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Kidney cancer drug attacks a major type of acute myeloid leukemia

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A drug used to treat kidney cancer also targets a genetic mutation active in about one third of patients with acute myeloid leukemia (AML), the most common and lethal form of adult leukemia, researchers at The University of Texas M. D. Anderson Cancer Center report in the Jan. 29 edition of the Journal of the National Cancer Institute.

In a Phase I clinical trial, the drug sorafenib reduced the median percentage of leukemia cells circulating in the blood from 81 percent to 7.5 percent and in the bone marrow from 75.5 percent to 34 percent among AML patients whose leukemia includes the FLT3-ITD mutation. Two patients had circulating leukemia cells, or blasts, drop to zero.

"AML patients with this mutation have a particularly poor prognosis, so this highly targeted drug appears to be a significant step forward in leukemia therapy," says senior author Michael Andreeff, M.D., Ph.D., professor in M. D. Anderson's Department of Stem Cell Transplantation and Cellular Therapy and Department of Leukemia.

The JNCI paper reports the drug's effect in lab experiments, a mouse model of the disease, and in a Phase I study of 16 patients with relapsed or resistant AML known to have the FLT3-ITD mutation.

There have been no major side effects in the clinical trial to date, so no maximum tolerated dose has been reached, Andreeff notes. The drug has little effect on cells with normal versions of the gene and does not interfere with normal blood cell formation.

A Phase I/Phase II clinical trial for AML is open at M. D. Anderson that combines sorafenib with the standard of care chemotherapy combination for AML, idarubicin and cytosine arabinoside. Presently, the trial is open for relapsed patients and those newly diagnosed with high-risk disease, says study co-author Jorge Cortes, M.D., professor in M. D. Anderson's Department of Leukemia. As safety and dose escalation research progress, sorafenib will be made available to other patients and assume a role in frontline therapy.

About 14,000 new cases of AML are diagnosed annually in the United States and the disease kills about 9,000 people each year. AML is characterized by swift proliferation of immature white blood cells in the blood and bone marrow that crowds out normal cells, leaving patients exposed to infection, severe anemia, and bleeding.

While major progress has been made treating some forms of leukemia and lymphoma, acute myeloid leukemia has seen less improvement in recent years. Andreeff says that's because AML exploits multiple molecular pathways and that these pathways differ from one type of AML to the next.

Andreeff and colleagues have shown that molecular pathways subverted and used by AML collude with each other, so when one pathway is blocked, the others redouble their efforts to fuel the disease.

"Here we have a great response against an important mutation, but sorafenib alone will not cure patients," Andreeff notes. Combination therapy will be required. Andreeff and colleagues are planning to examine other sorafenib combinations against FLT3-mutant disease.

After in vitro tests showed that sorafenib inhibited the growth of FLT3 mutant leukemia cell colonies, the research team tested the medication in a mouse model of the disease. Sorafenib-treated mice had a median

survival of 36.5 days compared with 20.5 days in untreated mice. Bioluminescence imaging showed widespread cancer growth in untreated mice and barely detectable disease in those that had received the drug.

Sorafenib, known commercially as Nexavar® and co-developed by Bayer AG and Onyx Pharmaceuticals, already is approved for advanced renal cell carcinoma and inoperable liver cancer by the U.S. Food and Drug Administration. It is being tested against other solid tumors.

The drug targets both tumor cell growth and angiogenesis - new blood vessels woven by cancer to sustain itself - by targeting two classes of kinases, which are enzymes that affect proteins by attaching phosphate groups to them.

Sorafenib's antileukemia effects appear to be superior to early results of new therapies under development that more narrowly target the FLT3 gene. Andreeff says the drug's ability to hit multiple kinases probably accounts for this, but the exact molecular mechanisms involved require further study.

Source: University of Texas M. D. Anderson Cancer Center