Drug makes leukemia more vulnerable to chemo

20 March 2012, By Julia Evangelou Strait

(Medical Xpress) -- Doctors at Washington University School of Medicine in St. Louis have shown that a new drug makes chemotherapy more effective in treating acute myeloid leukemia, a cancer of the white blood cells. Instead of attacking these cells directly, the drug helps drive them out of the bone marrow and into the bloodstream, where they are more vulnerable to chemotherapy.

"We're usually very good at clearing these leukemia cells from the blood," says Geoffrey L. Uy, MD, assistant professor of medicine and co-first author on the study published in the journal Blood. "But it's much harder to clear these cancerous cells from the bone marrow."

This combined phase 1 and 2 clinical trial included 52 patients with acute myeloid leukemia (AML) who had relapsed or whose AML was resistant to the standard chemotherapy regimen. In the phase 2 portion with 46 patients, all received the investigational drug, and 46 percent achieved complete remission, meaning no evidence of cancer could be found in the blood or bone marrow after treatment.

"In general, we see complete remission rates between 20 and 30 percent," says Uy, who treats patients at the Alivn J. Siteman Cancer Center at Washington University School of Medicine and Barnes-Jewish Hospital. "But a lot depends on individual patient characteristics."

Indeed, recent genetic studies have shown that mutations leading to AML may differ greatly among patients. But regardless of individual mutations, all of these leukemia cells rely in some way on the protective effects of the bone marrow, according to senior author John F. DiPersio, MD, PhD, the Virginia E. and Sam J. Golman Professor of Medicine.

"With DNA sequencing identifying so many mutations that are unique to one patient, it may be very hard to find therapies that work directly on the cancer," says DiPersio, who also treats patients at the Siteman Cancer Center. "Instead, we are targeting a common pathway that all leukemic cells are addicted to - in this case, the relatively normal environment of the bone marrow."
DiPersio calls the results of this study encouraging and worthy of additional exploration.

"If these results are repeated in a larger study, it would be transformative," he says. "It would change the standard way we treat these patients - we would use this approach with everybody. In addition, the approach of targeting the tumor microenvironment could also be exploited for the treatment of other hematologic and solid tumor malignancies."

Bone marrow protects leukemia cells by inhibiting the cell-suicide response that might otherwise lead AML cells to self-destruct. Although leukemia cells in the bone marrow do not rapidly divide, their stability makes them very resistant to treatment. And while chemotherapy can clear the bloodstream of leukemia for a period of time, these "protected" cells in the bone marrow may cause the cancer to return.

The drug used in this study, called plerixafor, blocks the leukemia cells from attaching to the bone marrow. Released from their protective environment into the bloodstream, the cells lose the bone marrow's survival signals and begin to divide. Rapidly dividing cells are more sensitive to chemotherapy.

Plerixafor received approval from the U.S. Food and Drug Administration in 2008 for use prior to a stem cell transplant to treat patients with two other types of blood cancers: multiple myeloma and non-Hodgkin's lymphoma. In these diseases, plerixafor is used to dislodge normal stem cells from the bone marrow. Once in the bloodstream, those stem cells can then be collected for a transplant. Returning

the patient's own stem cells after aggressive chemotherapy is a standard treatment for these two cancers.

"We helped in plerixafor's development for stem cell mobilization," DiPersio says. "So we thought if it makes normal stem cells leave the bone marrow to circulate, maybe it would do the same with leukemic cells."

In 2009, DiPersio and his colleagues showed that this concept worked in mice with a form of AML. Mice treated with plerixafor plus chemotherapy had improved survival over mice treated with chemotherapy alone. But DiPersio says plerixafor targets only one of many tethers anchoring these cells to the bone marrow.

"This is one of the first clinical examples of targeting the environment that leukemia cells live in," DiPersio says. "In the future, we may find other drugs, or combinations of drugs, that work better. There are now a number of groups around the world putting together similar approaches."

More information: Uy GL, Rettig MP, Motabi IH, McFarland K, Trinkaus KM, Hladnik LM, Kulkarni S, Abboud CN, Cashen AF, Stockerl-Goldstein KE, Vij R, Westervelt P, DiPersio JF. A phase 1/2 study of chemosensitization with the CXCR4 antagonist plerixafor in relapsed or refractory acute myeloid leukemia. *Blood*. February 2012.

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Provided by Washington University School of Medicine in St. Louis