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Idelalisib and Obinutuzumab Combination Shows Promise in Relapsed/Refractory Waldenström Macroglobu

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A combination regimen consisting of idelalisib and obinutuzumab led to promising response and survival rates in patients with relapsed and refractory Waldenström macroglobulinemia (WM), according to a study published in *Blood Advances*. However, these benefits came at the expense of several side effects in most patients. Lead author Cecile Tomowiak, MD, of University Hospital Center of Poitiers in France, noted that when the researchers designed this study in 2013, the main chemotherapy-free approaches in WM were rituximab monotherapy and a combination regimen comprising bortezomib, rituximab, and dexamethasone. Ibrutinib was not yet available in France and results of clinical trials with ibrutinib had not yet been published.

“The anti-CD20 antibody rituximab as single-agent therapy was widely used in WM, but this has limited activity with a median progression-free survival [PFS] of around 13 to 15 months,” explained Dr. Tomowiak. Obinutuzumab demonstrated “remarkable activity” in previous studies of follicular lymphoma, she added, as well as superiority to rituximab when combined with chlorambucil in chronic lymphocytic leukemia.

“Based on these observations, the use of chemotherapy-free monoclonal anti-CD20 antibody obinutuzumab in combination with oral idelalisib should induce responses in patients with WM,” Dr. Tomowiak said. “[It also] has the potential to improve care, especially in medically non-fit patients compared to current immunochemotherapy regimens that carry a high risk of myelotoxicity and/or neurotoxicity.”

“[This chemotherapy-free combination] has the potential to improve care, especially in medically non-fit patients.”

—Cecile Tomowiak, MD

The study included 49 patients with relapsed/refractory WM who received six cycles of continuous idelalisib 150 mg twice daily with intravenous obinutuzumab as

induction therapy. Following induction, patients received maintenance therapy with idelalisib alone for at least two years.

Investigators set PFS as the study's primary endpoint. Other endpoints included overall response rate (ORR), response rates at months 12 and 24, overall survival (OS), and time to next treatment.

A total of 48 patients were treated in the induction phase, and 27 patients proceeded to the maintenance therapy phase. Patients' median age was 68.5 years and participants had Eastern Cooperative Oncology Group scores of 0 (n=14), 1 (n=26), 2 (n=8), or unknown (n=1).

After a median follow-up of 6.5 months, the ORR was 71.4%. This included:

- 5 patients with very good partial response
- 27 patients with partial response
- 3 patients with minor response

Looking at PFS over more than two years of follow-up, the authors reported 12- and 24-month PFS rates of 75.5% and 55%, respectively. The 12- and 24-month OS rates were 97.8% and 89.8%.

In addition, the median time to treatment failure was 25.6 months. The cumulative incidence of starting a new therapy was 22.5% at 12 months and 36.8% at 24 months. Neither CXCR4 or TP53 genotypes affected responses or PFS, according to a univariate analysis. The TP53 mutation did have a deleterious effect on survival, but this association was not statistically significant.

No grade 5 adverse events (AEs) were reported, but a total of 26 patients discontinued the study treatment due to AEs, including neutropenia (9.4%), diarrhea (8.6%), and liver toxicity (9.3%).

"This is the first chemotherapy-free combination of immunotherapy and targeted treatment with a fixed-duration approach," Dr. Tomowiak said, "allowing the opportunity to spare treatments for the patient and reduce clonal selection." She noted the regimen may also help mitigate the financial toxicity and socioeconomic consequences of relapsed/refractory WM.

Dr. Tomowiak noted that there is currently an unmet medical need in patients who are refractory to Bruton tyrosine kinase inhibitors such as ibrutinib. The findings of the

present study suggest that this population may benefit from a combination of obinutuzumab with idelalisib or other PI3K inhibitors, pending results from further clinical trials.

The authors report no relevant conflicts of interest.

Reference

Tomowiak C, Poulain S, Herbaux C, et al. Obinutuzumab and idelalisib in symptomatic patients with relapsed/refractory Waldenström macroglobulinemia. *Blood Adv.* 2021;5(9):2438-2446.