Advances in personalized medicine for lung cancer

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Several new studies that may help doctors tailor lung cancer treatment to the characteristics of individual patients and of their tumors are being presented at the 3rd European Lung Cancer Conference in Geneva.

"A major goal of lung cancer treatment is to tailor the treatment to the individual," says Dr Fiona Blackhall from The Christie NHS Foundation Trust in Manchester, UK. "The studies that will be presented at ELCC 2012 are important practical steps to achieving this in the clinic. Methods ranging from convenient blood-based molecular tests, detailed genetic analysis of tumors and functional imaging techniques have been applied in patient populations receiving a range of treatments. These findings provide impetus to continue developing a personalized medicine approach to lung cancer with the overall aim of selecting the most effective treatment for the individual."

Proteins provide clues to outcomes

An international group of researchers report promising results with a test that may identify patients likely to benefit from first-line therapy with a particular drug combination.

Dr Oliver Gautschi from the Swiss Group for Clinical Cancer Research (SAKK), and collaborators from The Netherlands and the US company developing the test, conducted a retrospective analysis of two phase-II trials with a serum proteomic classifier called VeriStrat®. Their aim was

to evaluate the prognostic value of the test in patients with advanced non-small cell lung cancer receiving first-line treatment with bevacizumab and erlotinib.

VeriStrat® uses mass spectrometry to measure proteins in pre-treatment blood and assigns a result that correlates with outcome from treatment with a class of drugs known as EGFR inhibitors, which includes erlotinib and gefitinib. The test was initially developed and validated in patients who had already been treated with chemotherapy, and who then received an EGFR inhibitor in second line, Dr Gautschi explains.

"We conducted this project to see if the test is also prognostic in untreated patients who received an EGFR inhibitor in the first line. Until now, this has not been clear."

The researchers used VeriStrat® to analyze blood samples from 117 patients previously enrolled in two phase II trials and compared the results to the patients' progression-free survival and overall survival. The analysis showed that those classified by the test as likely to have better outcomes on EGFR inhibitor therapy did indeed live longer.

"The difference in overall survival between patients classified by the test as likely to have better or worse outcomes when receiving EGFR inhibitors was clinically relevant," Dr Gautschi said. However he noted that definitive conclusions about the use of this test in previously untreated patients requires further studies.

"There is an unmet need for reliable blood-based markers in patients with lung cancer, because lung tumors are harder to biopsy than breast tumours for example. The current study indicates that modern technologies, such as proteomics, are promising tools, which need further validation in large trials," he said. In this context, the European Thoracic Oncology Platform (ETOP) is currently launching a

prospective phase-III trial to futher validate this test in patients with lung cancer.

"Clinical trials involving robust predictive tools have potentially a great impact and can be of paramount relevance in defining the real role of personalized cancer medicine," commented Dr Rafael Rosell from the Catalan Institute of Oncology in Badalona, Spain, Member of the ESMO Chest Tumors Faculty group. "This broad proteomic analysis can provide useful information, circumventing the problem of tumor heterogeneity that can arise when a single tumor biopsy is examined," Dr Rosell added.

Micro RNA marks response to chemoprevention

Dr Celine Mascaux from the University of Colorado and collaborators report that the micro RNA miR-34c is a potential biomarker for histological response in lung cancer chemoprevention studies.

Chemoprevention is a way of preventing the development of cancer using medicines or other agents, including the prevention of cancer in at-risk individuals such as smokers.

Currently, the best intermediate endpoint for studies of chemoprevention is a histological grading of cells in the airways of the lungs. However, as Dr Mascaux's group notes, "more quantitative biomarkers of response would be desirable."

Dr Mascaux and colleagues analyzed the expression of selected micro RNAs as potential surrogate biomarkers in a lung cancer chemoprevention trial that compared a drug called iloprost to placebo in 125 former or current smokers.

In a recent study, oral iloprost has shown promise to prevent the

development of lung cancer in high-risk people.

After analyzing 14 different micro RNAs from 496 lung biopsies, they found that change in the expression of a particular micro RNA -- miR-34c -- in follow-up biopsies was inversely correlated with histological response.

Changes in the expression of this micro RNA may therefore be a quantitative biomarker of response in lung chemoprevention studies, they say.

RRM predicts shorter survival

Dr Giovanna Dal Bello and colleagues report that expression levels of ribonucleotide reductase subunit 2 (RRM2) predict shorter survival in patients whose non-small cell lung cancer had been surgically removed. In 82 patients, the Italian group found that RRM2 was an independent prognostic marker of shorter survival.

"The difference in overall survival between patients with high or low RRM2 levels was clinically relevant," said Dr Dal Bello from the National Institute for Cancer Research in Genoa, Italy. "In particular, mean survival time of patients with high RRM2 levels was 36.5 months compared to 46.1 months for those with low RRM2 levels."

"This is the first study that identifies RRM2 expression as a negative prognostic factor in resected stage I-III NSCLC," they report.

"RRM2 was identified as an unfavorable prognostic marker in our study population and this is in agreement with its crucial role in supplying deoxyribonucleotides for DNA synthesis and repair and with the finding that cells overexpressing RRM2 exhibit enhanced cellular invasiveness," Dr Dal Bello explained.

Because of the high and rapid recurrence rate of lung cancer, prognostic markers to identify patients with higher risk of relapse represent a high unmet medical need. "The prognostic role of RRM2 can help to identify patients at higher risk of relapse who may benefit from adjuvant chemotherapy," she noted.

Epigenetic clues distinguish tumor types

Dr David Shames from a San Francisco, California–based biotechnology company[1] and colleagues report that epithelial-like lung tumors, which have a better prognosis and exhibit greater sensitivity to inhibitors of the EGFR pathway, can be distinguished from mesenchymal-like tumors on the basis of global DNA methylation patterns.

DNA methylation is an important form of 'epigenetic' modification, which affects the expression of genes within cells.

Using cancer cell lines and surgically resected non-small cell lung cancer tumors, the researchers showed that patterns of DNA methylation can divide non-small cell lung cancer into two phenotypically distinct subtypes.

Their work also provides proof of principle, they say, that "differences in DNA methylation can be used as a platform for predictive biomarker discovery and development."

A promising biomarker of response to radiotherapy

In a further report, Dr Ioannis Trigonis from the Wolfson Molecular Imaging Centre and The Christie Hospital in Manchester, UK, describes the findings from an assessment of F-18 fluorothymidine (FLT), a tracer molecule used in PET scanning to measure tumor cell proliferation.

Dr Trigonis' group studied 14 patients with NSCLC who had a total of 31 dynamic FLT PET-CT scans before and within 1-2 weeks after the start of radical radiotherapy. They found that radiotherapy induced early significant decreases in tumor FLT uptake that varied across patients.

Their results indicate the potential of FLT PET to identify how well patients are responding to radiotherapy and guide therapeutic approaches, they say. More results will be presented at the meeting.

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