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Study identifies potential treatment for lethal childhood leukemia

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Columbia University Medical Center (CUMC) scientists have demonstrated that two related enzymes — phosphoinositide-3 kinase (PI3K) gamma and delta — play a key role in the development of T-cell acute lymphoblastic leukemia (T-ALL), a highly aggressive childhood leukemia that is difficult to treat. The study also showed that a dual PI3K gamma/delta inhibitor can significantly prolong survival in a mouse model of the disease. Further, the dual inhibitor was shown to prevent proliferation and to reduce the survival rate of human T-ALL cells in laboratory cultures, setting the stage for clinical trials. The study appears today in the online edition of *Cancer Cell*.

"Clearly, we have a drug that is extremely effective against this type of cancer in mice," said study leader Thomas Diacovo, MD, associate professor of pediatrics and pathology and cell biology at CUMC. "If this treatment strategy can safely and selectively target the activity of these enzymes in T-ALL tumors, we might be able to reduce the need for conventional chemotherapies that more broadly affect proliferating cells, including those in healthy tissues. This would be a major advancement in helping to reduce drug toxicities in young patients."

The dual inhibitor was developed by Gilead Sciences.

T-ALL is a cancer that arises during the development of T-cells, a type of white blood cell. The abnormal T cells multiply rapidly, invading and impairing the function of organs critical for sustaining life. T-ALL typically begins in childhood but can also appear later in life. The disease

is caused by mutations in DNA, which permit the cancer cell to continue growing and dividing, when a healthy cell would normally die. Left untreated, T-ALL is invariably fatal. It is highly resistant to chemotherapy, compared with other forms of leukemia. The relapse rate is about 25 percent in children and 50 percent in adults.

In studies of autoimmune disease done some years ago, Dr. Diacovo and his team found that inhibition of both PI3K gamma and delta not only reduced inflammation but also caused developing T cells to die at an accelerated rate. "This led us to ask in what disease states it would be advantageous to kill off aberrant T-cells," he said. "One of the first diseases that came to mind was T-ALL."

The current study was designed to take a closer look at the role of these enzymes in T-ALL and to see whether an experimental PI3K inhibitor called CAL-130 might affect disease progression.

In the first part of the study, using a mouse model of the disease, Dr. Diacovo and his team, led by Dr. Subramaniam, confirmed that both PI3K gamma and delta are essential for the development of T-ALL and the survival of leukemic (abnormal) cells. The researchers also demonstrated that administration of CAL-130 significantly lowered the number of leukemic T-cells in animals' general circulation. "The level of circulating leukemia cells dropped very rapidly, from an average of 100 million per ml to less than 1 million per ml within 24 to 48 hours," Dr. Diacovo said. "The counts remained low after just 7 days of therapy." The median survival time for mice treated with CAL-130 was 45 days, compared with 7.5 days for untreated controls.

The researchers also evaluated the effects of CAL-130 on blood samples taken from patients with T-ALL. The drug prevented proliferation of leukemic cells and promoted a self-destruct mechanism called apoptosis.

"We've made great strides in treating childhood acute lymphoblastic leukemias over the years, with an overall cure rate approaching 90 percent," said Dr. Diacovo. "Unfortunately, this is not the case for T-All. In addition, conventional treatment— chemotherapy — is quite toxic. This is a particular problem for children, who have an entire lifetime ahead of them and are likely to develop secondary cancers and other complications as a result of their treatment. So anything we can do to lessen associated toxicities would be a welcome advancement in the field."

Stephen G. Emerson, MD, PhD, director of the Herbert Irving Comprehensive Cancer Center at NewYork-Presbyterian Hospital/Columbia University Medical Center, said, "Even in difficult-to-treat cancers—such as this form of childhood leukemia—our researchers are continually searching for less toxic ways to treat our patients, in an effort to improve their quality of life and to enable them to lead long, healthy lives. This is one of the key approaches to the future of cancer care."

Clinical trials of a dual PI3K gamma/delta inhibitor in patients with leukemia are in the planning stages, said Dr. Diacovo.

More information: The paper is entitled, "Targeting non-classical oncogenes for therapy in T-ALL."

Provided by Columbia University Medical Center