Novel Agents for Waldenström Macroglobulinemia

Jorge J. Castillo[1,*]
[1]*Bing Center for Waldenström Macroglobulinemia, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA*
***Corresponding author:** jorgej_castillo@dfci.harvard.edu

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Abstract

Waldenström macroglobulinemia (WM) is a rare subtype of non-Hodgkin lymphoma characterized by the accumulation of malignant lymphoplasmacytic cells in the bone marrow and other organs that secrete a monoclonal IgM paraprotein. Whole genome sequencing studies have detected recurrent somatic mutations in *MYD88* and *CXCR4*, with a prevalence of 90% and 40%, respectively. Classic therapeutic options include alkylating agents and proteasome inhibitors, both in combination with rituximab. These regimens are associated with overall response rates (ORR) of 90% and median progression-free survival (PFS) between 4 and 6 years.

With an improved understanding of mutant MYD88 signaling, the Bruton tyrosine kinase (BTK) emerged as an essential driver of the disease and also a therapeutic target. The BTK inhibitor ibrutinib is one of the most effective agents in WM. In a phase II study in 63 patients with previously treated WM, ibrutinib was associated with an ORR of 90% and a major response rate of 70%.[1] The encouraging results of this study prompted the approval of ibrutinib in patients with WM by the FDA in 2015. Similar efficacy outcomes were reported in rituximab-refractory and treatment-naïve patients with WM. The INNOVATE study randomized 150 patients with WM to either the combination of ibrutinib plus rituximab or placebo plus rituximab.[2] The combination of ibrutinib plus rituximab was associated with a higher major response rate (72% versus 32%) and a higher 30-month PFS rate (82% versus 28%) than the combination of placebo plus rituximab, prompting the approval of the combination of ibrutinib plus rituximab for WM by the FDA in 2018. Despite the great advances in the treatment of WM, the disease remains incurable with standard treatment options and disease recurrence is the norm. Therefore, novel agents are needed.

Three novel covalent BTK inhibitors are under active investigation for WM: zanubrutinib, acalabrutinib and tirabrutinib. The ASPEN study randomized 201 patients to zanubrutinib or ibrutinib and showed that both agents are very effective at inducing durable responses in patients with WM.[3] The major response rates for zanubrutinib and ibrutinib were 77% and 78%, respectively, the very good partial response (VGPR) rates, the primary outcome of the study, were 28% and 19%, respectively, and the 18-month PFS rates were 84% and 85%, respectively. Zanubrutinib was associated with lower rates of atrial fibrillation (2% versus 15%) but higher rates of neutropenia than ibrutinib (29% versus 13%). Acalabrutinib was evaluated in 106 patients with WM and was associated with an ORR of 93% and a 24-month PFS rate between 80 and 90%.[4] Tirabrutinib was evaluated in 27 patients with WM and was associated with an ORR of 96% and a major response rate of 89%.[5] The results of these studies support the use of covalent BTK inhibitors as a standard of care in WM. Multiple studies combining covalent BTK inhibitors with chemoimmunotherapy and proteasome inhibitors are ongoing.

Many patients with WM will develop BTK mutations with subsequent resistance to covalent BTK inhibitors, however. The non-covalent BTK inhibitor pirtobrutinib was evaluated in a multicenter phase II study in 26 patients with WM of whom 18 (12 had progressed and 6 were intolerant) were previously exposed to a covalent BTK inhibitor.[6] The ORR to pirtobrutinib was 69%. Atrial fibrillation of any grade was reported in 1% of patients. The BCL2 antagonist venetoclax has shown to be safe and effective in previously treated WM.[7] In a multicenter phase II study, 30 patients with WM were exposed to venetoclax with an ORR of 90%, a major response rate of 83%, and a VGPR rate of 20%. The estimated 24-month PFS rate was 74%. There was no atrial fibrillation, neuropathy or IgM flare. Only one case of laboratory tumor lysis syndrome was reported. A study evaluating the combination of ibrutinib and venetoclax in treatment-naïve patients with WM is ongoing.

CXCR4, PI3K, CD38 and HCK are additional targets of interest in WM. The CXCR4 inhibitor mavorixafor is being evaluated in combination with ibrutinib in WM patients who carry CXCR4 mutations. The PI3K inhibitor idelalisib show early efficacy in patients with WM but it seems to be associated with a high rate of liver toxicity.[8] A multicenter study evaluating umbralisib in patients with WM has stopped accrual. The anti-CD38 monoclonal antibody daratumumab had a lower-than-expected efficacy rate in WM.[9] Dasatanib is an HCK inhibitor being studied in patients with WM progressing on covalent BTK inhibitors. The phospholipid-drug conjugate CLR-131 was recently granted a Fast-

Track Designation for WM patients having received two or more prior treatment regimens.

In all, the treatment of patients with WM continues evolving. There are many reasons to be optimistic about the future of the treatment landscape of patients with WM.

References

1. Treon SP, Tripsas CK, Meid K, Warren D, Varma G, Green R, *et al.* Ibrutinib in previously treated Waldenstrom's macroglobulinemia. N Engl J Med. 2015. 372(15): 1430-40.
2. Dimopoulos MA, Tedeschi A, Trotman J, Garcia-Sanz R, Macdonald D, Leblond V, *et al.* Phase 3 Trial of Ibrutinib plus Rituximab in Waldenstrom's Macroglobulinemia. N Engl J Med. 2018. 378(25): 2399-2410.
3. Tam CS, Opat S, D'Sa S, Jurczak W, Lee HP, Cull G, *et al.* A Randomized Phase 3 Trial of Zanubrutinib Versus Ibrutinib in Symptomatic Waldenstrom Macroglobulinemia:The Aspen Study. Blood. 2020: Epub ahead of print.
4. Owen RG, McCarthy H, Rule S, D'Sa S, Thomas SK, Tournilhac O, *et al.* Acalabrutinib monotherapy in patients with Waldenstrom macroglobulinemia: a single-arm, multicentre, phase 2 study. Lancet Haematol. 2020. 7(2): e112-e121.
5. Sekiguchi N, Rai S, Munakata W, Suzuki K, Handa H, Shibayama H, *et al.* A multicenter, open-label, phase II study of tirabrutinib (ONO/GS-4059) in patients with Waldenstrom's macroglobulinemia. Cancer Sci. 2020. 111(9): 3327-3337.
6. Mato AR, Shah NN, Jurczak W, Cheah CY, Pagel JM, Woyach JA, *et al.* Pirtobrutinib in relapsed or refractory B-cell malignancies (BRUIN): a phase 1/2 study. Lancet. 2021. 397(10277): 892-901.
7. Castillo J, Allan J, Siddiqi T, Advani R, Keezer A, Gustine J, *et al.* Multicenter prospective phase II study of venetoclax in patients with previously treated Waldenstrom macroglobulinemia. Clinical Lymphoma Myeloma and Leukemia. 2019. 19(10, Supplement): e39-e40.
8. Castillo JJ, Gustine JN, Meid K, Dubeau T, Yang G, Xu L, *et al.* Idelalisib in Waldenstrom macroglobulinemia: high incidence of hepatotoxicity. Leuk Lymphoma. 2017. 58(4): 1002-1004.
9. Castillo JJ, Libby EN, Ansell SM, Palomba ML, Meid K, Flynn CA, *et al.* Multicenter phase 2 study of daratumumab monotherapy in patients with previously treated Waldenstrom macroglobulinemia. Blood Adv. 2020. 4(20): 5089-5092.