ADVANCES IN LLM: CLL IN FOCUS

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Umbralisib and Ublituximab: An Upcoming Regimen for Chronic Lymphocytic Leukemia

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H&O What types of drugs are umbralisib and ublituximab?

JG Umbralisib (Ukoniq, TG Therapeutics) is a phosphoinositide 3 (PI3) kinase delta inhibitor. Umbralisib is approved for patients with relapsed/refractory follicular lymphoma or marginal zone lymphoma, but not yet for patients with chronic lymphocytic leukemia (CLL). Several PI3 kinase delta inhibitors are already approved for patients with CLL. Idelalisib (Zydelig, Gilead) was the first drug approved for CLL in this class. Umbralisib differs from idelalisib in that it is very specific for the delta isoform. The other PI3 kinase delta inhibitors hit both the delta and gamma isoforms to some extent. As a type of off-target effect, umbralisib also inhibits casein kinase 1 epsilon (CK1ε). It is unclear, however, whether inhibition of CK1ε contributes to the activity of umbralisib. As a pure delta inhibitor, umbralisib does not have the same inhibitory effect on T regulatory cells. Umbralisib appears to have a more favorable toxicity profile in terms of autoimmune effects compared with the other PI3 kinase delta inhibitors.

Ublituximab is an anti-CD20 monoclonal antibody. Several anti-CD20 monoclonal antibodies are already approved. Rituximab (Rituxan, Genentech/Biogen) was the first in class. Other agents include obinutuzumab (Gazyva, Genentech) and ofatumumab (Arzerra, Novartis). A novel aspect to ublituximab is the way it hits the target by binding to a different part of the CD20 molecule.

PI3 kinase delta inhibitors and anti-CD20 monoclonal antibodies appear to work synergistically in CLL and other B-cell malignancies. The combination of umbralisib plus ublituximab, known as the U2 regimen, aims to exploit this synergy.

H&O Could you discuss the design and results of the UNITY-CLL trial?

JG UNITY-CLL was a multicenter, randomized phase 3 trial that compared the U2 regimen vs chlorambucil and obinutuzumab, which represented the standard of care of chemotherapy and an antibody. Neither umbralisib nor ublituximab is approved in CLL, so the regimen was considered a novel-novel combination. Therefore, the regulators insisted that the study design include treatment arms that evaluated each agent as monotherapy in order to provide a run-in to the study to show it was feasible to combine the 2 agents. In an interim analysis, an independent review committee found that each of the monotherapy arms was inferior to the U2 arm. Both of the single-agent arms closed early, which allowed the study to focus on umbralisib plus ublituximab vs chlorambucil plus obinutuzumab.

A novel aspect to the study is that it included patients with treatment-naive or relapsed/refractory disease. More than 500 patients were enrolled. In the final analysis that compared the U2 combination vs obinutuzumab plus chlorambucil, approximately 220 patients were in each arm. The primary endpoint was progression-free survival (PFS) for U2 vs chlorambucil plus obinutuzumab as assessed by the independent review committee.

The study met the primary endpoint. Overall, the 2-year PFS was 60.8% for the U2 arm vs 40.4% for the chlorambucil/obinutuzumab arm. The median PFS was 31.9 months vs 17.9 months, respectively (hazard ratio [HR], 0.546; 95% CI, 0.413-0.720; $P<.0001$). The difference in PFS was even more stark in the treatment-naive patient population. For these patients, the median PFS

was 38.5 months with U2 vs 26.1 months with chlorambucil plus obinutuzumab (HR, 0.48; 95% CI, 0.31-0.73). For patients with relapsed/refractory disease, the median PFS was 19.5 months vs 12.9 months, respectively (HR, 0.60; 95% CI, 0.41-0.86). The chemotherapy-free combination therefore showed superiority over the chemotherapy-containing standard of care.

H&O What were the main toxicities associated with the U2 regimen?

JG The U2 regimen was well tolerated. The main toxicity consisted of a minimal amount of gastrointestinal upset. Some cases of diarrhea occurred, but the vast majority were mild. The rates of neutropenia were lower in the U2 arm than in the obinutuzumab/chlorambucil arm. The approved PI3 kinase delta inhibitors have a well-characterized toxicity profile that includes hepatic toxicity, colitis, and pneumonitis. A striking finding from the UNITY-CLL trial is that these toxicities were not common with the U2 regimen. There were low rates of hepatic toxicity, colitis, and pneumonitis. Therefore, the safety profile of the U2 regimen appeared favorable compared with the chemotherapy arm, as well as several of the other PI3 kinase delta inhibitors.

H&O Are there any other recent study data for these drugs in CLL?

JG There are preliminary data for studies evaluating the U2 regimen in combination with other agents, such as venetoclax (Venclexta, AbbVie/Genentech). Follow-up for these studies is awaited.

H&O Are there patients who are better candidates for the U2 regimen?

JG It will be necessary to consider where the U2 regimen fits into the very effective armamentarium for CLL, which includes Bruton's tyrosine kinase (BTK) inhibitors and venetoclax. Certain patients, such as those with a history of cardiac events, are not good candidates for a BTK inhibitor. In addition, there are patients for whom both the BTK inhibitors and venetoclax were intolerable or ineffective. In these cases, the U2 regimen represents a novel approach that appears favorable compared with the other PI3 kinase delta inhibitors.

H&O Do you have any other observations regarding the use of this regimen?

JG Clinicians were excited by the preliminary data for PI3 kinase delta inhibitors in CLL. Idelalisib, the first agent from the novel class of B-cell receptor antagonists, appeared to be effective. It was disappointing to see unexpected toxicity emerge in this setting. Umbralisib, which appears to be associated with a lower toxicity profile, opens up the opportunity to have another option for patients with CLL, in addition to the other effective therapies now available.

There are also other emerging agents in the field. It is of course beneficial for patients to have so many treatment options. Increasing numbers of patients with CLL have been exposed to BTK inhibitors and venetoclax. This class of drugs becomes very attractive for these patients. The U2 regimen might also be used as a bridge to other exciting therapies, such as chimeric antigen receptor T cells.

Disclosure

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Suggested Readings

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