'Smart drug' targets new mutation, dramatically shrinks aggressive sarcoma and lung cancer

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A new oral drug caused dramatic shrinkage of a patient's rare, aggressive form of soft-tissue cancer that was driven by an abnormally activated protein, physician-scientists from Dana-Farber Cancer Institute report in the Oct. 28 issue of the *New England Journal of Medicine*.

A second patient who had a similar tumor that was not fueled by the mutant protein, called ALK (named for the first disease in which it was found, anaplastic lymphoma kinase), failed to respond to the drug, said the researchers, confirming the inhibitor's specificity for the abnormal protein. The findings also highlight the value of "personalized medicine" gene-testing strategies to predict the best drug treatment for an individual's particular, genetically defined cancer.

The patient described in the NEJM Brief Report is a 44-year-old man diagnosed in 2007 with inflammatory myofibroblastic tumor (IMT), a type of sarcoma that typically develops in the chest or abdomen in children and young adults.

In approximately half the cases of IMT, ALK is fused to a different protein in the patients' cancer cells, spurring cancer development. The patient had been treated with standard chemotherapy drugs followed by the targeted compound Gleevec, but the cancer returned in the form of multiple tumors.

James Butrynski, MD and Geoffrey Shapiro, MD, PhD, Dana-Farber oncologists and the first and senior authors of the report, respectively, offered the patient participation in a Phase 1 trial of an experimental drug, crizotinib, which blocks ALK activity, as well as that of another oncogene, MET, that is abnormally activated in a number of cancers.

Crizotinib treatment shrank the tumors by more than 50 percent – technically called a "partial response." After several months of crizotinib, in December 2008, some of the tumors became resistant to the drug and started growing again. These tumors, as well as tumors still responsive to crizotinib, were removed surgically. Crizotinib was resumed after the surgery, and the patient remains without evidence of disease as of September 2010, according to the investigators.

The activity of crizotinib goes beyond this rare sarcoma. The current report accompanies a paper in the same journal describing striking activity of crizotinib in a group of patients with non-small cell lung cancers (NSCLC) containing the abnormal ALK protein. Researchers from Massachusetts General Hospital, Dana-Farber/Brigham and Women's Cancer Center, and other hospitals gave crizotinib to 82 patients after standard drugs failed to halt the tumors' growth. As part of the personalized medicine effort ongoing in the Dana-Farber/Brigham and Women's Cancer Center Thoracic Oncology Program, patients with abnormal ALK were identified for the trial, underscoring the importance of tumor profiling to match drug with patient.

Results showed that 47 patients had tumor shrinkage (complete disappearance in one patient) and the cancer stopped growing in 27 patients. The ALK rearrangements are found in a small subset, about 5 percent, of patients with NSCLC, but scientists are searching for other cancers that may also be susceptible to the ALK inhibitor.

Shapiro noted that even highly successful targeted drugs like crizotinib

are vulnerable to tumors' developing resistance against them. In fact, the IMT patient's tumors that developed resistance to crizotinib and were removed surgically have been studied by one of the reports co-authors, Pasi Janne, MD, PhD, also of Dana-Farber. In a paper appearing simultaneously in Cancer Research, Janne and his colleagues have identified a secondary mutation in ALK in the patient's tumor that conferred resistance to crizotinib. Furthermore, in work recently published by Janne, Shapiro and their Dana-Farber colleague, Kwok-Kin Wong, MD, PhD, the abnormal ALK proteins, including the protein with the secondary mutation that was resistant to crizotinib, were found to depend on a cellular chaperone, called Hsp90, for their stability. Inhibitors of Hsp90 are currently under clinical evaluation and have been shown to cause destruction of the aberrant ALK proteins.

Crizotinib is one of many targeted agents currently being evaluated by the Early Drug Development Center within the Experimental Therapeutics Program at Dana-Farber, with the aim of translating the best science into effective new therapies for patients with many forms of cancer that can be defined by sophisticated new molecular profiling techniques.

Provided by Dana-Farber Cancer Institute