

# Waldenström Macroglobulinemia – 2020 Update on Management and Future Directions

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## Introduction

Waldenström Macroglobulinemia (WM) is a low-grade B-cell lymphoproliferative disorder characterized by bone marrow infiltration with lymphoplasmacytic cells, together with an immunoglobulin M (IgM) monoclonal gammopathy. An estimated 1000–1500 new cases of WM are diagnosed in the United States each year, with an incidence rate of 3 cases per million people per year.<sup>1</sup> The incidence of WM is higher in whites (4.1 per million per year) than blacks (1.8 per million per year), and higher among men (0.92 per 100,000 person-years) than women (0.30 per 100,000 person-years). Median age (years) at diagnosis is 63 for blacks, and 73 for whites.<sup>2</sup> Median overall survival (OS) of patients diagnosed between 2001–2010 was 8 years.<sup>3</sup>

About 93–97% of patients with WM have a somatic mutation in MYD88, an adaptor protein in the B cell receptor pathway that triggers downstream signaling through BTK and IL-1 receptor-associated kinases, which, in turn, promotes NF- $\kappa$ B signaling.<sup>4</sup> Approximately, one-third of patients with the MYD88 mutation also have a mutation of CXCR4, a G protein-coupled receptor that promotes migration and activation of several pathways including RAS, Akt, and NF- $\kappa$ B.<sup>4</sup>

Patients with wild-type and mutated MYD88 have similar histopathologic features, but median baseline bone marrow infiltration and serum IgM levels are lower in *MYD88*<sup>WT</sup> compared with patients having the *MYD88L265P* variant. Yet, despite a higher disease burden, median OS is longer for patients having *MYD88L265P* WM (73 vs 90%).<sup>5</sup>

## Clinical presentation

WM belongs to a spectrum of IgM plasma cell dyscrasias. IgM monoclonal gammopathy of undetermined significance (MGUS) is a pre-cancerous condition with a rate of progression to WM of 1.5% per year, while symptomatic WM, is characterized by 10% or greater bone marrow infiltration by lymphoplasmacytic lymphoma, together with end organ damage related to tumor infiltration (cytopenias, hepatomegaly, splenomegaly, lymphadenopathy), circulating IgM (hyperviscosity, cryoglobulinemia, and/or cold

agglutinin hemolytic anemia) and/or tissue deposition of IgM (polyneuropathies, glomerular disease, amyloidosis). In between, are patients with smoldering WM, who have 10% or greater bone marrow infiltration, but without evidence of significant end organ damage. Smoldering WM is associated with a rate of progression to symptomatic WM, amyloidosis or lymphoma of 12% per year for the first 5 years from diagnosis, followed by 2% per year thereafter.<sup>6</sup>

Patients with MGUS and smoldering WM should be monitored, on observation, for progression to symptomatic WM. However, patients with symptomatic WM, defined as WM associated with a disease-related hemoglobin level of less than 10 g/dL, a platelet count of less than  $100 \times 10^9/L$ , bulky adenopathy or organomegaly, symptomatic hyperviscosity, severe neuropathy, amyloidosis, cryoglobulinemia, cold agglutinin disease, or evidence of disease transformation, should be considered for immediate therapy.<sup>7</sup>

## Frontline therapy

Choice of primary therapy is based on a patient's gene mutation profile, disease-related features, and co-morbid conditions. When autologous stem cell transplant (ASCT) may be considered at disease relapse, nucleoside analog-based therapy should be avoided prior to stem cell harvest. Frontline therapy with rituximab, in combination with either an alkylating agent or proteasome inhibitor +/- dexamethasone, is associated with rapid response, and its efficacy is independent of gene mutation profile. Combinations of bortezomib-rituximab +/- dexamethasone have been associated with major ( $\geq$  partial response) response rates (MRR) of 57–83%, while carfilzomib-rituximab-dexamethasone has shown an MRR of 68%, and ixazomib-rituximab-dexamethasone, an MRR of 50%.<sup>8–11</sup> By comparison, alkylating agent-based regimens (R-CHOP, R-CVP, rituximab-cyclophosphamide-dexamethasone, rituximab-bendamustine) have shown MRRs of 77–96%. Of these, rituximab-bendamustine is the preferred regimen in light of improved progression-free survival compared with R-CHOP and superior toxicity profile.<sup>12–13</sup> Rituximab monotherapy is generally a sub-optimal choice for patients needing systemic therapy, with overall response rates (minor + partial response) of 20–50%, and short progression-free survival (12–24 months).<sup>14</sup>

For patients whose WM exhibits the *MYD*<sup>L265P</sup>*CXCR4*<sup>WT</sup> gene mutation profile, ibrutinib, with or without rituximab, may also be considered frontline, due to its high MRR (92%) and rapid time

to response (4 weeks). The MRR falls to 62%, for those with an MYD<sup>L265P</sup>CXCR4<sup>WHIM</sup> gene mutation profile, and to 0% for those with MYD<sup>WT</sup>CXCR4<sup>WHIM</sup>.<sup>15-17</sup> Therefore, for double wild-type patients, alkylating agent- or proteasome inhibitor-based regimens, are preferred.

Bortezomib should be avoided in patients with baseline peripheral neuropathy, while carfilzomib should be used cautiously in those with underlying cardiac conditions. When considering ibrutinib, the risks of bleeding and atrial fibrillation must be considered; concurrent use of novel oral anticoagulants should be avoided, and patients with baseline or treatment emergent atrial fibrillation, should be co-managed with a cardiologist.

## Therapy at relapse

At disease relapse, patients may be re-treated with a previously effective regimen, if the initial remission lasted at least 1 year. When the initial disease-free interval was less than 1 year, another of the previously described regimens should be selected.

The role of ASCT in WM remains to be well defined. In a retrospective review of 158 patients, the 5-year PFS and OS with ASCT was 39.7% and 68.5%, respectively.<sup>18</sup> Allogeneic SCT should not be considered outside the context of a clinical trial, due to high rates of treatment-related mortality.

## Future directions

Gene expression and transcriptome studies have shown that BCL2 is highly expressed in WM cells, particularly in MYD88 L265P mutated WM, making BCL2 inhibition a promising mechanism to target. In a Phase II trial of patients with relapsed WM, venetoclax was associated with an MRR of 80%, with a median time-to-response of 9 weeks. Importantly, TTR was not affected by CXCR4 mutation status.<sup>19</sup>

Also promising is the second generation BTK inhibitor, zanubrutinib. Compared with ibrutinib, zanubrutinib has a comparable MRR (77.5 vs 77.8%), but superior  $\geq$  VGPR rate (28.4 vs. 17.4%). However, most compelling is the MRR of 50% seen in the MYD88<sup>WT</sup> cohort, with a VGPR rate of 26.9% and a 12-month PFS of 72%.<sup>20</sup>

Other promising agents under study include next generation BTK and BCL2 inhibitors, CXCR4 inhibitors (e.g., ulocuplumab) and ERK pathway inhibitors, as well as the anti-CD38 monoclonal antibody, daratumumab, and CAR-T cell therapies. The development of these and other novel agents will usher in a new era in the treatment of Waldenström macroglobulinemia.

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