Oncogene AEG-1 strongly predicts response to erlotinib treatment in EGFR-mutant lung cancer

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Spanish researchers have identified a gene whose expression level strongly predicts how well certain lung cancer patients will respond to treatment with the drug erlotinib.

Dr Rafael Rosell and colleagues reported their findings at the European Multidisciplinary Conference in Thoracic Oncology (EMCTO), 24-26 February 2011 in Lugano, Switzerland.

The researchers studied 55 patients with non-small cell lung cancer, whose tumors had mutations in the epidermal growth factor receptor (EGFR) gene. All were being treated with the drug erlotinib, which acts on the EGFR molecule.

"Currently we have no predictors for the duration of response to EGFR drugs in non-small cell lung cancer patients with EGFR mutation," Dr Rosell explained. "The median progression-free survival time for these patients ranges from 10 to 14 months, but there is a subgroup of patients with very short response while others have long lasting benefit."

Researchers in the Spanish Lung Cancer Group (SLCG), in cooperation with Pangaea Biotech, USP Dexeus University Institute, Barcelona -- which acts as one of the reference laboratories for the SLCG -- set out to find genes that predicted which patients would have a lasting benefit, and which would not. To do this, they used a technology called

NanoString. "NanoString is an integrated digital technology with high levels of precision and sensitivity that detects expression levels of hundreds of genes in a single reaction, making it suitable for clinical use," Dr Rosell explained.

Dr Rosell and colleagues used the technology to examine expression levels of 48 different genes in 43 patients with EGFR-mutant non-small cell lung cancer who were being treated with erlotinib.

They found that AEG (astrocye elevated gene 1, also known as metadherin) was the strongest predictor of progression-free survival in these patients. Progression-free survival was 27 months for those with low AEG-1 expression, compared to 12 months for those with high expression.

AEG-1 is a cancer-associated gene with multiple functions, which contribute to several hallmarks of cancer including drug-resistance.

Perhaps the greatest potential for AEG-1 expression would be to couple it with measurements of the expression of the BRCA1 gene, Dr Rosell said.

"Combining these two measurements could have very important clinical implications since defining a low-risk subgroup of patients can accurately predict situations when the simple administration of an oral EGFR drug could have an extremely durable effect, of more than two years."

"This could give confidence to the patient, their family and doctors, and eliminate the traditional anxiety of waiting for periodical CT scan reassessments," Dr Rosell said. "While radiographic monitoring will not be left to one side altogether, the patient and family can face these tests without anxiety."

For those patients in the high-risk group, the result can alert the clinical oncologist to be ready for early progression and look for alternative management strategy, Dr Rosell said.

Commenting on the research, which she was not involved in, Dr Fiona Blackhall, Consultant Medical Oncologist and Honorary Senior Lecturer at The Christie Hospital NHS Foundation Trust and Manchester Cancer Research Centre, UK, explained that Dr Rosell and colleagues applied innovative nanostring technology to address why, despite presence of EGFR gene mutation, clinical outcomes with erlotinib treatment (response rate and duration of response) are heterogeneous.

"They have discovered that AEG-1, a gene that activates several molecular pathways implicated in drug resistance, is a strong predictor of progression-free survival in the context of EGFR gene mutation and erlotinib treatment. This finding provides new insight into molecular mechanisms driving resistance to EGFR-tyrosine kinase inhibitors that may be exploited for therapeutic control."

AEG-1 gene expression levels could also be used in the clinic to identify 'low-risk' patients for less intensive radiological and clinical monitoring, she said. "These results highlight the potential for a new paradigm in personalized medicine in lung cancer in which biomarkers inform frequency of follow-up, and not just drug selection. A prospective validation study is now needed as the next step of translation of this important finding to the clinic."

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