Researchers find dual inhibitor may be safer for CLL patients

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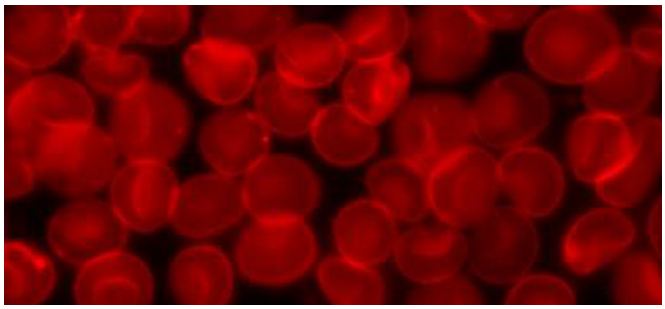

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Chronic lymphocytic leukemia (CLL) is the most common leukemia in adults. One in four new leukemia cases are CLL. Early-stage CLL patients often do not require therapy, but for those with aggressive disease or who have failed previous treatments, a targeted therapy approach may be necessary. One such targeted therapy is PI3K inhibitors, which are drugs that block a specific protein that controls cell growth.

While this type of treatment has proved beneficial for patients, it often comes with serious side effects , such as low blood count, liver damage, lung inflammation or intestinal issues. Moffitt Cancer Center researchers want to learn more about how this type of inhibitor works with the body's immune system to determine if there are ways to predict or mitigate associated adverse effects. Their findings were published in the July 14 issue of *Blood Advances*, a journal of the American Society of Hematology.

Phosphatidylinositol 3-kinase (PI3K) is one of the most important signaling pathways regulating cell growth, migration and survival. When activated, the PI3K pathway contributes to tumor growth and resistance to therapy. It is why this pathway has become a target for several new cancer drugs, including ones to treat CLL.

For this study, Moffitt investigators used mouse models to evaluate three PI3K inhibitors: two that are Food and Drug Administration approved—idelalisib and duvelisib—and one investigational drug, umbralisib.

"Toxicities for this class of PI3K inhibitors are thought to be immune-mediated, but we know little about what is going on within the immune system to cause these reactions," said Eva Sahakian, Ph.D., study author and research scientist in Moffitt's Immunology Program. "Our study sought to answer that question, looking specifically at how these drugs suppressed regulatory T cells and other immune cells."

Regulatory T cells (Tregs) are a small subset of cells that are actively involved in suppressing anti-tumor immune response through the targeting of other immune cells. They are thought to play a significant role in the progression of cancer and are generally increased in CLL patients.

The research team found that while all three PI3K inhibitors were effective in the treatment of CLL, idelalisib and duvelisib led to increased immune-mediated toxicities, as well as impaired function and a reduced number of Tregs. However, Treg volume and function were well maintained with umbralisib. The researchers believe this is because in addition to inhibiting PI3K, umbralisib is a dual inhibitor that also targets CK1?, a protein essential to regulating cell division and tumor growth.

"Our findings show the immune-mediated adverse reactions seen in CLL patients following PI3K inhibitor therapy can be counteracted with the addition of CK1? inhibition. The dual PI3K/ CK1? inhibitor umbralisib offers an improved safety profile for CLL patients," says Javier Pinilla-Ibarz, M.D., Ph.D., study author, senior member and head of the Lymphoma Section of the Malignant

Hematology Department at Moffitt.

The researchers suggest dual PI3K/CK1? inhibitor therapy could possibly be used in the treatment of other types of cancer. They would also like to investigate CK1? inhibitor therapy by itself and in combination with other therapies once an investigational drug becomes available.

More information: Kamira Maharaj et al, The dual PI3K?/CK1? inhibitor umbralisib exhibits unique immunomodulatory effects on CLL T cells, *Blood Advances* (2020). DOI: 10.1182/bloodadvances.2020001800

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