Medical Xpress

Clinical trials show promise in leukemia

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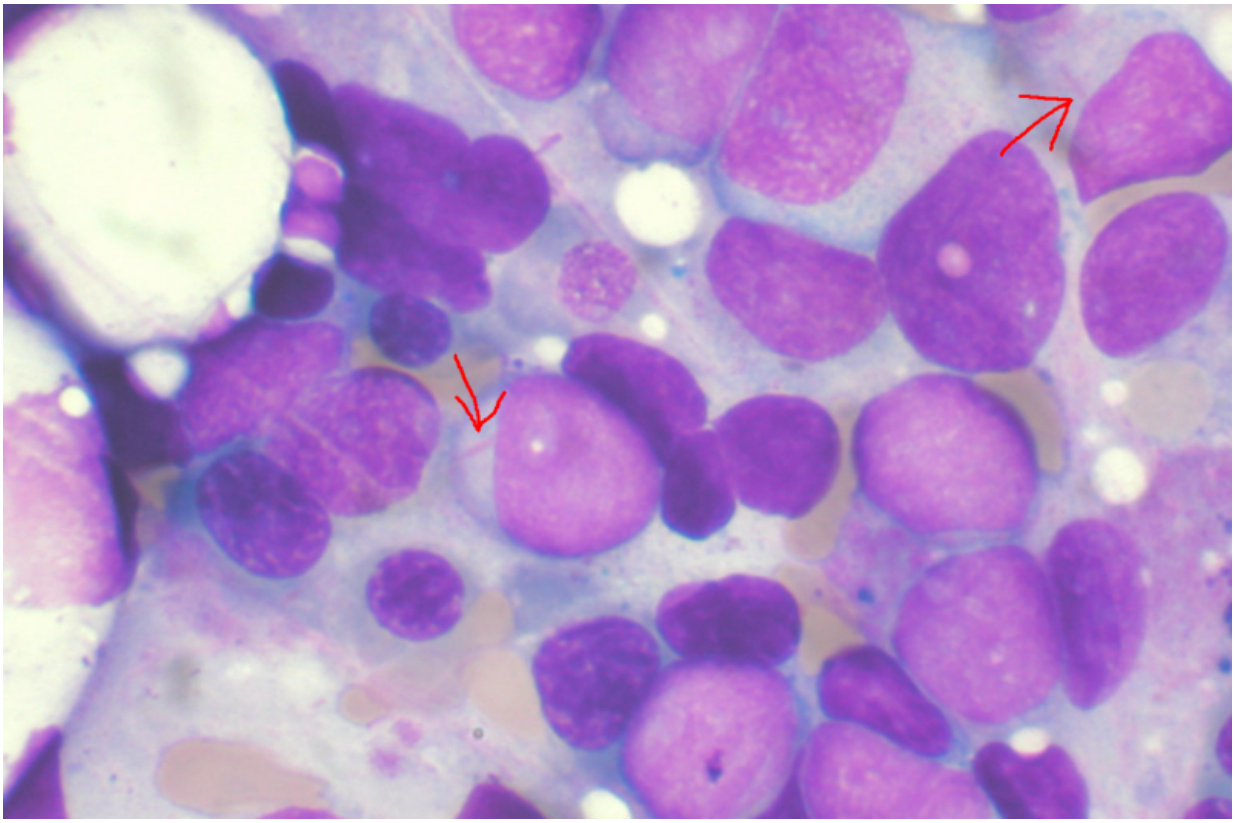

Bone marrow aspirate showing acute myeloid leukemia. Several blasts have Auer rods. Credit: Wikipedia

Two drugs that target different mutations showed encouraging results in treating leukemia, according to recent clinical trials published in the *New England Journal of Medicine* (*NEJM*) and *The Lancet Oncology*.

Jessica Altman, MD, '07 GME, associate professor of Medicine in the Division of Hematology and Oncology and director of the Acute Leukemia Program at the Robert H. Lurie Comprehensive Cancer Center of Northwestern University, was a co-author of both studies.

Acute myeloid leukemia (AML), the most common type of adult leukemia, is a cancer of the blood-forming cells of the bone marrow. Currently, most patients with AML are treated with standard chemotherapy. But recent scientific advances have revealed that there are many forms of the disease, each with different specific genetic changes that may affect cancer growth and treatment.

As such, there has been increasing research into the development of new targeted therapies that inhibit specific mutations found in AML. These therapies are especially important for patients who are unable to tolerate chemotherapy, or whose cancer has relapsed after standard treatment.

Targeting the IDH1 Enzyme

Mutations in the gene for an enzyme called isocitrate dehydrogenases 1 (IDH1) are found in roughly 5 to 10 percent of adults with AML, and these changes are thought to be a driver of the disease.

In a recent phase I clinical trial, a team of investigators evaluated the safety and efficacy of an oral medication that specifically inhibits mutated IDH1, called ivosidenib. The findings were published in the *NEJM*.

The trial included 258 patients with AML who were positive for the IDH1 mutation; 179 of them had relapsed or refractory AML.

The investigators found that ivosidenib, delivered at a dose of 500 mg daily, showed favorable results among patients with advanced relapsed

or refractory AML and was well tolerated with a low rate of serious adverse events. The complete remission rate (including patients who did not have a full blood count recovery) was around 30 percent.

"We saw an encouraging rate of response compared to standard chemotherapy in this patient population, with relatively few toxicities," Altman said.

Further investigations of ivosidenib are now ongoing. According to Altman, other inhibitors of IDH1 are also currently in development, and a drug called enasidenib that inhibits a related enzyme, IDH2, was approved by the Food and Drug Administration last year for adults with IDH2-mutated relapsed or refractory AML.

The *NEJM* study, a multi-center trial, was supported by Agios Pharmaceuticals, which owns ivosidenib.

Targeting the FLT3 Protein

About 30 percent of patients with AML have mutations in a different driver gene, called FLT3. The mutation is associated with particularly poor outcomes, especially among older patients and in those with a certain type of the mutation called FLT3-ITD.

In a phase II trial published in *The Lancet Oncology*, investigators assessed the efficacy and safety of quizartinib, a drug that inhibits FLT3, among patients with refractory or relapsed AML.

The study, which enrolled 333 patients, included two cohorts: one of patients 60 years or older with relapsed or refractory AML within one year of first-line therapy, and a second of patients 18 years or older with relapsed or refractory AML following chemotherapy or stem cell transplantation.

The trial found that quizartinib was generally well-tolerated and had a high rate of response, particularly among patients who were FLT3-ITD positive. The composite complete remission rate was around 50 percent.

According to the authors, the findings confirm that targeting the FLT3 mutation with a selective inhibitor is a promising strategy for improving outcomes in this patient population.

Randomized clinical trials evaluating quizartinib in other settings are ongoing, and other FLT3 inhibitors are also currently in development, Altman notes. There is also an already approved drug, called midostaurin, that has been shown to improve survival for patients with FLT3-mutated AML when combined with chemotherapy, compared to chemotherapy alone.

"Thus, it is possible we may be in a situation where there are choices of FLT3 inhibitors for patients with FLT3-mutated AML," Altman said.

More information: Courtney D. DiNardo et al. Durable Remissions with Ivosidenib in IDH1-Mutated Relapsed or Refractory AML, *New England Journal of Medicine* (2018). DOI: 10.1056/NEJMoa1716984

Jorge Cortes et al. Quizartinib, an FLT3 inhibitor, as monotherapy in patients with relapsed or refractory acute myeloid leukaemia: an open-label, multicentre, single-arm, phase 2 trial, *The Lancet Oncology* (2018). DOI: 10.1016/S1470-2045(18)30240-7

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