MedicalXpress

Researchers discover biomarkers that predict lung cancer patient response to therapy

January 31 2008

Researchers at UCLA's Jonsson Cancer Center have discovered biomarkers that predict which patients with advanced non-small cell lung cancer will respond to a combination treatment of the anti-inflammatory drug Celebrex and the growth factor receptor blocker Tarceva.

The findings, published in the Feb. 1, 2008 issue of the *Journal of Thoracic Oncology*, may help oncologists personalize treatment, prescribing drugs they know patients will respond to and sparing them from therapies that won't work. Both drugs are taken in pill form once a day and result in fewer side effects than conventional treatments such as chemotherapy.

If the findings are confirmed in further studies, the personalized drug combination would offer an alternative therapy in a disease population in which new, more effective treatments are needed, said Dr. Steven Dubinett, a professor of pulmonary and critical care medicine and senior author of the study. This year alone, more than 213,000 Americans will be diagnosed with lung cancer. Of those, more than 160,000 will die.

"We need good predictors of response to targeted therapy in lung cancer so individual patients receive the specific therapy that targets the particular molecular abnormalities of their tumors," said Dubinett, who also serves as director of the cancer center's Specialized Program of Research Excellence (SPORE) in lung cancer.

The findings grew out of a Phase I dose-escalation study of the drug

combination in a small group of patients who had failed all other treatment options. The early phase study resulted in more patient responses than expected in people with advanced lung cancer, the most deadly stage of the disease. About 50 percent of patients in the study had tumors that decreased in size by more than 30 percent or had tumors that did not grow, a state called stable disease that is considered a positive outcome.

UCLA researchers studied tumor, blood and urine samples from the patients to discover why some patients did well and others did not. Their findings identified several biomarkers that could potentially help identify patients likely to respond to the Tarceva and Celebrex combination therapy and those who likely would not respond.

Researchers found higher levels of certain proteins in the blood of patients who did not respond to therapy. Other proteins were found that declined in patients who did respond to the treatment. Dubinett said that changes in these proteins levels may help explain the potential benefit of Celebrex in rendering the tumor cells more vulnerable to Tarceva.

About 80 to 85 percent of lung tumors overexpress cycloxygenase-2 (COX-2), an enzyme that causes inflammation, makes cancer cells resistant to death and more invasive and vascular, meaning the tumors create an independent blood supply to nourish themselves. COX-2 also appears to cause resistance to drugs like Tarceva that inhibit epidermal growth factor receptors, which are found on the surface of cancer cells and receive signals to reproduce, causing the cancer to grow.

Only about 15 percent of lung cancer patients respond to Tarceva and they later become resistant. Dubinett and his team determined in the lab that if they inhibited the COX-2 pathway, they were able to restore the sensitivity of lung cancer tumor cells to Tarceva. That finding led to the Phase I study of Celebrex, which inhibits COX-2, with Tarceva. The

study is part of the lung cancer SPORE program, funded by the National Cancer Institute, with additional support from the Nickoll Family Gift for Emerging Therapies in Lung Cancer.

In analyzing the samples from the Phase I patients, the research team found that patients with low levels of MMP9 before treatment had the best response to the combination therapy. That protein biomarker might be used one day to stratify patients into groups. If these results are confirmed in larger studies, those patients with low blood levels of MMP9 could receive the Celebrex and Tarceva and expect to respond.

The work is now being tested in a much larger, multi-site Phase II study of 100 patients. The samples taken from patients at all the study sites - before and after treatment - will be analyzed in Jonsson Cancer Center laboratories. Investigators will seek to confirm whether there's a connection between tumors that express the proteins identified in the Phase I study and a response to the combination therapy.

This larger study could provide evidence that effective combination targeted therapies for lung cancer can be developed in the near future and provided to patients whose blood tests suggest they are most likely to benefit. It also could determine why all lung cancers don't respond to the same treatment and promote a personalized medicine approach that would group patients by the molecular signatures found in their tumors and bloodstream rather than by cancer type.

"This study could determine whether these biomarkers can be used in the future before treatment to select the patients likely to respond," said Dubinett.

Source: University of California - Los Angeles