Double assault on tough types of leukemias

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Investigators at Northwestern University Feinberg School of Medicine have identified two promising therapies to treat patients with acute megakaryocytic leukemia (AMKL), a rare form of leukemia where the number of cases is expected to increase with the aging population.

The disease is characterized by an overload of white blood cells that remain forever young because they can't mature into specialized cells. Published in a recent issue of the journal *Cell*, the study found that the drug with the generic name alisertib (MLN8237), induced division and growth of healthy cells to overtake the proliferation or "blasts" of immature cells.

In the study, a mouse model with this leukemia that was treated with alisertib showed a striking reduction in the number of leukemia cells, including dramatic reductions in overwhelming white cell counts and the weights of their spleens and livers, which are indications of leukemia.

Alisertib has been tested before in humans with limited success to treat other types of leukemia and lymphoma, a cancer of the immune system. However, the drug should be effective against AKML in humans because it specifically targets the enzyme Aurora A kinase, said study senior author John Crispino, the Robert I. Lurie, MD, and Lora S. Lurie Professor of Hematology/Oncology at Feinberg. In normal cell development, this enzyme enables healthy cells to proliferate correctly, but with leukemia, is also allows adolescent cells to multiply unchecked if they are in the mix.

Crispino also is a member of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University.

"Alisertib was really potent against the proliferation of cancer cells," Crispino said. "We were incredibly excited when we found that the drug we predict will reverse AMKL is already far along in clinical development. The fact that we don't have to start from scratch means we could be years closer to finding an effective therapy."

Crispino expects alisertib will be a more gentle cancer drug without the ravaging side effects of conventional chemotherapies. This is because the drug specifically targets a key enzyme, avoids healthy cells in the bone marrow and blood, and will probably be more effective at lower doses than drugs tested in previous studies.

"This study has given us a scientific rationale to take this drug to an early phase clinical trial in this very challenging form of leukemia," said Jessica Altman, M.D., assistant professor in hematology/oncology at Feinberg and an oncologist at Northwestern Memorial Hospital. Altman also is a member of the Lurie Cancer Center. Together with other leukemia specialists, she is designing a multi-center clinical trial planned to open in 2013.

Investigators also identified another attack plan for other types of leukemias. Sifting through 9,000 chemical compounds during the study, they found that dimethylfasudil boosted the number of mature bone marrow cells and shot down malignant ones.

Dimethylfasudil could be useful against AMKL and tolerated better by patients, Crispino says. However, he adds that alisertib is moving forward now because there is urgent need and the drug is available. Meanwhile, Crispino's team and other scientists at Northwestern's Center for Molecular Innovation and Drug Discovery are developing the

compound dimethylfasudil into an acceptable anticancer drug for clinical trials, which may take two to three years.

Investigators believe dimethylfasudil may be valuable to fight other types of leukemias because it has broad action against other enzymes that let cancer cells reproduce.

Provided by Northwestern University