Study identifies potential drug combination for mantle cell lymphoma and chronic lymphocytic leukemia

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Using the molecularly targeted drug ibrutinib (Imbruvica) together with the investigational anticancer agent ABT-199 may improve outcomes for patients with mantle cell lymphoma (MCL) and chronic lymphocytic leukemia (CLL), according to preclinical data presented at the American Association for Cancer Research special conference, Hematologic Malignancies: Translating Discoveries to Novel Therapies, held Sept. 20-23.

"Ibrutinib was recently approved by the FDA [U.S. Food and Drug Administration] for the treatment of both mantle cell lymphoma and chronic lymphocytic leukemia," said Michael J. Weber, PhD, professor of microbiology, immunology, and cancer biology at the University of Virginia School of Medicine in Charlottesville. "Unfortunately, about one-third of patients have disease that is resistant to ibrutinib, and even for those who have disease that responds, in very few cases is it a complete response. This problem of treatment resistance is one of the biggest challenges in cancer treatment at the moment.

"We took an empirical but systematic approach to identify combinations of drugs that might improve the ability of ibrutinib to kill cancer cells," continued Weber. "The combination of ibrutinib and ABT-199 was by far the most effective in our assays, and we are in the very earliest stages of planning a clinical trial to test this combination in the clinic."

In previously reported studies, Weber and colleagues found that ibrutinib and ABT-199 synergized to kill, by a process called apoptosis, MCL cell lines. In this study, they assessed the effects of exposure to the combination on blood samples from 16 patients who had MCL or CLL cells detectable in the blood. The percentage of cells undergoing apoptosis was sixfold higher in samples exposed to the combination compared with samples exposed to either drug alone: 23 percent of cells exposed to the combination underwent apoptosis compared with 3.8 and 3 percent of cells exposed to ibrutinib and ABT-199, respectively.

Further analysis showed that the combination of ibrutinib and ABT-199 worked synergistically to cause apoptosis in leukemic cells from five of nine patients with CLL. According to Weber, the variable response to this combination points to the importance of understanding how these combinations work, so that we can match the treatments with the most appropriate patients.

"Ibrutinib and ABT-199 target different pathways involved in promoting cancer cell survival and growth," said Weber. "This is very intriguing because in most instances where cancer cells are resistant to a particular molecularly targeted drug, we find that cancer cells adapt and find new ways to reactivate the pathway being targeted by the drug and that combinations of drugs targeting this pathway in different ways can improve outcomes. Here, we found that targeting a pathway outside the primary pathway was effective."

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