Study reveals need for personalized approach in treatment of AML

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A new discovery in mice by researchers at Wake Forest Baptist Medical Center may one day allow doctors to spare some patients with acute myeloid leukemia (AML) from toxic treatments, while also opening the door for new therapeutic research.

AML, the most common form of acute leukemia seen in adults, is an aggressive form of cancer that primarily affects the elderly. Despite years of research, outcomes for most patients remain poor, particularly for one subset of patients with a specific mutation of the FLT3 receptor.

At a microscopic level, each cell's surface is covered in proteins that allow for signals on the outside of a cell to "turn on" various activities inside that cell. FLT3 is one of those receptor proteins. Mutations of the FLT3 receptor are among the most common mutations seen in the disease – affecting about 20 to 30 percent of AML patients – and have been associated with worse prognosis.

A new study, published recently in the journal *Experimental Hematology*, reveals that one particular mutation of the FLT3 receptor, called internal tandem duplication (ITD), alters the patient's responsiveness to standard therapy.

"This research uses a mouse model to define the changes in chemotherapy response that the presence of the FLT3-ITD causes," said Timothy S. Pardee, M.D., Ph.D., an assistant professor of hematology and oncology and lead author of the study. "While its affect on prognosis

has been well documented, its affect on therapy response has been poorly understood."

Pardee and colleagues used mice that had leukemia, either with or without the FLT3-ITD, to examine the effects of the mutation on responsiveness to two drugs used in combination as standard chemotherapy treatment for AML patients: cytarabine and doxorubicin. Both drugs work by altering the DNA of cells in different ways, causing them to essentially commit suicide.

The researchers found that the presence of the FLT3-ITD mutation makes cells resistant to doxorubicin, but makes them extra sensitive to cytarabine, when the drugs are administered separately. More importantly, the mutation causes the cells to be resistant overall to the combination of the two drugs, the most common clinical application.

When the mutation occurs, it is a cancer-initiating event. The receptor is no longer able to turn itself off, so it continuously signals the cells to grow and repair damage, such as the damage intentionally caused by doxorubicin.

"The mice who had this mutation seemed to be able to repair certain kinds of DNA damage, specifically, the double strand DNA breaks that the doxorubicin creates," Pardee said. "The FLT3-ITD mutation is telling the cell to repair itself at a pace that keeps up with the amount of damage the drug is designed to cause. If you have a cancer cell that you're trying to kill by doing a certain type of damage and that cell is better at repairing that kind of damage, you have to do more damage to get the cell to die. The mice that were treated with just doxorubicin died at the same rate as those that received no treatment at all."

And, while the FLT3-ITD mutation seems to make cells more sensitive to the impact of cytarabine when exposed to just the one drug, the

mutation lessens the impact of the combination of the two drugs together.

"It's almost like the doxorubicin is protecting the cancer cells somewhat from the impact of the cytarabine, which is trying to kill the cell," Pardee said. "When this mutation is present, there is no benefit to adding the doxorubicin. The amount of leukemia does not lessen with the use of it."

Doxorubicin falls into a class of extremely toxic drugs known as anthracyclines. As with other chemotherapy agents, they are known to cause hair loss. However, they are also known to suppress normal cells in the bone marrow and to cause cardiac toxicity. Treatment with drugs of this class can directly injure the heart muscle and sometimes even cause heart failure, Pardee explained.

"Virtually every AML patient in America and Europe who can handle this combination of drugs will receive this standard treatment under current practice guidelines," Pardee said. "More studies are needed to determine the applicability of these findings in humans, but this study shows, in an animal model, that those with the FLT3-ITD mutation are deriving no benefit from the addition of doxorubicin.

"We're hopeful that in the future, these findings will lead to more personalized patient care," he said. "The 'one-size-fits-all' approach to treating AML needs to be re-examined."

In addition to investigating ways to personalize approaches in treatment, Pardee said that future research may focus on developing drugs that can be combined with cytarabine in patients with this mutation and be effective, perhaps by inhibiting the FLT3 receptor or working in ways other than creating double strand DNA breaks.