Targeted Therapy Shows Promise for Lymphoma

Umbralisib may offer a chemotherapy-free option for people with relapsed or nonresponsive marginal zone lymphoma.

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Umbralisib, an experimental therapy that targets the PI3K cell growth pathway, showed good activity and a favorable safety profile in people with marginal zone lymphoma (MZL), according to early study findings presented at the 2019 American Association for Cancer Research (AACR) annual meeting last week in Atlanta.

More than half of participants in a Phase IIb clinical trial experienced complete or partial cancer regression using umbralisib without chemotherapy, and the median duration of response has not yet been reached, reported Nathan Fowler, MD, of the University of Texas MD Anderson Cancer Center in Houston.

MZL, which accounts for around 10 percent of all non-Hodgkin lymphoma, is a slow-growing cancer that involves B cells, the immune system cells that produce antibodies. Treatment with rituximab (Rituxan or biosimilars), a monoclonal antibody that binds to the CD20 receptor on B cells, has improved outcomes, but relapse is common, and these patients have limited options, Fowler noted as background.

Fowler’s team evaluated umbralisib as a follow-up treatment for people with relapsed or refractory (nonresponsive) MZL.

Umbralisib, which is being developed by TG Therapeutics, interferes with the delta form of phosphoinositide-3 kinase (PI3K-delta), an enzyme involved in a signaling pathway that plays a role in B-cell survival and growth. Umbralisib also inhibits CK1-epsilon, which regulates certain T cells. Other PI3K inhibitors in development mainly target the alpha form and have different side effects. Previous studies suggest that umbralisib is likely to cause fewer immune-mediated side effects than earlier drugs in its class. In January, umbralisib received a breakthrough therapy designation from the Food and Drug Administration.

The MZL cohort of the UNITY-NHL trial enrolled 69 treatment-experienced patients who had previously tried rituximab or another CD20 antibody, usually in combination with chemotherapy. All participants received oral umbralisib once daily until disease progression or unacceptable
toxicity.

Fowler presented interim data from 42 people who had at least nine monthly cycles of treatment with umbralisib. A majority were women, and the median age was 67. Of these, 23 had extranodal MZL that started outside the lymph nodes, 12 had nodal cancer that starts and usually stays in the lymph nodes, and seven had MZL involving the spleen.

After a median of 12.5 months of follow-up, the overall response rate—meaning complete or partial cancer regression—was 52 percent. Nineteen percent had complete responses, 33 percent had partial responses and some additional patients had some regression that did not meet the trial’s response thresholds. In addition, 36 percent had stable disease without further progression. The overall response rate rose to 57 percent for patients with extranodal MZL. The median duration of response has not yet been reached because a majority of patients are still responding.

After a year of treatment, the estimated progression-free survival (PFS) rate—meaning participants are still alive without worsening of disease—was 66 percent. The median PFS duration also was not reached. Overall survival results are not yet mature.

Treatment with umbralisib was generally safe and “fairly well tolerated,” although side effects were common, Fowler reported. The most frequent adverse events were diarrhea, nausea and fatigue. More than half had diarrhea, but it was usually mild or moderate and often improved with time. The most common severe side effects were diarrhea, neutropenia (decreased white blood cell count) and elevated liver enzymes; no one developed colitis (colon inflammation). Ten people stopped treatment because of drug-related adverse events. In general, side effects did not worsen with continued use of umbralisib, Fowler said.

Based on these findings, the researchers concluded, “PI3K-delta inhibition with single-agent umbralisib is active and well tolerated in patients with relapsed or refractory MZL, achieving durable responses with chemotherapy-free therapy.”

This study is ongoing, and all complete responders are still on treatment, according to Fowler. It is part of a larger trial that is also evaluating umbralisib in combination with ublituximab (an experimental CD20-targeting antibody) and chemotherapy and will look at other types of NHL.

“The adverse event and clinical activity data are highly encouraging at this early timepoint,” Fowler said in an AACR press release. “We are excited to continue following patients for a longer time to further establish the long-term activity and side effects of umbralisib. With the results reported so far, umbralisib has the potential to make a real difference for patients with relapsed/refractory marginal zone lymphoma.”

Click here to read the study abstract.

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