Treatment paradigm in Waldenström macroglobulinemia: frontline therapy and beyond

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***Abstract*:** Waldenström macroglobulinemia (WM) is an indolent lymphoplasmacytic lymphoma. Recent strides made in the genomic profiling of patients with WM have led to the identification of many novel therapeutic targets. Patients with WM can present with asymptomatic disease and not all patients require treatment. When criteria for initiating systemic therapy are met, the choice of therapy depends on the tumor genotype (*MYD88* and *CXCR4* mutation status), patient preference (fixed *versus* continuous duration therapy, oral *versus* intravenous route, cost), associated medical comorbidities, and adverse effect profile of the treatment. In the absence of head-to-head comparison between chemoimmunotherapy and Bruton's tyrosine kinase inhibitors in otherwise fit patients with a *MYD88*[L265P] mutation, our preference is fixed duration therapy with four to six cycles of chemoimmunotherapy with bendamustine–rituximab. In this review, we discuss the role of *MYD88* and *CXCR4* mutation in treatment selection, and current data for frontline and salvage treatment options in patients with WM.

Keywords: bendamustine–rituximab, BTK, CXCR4, DRC, ibrutinib, lymphoplasmacytic lymphoma, MYD88

Introduction

Waldenström macroglobulinemia (WM) is a B-cell lymphoplasmacytic lymphoma (LPL) that typically follows an indolent course.[1] It is a relatively uncommon malignancy with roughly 1,500–2,000 new cases diagnosed in the United States.[2,3] The median age at presentation is 70 years and prevalence of WM is higher in Caucasian individuals. Surveillance, epidemiology, and end results data studies have demonstrated the annual incidence rate to be higher in Caucasian population (0.52 per 100,000; 95% CI: 0.50–0.53) compared with African American population (0.29 per 100,000, 95% CI: 0.26–0.33).[4] Waldenström macroglobulinemia lies on a spectrum of disorders ranging from an immunoglobulin M (IgM) monoclonal gammopathy of undetermined significance (MGUS), to asymptomatic/smoldering WM and eventually symptomatic disease.[1] The common underlying feature in these disorders is the presence of circulating monoclonal IgM protein. Patients with MGUS have a monoclonal IgM protein with less than 10% bone marrow involvement by LPL. Asymptomatic/smoldering WM is characterized by ⩾10% involvement of the bone marrow by LPL and do not have any signs or symptoms of malignancies. Like other indolent lymphomas, not all patients with WM require treatment at diagnosis and one-fifths of patients with WM present with asymptomatic or smoldering disease.[5,6] Diagnosis of active WM requires the presence of bone marrow infiltration by ⩾10% lymphoplasmacytic cells along with symptomatic disease.[7,8] The indications for initiation of systemic therapy are guided by the 2002 consensus criteria and, most recently, International Workshop on Waldenström's Macroglobulinemia (IWWM)-10, which include significant cytopenias (hemoglobin < 10 g/dL, platelet count of < 100 × 10^9/

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liters), symptomatic hyperviscosity, symptomatic cryoglobulinemia, cold agglutinin disease, renal dysfunction due to coagulopathy, central nerve system involved by LPL (Bing Neel syndrome), constitutional signs and symptoms of malignancy (B-symptoms), bulky organomegaly/adenopathy, and moderate to severe WM-induced peripheral neuropathy.[9] Rarely, transformation to an aggressive B-cell lymphoma (BCL) can be an initial presentation of WM and necessitates management similar to that for an aggressive non-Hodgkin lymphoma.[10] Development of amyloid light-chain (AL) amyloidosis can also complicate the disease course in 7–10% patients with WM, requiring treatment initiation directed against the WM clone.[11,12] While these criteria for treatment initiation are largely uniform, the choice of initial systemic therapy is not as well-defined. In this review, we discuss the current understanding of the genomic landscape of WM and the choice of systemic therapy in frontline and relapsed/refractory setting.

Immunophenotype, *MYD88* and *CXCR4* mutations in WM

Immunophenotype of lymphoplasmacytic cells in WM carries findings of both lymphocytic and plasmacytic cellular components. The lymphocytic components demonstrate CD10–, CD11c–, CD19+, CD20+, CD22+, CD79a+, CD23–, CD25+, CD27+, FMC7+, CD56–, CD103–, and CD138–, while the plasmacytic component is CD138+, CD38+, and CD45– or dim. The lymphocytic and plasmacytic cells would be positive for IgM. Absence of CD56 in WM helps to differentiate LPL cells from plasma cells seen in the bone marrow in patients with multiple myeloma.[13] During the past decade, whole genome sequencing data have led to identification of many recurrent mutations in patients with WM, the most common being the $MYD88^{L265P}$ point mutation identified in up to 95% of patients.[14,15] Although not pathognomonic or diagnostic for WM by itself, the presence of the $MYD88^{L265P}$ mutation is strongly supportive of a diagnosis of WM in the presence of appropriate clinical and histologic features.[7] The $MYD88^{L265P}$ mutation leads to homodimerization of the MYD88 adaptor protein and constitutive signaling through Bruton's tyrosine kinase (BTK), a non-receptor tyrosine kinase downstream from the B-cell receptor.[16] BTK plays a crucial role in B-cell survival and growth through downstream nuclear factor kappa beta (NF-kB) pathway activation.

Another commonly encountered mutation in WM is noted in the C-terminal of the *CXCR4* gene and is identified in 30–40% patients.[15,17] The *CXCR4* mutation identified in WM is similar to the one described in WHIM (warts, hypogammaglobulinemia, infections and myelokathexis) and hence commonly referred to as the $CXCR4^{WHIM}$ mutation.[18] The C-terminal mutation of *CXCR4* gene results in receptor internalization upon stromal cell-derived factor 1a (SDF-1a) stimulation, leading to a persistent active state of *CXCR4* gene and downstream activation of AK strain transforming (AKT) and extracellular signal-regulated kinase (ERK) signaling pathways.[19]

The impact of $MYD88^{L265P}$ mutation on overall survival (OS) is debated with some studies demonstrating an inferior OS, whereas others not demonstrating any impact on OS.[17,20] Interestingly, $MYD88^{WT}$ status and not $MYD88^{L265P}$ mutated status is associated with a higher risk of histologic transformation to an aggressive lymphoma.[21] Patients with $MYD88^{WT}$ have also demonstrated a shorter time from smoldering WM to development of active disease.[6,22] In addition, the *MYD88* mutation serves as a reliable biomarker for response to BTK inhibitor therapy.[23,24] The response rates for ibrutinib in patients with WM harboring the $MYD88^{L265P}$ mutation and *CXCR4* wild-type ($CXCR4^{WT}$) are close to 100% in the frontline setting and upward of 90% in relapsed/refractory setting.[23,25] A concurrent *CXCR4* mutation can confer resistance to ibrutinib therapy. In a study addressing impact of *CXCR4* mutations, SDF-1a treated $CXCR4^{S338X}$ cell lines demonstrated sustained AKT and ERK activation compared with $CXCR^{WT}$ cell lines when treated with ibrutinib.[26] In a retrospective study of patients treated with ibrutinib, the presence of *CXCR4* non sense ($CXCR4^{NS}$), but not frameshift mutations, was associated inferior response rates (major response rates (MRRs) of 85% *versus* 55% for $CXCR4^{WT}$ and $CXCR^{NS}$ mutations, respectively) and progression-free survival (PFS).[27] In a prospective trial comparing zanubrutinib and ibrutinib, the MRRs for *CXCR mutated* were numerically lower compared with the *CXCR4WT* patient subsets, but were overall comparable across treatment arms (63% *versus* 64% and 80% *versus* 79%, for ibrutinib and zanubrutinib, respectively).[28] Limited evidence also suggests that the presence of $CXCR4^{NS}$ mutations in smoldering WM is associated with a shorter time to treatment initiation compared with

smoldering WM with $CXCR^{WT}$, but does not impact OS from diagnosis.[15,29] Mutations in *MYD88* and *CXCR4* genes have not been demonstrated to impact outcomes, that is, PFS or OS, for patients treated with proteasome inhibitors (PIs), although the time to achieve a response appears to be longer in patients with *CXCR4* mutations.[30,31] Similarly, early data suggest that BCL-2 inhibition with venetoclax is efficacious irrespective of the *CXCR4* mutation status.[32,33] The mutational data for *MYD88* and *CXCR4* genes have helped to pave the way for personalized therapy for WM, especially with regards to BTK inhibitors, but its impact on outcomes with conventional chemoimmunotherapy remains to be studied. Therefore, in our current practice, we routinely check *MYD88* and *CXCR4* mutation status regardless of selection of frontline fixed duration chemoimmunotherapy or continues duration BTK inhibitor-based therapy. The *CXCR4* mutation testing is also important when treating patients with BTK inhibitors with or without rituximab due to the aforementioned differential response to BTK inhibitors based on *CXCR4* mutation status.

Frontline therapy for patients with WM

Treatment options for WM have expanded significantly over the past two decades. Purine analog-based regimens (fludarabine with or without rituximab) demonstrated improved survival in patients with WM compared with chlorambucil, but have largely been relegated over the last decade due to the better safety and tolerability of the newer regimens.[34,35] One of the emergent presentations of WM includes symptomatic hyperviscosity, a clinical syndrome with symptoms including confusion, headache, blurry vision, mucosal or cutaneous bleeding and rarely, and catastrophic neurologic sequelae, including stroke. Patients presenting with symptomatic hyperviscosity at the time of diagnosis should undergo urgent plasmapheresis followed by systemic therapy.[36,37] In the absence of symptomatic hyperviscosity, most patients with WM requiring treatment are treated with systemic therapy.

The current commonly used frontline systemic therapy categories can be categorized as chemo-immunotherapy, PI-based therapy, and BTK inhibitor-based therapy. Rituximab is an anti-CD20 monoclonal antibody that demonstrates response rates of 30–40% as a single-agent therapy in patients with WM.[38] Treatment with single-agent rituximab has largely been superseded by chemoimmunotherapy regimens that have demonstrated superior responses and outcomes. Chemoimmunotherapy regimens include anti-CD20 monoclonal antibody rituximab as the backbone along with an alkylating agent like bendamustine or cyclophosphamide. The relevant data on frontline therapies in WM are discussed below.

Chemoimmunotherapy in frontline setting in WM

Bendamustine in combination with rituximab (BR) represents a commonly employed frontline chemoimmunotherapy for WM. The landmark phase 3 randomized clinical trial (StiL trial) compared six cycles of BR *versus* rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) in 447 patients with indolent lymphomas, including 41 patients with LPL/WM.[39] Although not powered for the subset of patients with LPL/WM ($n = 41$), median PFS with BR was 69.5 months (interquartile range (IQR) 36.6–73 months) compared with 28.1 months ((IQR 17.8–51 months), hazard ratio (HR) = 0.33, $p = 0.0033$) with R-CHOP treatment.[39] After an extended follow-up, the benefit in time-to-next treatment was sustained for the BR arm compared with R-CHOP, although OS was comparable in the two arms.[40] The overall response rate (ORR) with BR was 93%, which was comparable with R-CHOP, however, BR achieved in a higher rate of complete response (CR) rates (40% *versus* 30%, $p = 0.02$) using the standard World Health Organization (WHO) response criteria.[39] In line with the StiL trial data, the BRIGHT trial comparing BR *versus* R-CHOP/R-CVP in indolent lymphomas and mantle cell lymphoma demonstrated superiority of BR with regard to PFS (5-year PFS of 65% *versus* 56%, HR = 0.6, $p = 0.002$), however, only 11 out of the 447 patients had a diagnosis of LPL/WM.[41]

The BR regimen consists of bendamustine 90 mg/m^2 days 1 and 2, and rituximab 375 mg/m^2 on day 1 of each cycle, administered every 28 days for total of six cycles. The regimen was well tolerated, and major adverse effects were cytopenias with grade 4 neutropenia and thrombocytopenia was noted in 9% and 6%, respectively, in patients receiving BR. Rate of all grade infection was 37% with BR compared with 50% with R-CHOP, $p = 0.002$. Unlike R-CHOP, alopecia is not a

notable adverse effect with this regimen (0% in the StiL trial) and rates of paresthesias are lower with BR. Cutaneous adverse events (erythema (16% *versus* 9%) and allergic skin reaction (15% *versus* 6%)) were higher with BR.[39] When patients were treated with alkylator-based chemoimmunotherapy, secondary malignancies are of concern. In the StiL trial, one patient each in the BR (1 out of 261) and R-CHOP (1 out of 253) arms in the StiL trial were noted to develop myelodysplastic syndrome (MDS) during the follow-up period of 45 months.[39] Another retrospective study with a 9-year median follow-up reported 0.5%/person/year of developing MDS or acute myeloid leukemia (AML), which translated to a cumulative incidence of 6.2% after treatment with bendamustine in patients with non-Hodgkin lymphoma.[42] Furthermore, multiple retrospective studies have since demonstrated excellent efficacy and safety profile for BR in WM.[43–45]

Another common chemoimmunotherapy regimen utilized in the treatment of WM is dexamethasone–rituximab–cyclophosphamide (DRC). A phase 2 study of 72 patients with previously untreated WM was treated with DRC regimen that consisted of six 21-day courses of dexamethasone intravenous (IV) 20 mg and rituximab IV 375 mg/m^2 on day 1 and oral cyclophosphamide 100 mg/m^2 twice daily (days 1–5).[46] The ORR for the study population was 83% with 67% of these patients achieving a partial response (PR) and 7% achieving a CR. In this study, the median PFS was 35 months, median time to next treatment was 51 months and median OS was 95 months (8-year OS of 47%). Notably, 3% patients developed MDS during a median follow-up period of 8 years.[46]

PI-based therapies

Various PIs, including bortezomib, ixazomib, and carfilzomib have been evaluated in WM and have demonstrated good clinical efficacy. Historically, bortezomib, dexamethasone, and rituximab (BDR) has been a commonly employed PI-based regimen in WM. A phase 2 study of 59 patients with previously untreated WM demonstrated an ORR of 85%, with majority of responses (58%) being PRs, with and 7% achieving very good partial responses (VGPRs) and 3% achieving a CR. With an extended follow-up, the median PFS was 43 months and 7-year OS was 66%.[47] None of the patients treated with BDR developed a secondary

MDS after a median follow-up of 7 years. However, peripheral neuropathy was noted in 46% of patients (≥ grade 3 in 7%), and all patients demonstrated improvement in the neuropathy to grade 1 or lower at the time of last follow-up.[47] It is important to emphasize that this trial had utilized twice weekly intravenous bortezomib, whereas the current subcutaneous once weekly regimens are associated with significantly lower rates of peripheral neuropathy.[48,49]

A recent randomized phase 2 clinical trial of 204 patients with previously untreated WM studied the addition of bortezomib to DRC (B-DRC *versus* DRC), with a primary endpoint of PFS. The MRR was 79% *versus* 68% for B-DRC and DRC, respectively. The 2-year PFS was not significantly different between the two arms (80.6% (95% CI: 69.5, 88.0) with B-DRC *versus* 72.8% (95% CI: 61.3, 81.3) with DRC; *p* = 0.32), and rates of peripheral neuropathy were expectedly more common in the B-DRC population.[50] Carfilzomib, a neuropathy-sparing PI, was studied in combination with rituximab and dexamethasone (CaRD) in 31 patients with treatment-naïve WM and demonstrated ORR and MRR of 80% and 71%, respectively, with a median PFS of 45 months. Reversible cardiomyopathy was noted in 3% of the patients.[51] A study of 26 patients with ixazomib–dexamethasone–rituximab (IDR) demonstrated an ORR of 96% and MRR of 78%, with median PFS not reached at 22 months of follow-up.[31] It is important to note that both the CaRD and IDR regimens had a maintenance phase treatment with the respective agents in their study designs, which is not a uniform or commonly employed practice in managing patients with WM outside of clinical trial setting.

BTK inhibitors in frontline setting

Ibrutinib was the first BTK inhibitor that received approval from the Food and Drug Administration (FDA) in 2015 for treatment of patients with WM based on a study demonstrating excellent efficacy in patients with relapsed/refractory WM (RRWM).[23] Ibrutinib has been studied in the frontline setting in 30 patients with WM, all harboring the *MYD88*[L265P] mutation. Ibrutinib was initiated at a dose of 420 mg/day till progression, death or intolerable adverse effects and long-term results of the study were recently published.[25,52] Ibrutinib demonstrated excellent response rates, with an ORR of 100% and MRR of 87% (VGPR

rates of 30% and PR rates of 57%). However, as noted in RRWM patients treated with ibrutinib, CRs continued to remain elusive with only one reported case so far.[53] The response rates were lower in patients with *CXCR4* mutations (VGPR rates of 14% *versus* 44% for patients with and without *CXCR4* mutations, respectively), and patients with *CXCR4* mutations also had longer time to achieving a major response. After a median follow-up of 50 months, the median PFS was not reached in the study and 4-year PFS was 76%. The 4-year PFS was lower for patients with *CXCR4* mutations (59%, 95% CI: 28–81%) *versus* $CXCR4^{WT}$ genotype (92%, 95% CI: 57–99%; $p = 0.06$), with the lack of statistical significance being likely from the study not being powered to detect this difference. The rate of atrial fibrillation in this study population was 20%.[52] Acalabrutinib, another BTK inhibitor, has also demonstrated efficacy in RRWM.[54] While no randomized study has compared acalabrutinib with ibrutinib in patients with WM, a phase 3 study comparing acalabrutinib and ibrutinib in frontline treatment of patients with chronic lymphocytic leukemia demonstrated comparable PFS. Importantly, the rate of atrial fibrillation/flutter was significantly lower with acalabrutinib (9.4%) *versus* ibrutinib (16%, $p = 0.02$).[55] Overall cardiac events and hypertension were also lower in patients with acalabrutinib compared with ibrutinib in this study.[55]

Zanubrutinib, a more selective BTK inhibitor with fewer off target side effects was studied in the phase 3 ASPEN trial.[28] The study randomized 164 patients with RRWM and 37 patients with treatment-naïve WM to zanubrutinib and ibrutinib, with a primary endpoint of rates of VGPR or better ($\geqslant$VGPR) with these two BTK inhibitors. The study did not meet its primary endpoint of higher rates of $\geqslant$VGPR with zanubrutinib (28% *versus* 19% with ibrutinib, $p = 0.09$). However, zanubrutinib demonstrated significantly lower rates of atrial fibrillation (2%) compared with ibrutinib (15%). Other adverse effects, including diarrhea, hemorrhages and hypertension were also lower with zanubrutinib compared with ibrutinib. The rates of neutropenia were higher with zanubrutinib, but infection rates were comparable between the two arms.[28] Taking the acalabrutinib and zanubrutinib data together, it is likely that these drugs have a better safety profile compared with ibrutinib. In a subset analysis of the ASPEN study looking at $MYD88^{WT}$ patients

($n = 26$, with 23/26 being $CXCR4^{WT}$), the MRR was 50% with 18% achieved a VGPR with zanubrutinib treatment.[56]

The data for BTK inhibitor-based combination therapy in frontline setting is currently limited. The phase 3 iNNOVATE trial compared ibrutinib with rituximab (IR) to rituximab-placebo (placebo-R) in a phase 3 double blind randomized clinical trial. The study randomized 150 patients to IR and placebo-R with 45% of the study population not receiving any prior systemic therapy. In the overall study population, the IR regimen was associated with a significantly higher response rates (MRR of 72% *versus* 30%, $p < 0.001$) and PFS (30-month PFS rate of 82% with IR *versus* 28% with placebo-R, HR 0.2, $p < 0.01$).[57] While not powered to analyze the subset of treatment-naive cohort ($n = 68$), IR demonstrated a significantly improved 24-month PFS of 84% compared with 59% in the placebo-R arm (HR = 0.34; 95% CI: 0.12–0.95) in this cohort of patients.[57] The major limitation of this study is the comparator arm of rituximab monotherapy, which is no longer considered a standard frontline treatment for otherwise fit patients with WM. Nonetheless, the iNNOVATE study establishes safety and efficacy of the IR combination, and this represents another option for frontline therapy in WM.

Rituximab maintenance
Till recently, the role of maintenance therapy with rituximab in patients with WM was supported by limited evidence. Few retrospective studies have demonstrated improvement in outcomes for patients with WM treated with rituximab maintenance following four to six cycles of chemoimmunotherapy.[58,59] The phase 3 randomized NHL7-2008 MAINTAIN trial addressed the question of rituximab maintenance in patients with previously untreated WM treated with six cycles of BR. The patients in the maintenance arm received rituximab at a dose of 375 mg/m^2 every 2 months for a total of 2 years. Among patients responding to BR, the median PFS was 101 months in the rituximab maintenance cohort *versus* 83 months in the BR alone cohort, but this improvement was not statistically significant (HR = 0.80 (95% CI: 0.51–1.25, $p = 0.32$)).[60] No difference in OS was noted after a median follow-up of close of 70 months. In addition to establishing the limited role of rituximab maintenance, the study affirmed the prolonged and sustained

responses with BR in the frontline setting for WM. In addition to the lack of PFS benefit, the rates of infections were higher among patients treated with rituximab maintenance.[60] Treatment with rituximab has also been associated with poor humoral response to COVID-19 vaccination. Therefore, treating physicians should be cautious in recommending maintenance rituximab in WM, especially in the absence of an OS benefit.[61,62] In our practice, we do not recommend routine rituximab maintenance therapy after four to six cycles of induction chemoimmunotherapy.[8]

Choosing the optimal frontline therapy for patients with WM

The past decade has seen the rise of multiple efficacious and safe treatments in the frontline setting in WM. However, few randomized trials exist to establish superiority of one regimen over the other. Various factors play into the decision-making for optimal frontline therapy, including mutational profile, patient preference, general performance status, and medical comorbidities in the patients. Among patients with a $MYD88^{WT}$ genotype, the efficacy of non-BTK-based therapy is well established and is our preferred strategy for frontline therapy. As discussed above, the depth and kinetics of response along with PFS in patients with $CXCR4$ mutations are inferior compared with patients carrying $CXCR4^{WT}$ genotype when treated with ibrutinib. Based on these data, our preference in patients with $CXCR4$ mutations is to treat with chemoimmunotherapy rather than BTK inhibitors. At present, there are limited data on the impact of $CXCR4$ mutations on response and outcomes with chemoimmunotherapy regimens. For patients with $MYD88^{L265P}CXCR^{WT}$ genotype, both chemoimmunotherapy and BTK inhibitors are reasonable alternatives. The main distinguishing feature between chemoimmunotherapy and BTK inhibitors is the duration of therapy, toxicity profile, and route of administration. Chemoimmunotherapy regimens have the traditional adverse effects from chemotherapy, including cytopenias and nausea/vomiting but are typically used in a fixed duration of four to six cycles. These regimens do require intravenous administration. As discussed above, secondary malignancies due to chemotherapy is also a concern.[39,42,63] On the other hand, BTK inhibitor monotherapy has the convenience of oral administration and limited cytopenias compared with chemoimmunotherapies or PI-based treatments.

However, the atrial fibrillation rate of 15–20% is quite concerning,[28,52] especially in what is usually an elderly patient population. Bleeding complications are also noted with BTK inhibitors and need to be factored in while initiating treatment.[63] A recent global registry study demonstrated substantially longer time-to-next therapy with BR ($n = 74$) compared with BTK inhibitors ($n = 723$) in the frontline setting, but data on genotyping and baseline characteristics were not available in this study.[64] Keeping these caveats in mind, addressing the question of BTK inhibitors *versus* chemoimmunotherapy as frontline therapy needs more data.

With regard to the choice of non-BTK therapy in the frontline setting, BR is fast emerging as the accepted standard frontline therapy. There is no prospective study comparing BR with the other common regimens like DRC or BDR. A recent retrospective study comparing BR ($n = 83$) demonstrated superior ORR (98%), in comparison with DRC ($n = 2$, ORR: 78%) and BDR ($n = 45$, ORR: 84%) cohorts ($p = 0.003$) in the frontline setting. The median PFS was also noted to be superior with BR (median 5.2 years with BR *versus* 4.3 for DRC *versus* 1.8 years for BDR, $p < 0.001$).[65] There was no difference in the OS between these regimens. It is notable that the PFS with BDR was significantly inferior to the previously published reports in prospective studies and the study also fails to address the impact of $CXCR4$ mutation on the different chemoimmunotherapies.[65] Notably, the response rates for BR, DRC, or BDR regimens were not affected by the $MYD88$ mutation status.[65] The superiority of BR compared with other chemoimmunotherapy regimens has also been demonstrated in other retrospective studies.[66]

Our preferred approach for frontline treatment for all patients with treatment naïve WM is four to six cycles of BR without maintenance rituximab, especially pertinent in patients with $MYD88^{WT}$ and $MYD88^{L265P}/CXCR4^{MUT}$ genotypes, where ibrutinib has much lower efficacy. The rationale for our preference for BR irrespective of the mutational profile is the fixed duration of therapy along with good safety and efficacy profile. We also prefer to use BR especially in patients with bulky lymphadenopathy or extensive liver disease in order to achieve a quick response. In patients with a serum IgM value of more than 4,000–5,000 mg/dL, rituximab can be omitted from the initial few

cycles of chemoimmunotherapy to avoid an IgM flare.[67] In addition, while the standard recommended dose of bendamustine is 90 mg/m² on days 1 and 2, we do consider dose reduction to 70 mg/m² in elderly or frail patients. We have highlighted some of these important studies in Table 1 and also present an algorithmic approach to frontline therapy in Figure 1.

Treatment options for RRWM

Similar to the treatment indications in the frontline setting, the initiation of therapy in the relapsed setting should be based on constitutional signs and symptoms of malignancies, and disease-related cytopenias and not merely the serum IgM level.[9] In the absence of comparative prospective studies to guide treatment for RRWM, there is no standard treatment adopted universally and most guidelines are based on previous treatments, clinician preference, and data from small retrospective and prospective studies. In patients with progression after frontline therapy, our preferred strategy for subsequent treatment is with a different treatment regimen and drug class that has not been utilized before. For instance, in patients treated with BR with subsequent progression, we prefer treatment with a BTK inhibitor and vice versa. Akin to decision-making in frontline setting, patient's comorbidities and preference for continuous *versus* fixed duration treatment, treatment availability and physician comfort level along with financial toxicity should also be taken to count when selecting best treatment options for patients with WM. Occasionally, patients who have had a sustained disease remission with frontline chemoimmunotherapy (typically a time-to-next treatment of 3–4 years or longer after completion of frontline therapy) can be offered a retrial of the same regimen.[8]

Non-BTK inhibitor-based therapy

BR has shown to be effective in achieving durable responses in RRWM. A retrospective study looking at 71 patients with RRWM treated with BR in the salvage setting demonstrated an ORR of 80% with 7% achieving CR, 15% achieving VGPR, and 52% achieving PR.[44] None of the 71 patients were treated with a BTK inhibitor-based therapy; 90% of patients were treated with an alkylating agent in combined with rituximab before initiation of BR and 34% of patients were refractory to alkylator-based therapy. The ORR for patients who were not refractory to alkylator-based treatments was 87% compared with 67% in patients who had refractory disease to alkylator-based therapy. Patients with an IgM level < 3,000 mg/dL at the time of treatment initiation had a better quality of response with higher CR and VGPR rates compared with patients with IgM level ⩾ 3,000 mg/dL. In addition, a higher dose of bendamustine at 90 mg/m² had a comparable ORR and MRR for doses < 90 mg/m², but the deeper responses were noted with the higher dose (CR and VGPR rate of 37% *versus* 10%). In this study, after a median follow-up of 19 months, the median PFS was not reached and the 4-year OS was 72%.[44]

Another retrospective study in RRWM compared 44 patients treated with BR and 50 patients treated with DRC. For patients treated with BR, the ORR was 95% with MRR of 81%; CR (3%), VGPR (38%), and PR (41%). After a median follow-up of 32 months, the estimated median PFS was 58 months. Patients with RRWM treated with BR had a trend toward improved PFS (median PFS, 58 months with BR *versus* 31 months with DRC, $p = 0.08$).[43] In a retrospective study by Paludo *et al.*, 50 patients with RRWM were treated with DRC and ORR was seen at 87%, including 4% with VGPR and 64% with PR. After a median follow-up of 51 months, the median PFS was 32 months and median time-to-next therapy was 50 months.[69]

In addition to chemoimmunotherapy, purine analog-based therapies, PIs and novel agents have all demonstrated efficacy in RRWM. Purine analogs have good efficacy in RRWM, but largely fallen out of favor due to the adverse toxicity profile of these class of drugs, especially the prolonged immunosuppression. Cytopenias can also be persistent, especially in patients previously treated with chemoimmunotherapies.[70] In a prospective study, fludarabine and rituximab (FR) combination was studied in patients with WM (27 patients in the treatment naïve and 16 patients in the RR setting) demonstrated an ORR of 95% with a MRR of 86%, with 5% achieving a CR.[71] After a median follow-up of 40.3 months, the median estimated PFS for the entire cohort was 51.2 months and was significantly shorter in patients who received FR in the salvage setting (38.4 months) compared with patients who received FR in the upfront setting (77.6 months). In this study, 7% of patients transformed to

Table 1. Summary of selected important comparative studies for frontline therapy in patients with Waldenström macroglobulinemia.

References	Study type and regimen	Median follow-up	Response rate	Median PFS	OS
Rummel *et al.*[39] STiL NHL1-2003Trial	Phase 3 BR *versus* R-CHOP (*n* = 41 for WM subset)	45 months (entire cohort)	91%	69.5 months (BR) *versus* 28.1 months (R-CHOP); *p* = 0.003	Median OS not reached
Rummel *et al.*[60] StiL NHL7-2008 MAINTAIN Trial	Phase 3 induction × six cycles *versus* induction × 6 cycles followed by R maintenance 2 months × 2 years	70 months	91.4%	83 months in observation (65.3 months with BR) *versus* 101 months in maintenance arm (HR = 0.8; *p* = 0.32)	Median OS not reached in either arm
Dimopoulos *et al.*[57] Buske *et al.*[68] iNNOVATE trial	Phase 3 IR (*n* = 75) *versus* placebo-R (*n* = 75) frontline *n* = 68	50 months	Response for IR: 92%, MRR: 72%;*MYD88*[L265P]*/CXCR4*[WT]: 94%, MRR: 78%, *MYD88*[L265P]*/CXCR4*[WHIM]: 100%, MRR: 73%[a] *MYD88*[WT]*/CXCR4*[WT]: 81%, MRR: 63%[a]	Median PFS NR (57–NR) *versus* 20.3 months (13–28) frontline cohort (*n* = 68): HR = 0.34 (95% CI: 0.12–0.95) for IR *versus* placebo-R	Median OS not reached for either arm. HR = 0.81 for IR *versus* placebo-R (*p* = 0.64)
Buske *et al.*[50]	Prospective randomized phase 2 B-DRC (*n* = 100) versus DRC (*n* = 100)	27.5 months	91.2%, MRR: 79% *versus* 86.7%, MRR: 69%	24-month PFS, %; 80.6% (69–88) for B-DRC *versus* 72.8% (61–81) for DRC (*p* = 0.32)	Median OS not reached in both arms
Abeykoon *et al.*[65]	Retrospective BR (*n* = 83) *versus* DRC (*n* = 92) *versus* BDR (*n* = 45)	54 months	98% *versus* 78% *versus* 84%	Median PFS, 5.2 years (BR) *versus* 4.3 years (DRC) *versus* 1.8 years (BDR); *p* < 0.0001	4-year OS 90% (BR) *versus* 87% (DRC) *versus* 87% (BDR) *p* = 0.77
Castillo *et al.*[66]	Retrospective BR (*n* = 57) *versus* DRC (*n* = 87) *versus* CDR (*n* = 38), with or without R-maintenance	42 months	98%, MRR: 94% *versus* 90%, MRR: 83% *versus* 89%, MRR: 84%	Median PFS 66 months (BR) *versus* 59 months (DRC); *p* = 0.1[a] *versus* 71 months (BDR), *p* = 0.1[a]	5-year OS, 95% (BR) *versus* 81% (DRC) *versus* 96% (BDR); *p* = 0.06 (overall)
Tam *et al.*[28] ASPEN study	Prospective randomized phase 3, ibrutinib (*n* = 18) *versus* zanubrutinib (*n* = 19)[b]	18 and 18.5 months[b]	89%, MRR: 67% *versus* 95%, MRR: 74% MRR for *CXCR*[WHIM] and *CXCR*[WT]: 63% *versus* 64% for ibrutinib and 80% *versus* 79% for zanubrutinib[b]	Median PFS NR (0-31) *versus* NR(0-31)[b]	18 months OS, 97% *versus* 93%[b]
Dimopoulos *et al.*,[56] ASPEN subset analysis of *MYD88*[WT] cohort	Zanubrutinib (*n* = 28)[b]	17.9 months[b]	80%, MRR: 40%[b]	12 and 18 months: 80% and 60%[b]	12 and 18 months: 100% and 80%[b]

BR, bendamustine–rituximab; BDR- bortezomib, dexamethasone, rituximab; DRC, dexamethasone–rituximab–cyclophosphamide; IR, ibrutinib–rituximab; NA, not available; NR, not reached; PFS, progression-free survival; OS, overall survival; R, rituximab; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; WM, Waldenström macroglobulinemia.
[a]No documented complete responses.
[b]Includes both treatment naïve patients and relapsed/refractory patients.
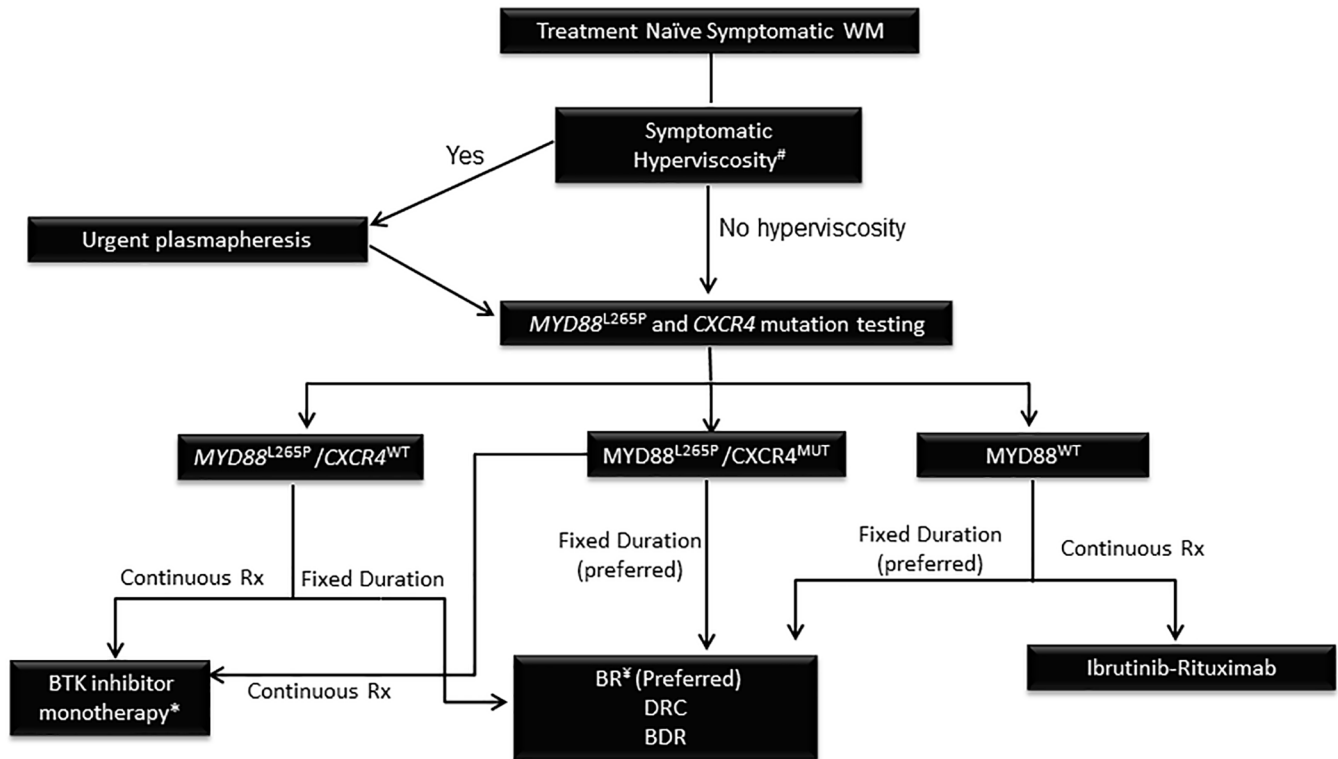
Figure 1. Algorithm for management of newly diagnosed Waldenström macroglobulinemia.
BTK, Bruton tyrosine kinase; BR, bendamustine-rituximab; BDR, bortezomib-rituximab-cyclophosphamide; $CXCR4^{MUT}$, CXCR mutated; $CXCR4^{WT}$, CXCR wild type; DRC, dexamethasone-rituximab-cyclophosphamide; WM, Waldenström Macroglobulinemia
#Symptoms of hyperviscosity include, but are not limited to, headaches, visual disturbance, abnormal bleeding, altered mental status, strokes and acute coronary syndrome.
*Include ibrutinib, acalabrutinib, zanubrutinib.
¥In case of serum IgM > 4000 mg/dl, consider omitting rituximab from BR for first couple of cycles to avoid IgM flare from rituximab.

aggressive lymphoma while another 7% of patients had developed AML and MDS at a median time of 21 and 39 months, respectively, from the initiation of FR.[71]

PIs are also efficacious agents in RRWM. Bortezomib given intravenously in 27 patients with RRWM demonstrated excellent response rates (ORR of 85%), but was complicated by high rates of ≥grade 3 neuropathy.[72] Carfilzomib has also been studied with rituximab and dexamethasone (CaRD) in a phase 2 study in RRWM patients who were not treated with bortezomib or rituximab-based therapy. In this study, ORR and MRR were observed at 87% and 68%, respectively, and CR/VGPR was achieved in 36%. Although this is an attractive regimen where less neuropathy was seen compared with bortezomib-based regimens, in current era, patients who have relapsed disease and were not exposed to rituximab-based therapy remains very rare. Hence, the applicability of this data in patients with RRWM remains limited.[73]

A phosphatidylinositol 3-kinase inhibitor, idelalisib, was studied in combination with obinutuzumab in a phase 2 clinical trial in 48 patients with RRWM. The ORR was 71% while the MRR was 65%, with none achieving CR. After a median follow-up of 26 months, the median PFS was 25 months. In this study, *CXCR4* mutation status had no impact on response and the impact of $MYD88^{L265P}$ mutation status was not assessed. Importantly, 53% of patients discounted idelalisib due to toxicity after a median of three cycles and ≥grade 3 neutropenia, anemia, and thrombocytopenias were observed at 19%, 6%, and 4%, respectively.[74]

Venetoclax, a small molecule BCL-2 inhibitor, was evaluated in a phase 2 clinical trial of

32 patients with RRWM, including 16 patients that were previously exposed to BTK inhibitors.[75] All patients were *MYD88*[L265P] mutated and 17 harbored a *CXCR4* mutation. The ORR and MRR were 84% and 81%, respectively, and no CRs were noted. The MRR for patients with refractory disease was 50% as compared with 95% in patients who had relapsed disease without refractoriness to prior therapy. The CXCR4 mutation status did not seem to impact response, but the cohort size was small. After a median follow-up of 33 months, the median PFS was 30 months and ⩾ grade 3 neutropenia was seen in 45% of patients.[75] The role of venetoclax in *MYD88*[WT] genotype remains to be studied. Daratumumab, a CD38 monoclonal antibody, was studied in a phase 2 trial in 13 patients with RRWM. The efficacy of daratumumab was modest at best and ORR was only 23% with a short median PFS at 2 months.[76]

BTK inhibitor-based therapy

Ibrutinib, acalabrutinib, and zanubrutinib are all active and effective agents for patients with RRWM. Ibrutinib is the first-generation BTK inhibitor that was initially studied in 63 patients with RRWM. Of these patients, 51% had alkylator-based therapy before initiation of ibrutinib. In this study, ORR was seen in 90.5% and MRR in 73%. The best responses were seen in patients with *MYD88*[L265P]/ *CXCR4*[WT].[23] In RRWM with rituximab-refractory disease, ibrutinib demonstrated ORR and MRR of 87% and 77%, respectively, and most patients (except one) in this study had *MYD88*[L265P] genotype. After 58 months of follow-up, the median PFS was 39 months. Interestingly, in this rituximab-refractory patient population, no events of atrial fibrillation or hemorrhagic complications were reported as an adverse event from ibrutinib single-agent treatment.[24,77] The results of the iNNOVATE study comparing IR with placebo-R have been discussed previously, with IR demonstrating robust responses close to 80% or above with responses seen across all *MYD88* and *CXCR4* genotype subsets, suggesting that the addition of rituximab to ibrutinib can potentially overcome the relatively low responses seen with ibrutinib single-agent treatment in *MYD88*[WT] and *CXCR4*[WHIM] mutated genotypes.[57]

Acalabrutinib was studied in 92 patients with RRWM and demonstrated an ORR and MRR of 93% and 78%, respectively. As expected, the ORR and MRR were higher in patients with *MYD88*[L265P] genotype (94% and 78%, respectively) compared with *MYD88*[WT] genotype (ORR: 79% and MRR: 57%). Abnormalities in hemostasis occurred in 58% of patients and atrial fibrillation was reported in 4% of patients with RRWM.[78] In the seminal phase 3 ASPEN clinical trial discussed previously, zanubrutinib was studied and was compared head-to-head with ibrutinib. While the study did not meet its primary endpoint of significantly higher rate of deeper responses with zanubrutinib, the toxicity profile for zanubrutinib is favorable when compared with ibrutinib.[28] In the subset analysis of the ASPEN study looking at *MYD88*[WT] patients (23 out of 28 were relapsed/refractory), the MRR was 50% with 18% achieved a VGPR with zanubrutinib treatment.[56]

Stem cell transplant-based therapy

Autologous stem cell transplant (ASCT) is an uncommonly used treatment modality in patients with RRWM and allogenic stem cell transplant (allo-SCT) should not be used outside of a clinical trial setting due to its associated treatment-related morbidity and mortality. A European Group for Blood and Marrow Transplantation (EBMT) study for ASCT demonstrated 5-year PFS and OS rates of 40% and 70% in a cohort of 158 patients with RRWM, but was associated with a high rate of secondary malignancies (8.4% at 5 years).[79] Given the favorable genetic profile and slow kinetics in WM, some studies have also documented promising outcomes with ASCT.[80] However, with increasingly effective and well-tolerated options becoming available for treatment of RRWM, in the current era the role of ASCT is mostly relegated to transformation to an aggressive lymphoma. If ASCT is being considered as treatment for patients with RRWM in the absence of transformed disease, we recommend selection of patients with good performance status in whom treatment options with fixed duration chemoimmunotherapy, PI-based therapy, and BTK inhibitor-based therapy have been exhausted, but remains to be chemosensitive. A synopsis of treatment options and associated responses for patients with RRWM could be found in Table 2.

Histologic transformation in WM

The cumulative incidence of transformation of WM to an aggressive malignancy has been demonstrated in 2–11% of patients and tends to

Table 2. Summary of select treatment regimens for patients with relapsed/refractory Waldenström macroglobulinemia.

Regimen, study, and number of patients	Study type	ORR (%)	MRR (%)	PFS, EFS or TTP (months)
Bendamustine and rituximab Paludo et al.[43] (n = 43) Tedeschi et al.[44] (n = 53)	Retrospective Retrospective	95 80	81 75	58 30-month PFS: 60%
Dexamethasone, rituximab, and cyclophosphamide Paludo et al.[69] (n = 50)	Retrospective	87	68	32
Cladribine and rituximab Laszlo et al.[70] (n = 13)	Prospective	85	–	–
Fludarabine and rituximab Treon et al.[71] (n = 16)	Prospective	94	81	38.4
Fludarabine, cyclophosphamide, and rituximab Tedeschi et al.[81] (n = 15)	Retrospective	79	77	50*
Carfilzomib, rituximab, dexamethasone Treon et al.[73] (n = 30)	Prospective	87	68	15-month PFS 64.5
Thalidomide and rituximab Treon et al.[82] (n = 25)	Prospective	72	64	15.25
Lenalidomide with rituximab# Treon et al.[83] (n = 16, 12 previously untreated)	Prospective	50	25	17
Idelalisib with obinutuzumab Tomowiak et al.[74] (n = 48)	Prospective	71	65	25
Venetoclax Castillo et al.[75] (n = 32)	Prospective	84	81	30
Daratumumab Castillo et al.[76] (n = 13)	Prospective	23	15	2
Ibrutinib Abeykoon et al.,[20] Treon et al.[84] (n = 63) Dimopoulos et al.,[57] Trotman et al.[77] (n = 31)	Prospective Prospective	90.5 91	79 71	5-year PFS 54% Median PFS 39 months
Ibrutinib plus rituximab (IR) Dimopoulos et al.,[57] Buske et al.[85] (n = 150; 75 in IR arm)	Prospective phase 3	92	76	48-month PFS: 71%
Acalabrutinib Owen et al.[78] (n = ; 92 had relapsed or refractory disease)	Prospective	93	78	24-month PFS: 90%
Zanubrutinib Tam et al.[28] (n = 164)	Prospective	94	78	18-month PFS: 85%
ASCT Parrondo et al.[86] (n = 278) **Allogenic SCT** Parrondo et al.[86] (n = 311)	Meta-analysis Meta-analysis	85 81	80 76	55 49

*EFS: event-free survival; PFS: progression-free survival; ORR: overall response rate; MRR: major response rate; m: months; ASCT: autologous stem cell transplant; allo-SCT: allogeneic stem cell transplant.
#Lenalidomide produced clinically significant acute anemia.

increase with a longer follow-up.[21,34,87] The most common type of aggressive lymphoma which rises from WM transformation is diffuse large B-cell lymphoma (DLBCL). Prior alkylator-based and purine nucleoside-based therapies increase risk of transformation and one study noted a 6-year cumulative incidence of transformation to be 7.7% and 11.1% in patients treated with fludarabine and chlorambucil, respectively.[21,34] However, these agents are now infrequently used in treating patients with WM and recent studies have documented the risk of transformation to be less than 5% during a follow-up period of close to 10 years and have identified $MYD88^{WT}$ to be an independent risk factor for transformation.[20,21] Although the biological explanation for this is not completely understood, the genomic profile for $MYD88^{WT}$ WM, as compared with $MYD88$ mutated counterparts, have shown to have overactive NF-κB activation, higher mutations in DNA damage repair proteins, such as ataxia telangiectasia mutated (ATM) thus impairing DNA repair response, and genomic dysregulation, which might contribute to increased risk of histological transformation.[88]

The treatment strategies for transformed WM parallels what is used in aggressive DLBCL and most commonly used chemoimmunotherapy option is R-CHOP or other similar chemoimmunotherapy therapy with response rates ranging from 61 to 83% (CR 48–60%).[89] Despite therapeutic advancements made in WM, the prognosis for transformed WM remains poor and the median OS ranges from 16 to 36 months.[21,89]

Summary
The treatment options for patients with WM have expanded over the past decade with the current choice of frontline therapy commonly being between a BTK inhibitor and chemoimmunotherapy regimens. The genotype of the tumor and the patient preferences plays a crucial role in determining optimal frontline therapy. We prefer a fixed duration chemoimmunotherapy with four to six cycles of BR without any maintenance therapy for patients with newly diagnosed WM with indication for treatment. Additional data are needed on the impact of CXCR4 mutations on outcomes with chemoimmunotherapy regimens to further tailor the treatment. With the relatively similar efficacy of zanubrutinib and ibrutinib, the choice between various BTK inhibitors is directed by the differing safety profile. Cure still remains elusive in WM and limiting long-term toxicities should be an important component while choosing therapy for patients with WM.

Author contribution(s)
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Jithma P. Abeykoon: Conceptualization; Data curation; Methodology; Writing – original draft; Writing – review & editing.

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