Targeted Therapies Improve Outcomes for People With Chronic Lymphocytic Leukemia

Venclexta combination therapy clears leukemia in blood and bone marrow, recent studies show.

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Regimens combining Venclexta (venetoclax) with other targeted therapies led to longer progression-free survival and improvement in other clinical outcomes for people with chronic lymphocytic leukemia (CLL), according to studies presented at the American Society of Hematology annual meeting this week in Atlanta.

CLL, the most common type of adult leukemia, involves overproduction of abnormal lymphocytes, usually B cells. As these abnormal cells grow out of control, they can crowd out normal blood cells, leading to increased susceptibility to infections, anemia and other complications.

CLL is difficult to cure. Treatment usually involves chemoimmunotherapy, a combination of traditional chemotherapy and medications that help the immune system fight cancer. While standard therapy can often put leukemia into remission, it usually doesn't eliminate all the cancer, and relapse is common.

Venclexta is a small-molecule targeted therapy that interferes with the BCL-2 protein, which plays a role in regulating cell apoptosis (programmed cell death). Blocking BCL-2 may restore cell signaling that tells cancer cells to self-destruct, according to Genentech, which is developing the drug in collaboration with AbbVie.

Venclexta monotherapy has received accelerated approval from the Food and Drug Administration (FDA) for CLL with 17p deletion, a genetic mutation associated with faster disease progression and poor treatment response; Venclexta plus Rituxan (rituximab) has a breakthrough therapy designation.

Venclexta + Rituxan

John Seymour, MBBS, PhD, of Royal Melbourne Hospital presented late-breaking findings from the Phase III MURANO study, evaluating Venclexta plus Rituxan, a monoclonal antibody that targets the CD20 protein on B cells, in people with advanced CLL.

This international study included 389 people with relapsed or refractory (nonresponsive) CLL who had previously been treated with at least one, but no more than three, prior therapies. The median age was 65, and about a quarter had 17p deletion.

Participants were randomly assigned to receive Rituxan plus either Venclexta or the chemotherapy drug bendamustine (Bendeka, Treanda or generics). Venclexta was taken as a daily pill, with the dose ramped up slowly to 400 milligrams to lessen side effects, for two years or until disease progression or unacceptable side effects occurred. Rituxan and bendamustine were given by IV infusion one or two days a month for six monthly cycles.

People treated with Venclexta plus Rituxan had an 83 percent lower risk of disease progression or death and significantly longer progression-free survival (PFS) than the chemotherapy group. After two years, 85 percent of people taking Venclexta were still alive without their disease worsening, compared with 36 percent of those taking bendamustine, Seymour reported. The median PFS was 17 months in the chemotherapy group but had not yet been reached in the Venclexta group because a majority of patients are still doing well. Response rates were good for people considered at high risk or low risk for disease progression.

Overall response rates, meaning complete or partial remission, were 93 percent in the Venclexta plus Rituxan group and 68 percent in the Rituxan plus bendamustine group; complete response rates were 27 percent and 8 percent, respectively. More people in the Venclexta group had undetectable minimal residual disease (MRD), or less than 1 leukemia cell per 10,000 white blood cells (84 percent versus 23 percent, respectively). Median overall survival could not yet be determined in either group because a majority of patients are still alive.

Side effects were common, but they usually could be managed and most patients stayed on treatment. In this study, 46 percent of patients taking Venclexta and 43 percent of those taking bendamustine had serious adverse events. People in the Venclexta group were more likely to develop white blood cell deficiencies, while those taking bendamustine were more likely to have low red blood cell counts and low platelet counts.

A major potential side effect of Venclexta is tumor lysis syndrome (TLS), which can occur when a large number of cancer cells are killed at once, releasing their contents into the blood and causing chemical imbalances. This occurred in 3 percent of Venclexta recipients and 1 percent of bendamustine recipients.

Venclexta + Imbruvica

Peter Hillmen, MBChB, PhD, of the University of Leeds in the United Kingdom presented results from the earlier-stage CLARITY trial, a feasibility study testing Venclexta plus Imbruvica (ibrutinib). Imbruvica is a BTK inhibitor that interferes with a signaling pathway that regulates B-cell growth. The FDA has granted it accelerated approval for CLL and small lymphocytic lymphoma.

This study included 54 people with relapsed or refractory CLL. The median age was 64, 20 percent had 17p deletion and most had previously tried chemoimmunotherapy. They took Imbruvica alone

for eight weeks and then added Venclexta, again starting with a low dose and ramping up.

After six months on treatment, all patients who had reached this time point responded to some extent, with 39 percent of them achieving complete responses. About a third had no remaining leukemia in their blood or bone marrow. One person developed TLS, stopped treatment until biochemical abnormalities resolved and was able to restart Venclexta.

Patients in this study will continue on Venclexta plus Imbruvica for twice as long as it takes them to achieve a complete response—in the hope of eliminating all residual disease—at which point they will stop treatment to see whether response is durable. The Phase III FLAIR trial will evaluate this combination as first-line therapy in a larger population.

Venclexta + Gazyva

Ian Flinn, MD, PhD, of the Sarah Cannon Research Institute in Nashville reported findings from a Phase Ib trial of Venclexta plus Gazyva (obinutuzumab), a newer CD20-targeting monoclonal antibody that has been shown to work better than Rituxan in some studies.

This study included 32 patients with advanced CLL who, unlike participants in the other trials, were being treated for the first time. The median age was 63, and 16 percent had 17p deletion. They received IV infusions of Venclexta and Gazyva for six monthly cycles, followed by Venclexta alone for another six months.

Here, too, the overall response rate was 100 percent, with 56 percent having complete responses, according to the study abstract. Everyone achieved MRD negativity in their blood and two thirds had no residual leukemia in their bone marrow. No one in this study developed TLS.

The “deep and durable” responses and “unprecedented” MRD negativity rates in this study suggest that combination targeted therapy may work better for initial treatment rather than waiting until after chemotherapy fails.

Another study looked at a three-drug regimen of Venclexta, Imbruvica and Gazyva in 25 previously untreated CLL patients. Again, all participants responded, including half with complete responses, and about 60 percent had MRD negativity in their blood and bone marrow, according to the study abstract. Although triple therapy was safe, with no cases of TLS, it did not appear to work better than two-drug combinations.

Commenting on the CLARITY findings at an ASH press briefing, Laurie Sehn, MD, of the British Columbia Cancer Agency suggested that we are moving into an era where targeted therapies will replace toxic chemotherapy for blood cancers, and results to date suggest that some patients can be cured.

Click here to read the Venclexta plus Rituxan abstract.

Click here to read the Venclexta plus Imbruvica abstract.

Click here to read the Venclexta plus Gazyva abstract.

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