Experimental drug combination selectively destroys lymphoma cells

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This is Steven Grant, M.D. Credit: Virginia Commonwealth University Massey Cancer Center

Laboratory experiments conducted by scientists at Virginia Commonwealth University Massey Cancer Center suggest that a novel combination of the drugs ibrutinib and bortezomib could potentially be an effective new therapy for several forms of blood cancer, including diffuse large B-cell lymphoma (DLBCL) and mantle cell lymphoma (MCL).

The study, published in the *British Journal of Hematology*, showed that the experimental drug combination killed cancer cells through a form of cell suicide known as apoptosis, but was relatively non-toxic to normal, healthy cells. Ibrutinib is a new agent that inhibits the B-cell receptor (BCR) signaling complex, which plays an important role in the survival of malignant B-cells. It has shown very promising initial results in the treatment of patients with B-cell malignancies, including chronic lymphocytic leukemia (CLL), DLBCL and MCL. The synergistic interaction of the two drugs proved lethal even to lymphoma cells that had become resistant to bortezomib, when used alone.

"Bortezomib is currently used to treat MCL and multiple myeloma, but, unfortunately, many patients develop resistance to the drug," says the study's principle investigator Steven Grant, M.D., Shirley Carter Olsson and Sture Gordon Olsson Chair in Oncology Research, associate director for translational research, program co-leader of Developmental Therapeutics and Cancer Cell Signaling research member at VCU Massey Cancer Center. "We are hopeful that this combination therapy may circumvent such resistance and eventually help fill an urgent need for more effective therapies for patients with these uncommon blood disorders."

With cultured DLBCL and MCL cells in laboratory experiments spearheaded by Girija Dasmahapatra, Ph.D., lead author of the study's manuscript and instructor in the Department of Internal Medicine at VCU School of Medicine, the scientists found that ibrutinib blocked several molecular pathways that the cancer cells use for growth and survival. When ibrutinib was combined with bortezomib, the scientists observed a high level of synergism between the two drugs that resulted in profound cell death due to DNA damage, culminating in apoptosis. The research findings suggest that the effectiveness of the combination therapy against bortezomib-resistant lymphoma cells may stem from ibrutinib's ability to block signaling pathways used by the cancer cells to

survive bortezomib exposure.

Specifically, exposure of DLBCL and MCL cells to ibrutinib blocked the cancer-promoting NF-κB, AKT and ERK1/2 signaling pathways. These signaling pathways provide cells with the ability to adapt to otherwise harmful environmental stimuli by transmitting messages from receptors located at the cell's surface to proteins within the cell that trigger a variety of biological processes. In particular, NF-κB, AKT and ERK1/2 have been shown to carry out many functions that allow cancer cells to survive and proliferate. Significantly, each of these pathways has been implicated in the development of resistance to proteasome inhibitors such as bortezomib.

"We have provided a framework for understanding how an agent like ibrutinib might be employed to enhance the activity of an established anti-cancer agent like bortezomib," says Grant. "We are currently working with representatives from the pharmaceutical industry and the National Cancer Institute to develop a new treatment strategy in which ibrutinib will be combined with proteasome inhibitors like bortezomib for the treatment of patients with lymphomas and potentially other blood cancers."

More information: onlinelibrary.wiley.com/doi/10 … 1/bjh.12206/abstract

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