Childhood leukemia study reveals disease subtypes, new treatment option

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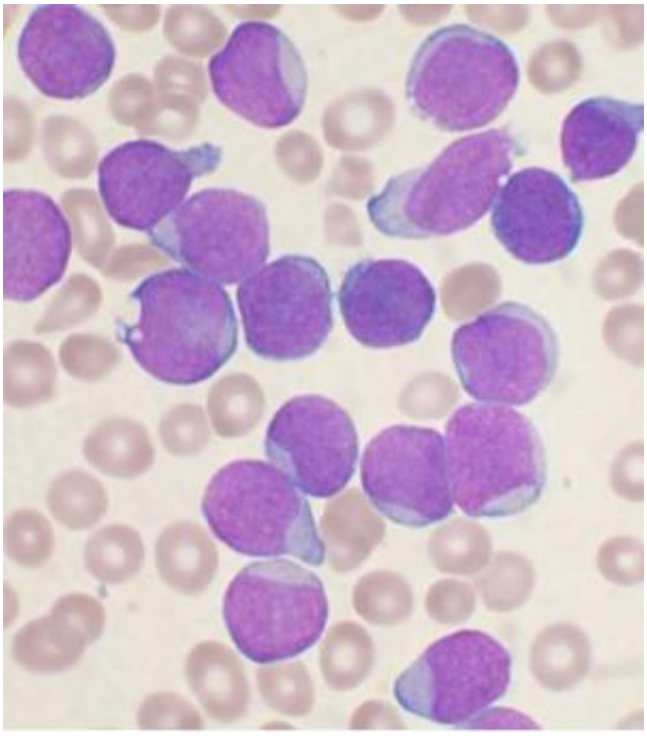

A Wright's stained bone marrow aspirate smear from a patient with precursor B-cell acute lymphoblastic leukemia. Credit: VashiDonsk/Wikipedia

A new study of acute lymphoblastic leukemia (ALL), a blood cancer that primarily affects young children, has revealed that the disease has two distinct subtypes, and provides preliminary evidence that about 13 percent of ALL cases may be successfully treated with targeted drugs that have proved highly effective in the treatment of lymphomas in

adults.

Usually emerging in children between 2 and 5 years of age, ALL occurs when the proliferation of white blood cells known as lymphocytes spirals out of control. The current standard of care for ALL employs high doses of chemotherapy that usually cure the disease, but may also have serious long-term effects on brain development, bone growth and fertility, so there is an unmet need for better therapies.

In addition to discovering the two ALL subtypes, the researchers, led by scientists from UC San Francisco (UCSF) and Oregon Health & Science University (OHSU), developed a simple lab test that determines whether patients fall into the less-common subtype that may respond to targeted therapy. One author of the new study, affiliated with MD Anderson Cancer Center in Texas, is already using this new test to recruit patients for a Phase 1 clinical trial evaluating the use of targeted drugs for ALL.

The research and resulting clinical trial exemplify one of the main goals of precision medicine—improving health by identifying subtypes of disease that can be specifically targeted with drugs or other therapies.

"We hope patients in this newly identified subset can be treated with these targeted drugs, which have worked very well in patients with lymphoma and which are powerfully effective in the mouse experiments we have conducted on ALL," said co-senior author Markus Müschen, MD, PhD, professor of laboratory medicine at UCSF and a member of the UCSF Helen Diller Family Comprehensive Cancer Center (HDFCCC). "These drugs have essentially no side-effects and relatively few effects on quality of life."

Müschen said the new work, reported online in *Cancer Cell* on March 9, 2015, grew out of a line of research on new treatments for lymphoma, which usually affects adults. That work, which culminated in papers

published in The *New England Journal of Medicine* in 2013, showed that various forms of lymphoma respond well to treatment with ibrutinib (trade name Imbruvica) or idelalisib (trade name Zydelig), two drugs that precisely target the B-cell antigen receptor, a protein found in white blood cells.

"Because B-cells are also involved in ALL, we essentially recapitulated these studies, starting out with the basic science by studying genetic components of the B-cell antigen receptor in mice," said Müschen. "We were surprised to find that, depending on the initial cancer-causing mutation, B-cell antigen receptor signaling is sometimes present in ALL, which suggested that ALL might also respond to the drugs that had been used in lymphoma."

Led by first authors Huimin Geng, PhD, assistant professor of laboratory medicine at UCSF, postdoctoral fellow Christian Hurtz, PhD, also of UCSF, and Kyle Lenz, research assistant at OHSU, the group found that cells that exhibit B-cell antigen receptor signaling also express very high levels of a protein known as BCL-6. Then, using BCL-6 as a biomarker, the team used several methods to inhibit B-cell antigen receptor signaling, including treating cells with targeted compounds used in human lymphoma. All of these approaches successfully and selectively killed ALL cells, and similar results were seen in a mouse model of ALL.

The research group next studied 830 patients enrolled in four ongoing ALL clinical trials, in part to assess whether testing for BCL-6 expression would be a practical biomarker in the clinic to identify candidates for targeted therapy.

Virtually all of the bone marrow slices from 112 patients (13.5 percent) with active B-cell antigen receptor signaling showed "beautiful staining" of BCL-6 expression, Müschen said (in two patients only weak staining

was seen). On the other hand, no BCL-6 staining was observed in patients lacking B-cell antigen receptor signaling. These results suggest that the BCL-6 test may have sufficient sensitivity and specificity to select patients for targeted therapy.

"Children are given high doses of chemotherapy for ALL because they are considered more resilient than adults, but there are long-term consequences that may not be obvious in childhood," Müschen said. "Our idea is that by adding these new drugs we can reduce the amount of conventional chemotherapy or even replace it. In our experiments with mice, both combination therapy with low-dose chemotherapy and single-agent targeted therapy each worked very well. The new clinical trial using the BCL-6 biomarker should begin to bring us the answers."

Provided by University of California, San Francisco