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Novel compound shows promise as potential treatment for acute myeloid leukemia

Published on March 21, 2016 at 5:28 AM

A novel compound has shown promise in preclinical studies as a treatment for acute myeloid leukemia, more than doubling median days of survival even in a drug-resistant form of the disease.

Researchers at UNC Lineberger Comprehensive Cancer Center, UNC Eshelman School of Pharmacy, the Aflac Cancer & Blood Disorders Center in Atlanta, Emory University School of Medicine, and at other institutions report that MRX-2843 blocked the growth of acute myeloid leukemia cells, led to a significant level of cancer cell death and more than doubled the median days of survival in laboratory models with a drug-resistant form of the disease.

The researchers say the findings, published March 17 in the journal JCI Insight, could pave the way for human clinical trials.

"Our data indicate that this could be a superior drug for certain resistant forms of acute myeloid leukemia; however, it has to be tested in clinical trials," said Shelton Earp, MD, director of UNC Cancer Care and Lineberger Professor of Cancer Research. "We know that leukemia can develop resistance to drugs similar to ours. The questions is: Would this new UNC inhibitor give patients with resistant acute myeloid leukemia longer survival? This is a particularly salient question for older AML patients who can't tolerate high doses of chemotherapy and bone marrow transplant."

MRX-2843 was designed to specifically target two cell signaling proteins called tyrosine kinases that help drive abnormal cell growth in acute myeloid leukemia, non-small cell lung cancer, melanoma and glioblastoma.

The researchers had set out to create a compound that would block MERTK, a protein the researchers found to be over-expressed in acute myeloid leukemia cells. But they later determined that the compound could also block the FLT3 protein. FLT3 is mutated in 20 to 30 percent of adults, and in 10 to 15 percent of children, with acute myeloid leukemia, and is associated with worse outcomes in patients.

The compound was developed in the UNC Center for Integrative Chemical Biology and Drug Discovery, led by Stephen Frye, PhD, a UNC Lineberger member and the Fred Eshelman Distinguished Professor in the UNC Eshelman School of Pharmacy, with funding from the NCI Experimental Therapeutics program, or NCI NeXT. Frye's group made more than 1,500 compounds targeting MERTK.

"We examined the structure of a small molecule bound at the active site of the MERTK tyrosine kinase enzyme, and then we designed compounds to be more potent or selective," Frye said. "Research faculty Xiaodong Wang and Dmitri Kireev, multiple chemists and postdoctoral fellows in my lab contributed to this discovery."

The MERTK protein itself was originally discovered by Doug Graham, MD, PhD, when he was a graduate and medical student in the Earp lab at UNC Lineberger. Graham is now director of the Aflac Cancer & Blood Disorders Center at Children's Healthcare of Atlanta and chief of the Emory University School of Medicine Pediatric Hematology/Oncology/BMT division. After graduating from UNC, he continued researching MERTK in his lab at the Children's Hospital of Colorado and Children's Healthcare of Atlanta.

"Our research has shown that when the MERTK protein in a cell is 'turned on,' it can give a cancer cell a survival advantage and often make the cancer cell less responsive to traditional chemotherapy drugs," Graham said. "We have been working as a team across multiple labs to develop drugs that effectively 'turn off' the MERTK protein. The MRX-2843 compound is effective at targeting cancer cells with activated MERTK. With the FDA's IND approval to start a first-in-human clinical trial, we hope to bring this drug to adults battling these specific cancers, and ultimately if successful in adults, to the pediatric population."

In tests using multiple preclinical models, researchers demonstrated that MRX-2843 blocked the growth of acute myeloid leukemia cells, and led to a significant level of cancer cell death. They also determined that giving the compound orally once a day to mice with human AML tissue increased the mice's survival two to three times.

The drug also remained effective against acute myeloid leukemia models that developed resistance to another potential drug. In mice with one of two additional FLT3 mutations that drive drug resistance, treatment with MRX-2843 increased survival from 35.5 to 94 days, while another drug in development for acute myeloid leukemia and

mutated FLT3 increased survival from 36 to 45 days.

"We know that mutations arise where other compounds bind in the active site of FLT3 so that they will no longer bind," Frye said. "Data from this study show that our compound is still potent against these resistant mutants because ours has a different binding mode."

Source:
University of North Carolina Health Care System