Tailoring Therapy in Waldenström Macroglobulinemia

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Abstract
The rarity of WM limits the ability to perform large randomized clinical trials comparing treatment regimens. Prospective single-arm studies, however, have led to the development of effective therapies. The choice of treatment should consider patient-specific characteristics and anticipated toxicities, as well as patient and provider preference. Additionally, *MYD88* and *CXCR4* mutations are known to affect treatment response and progression-free survival (PFS).

Approximately 50-60% of patients with WM would have mutations in MYD88 without mutations in CXCR4 (*MYD88*^{MUT} and CXCR4^{WT}).[1] The oral Bruton tyrosine kinase (BTK) inhibitor ibrutinib is an ideal treatment option for patients with *MYD88*^{MUT} and *CXCR4*^{WT} disease, as ibrutinib monotherapy has been associated with an overall response rate (ORR) of 100% and 5-year PFS rate of 70%.[2] There are some patient characteristics that should be considered, however. In patients with a history of cardiovascular disease or pre-existing cardiac arrhythmia, the risk of atrial fibrillation is higher and can occur at an earlier time point on ibrutinib therapy. In these cases, patients should be monitored closely, or other treatment options can be considered. Additionally, due to risk of bleeding associated with ibrutinib, alternative treatment options can be considered in those patients on therapeutic anticoagulation. Using direct oral anticoagulants, rather than vitamin K antagonists, may lower the risk of bleeding when used in combination with BTK inhibitors. Patients and clinicians should also be aware that BTK inhibitors are prescribed as indefinite therapy, which should be continued until the time of disease progression or development of intolerable adverse effects. Temporary or permanent cessation of BTK inhibitors can lead to withdrawal symptoms and a rapid serum IgM level rebound.

The *MYD88*^{MUT} and *CXCR4*^{MUT} profile has been reported in 30–40% of patients with WM. Patients with *CXCR4*^{MUT} disease are more likely to present with higher serum IgM levels, symptomatic hyperviscosity and acquired von Willebrand disease.[3] In these patients, ibrutinib monotherapy is less preferred, as a lower major response rate, a prolonged time to response, and a shorter PFS have been reported.[4,5] Chemoimmunotherapy or proteasome inhibitor-based regimens are appropriate in these setting. Data from a retrospective review of 63 patients, with known *CXCR4* mutational status in 49 patients, treated with bortezomib and rituximab showed no significant difference in PFS or OS when comparing patients with or without *CXCR4* mutations.[6] A prospective study of 69 patients treated with bendamustine plus rituximab showed no difference in disease response or survival outcomes based on the *CXCR4* mutational status.[7] Similar results were also reported in a pooled analysis of patients treated with bortezomib, carfilzomib, or ixazomib in the frontline setting.[8] No difference in response rates, PFS or OS after frontline treatment initiation was noted between patients with and without *CXCR4* mutations. The combination of ibrutinib plus rituximab was proven to be safe and efficacious in patients with WM based on the results of the INNOVATE study.[9] The low rate of IgM flare of 8% reported in this trial with no patients requiring plasmapheresis makes the combination of ibrutinib plus rituximab a suitable option in patients with *CXCR4* mutations. Response rates and PFS were similar among patients with or without *CXCR4* mutations. Therefore, this regimen could be used in this cohort with consideration for the most common toxicities of infusion-related reactions to rituximab, in addition to the side effects expected with ibrutinib.

Patients with *MYD88*^{WT} and *CXCR4*^{WT} disease, which constitute 5–10% of patients with WM, have specific clinical characteristics, such as shorter overall survival (OS) and increased risk of transformation to aggressive lymphoma.[10–12] Bendamustine plus rituximab should be considered an option given reported efficacy in a retrospective study.[13] However, a prospective study suggested a shorter PFS in the six *MYD88*^{WT} patients.[2] Lower response rates to single agent ibrutinib were reported in a study using an allele-specific polymerase chain reaction (AS-PCR) assay in CD19-selected bone marrow cells to assess *MYD88* mutational status.[14] In the INNOVATE study, the combination of ibrutinib plus rituximab was associated with an ORR of 81%, a major response rate of 63%, a VGPR rate or 27% and a 30-month PFS rate of 80% in patients with *MYD88*^{WT} and *CXCR4*^{WT} disease.[9] In this study, however, the *MYD88* mutational status was assessed in 136 patients using next-generation sequencing (NGS) in unselected bone marrow cells. Twenty patients (15%) had *MYD88*^{WT} and *CXCR4*^{WT} disease. NGS may be less sensitive than AS-PCR, particularly for patients with low disease burden.[15] Prospective studies have reported that the novel BTK inhibitors

acalabrutinib and zanubrutinib are effective in WM patients with *MYD88*^{WT} disease. In the acalabrutinib study, 50 of 106 (47%) of the participants were genotyped and 14 (28%) had *MYD88*^{WT} disease. MYD88 genotyping was performed at the discretion of the participating centers and used different methods of detection. The ORR and major response rate in these patients were 78% and 57%. In the ASPEN cohort 2 substudy, 28 WM patients with *MYD88*^{WT} disease were exposed to zanubrutinib.[16] *MYD88* mutational status was assessed using NGS in unselected bone marrow tissue. Zanubrutinib therapy was associated with an ORR, major response rate and VGPR rate of 80%, 50% and 27%, with an 18-month PFS rate of 68%.

Genomic profiling has emerged as a potential approach to tailoring treatment options in 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. Treon SP, Meid K, Gustine J, Yang G, Xu L, Liu X, *et al.* Long-Term Follow-Up of Ibrutinib Monotherapy in Symptomatic, Previously Treated Patients With Waldenstrom Macroglobulinemia. J Clin Oncol. 2021. 39(6): 565-575.
3. Castillo JJ, Moreno DF, Arbelaez MI, Hunter ZR, Treon SP. CXCR4 mutations affect presentation and outcomes in patients with Waldenstrom macroglobulinemia: A systematic review. Expert Rev Hematol. 2019. 12(10): 873-881.
4. Gustine JN, Xu L, Tsakmaklis N, Demos MG, Kofides A, Chen JG, *et al.* CXCR4 (S338X) clonality is an important determinant of ibrutinib outcomes in patients with Waldenstrom macroglobulinemia. Blood Adv. 2019. 3(19): 2800-2803.
5. Castillo JJ, Xu L, Gustine JN, Keezer A, Meid K, Dubeau TE, *et al.* CXCR4 mutation subtypes impact response and survival outcomes in patients with Waldenstrom macroglobulinaemia treated with ibrutinib. Br J Haematol. 2019. 187(3): 356-363.
6. Sklavenitis-Pistofidis R, Capelletti M, Liu CJ, Reidy M, Zavidij O, Huynh D, *et al.* Bortezomib overcomes the negative impact of CXCR4 mutations on survival of Waldenstrom macroglobulinemia patients. Blood. 2018. 132(24): 2608-2612.
7. Laribi K, Poulain S, Willems L, Merabet F, Le Calloch R, Eveillard JR, *et al.* Bendamustine plus rituximab in newly-diagnosed Waldenstrom macroglobulinaemia patients. A study on behalf of the French Innovative Leukaemia Organization (FILO). Br J Haematol. 2019. 186(1): 146-149.
8. Castillo JJ, Gustine JN, Meid K, Flynn CA, Demos MG, Guerrera ML, *et al.* CXCR4 mutational status does not impact outcomes in patients with Waldenstrom macroglobulinemia treated with proteasome inhibitors. Am J Hematol. 2020.
9. 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.
10. Abeykoon JP, Paludo J, King RL, Ansell SM, Gertz MA, LaPlant BR, *et al.* MYD88 mutation status does not impact overall survival in Waldenstrom macroglobulinemia. Am J Hematol. 2018. 93(2): 187-194.
11. Treon SP, Cao Y, Xu L, Yang G, Liu X, Hunter ZR. Somatic mutations in MYD88 and CXCR4 are determinants of clinical presentation and overall survival in Waldenstrom macroglobulinemia. Blood. 2014. 123(18): 2791-6.
12. Treon SP, Gustine J, Xu L, Manning RJ, Tsakmaklis N, Demos M, *et al.* MYD88 wild-type Waldenstrom Macroglobulinaemia: differential diagnosis, risk of histological transformation, and overall survival. Br J Haematol. 2018. 180(3): 374-380.
13. Paludo J, Abeykoon JP, Shreders A, Ansell SM, Kumar S, Ailawadhi S, *et al.* Bendamustine and rituximab (BR) versus dexamethasone, rituximab, and cyclophosphamide (DRC) in patients with Waldenstrom macroglobulinemia. Ann Hematol. 2018. 97(8): 1417-1425.
14. Treon SP, Xu L, Hunter Z. MYD88 Mutations and Response to Ibrutinib in Waldenstrom's Macroglobulinemia. N Engl J Med. 2015. 373(6): 584-6.
15. Kofides A, Demos M, Tsakmaklis N, Xu L, Liu X, Patterson C, *et al.* Alternative Mutations and Isoform Dysregulation in MYD88 in Waldenstrom's Macroglobulinemia. Blood. 2018. 132(Supplement 1): 1566.
16. Dimopoulos M, Sanz RG, Lee HP, Trneny M, Varettoni M, Opat S, *et al.* Zanubrutinib for the treatment of MYD88 wild-type Waldenstrom macroglobulinemia: a substudy of the phase 3 ASPEN trial. Blood Adv. 2020. 4(23): 6009-6018.