Not all lung cancer patients who could benefit from crizotinib are identified by FDA-approved test

August 28 2012

Break apart a couple worm-like chromosomes and they may reconnect with mismatched tips and tails – such is the case of the EML4-ALK fusion gene that creates 2-7 percent of lung cancers. Almost exactly a year ago, the FDA approved the drug crizotinib to treat these ALK+ lung cancer patients, who were likely never smokers. Informed doctors use the test called a FISH assay to check for the EML4-ALK fusion gene, and then if the test is positive, ALK+ patients benefit greatly from crizotinib.

A recent University of Colorado Cancer Center case study published in the Journal of Thoracic Oncology describes the never-before-seen case of a patient who tested negative for EML4-ALK fusion based on the well-defined criteria for FISH assay as approved by FDA, but nevertheless experienced remission after treatment with crizotinib.

"The case implies that not all patients who might benefit from the drug are captured by the FDA-approved FISH assay. Perhaps despite the FDA pairing of crizotinib with FISH, other assays or other criteria for ALK/FISH positivity could be used," says paper co-author, Fred R. Hirsch, MD, PhD, investigator at the CU Cancer Center and professor of medical oncology and pathology at the CU School of Medicine.

In fact, it was by chance that after the patient's negative FISH, Hirsch and colleagues chose to look deeper. Besides using FISH to stain sections

of chromosomes with the EML4-ALK fusion gene, the team used immunohistochemistry to look for the protein products of this fusion gene – not the faulty plans but the faulty results. Sure enough, in this case, the patient had the EML4-ALK fusion protein but apparently without the typical EML4-ALK fusion gene that should code for it.

The team looked deeper, using next-gen sequencing to discover what, exactly, was going on in the short arm of chromosome number 2, which harbors the EML4-ALK fusion gene. What they found looked less like a pair of clean breaks that reattached in the wrong places – say, like a snapped radius and ulna that found the wrong reattachments to make a rulna and an ulnius – but more like shattered fragments with genetic shards embedded in and around the primary sections.

"We think these genetic shards made the resulting gene look different enough from the typical EML4-ALK fusion gene to avoid detection by the FDA approved FISH assay," Hirsch says.

Within two weeks of starting crizotinib, the patient reported improved pain symptoms and energy. Four months after starting the drug, a PET scan, which shows the sugar signatures of rapidly developing cancer cells, was negative. A chest CT scan showed the primary tumor had shrunk by 75 percent.

"Certainly FISH is a valuable assay to check for ALK-positive lung cancer," Hirsch says. "But we hope this work demonstrates the need to further refine this test, to ensure that all the patients who could benefit from crizotinib in fact receive the drug."

Together with CU Cancer Center colleagues including Drs. Doebele, Garcia, Aisner and Camidge, Hirsch is participating in a larger study comparing different assays for ALK testing to determine which assay or combination of assays identifies the most patients likely to benefit from

crizotinib.

Provided by University of Colorado Denver