CLL IN FOCUS

Current Developments in the Management of Chronic Lymphocytic Leukemia

Is There Still a Role for PI3K Inhibitors in CLL?

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H&O What did the DUO trial find regarding the use of duvelisib in previously treated chronic lymphocytic leukemia (CLL) or small lymphocytic leukemia (SLL)?

IWF The DUO trial was a large, randomized phase 3 study that compared monotherapy with the phosphoinositide 3-kinase (PI3K) inhibitor duvelisib (Copiktra, Secura Bio) vs monotherapy with the monoclonal antibody ofatumumab (Arzerra, Novartis) in 319 patients with relapsed or refractory (R/R) CLL or SLL who had received at least 1 prior therapy. The initial results of the study, with a median follow-up of 22.4 months, showed a significant improvement in median progression-free survival (PFS) among patients in the duvelisib group compared with those in the ofatumumab group, at 13.3 vs 9.9 months, respectively (hazard ratio [HR], 0.52, $P<.0001$). These results were published in *Blood* in 2018.

Further follow-up revealed that the benefit was greatest in patients who received 2 or more prior therapies, which was the the group that received US Food and Drug Administration (FDA) approval. The most common adverse reactions among patients taking duvelisib were diarrhea or colitis, neutropenia, rash, fatigue, pyrexia, cough, nausea, upper respiratory infection, pneumonia, musculoskeletal pain, and anemia. These findings led to the September 2018 FDA full approval of duvelisib as third-line or later treatment for CLL/SLL. At that time, the FDA also granted accelerated approval to duvelisib for adults with R/R follicular lymphoma (FL) after at least 2 prior therapies based on findings from the phase 2 DYNAMO trial. However, Secura Bio voluntarily withdrew the indication of duvelisib for R/R FL in December 2021.

The FDA required Secura Bio to submit the final analysis of DUO at 5 years to evaluate the long-term safety of the drug.

H&O Could you discuss the follow-up data regarding duvelisib?

IWF At a median follow-up of 63 months, the results of DUO revealed a possible increased risk of death with duvelisib vs ofatumumab (HR, 1.09; 95% CI, 0.79-1.51). This concern persisted among patients who received at least 2 prior lines of therapy, with an HR of 1.06 (95% CI, 0.71-1.58). The median overall survival (OS) was 52.3 months (95% CI, 41.8-68.0) in the duvelisib group and 63.3 months (95% CI, 41.2 to not estimable) in the ofatumumab group. As a result, the FDA announced a warning to the public on June 30, 2022, of a possible increased risk of death with duvelisib. Although the drug is still marketed with additional warnings on the label, I have not used it in several years because other alternatives are available. Duvelisib carries a boxed warning regarding 4 fatal and/or serious toxicities: infections, diarrhea or colitis, cutaneous reactions, and pneumonitis.

The warning regarding duvelisib was not unexpected. On February 3, 2022, the FDA issued a drug safety alert about a possible increased risk of death among people who received the PI3K-δ inhibitor umbralisib for marginal zone lymphoma or FL. Some of the deaths in that study were caused by COVID-19, but not all of them were. In April 21, 2022, the FDA's Oncologic Drugs Advisory Committee met to discuss concerns about safety regarding the entire PI3K drug class. Less than 2 months later, on June 1, the FDA withdrew its approval of umbralisib.

Since last year, the FDA has required manufacturers of PI3K inhibitors to conduct comparative trials rather than single-arm trials to obtain approval. This requirement applies to the development of the PI3K-δ inhibitor zandelisib in FL.

H&O Are there any differences among the PI3K inhibitors that might make some safer than others?

IWF Although umbralisib and idelalisib (Zydelig, Gilead) are inhibitors of PI3K-δ and duvelisib is an inhibitor of both PI3K-δ and PI3K-γ, the differences between these categories are more theoretical than clinical. Even though duvelisib and idelalisib are still available, the adverse event profiles are almost identical to those of umbralisib. The agent copanlisib (Aliqopa, Bayer), which is still available for use in FL, is a pan-PI3K inhibitor that is administered intravenously. These factors make copanlisib slightly different from the other PI3K inhibitors, but the same concerns remain as with umbralisib.

I see PI3K inhibitors being used only in a very small fraction of patients who are either refractory to or intolerant of the other available agents.

H&O Are there any approaches to PI3K inhibitor treatment that could make it safer?

IWF Researchers are exploring different ways of giving these drugs so they are not constantly blocking PI3K, such as intermittent dosing, lower dosing, and dose loading followed by lower dosing. These approaches are worth exploring. Patients need to be well-informed about the risks of complications with these agents, including infectious complications. The use of antibiotics is indicated for prophylaxis against herpes viruses, *Pneumocystis jirovecii* pneumonia, and other opportunistic infections.

Even before the FDA warning about duvelisib and withdrawal of umbralisib in 2022, PI3K inhibitors had fallen out of favor for most patients with CLL. The most important agents in CLL are the B-cell lymphoma 2 (BCL2) inhibitor venetoclax (Venclexta, AbbVie/Genentech), the monoclonal antibodies rituximab and obinutuzumab (Gazyva, Genentech), and the Bruton tyrosine kinase (BTK) inhibitors ibrutinib (Imbruvica, Pharmacyclics/Janssen), acalabrutinib (Calquence, AstraZeneca), and zanubrutinib (Brukinsa, BeiGene). Pirtobrutinib (Jaypirca, Lilly) is currently approved for use in mantle cell lymphoma and is expected to gain approval for use in CLL. All these therapies are safer than PI3K inhibitors in most patients.

H&O Do you see any role for the use of PI3K inhibitors in CLL at this point?

IWF I see PI3K inhibitors being used only in a very small fraction of patients who are either refractory to or intolerant of other available agents. Our expectations regarding outcomes with these agents would be limited if the patient had already experienced relapse despite treatment with a BTK inhibitor and venetoclax. I would only turn to PI3K inhibitors in CLL if they were the only option.

H&O If a PI3K inhibitor were the only option, would you use a strategy such as intermittent dosing?

IWF Although the optimal approach remains unproven, it appears we can safely administer lower doses of PI3K inhibitors. In an analysis of the DUO trial that we presented as a poster at the 2019 Society of Hematologic Oncology Annual Meeting, we found that reducing or interrupting duvelisib treatment for toxicity did not negatively affect outcomes in patients with R/R CLL/SLL. This finding was consistent with my own clinical experience with the drug. Of note, some of the patients who remained on duvelisib for the longest duration were those who required a lower dose than what is recommended on the label. Alternative dosing and schedules are being tested in clinical trials.

Disclosures

Dr Flinn has received consulting fees to his institution from AbbVie, BeiGene, Century Therapeutics, Genentech, Genmab, Hutchison MediPharma, InnoCare Pharma, Kite Pharma, Myeloid Therapeutics, Novartis, Secura Bio, Servier Pharmaceuticals, TG Therapeutics, Vincerx Pharma, and Xencor, and has received research grants to his institution from AbbVie, Acerta Pharma, Agios, ArQule, AstraZeneca, BeiGene, Bio-Path Holdings, Bristol Myers Squibb, Calibr, Cancer and Leukemia Group B, Celgene, City of Hope National Medical Center, MorphoSys, Curis, CTI BioPharma, Epizyme, Fate Therapeutics, Forma Therapeutics, Gilead, Genentech, Gilead Sciences, InnoCare Pharma, IGM Biosciences, Incyte, Infinity Pharmaceuticals,

Janssen, Kite Pharma, Loxo, Marker Therapeutics, Merck, Millennium Pharmaceuticals, MorphoSys, Myeloid Therapeutics, Novartis, Nurix, Pfizer, Pharmacyclics, Portola Pharmaceuticals, Rhizen Pharmaceuticals, Roche, Seagen, Step Pharma, Tessa Therapeutics, TG Therapeutics, Trillium Therapeutics, Triphase Research & Development Corp, Cogent Biosciences, Verastem, Vincerx Pharma, and 2seventy bio.

Suggested Readings

April 21-22, 2022: meeting of the Oncologic Drugs Advisory Committee meeting announcement. US Food and Drug Administration. https://www.fda.gov/advisory-committees/advisory-committee-calendar/updated-information-april-21-22-2022-meeting-oncologic-drugs-advisory-committee-meeting-announcement. Posted April 15, 2022. Accessed March 14, 2023.

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FDA warns about possible increased risk of death and serious side effects with cancer drug Copiktra (duvelisib) [news release]. US Food and Drug Administration. https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-possible-increased-risk-death-and-serious-side-effects-cancer-drug-copiktra. Posted June 30, 2022. Accessed March 14, 2023.

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Secura Bio announces Copiktra (duvelisib) strategic focus on T-cell lymphoma and voluntary US withdrawal of the relapsed or refractory follicular lymphoma indication [news release]. Secura Bio, Inc. https://www.prnewswire.com/news-releases/secura-bio-announces-copiktra-duvelisib-strategic-focus-on-t-cell-lymphoma-and-voluntary-us-withdrawal-of-the-relapsed-or-refractory-follicular-lymphoma-indication-301436834.html. Posted December 3, 2021. Accessed March 13, 2023.