Using Biology to Determine Type and Duration of Treatment in Waldenström Macroglobulinemia

Jorge Castillo, MD[1,*]
[1]*Dana-Farber Cancer Institute, Boston, MA, USA*
***Corresponding author:** jorgej_castillo@dfci.harvard.edu

Waldenström Macroglobulinemia (WM) is a lymphoplasmacytic lymphoma characterized by the accumulation of malignant immunoglobulin M (IgM)-secreting lymphoplasmacytic cells in the bone marrow and other organs. The clinical features of WM are diverse and include anemia, hyperviscosity, extramedullary disease (e.g., lymphadenopathy, splenomegaly, pleural effusions, kidney involvement), and peripheral neuropathy, among others (e.g., amyloidosis, cryoglobulinemia, cold agglutinin disease). In some cases, WM patients can be asymptomatic at diagnosis and remain asymptomatic for several years.

From a biological perspective, recurrent somatic mutations in *MYD88* and *CXCR4* have been described in more than 90% and approximately 40% of patients with WM, respectively[1,2]. The majority (98%) of the *MYD88* mutations occur in locus 265 (*L265P*) with a minority (2%) located outside of the locus 265 (e.g., 219, 243). More than 30 *CXCR4* mutations have been described and can be divided into nonsense and frameshift mutations. Based on the genomic profile, patients with WM can be classified into three groups: *MYD88* mutated and *CXCR4* wildtype ($MYD88^{MUT}/CXCR4^{WT}$), which comprises 50-60%, *MYD88* and *CXCR4* mutated ($MYD88^{MUT}/CXCR4^{MUT}$), which comprises 30-35%, and *MYD88* and *CXCR4* wildtype ($MYD88^{WT}/CXCR4^{WT}$), which comprises 5-10% of all cases.

Clinically, these three genomic categories are associated with distinct clinical features. Patients with $MYD88^{MUT}/CXCR4^{MUT}$ disease present with higher burden of disease in the bone marrow, higher serum IgM levels, symptomatic hyperviscosity and acquired von Willebrand disease[3]. On the other hand, patients with $MYD88^{WT}/CXCR4^{WT}$ disease are more likely to present with extramedullary disease and have a higher risk of transformation to diffuse large B-cell lymphoma[4]. Patients with $MYD88^{MUT}/CXCR4^{MUT}$ or $MYD88^{WT}/CXCR4^{WT}$ have also been associated with a shorter time from diagnosis to treatment initiation than patients with $MYD88^{MUT}/CXCR4^{WT}$ disease[5].

The genomic profile of patients with WM can help tailor treatment options for these patients, especially when Bruton tyrosine kinase (BTK) inhibitors are being considered. In the seminal phase II study evaluating ibrutinib in 63 patients with previously treated WM, the 22 patients with $MYD88^{MUT}/CXCR4^{MUT}$ disease had lower rates of partial response or better (major response; 68% vs. 97%) and very good partial response (VGPR; 9% vs. 47%) than the 36 patients with $MYD88^{MUT}/CXCR4^{WT}$ disease[6,7]. In addition, the time to a major response was longer (4.7 vs. 1.8 months), and the 5-year progression-free survival (PFS) rate was lower (38% vs. 70%), suggesting a *CXCR4* mutational status as a resistance mechanism to BTK inhibition. Furthermore, in patients with $MYD88^{WT}/CXCR4^{WT}$ disease, the overall response rate was 60% but the rates of major response and VGPR were 0% with a median PFS of 24 months. In a phase II study evaluating 30 patients with previously untreated WM, the 14 patients with $MYD88^{MUT}/CXCR4^{MUT}$ disease had a longer time to response (7.3 vs. 1.8 months), lower rates of major response (78% vs. 94%) and VGPR (44% vs. 14%), and lower 4-year PFS rates (59% vs. 92%) than the 16 patients with $MYD88^{MUT}/CXCR4^{WT}$ disease[8,9]. No patients with $MYD88^{WT}/CXCR4^{WT}$ disease were enrolled in this study.

In the randomized INNOVATE study, 150 patients with previously treated and treatment naïve WM were randomized 1:1 to ibrutinib plus rituximab and placebo plus rituximab[10,11]. The addition of rituximab to ibrutinib was associated with a time to response of 3 vs. 1 month, a major response rate of 77% vs. 81%, a VGPR or better rate of 23% vs. 44%, and a 54-month PFS rate of 63% vs. 72% in patients with $MYD88^{MUT}/CXCR4^{MUT}$ when compared with patients with $MYD88^{MUT}/CXCR4^{WT}$ disease. Patients with $MYD88^{WT}/CXCR4^{WT}$ disease had a 73% major response rate with a VGPR rate of 27% and a 54-month PFS rate of 70%, suggesting that the addition of rituximab to ibrutinib might improve outcomes in this genomic group although a formal comparison between ibrutinib plus rituximab and ibrutinib monotherapy has not been made. In the randomized ASPEN study, zanubrutinib was associated with a similar time to major response (3.1 vs. 2.8 months) and lower rates of VGPR (18% vs. 34%) in patients with $MYD88^{MUT}/CXCR4^{MUT}$ when compared with patients with $MYD88^{MUT}/CXCR4^{WT}$ disease[12]. Patients with $MYD88^{WT}/CXCR4^{WT}$ disease had a major response rate of 50% and a VGPR rate of 27% to zanubrutinib suggesting that novel covalent BTK inhibitors might induce deeper responses in this genomic group. However, one must be aware of the substantial differences in *MYD88* and *CXCR4* mutational status assessment techniques between these studies.

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Therefore, and based on the above, BTK inhibitor monotherapy is preferred in patients with *MYD88*^{MUT}/*CXCR4*^{WT} disease, while the addition of rituximab to ibrutinib or zanubrutinib can be considered in patients with *MYD88*^{MUT}/*CXCR4*^{MUT} or *MYD88*^{MUT}/*CXCR4*^{WT} disease. Rituximab-containing regimens such as bendamustine and rituximab, or bortezomib, dexamethasone and rituximab are safe and highly effective options in WM patients regardless of *MYD88* or *CXCR4* mutational status[13,14]. The BCL2 antagonist venetoclax is another option in the relapsed setting. *MYD88*^{MUT}/*CXCR4*^{MUT} disease was associated with a lower VGPR rate (12% vs. 29%) but major response (76% vs. 86%) and median PFS (~30 months) were similar to *MYD88*^{MUT}/*CXCR4*^{WT} disease[15]. Rituximab monotherapy can be used in WM patients regardless of genomic profile. However, it is associated with lower rates of major response (31%) and VGPR or better (5%) as well as shorter PFS (median 20 months)[10].

Ongoing clinical trials are investigating triple, fixed-duration BTK inhibitors-containing regimens as well as non-covalent BTK inhibitors and immunotherapeutic agents such as the phospholipid-drug conjugate CLR-131, the anti-CD19 antibody-drug conjugate loncastuximab, and chimeric antigen receptor T-cells. It would be of great interest to investigate the impact that the genomic profile of patients WM might have on these novel agents. Also, additional research is needed to standardize *MYD88* and *CXCR4* mutational testing to further optimize the applicability of genomic profile in the management of patients with WM.

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