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Combination therapy shows promise for chronic myeloid leukemia

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A study in mice combining two inhibitor drugs for treatment of chronic myeloid leukemia (CML) has revealed potential for not only stopping the disease completely, but also significantly lowering the cost for treatment. CML is a cancer of the white blood cells accounting for 20 percent of adult leukemia.

The study at The University of Texas MD Anderson Cancer Center was led by Michael Andreeff, M.D., professor, and Bing Carter, Ph.D., professor, both of the department of Leukemia. Findings were published in the Sept. 7 online issue of *Science Translational Medicine*.

Researchers combined the BCR-ABL tyrosine kinase inhibitor (TKI), with another inhibitor drug known as venetoclax, and observed encouraging response and cure rates for both the chronic phase of the disease and its fatal end-stage phase called blast crisis. BCR-ABL inhibitors are the current standard-of-care treatment allowing most patients to remain in remission, but they do not entirely eradicate the cancer cells. In some patients, the cancer returns in a form that is untreatable. Approximately 100,000 patients in the U.S. are kept on life-long TKI therapy at a cost of $100,000 annually, a treatment that is unaffordable for many patients.

"Our results demonstrate that this study in mice employing combined blockade of BCL-2 and BCR-ABL has the potential for curing CML and significantly improving outcomes for patients with blast crisis, and, as such, warrants clinical testing," said Andreeff. "This combination

strategy may also apply to other malignancies that depend on kinase signaling for progression and maintenance."

TKIs for CML are the most successful class of molecular targeted therapy of any malignant disease, but are not effective in eliminating CML stem cells. Since the persistent stem cells could allow the cancer to return and advance to the fatal blast crisis stage, patients must remain on the drugs for the rest of their lives.

"It is believed that TKIs do not eliminate residual stem cells because they are not dependent on BCR-ABL signaling," said Carter. "Hence cures of CML with TKIs are rare."

Carter has worked for several years on eliminating the residual CML stem cells, which could mean CML patients no longer would require expensive lifelong TKIs. Based on this study, combining TKIs with BCL-2 inhibitor, an agent pioneered by Andreeff's group for use in both acute and chronic myeloid leukemias, may be a solution.

"Long-term treatment with TKIs comes at a high cost, both in terms of side effects and financially," she said. "Worldwide, most CML patients cannot afford the extraordinary expenses associated with TKI-based therapy. And, unfortunately, for patients who progress to blast crisis, there are no meaningful treatments and survival is counted in weeks or months."

More information: "Combined targeting of BCL-2 and BCR-ABL tyrosine kinase eradicates chronic myeloid leukemia stem cells," *Science Translational Medicine*, stm.sciencemag.org/lookup/doi/ … scitranslmed.aag1180

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