

Novel drug preventing protein recycling shows potential for treating leukemia

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Researchers from the Children's Cancer Hospital at The University of Texas M. D. Anderson Cancer Center have found that a novel targeted therapy effectively treats acute leukemia in animal models by preventing cancer cells from being purged of damaged proteins.

In the March online issue of the journal *Blood*, investigators reported that the new proteasome inhibitor, NPI-0052, not only successfully kills leukemia cells, but also shows greater efficacy than its predecessor bortezomib when combined with other agents in animal models.

According to researchers, proteasomes clean out mutated or damaged proteins within cells, which promotes cell growth and allows cancer cells to rapidly reproduce. Proteasome inhibitors block this process, resulting in apoptosis, or cell death, of the malignant cells.

Bortezomib is the first and only FDA-approved proteasome inhibitor. Although it is effective for treating multiple myeloma and mantle cell lymphoma, it was proven to be ineffective as a single agent against leukemia in clinical trials. NPI-0052 varies from bortezomib in ways that researchers at M. D. Anderson hope will make NPI-0052 effective in a human clinical trial.

"NPI-0052 targets the proteasome through different intermediaries and is more potent than bortezomib in leukemia cells," says senior author Joya Chandra, Ph.D., assistant professor of pediatrics from the Children's Cancer Hospital at M. D. Anderson. "Therefore we can use less of the drug to inhibit the proteasome."

NPI-0052 inhibits the main enzymatic activity of the proteasome three times more effectively than bortezomib as a single agent. When combined with a histone deacetylase (HDAC) inhibitor, another anti-cancer agent, NPI-0052 achieves four-fold greater synergistic effects than bortezomib.

M. D. Anderson currently has a Phase I clinical trial led by principal investigator Razelle Kurzrock, M.D., to test NPI-0052 on adult patients with solid tumor malignancies and recurrent lymphoma. Chandra's group is the first group to be studying the effects of the drug in acute leukemia models.

"This drug, so far, has shown efficacy in animal models of leukemia, myeloma and colon cancer, and it has worked to kill multiple myeloma cells resistant to bortezomib," says Chandra. "As a result of our research, we're looking at the feasibility of combining NPI-0052 with HDAC inhibitors in the future to treat leukemia."

Source: University of Texas M. D. Anderson Cancer Center

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