Study ties abnormal cells in blood to lung cancer

July 22 2010

A novel approach detects genetically abnormal cells in the blood of non-small cell lung cancer patients that match abnormalities found in tumor cells and increase in number with the severity of the disease, a research team led by scientists at The University of Texas MD Anderson Cancer Center report in the journal *Clinical Cancer Research*.

Lung cancer patients in the study also had many times the number of these circulating abnormal cells than study volunteers in a closely matched control group.

"We suspect additional research will show that these circulating abnormal cells are circulating non-small cell lung cancer cells," said study corresponding author Ruth Katz, M.D., professor in MD Anderson's Department of Pathology. "Blood tests for these circulating tumor cells could be used to diagnose lung cancer earlier, monitor response to therapy and detect residual disease in patients after treatment."

Katz and colleagues conducted what they believe to be the first study to use a technique called fluorescence in situ hybridization (FISH) to detect abnormal circulating cells that have aberrations found in non-small cell lung cancer. FISH detects and quantifies abnormal cells by using dye-labeled DNA probes of cell chromosomes that cause cells with the targeted genetic abnormalities to light up when viewed under a fluorescent microscope.

"We were surprised to find many more abnormal circulating cells in lung cancer patients compared with what had been seen previously using other techniques," Katz said.

The researchers used 12 biomarker probes that target aberrations previously connected to lung cancer to analyze 59 cases of non-small cell lung cancer and 24 controls, people without lung cancer, including smokers and non-smokers. Their findings include:

- Highly significant differences in the average number of abnormal cells in the bloodstream between patients and controls. For example, deletion of a gene at an address on chromosome 3 called 3p22.1 occurred on average in 7.04 cells per micro liter of blood in controls, while cases averaged 45.52 cells per micro liter with that deletion.

- Abnormal cells were significantly associated with disease stage, with cells that contained certain abnormalities increasing significantly as cancer progressed from early to advanced stage disease.

- Eight of the biomarkers had a strong overall correlation between abnormal circulating cells and tumors. Chromosomal gain of the EGFR gene in circulating cells was significantly associated with the same gain in tumors, most notably among patients with stage III or stage IV disease.

Some biomarkers were associated with lung cancer recurrence and overall survival, but none were statistically significant after adjusting for age, sex and disease stage. Larger clinical trials are needed to address these associations, Katz said.

The FISH analysis used by the team detected more circulating abnormal cells - by orders of magnitude - than existing methods that rely on immunomagnetic beads to attach to an antibody found on the surface of circulating cells that originate in an organ's epithelium. Epithelial tissue lines the surfaces and cavities of organs and 80 percent of all solid tumor cancers originate in the epithelium. Detection methods for circulating tumor cells have focused strictly on epithelial cells.

While the FISH analysis detected up to 45,000 abnormal cells per milliliter of blood, studies using the antibody-based epithelial method typically find fewer than 10 abnormal cells per milliliter.

Katz believes part of the difference is that FISH is not limited to epithelial cells, so it picks up mesenchymal cells, thought to be involved in the spread of primary cancer to other organs, stem cell precursor cells and a variety of other cell types in addition to epithelial cells.

"That's what differentiates this study from others, we use DNA probes through FISH to look at chromosomal changes in the cell nucleus, regardless of the cell's origin," Katz said.

Katz said future plans include studies with larger numbers of patients to validate that circulating abnormal cells are related to disease stage, relapse and survival. They also will evaluate epithelial, mesenchymal, stem cell and blood and lymphocyte markers, combined with FISH, to track down the origin of circulating abnormal cells and their associated traits.

Work is under way to develop a clinical test based on FISH.

Provided by University of Texas M. D. Anderson Cancer Center