Combined therapy shows promise for chronic lymphocytic leukemia

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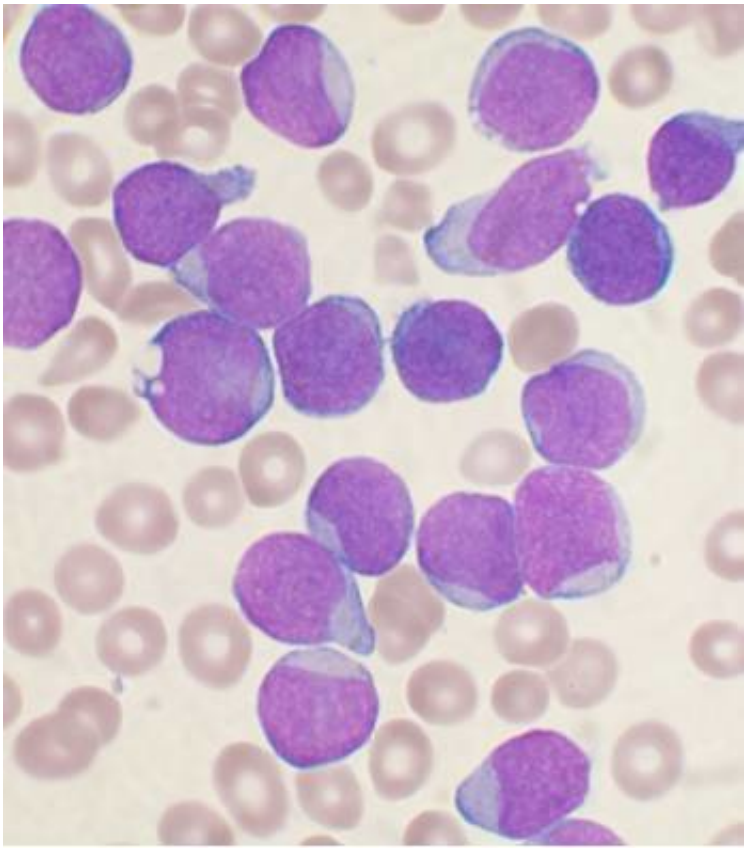

A Wright's stained bone marrow aspirate smear of patient with precursor B-cell acute lymphoblastic leukemia. Credit: VashiDonsk/Wikimedia/CC BY-SA 3.0

A combination therapy pairing a small molecule inhibitor with monoclonal antibody immunotherapy improved patient outcomes for relapsed chronic lymphocytic leukemia (CLL), according to a

Northwestern Medicine clinical trial published in *Blood*.

The findings support the practice of fixed-duration therapy for a venetoclax-based treatment in CLL, according to Shuo Ma, MD, '00 Ph.D., associate professor of Medicine in the Division of Hematology and Oncology and co-first author of the study.

CLL is the most common type of leukemia in older adults, when B-lymphocytes, a type of white blood cell, develop into cancer cells in the bone marrow, blood and lymphatic system. Patients typically don't experience symptoms at initial diagnosis, but over time the cancer cells proliferate and can cause symptoms or impairment of bone marrow function, requiring treatment.

Conventional chemoimmunotherapy used to be the standard choice for treatment, but over the past several years, therapeutic strategies have shifted to primarily small molecule inhibitors that target enzymes in the B-cell receptor (BCR) signaling pathway or the apoptosis pathway. BCR pathway inhibitors prevent cancer cell proliferation and growth by blocking communication between leukemia cells and the tumor's microenvironment.

"These inhibitors require continuous and indefinite treatment," said Ma, who is also a member of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University.

The other class of targeted therapy, represented by venetoclax, targets the protective protein BCL2 and induces rapid tumor killing by programmed cell death.

Previous work published in *Lancet Oncology*, of which Ma was also co-first author, reported a phase 1b study of a novel combination treatment of venetoclax and a monoclonal antibody immunotherapy called

rituximab was highly effective for patients with relapsed or refractory CLL.

For the study, patients had received 200 to 600 milligrams of venetoclax daily and rituximab for six months, followed by venetoclax monotherapy. Rituximab, which targets the CD20 molecule expressed on the surface of B-cells, is currently widely used for various types of B-cell lymphomas and leukemias, including CLL, in combination with chemotherapy or other targeted therapies.

Ma and collaborators showed that the venetoclax-rituximab combination treatment was highly effective in producing a rapid reduction of leukemia burden, with the majority of patients achieving a deep response with no minimal residual disease. Patients who achieved a deep response to venetoclax-rituximab treatment were also given the option to continue venetoclax alone or to stop treatment all together.

In the current follow-up report, Ma and colleagues evaluated five-year patient outcomes for the venetoclax-rituximab combined treatment. Patients' overall survival, progression-free survival and duration of treatment response after five years were 86 percent, 56 percent and 58 percent, respectively. Additionally, 74 percent of patients who achieved a deep response to the combination therapy and who chose to stop treatment had sustained remission, which was also similar to patients who chose to continue treatment, according to the authors.

The findings support the fixed-duration venetoclax-based therapy, which has now become the standard of care, according to Ma.

"We also reported effectiveness of venetoclax-rituximab re-treatment for those patients who progressed after completing the initial treatment course, further extending the clinical benefit of venetoclax-based therapy," Ma added.

More information: Shuo Ma et al, Efficacy of venetoclax plus rituximab for relapsed CLL: Five-year follow-up of continuous or limited-duration therapy, *Blood* (2021). DOI: 10.1182/blood.2020009578

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