to be educated, so does the medical community. "These patients are out there and have health risks and need to be followed," Dr. Daniel A. Mulrooney said in a separate interview. Today's physicians learned next to nothing about childhood cancer survivors in their medical training, and it's unlikely that current medical school curricula cover the topic either, he suggested.

"The cumulative incidence curves for secondary cancers [in childhood cancer survivors] have not yet plateaued—we haven't seen any type of downturn," said Dr. Mulrooney, a pediatric hematologist/oncologist at the University of Minnesota, Minneapolis. "These cancers develop earlier than expected and are likely to increase over time." It will be challenging, because these patients will grow to the age when cancers are more common.

All of the physicians interviewed for this article declared that they have no conflicts of interest. ■