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Current approach to Waldenström Macroglobulinemia

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ABSTRACT

Waldenström Macroglobulinemia (WM) is a unique, low grade, IgM lymphoplasmacytic lymphoma with a heterogeneous clinical course. A paucity of high-grade evidence from large phase 3 trials remains a major issue in the field despite a rapidly expanding therapeutic armamentarium against WM. Prior knowledge of the patients' $MYD88^{L265P}$ and CXCR4 mutation status aids in treatment decision making if Bruton's tyrosine kinase (BTK) inhibitor therapy is being considered. Head-to head comparative data to inform optimal approach are lacking, and a particularly vexing issue for the clinicians is choosing between fixed-duration bendamustine-rituximab (BR) therapy and an indefinite BTK inhibitor-based regimen, given that both approaches are well tolerated and effective, particularly for the patient population harboring $MYD88^{L265P}$ mutation. For the patients with $MYD88^{WT}$ genotype, chemo-immunotherapy such as BR is preferred, although zanubrutinib, a potent second generation BTK inhibitor, with its reduced off target effects and greater BTK occupancy compared to its predecessor, ibrutinib, has also recently shown activity in $MYD88^{WT}$ WM. This review summarizes the current literature pertaining to the diagnosis, prognosis, and the treatment of WM.

Introduction

Waldenström macroglobulinemia (WM) is a distinct, indolent, non-Hodgkin lymphoma (NHL) characterized by circulating monoclonal immunoglobulin (Ig) M and lymphoplasmacytic bone marrow infiltration. With the identification of mutations in the *MYD88* and *CXCR4* genes and a critical actionable target, Bruton's tyrosine kinase (BTK), newer therapies are being evaluated at an unprecedented pace. This review appraises the current literature impacting our approach to patients with WM, a unique B cell malignancy.

Epidemiology

WM has an estimated incidence of 1000–1500 new cases per year in the US [1, 2]. The median age at diagnosis is approximately 70 years. Albeit a rare hematologic malignancy, WM is twice as common among males (3.4 per million/year) [3] and predominantly affects Caucasians [4]. Encouragingly, the 5-year survival has improved to 78% among those diagnosed between 2000 and 2010 in comparison to67% among those diagnosed earlier. [5] With improved therapies, there are emerging data that the in-hospital mortality rates as well as the need for hospital admissions are also declining [6]. Although there is no proven inheritance pattern, a Swedish population-study has observed a 20-fold increased risk of developing LPL in the first degree relatives of patients with WM. [7] In addition, there is 3, 3.4 and a 5- fold increased risk of developing non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL) and monoclonal gammopathy of unknown significance (MGUS), respectively, among the first degree relatives of patients with WM. [7] A family history of WM may be associated with a shorter progression-free survival (PFS) and time to next treatment (TTNT), without a discernable difference in overall survival (OS). [8, 9]

Pathogenesis

The identification of a somatic mutation in the myeloid differentiation factor 88 (*MYD88*) gene by whole genome sequencing has provided critical insight into pathways driving proliferation and survival of WM cells. A somatic variant (T→C) at position 38,182,641 of chromosome 3p22.2 results in substitution of leucine to proline (L265P), an amino acid sequence alteration that has been observed even at the precursor IgM MGUS stage. [10] This gain-of-function mutation activates the nuclear factor kappa B (NF-κB) and MAPK signaling pathways through IL-1 receptor associated kinase (IRAK4) and BTK enzymes, promoting WM cell survival and oncogenesis. [11, 12] Notably, the response to BTK inhibitors[13] and progression rate from IgM MGUS to active WM [14] is higher in the setting of MYD88 mutation. This acquired mutation may

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be encountered in upto 95% of cases with WM [11] [13] and upto 80% of patients with IgM MGUS [13]. Targeted next-generation sequencing (NGS) has identified mutations other than the classical L265P in the *MYD88* gene in a small subset of patients who respond to BTK inhibitors as well as their counterparts with L255P mutation.

Unique subclonal somatic mutation(s) involving the C terminal domain of the G-protein coupled chemokine receptor, CXCR4 are identified in upto 40% of patients with WM [15, 16], leading to loss of regulatory serines [17], and are akin to the germline mutation in *CXCR4* encountered in patients with WHIM syndrome, an autosomal dominant disorder with **W**arts, **H**ypogammaglobulinemia, **I**nfections, Myelokatheksis [16]. When its ligand, the stromal derived factor-1 (SDF-1/CXCL12) binds to mutated CXCR4, sustained downstream activation of prosurvival protein kinase B (AKT) and extracellular signal-regulated kinase (ERK) pathways is observed, supporting migration and adhesion of WM cells to bone marrow stroma as well as resistance to BTK inhibitors. [18] Over 40 different types of nonsense and frameshift mutations of CXCR4 have been identified in patients with WM. [15, 18-20] $CXCR4^{S338X}$ is the most common sub-clonal nonsense CXCR4 mutation and can be detected by allele-specific polymerase chain reaction (AS-PCR) assay [16]. The patients harboring CXCR4 mutation (s) typically show a higher bone marrow burden but lymphadenopathy is not as frequently observed [21]. *CXCR4* mutations are observed in IgM-MGUS as well, albeit at a lower frequency than WM (7% versus 24%, $P < 0.02$). [22] Mutations in other genes *KMT2D* (24%), *PRDM1* (6%),*NOTCH2* (5%), *ARID1A* (5%), *CD79b* (3%), and *TRAF3* (2%)exist but their prognostic impact remains unknown [23].

Patients with $MYD88^{WT}$ signature present at an older age, with less bone marrow involvement, but higher B2 microglobulin levels, [21] lower IgM levels and higher extramedullary involvement. [23] Moreover this signature is associated with a higher risk of histologic transformation compared to $MYD88^{L265P}$ (18% vs 4%) although the 5-year OS rates appear to be similar (85% vs 82%) [24]. The patients with $MYD88^{265P+}$/$CXCR4^{WHIM/FS}$ have an intermediate disease course when treated with ibrutinib, a first- in-class BTK inhibitor, but exhibit higher IgM levels and increased bone marrow involvement, with a higher rate of symptomatic hyperviscosity. [21]

The other cytogenetic abnormalities reported in patients with MYD88 mutation include deletion of 6q(7–30% with conventional cytogenetics and 54% with M-FISH) [25, 26], gain of 4q, 8q, 12q,loss of 11q,13q and 17p[17] . Del 6q was most common cytogenetic abnormality in a Chinese study of 181 patients with LPL and was associated with complex karyotype and high risk IPSSWM[27] but did not impact PFS or OS. However, another recent study showed that WM patients with del 6q exhibited shorter PFS (median 20 vs. 47 months, $P < 0•001$) and OS (median OS of 90 compared with 131 months in non-del6q patients $P= 0•01$) [28]. Del 6q results in the loss of B-lymphocyte-induced maturation protein 1 (*BLIMP1*) and tumor necrosis factor alpha-induced protein 3 (*TNFAIP3*) which is a negative regulator of the NF-κB pathway, perhaps accounting for a more aggressive disease course. [28] Importantly, a minimal region of deletion (MDR) for 6q (6q14.1–6q27) reportedly includes a host of genes involving regulatory functions including *IBTK* (BTK/B-cell receptor), *FOXO3, BCLAF1* (apoptosis), and *TNFAIP3, HIVEP2 (*NF-kB) in WM [29]. Del 17p seen in upto 8% of patients, is more frequent in patients with translocation than without (43% vs 5%,$p = 0.03$) and associated with a shorter disease-free survival (7.8 vs 28.8 months, $p = 0.001$) and PFS (18.7 vs 30 months, $p = 0.05$). [26] PI3K/AKT pathway has been shown to decrease apoptosis and aid in homing and adhesion of WM cells to the marrow milieu; inhibition of this pathway with perifosine blocks WM cells from homing into their protective niches. [30]

Diagnostic criteria

The Mayo Clinic Criteria for the diagnosis of WM require the presence of monoclonal serum IgM of any size plus bone marrow lymphoplasmacytic infiltration of at least 10%. The characteristic immunophenotypic signature of WM cell reveals surface IgM^{+}, $CD5^{\pm}$, $CD19^{+}$, $CD20^{+}$, $CD22^{+}$,$CD79a^{+}$,$CD23^{-}$, $CD25^{+}$,$CD27^{+}$,$FMC7^{+}$, $CD138^{+}$,$CD103^{-}$[31]. CD11c and CD23 may be observed in 81% and 61% respectively, [32] and CD10 was positive in 7% [33] thus accounting for the diagnostic complexity.

In addition to the bone marrow, lymph nodes and spleen may be infiltrated by lymphocytes and plasmacytic cells in WM. Though IgM WM is the most common LPL, ≤ 5% LPLs can have IgG, IgA and non-secretory types, with have higher extramedullary involvement [34, 35].. MYD88 mutation has been encountered in upto 43% of non-IgM LPL [36]. No difference in PFS or OS compared to IgM LPL (WM) counterparts has been observed. [34]

Initial investigations

A detailed history, including the family history and thorough physical exam are essential in all patients suspected to have WM. It is critical to differentiate IgM MGUS and active WM as the management differs significantly. The clinical presentations in a patient suspected to have WM are summarized in Table 1. Additional testing is based on clinical suspicion and treatment decision.

Risk stratification and prognosis

The International Prognostic Scoring System for Waldenström Macroglobulinemia (IPSSWM)[37] has been widely used to risk stratify WM prior to initiating therapy, however its role in the treatment decision making is limited. Given the increasing incidence of WM with age and the emergence of newer prognostic markers R-IPSSWM was introduced in 2019. [38] In a Mayo Clinic study of 889 patients, age > 65 years (RR 1.8,95%CI 1.2–2.8,$p = 0.01$), LDH > upper limit of normal (RR 2.5, 95%CI 1.3–4.6,=0.003) and serum albumin <3.5 g/dL (RR 1.6, 95%CI 1.1–2.5,$p = 0.02$) were found to be independently prognostic [39]. Patients were stratified into low-risk, intermediate-risk and high risk based on presence of 0,1 or ≥2 risk factors. The median OS for low risk in this simplified model was 14.6 years (95%CI 12.1-NR), intermediate risk group was 11 years (95%CI 8.1–14.7 years) and the high-risk group was 7.2 years (95% CI: 5.4–10 years)[39].

Table 1
Evaluation of Patients with Suspected Waldenström macroglobulinemia.

Clinical	Investigations
Signs and symptoms related to tumor burden Lymphadenopathy Organomegaly, early satiety B symptoms **Signs and symptoms related to IgM Hyperviscosity:** Headache, blurry vision, impaired balance, encephalopathy, mucocutaneous bleeding, peripheral neuropathy; requires fundoscopic examination **Coexisting AL, AH or AHL Amyloidosis:** - Peripheral /autonomic neuropathy - Volume overload - Diarrhea, constipation - Easy bruising - Dyspnea, palpitations, jaw claudication, macroglossia, periorbital purpura, xerostomia, dysgeusia **Cryoglobulinemia:** - Vasculitis, purpura, acrocyanosis, cutaneous ulcers - Raynaud's phenomenon, arthralgias, renal dysfunction	-CBC with differential -Renal and liver function - SPEP and 24-hour UPEP with immunofixation -Quantitative immunoglobulins - Serum free light chains - Uric acid, β2microglobulin, LDH - Bone marrow aspirate and biopsy with immunohistochemstry - MYD88 L265P mutation testing with AS-PCR in bone marrow. - CXCR4 mutational analysis (if available) Serum viscosity, cryoglobulin and cold agglutinin titer in select cases CT scan chest, abdomen and pelvis

Management

Smoldering WM (SWM)

WM is a heterogeneous disease, with variable outcomes [40, 41]; the median disease-specific survival is approximately 11years [42]. There are specific indications for initiating therapy and a substantial subset (15–25%) of patients diagnosed with WM does not require treatment at presentation. SWM is characterized by the asymptomatic presence of IgM monoclonal protein >3 g/dL and/or ≥10% involvement of bone marrow with lymphoplasmacytic cells in the absence of WM-related end-organ damage, i.e. indications to initiate treatment. [40] The patients with SWM have a higher risk of progression to active WM or AHL amyloidosis compared to IgM MGUS (68% vs 18% at 10 years). [40, 43] In a Mayo Clinic study of 87 patients between 1974 and 1995 the cumulative progression of SWM was 6% at 1 year, 39% at 3 years, 59% at 5 years and 68% at 10 years. [40] The rate of progression was 12% per year in first 5 years and decreased to 2% per year for next 5 years. [40] Bone marrow involvement of over 50% and IgM levels > 3 g/dL have been associated with an increased risk of progression [40]. In another recent study IgM levels > 4.5 g/dl, bone marrow involvement > 70%, albumin ≤ 3.5 g/dl, β2microglobulin >4 mg/dl [44] and $MYD88^{WT}$ were associated with a higher rate of progression to active disease requiring therapy [45].

Indications for treatment

Specific indications for the treatment of WM have been clearly outlined based on the 2nd IWWM Consensus [46]. WM cell directed therapy can be initiated if the following scenarios are directly attributable to WM: a) the presence of constitutional symptoms, b) profound cytopenias (Hb < 10 g/dl, PLT <100,000/μL, c) bulky lymph nodes/organomegaly, d) symptomatic hyperviscosity, e) cryoglobulinemia, f) symptomatic cold agglutinin disease, g) moderate to severe neuropathy, h) AL/AH amyloidosis. The absolute size of IgM protein should not be a determinant of the timing of commencement of therapy, but SWM patients with progressively increasing IgM levels require much closer monitoring in the absence of specific indications for therapy. Additionally, clinicians should be vigilant for any symptoms of hyperviscosity, specifically in patients with IgM levels over 4000 mg/dL. A funduscopic examination to rule out any hyperviscosity related retinal changes is imperative in such cases.

Treatment

Anti-CD20 antibodies

CD20 is uniformly expressed on WM cells. Rituximab monotherapy in 4 weekly doses was initially evaluated in a phase 2 ECOG trial, E3A98 (Table 2) in both frontline and relapsed/refractory (R/R)setting and demonstrated an ORR of 52%. [47] Rituximab intolerance secondary to infusion reactions, cytopenias and infection can develop with prolonged treatment. [48] Another anti-CD20 monoclonal antibody, ofatumumab showed ORR 59% [49] and IgM flare at a rate (9%) that appeared lower compared to that observed with rituximab monotherapy (50%) [49] and may be used in patients with rituximab intolerance. A combination of idelalisib and obinutuzumab in the R/R setting in a phase 2 PHYLLO trial showed impressive major response rate (MRR/ partial response or better) of 76% and an overall response rate (ORR) of 90% after induction [50] Anti-CD20 antibodies can easily be integrated with chemotherapy, BTK inhibitors and proteasome inhibitors (PIs), without substantially affecting the toxicity profiles of the regimens.

Chemoimmunotherapy

Bendamustine-Rituximab (BR) is a safe, well-tolerated regimen, used widely in the frontline and R/R setting in WM. Non-inferiority of BR compared to combination of rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone along with (R-CHOP) was first shown in STiLNHL1–2003 phase 3 trial, [51] with similar ORR (93% vs 91%) for the two regimens, but lesser toxicity in the BR arm. The median PFS of approximately 70 months with BR was impressive compared to only 28 months with R CHOP (**Table 3**). More recently, the results of the STiL NHL-MAINTAIN study [52] confirmed the efficacy of BR regimen (median PFS 68 months), but rituximab maintenance for 2 years following BR induction and 2 cycles of rituximab consolidation in those that had achieved at least a partial remission was not associated with a statistically improved PFS. At nearly 7 years follow-up, median PFS for those in the observation cohort was 106.3 months and median PFS for patients in the maintenance treatment group was 118.4 months (hazard ratio [HR], 1.21; 95% CI, 0.78–1.89; P= 0.3982). Additionally, there was no OS benefit noted (hazard ratio [HR], 0.85; 95% CI, 0.46–1.55; P= 0.5962).

BR was compared to dexamethasone, rituximab and cyclophosphamide (DRC) and BDR in a Mayo Clinic retrospective study[53] and ORR was superior in BR compared to DRC (98% vs 85%, $p = 0.01$) as well as when compared to BDR (98% vs 76%, $p = 0.004$). TTNT was also prolonged in the BR group [NR (3.7-NR)] compared to DRC [4.3 yrs [3–7]] and BDR [1.8 years (0.8-NR)]. Additionally, in a recent larger retrospective Mayo Clinic study, superior ORR, PFS and TTNT noted with BR in comparison to both DRC or BDR (bortezomib, dexamethasone and rituximab) in treatment-naïve patients with active WM. Importantly, the patient outcomes with any one of these three regimens were unaffected by the patients' $MYD88^{L265P}$ mutation status[54]

Purine analogs have also been successfully combined with rituximab, although their use has declined substantially in WM patients given the stem cell toxicity associated with this class of agents.

Chemotherapies

WM1, a phase 3 trial[55] compared single-agent fludarabine to chlorambucil as primary therapy in WM, and reported improved ORR (47.8% vs 38.6%, $p = 0.07$), PFS (median 36.3 vs 27.1 months, $p = 0.012$) and duration of response (38.3 vs 19.9 months, $p < 0.001$) with oral fludarabine. A higher rate of cytopenias were encountered with fludarabine (36% vs 17.8%, $p < 0.001$) but chlorambucil was associated with an increased risk of second malignancies (20.6% vs 3.6%,$p = 0.001$) [55]. Oral fludarabine is unavailable in the U.S, and chlorambucil use has declined substantially, perhaps due to these findings and greater availability of better tolerated agents.

Table 2
Efficacy and Toxicity of AntiCD20 antibodies as monotherapy

Trial Phase	Agent	Treatment setting	No of patients	ORR (%)	MRR (%)	PFS	Common and Unique Toxicities
2 [47, 101]	Rituximab		69				IgM flare
		R/R	35	51	20	46% at 2 yrs	Infusion reactions
		TN	34	53	35	51% at 2 yrs	Prolonged neutropenia
2[102]	Rituximab	TN, R/R	27	NR	44	16 m*	
2[103]	Rituximab (extended dose schedule)	R/R	29	66	48	14 m*	
2[49]	Ofatumumab	TN, R/R	37	59	41	18 m	IgM Flare

NR not reported, m months, *TTP Time to Progression, Treatment naïve TN, Relapsed/ Refractory R/R.

Table 3
Major Chemo-immunotherapies for WM

Trial Phase	Agent	Setting	Size	ORR (%)	MRR (%)	PFS (median)	Major Toxicities
3 [104, 105]	Bendamustine, Rituximab (BR) vs Rituximab,Cyclophosphamide, Doxorubicin, Vincristine, Prednisone (RCHOP)	TN	22 19	93 91	NA	70 28	BR rash, cytopenias R CHOP: infections, cytopenias, PN, stomatitis
2[106]	Dexamethasone, Rituximab, Cyclophosphamide (DRC)	TN	72	83	74	67% at 2y	Neutropenia, infusion reactions, infections
2[107]	Bortezomib-DRC vs DRC	TN	101 101	91 87	79 69	81% at 2y 73% at 2y	PNwith bortezomib
3[55]	Chlorambucil vs Fludarabine	TN	169 170	36 46	NA	27 mo 38 mo	Chlorambucil: Risk of SPM Fludarabine: neutropenia,SPM
2[108]	Cladribine +Rituximab	TN R/R	29	90	79	NR*	Mild hematologic toxicity
2[109]	Fludarabine+Rituximab	TN R/R	27 16	96 94	89 81	67% at 2y 28% at 2y	Cytopenia, PJP, transformation to aggressive lymphomas.
2[110]	Fludarabine, Cyclophosphamide and Rituximab (FCR)	TN, R/R	43	79	74	NR	neutropenia

* median time to treatment failure, NR- not reached, PN peripheral neuropathy, NA- Not available, SPM second primary malignancy.

BTK inhibitors

Ibrutinib is an oral agent that inhibits BTK activity by covalently binding with a cysteine residue of BTK enzyme active site. Ibrutinib received accelerated approval by the FDA for adult patients with WM based on phase 2 trial data showing impressive rates of overall (91%) and major (73%) responses with ibrutinib as single agent in previously treated patients (Table 4). Ibrutinib was the first BTK inhibitor approved for both treatment-naive and R/R WM. [56, 57] $MYD88^{L265P/}$ $CXCR4^{WT}$ genotype was associated with ORR of 100%, but coexisting $CXCR4^{WHIM}$ mutation rendered resistance, with an ORR of 85.7%. $MYD88^{WT}/CXCR4^{WT}$ signature was associated with the lowest ORR (71.4%) with ibrutinib [57]. Notably, no patient harboring $MYD88^{WT}$ signature achieved PR or better [57]. The updated results from extended follow-up study of ibrutinib monotherapy[58] has recently revealed that the patients with RR WM who harbored only MYD88 mutation at baseline showed an impressive 75% PFS rate at a follow-up of nearly 5 years vs a median PFS of only 5 months in those with $MYD88^{WT}$ genotype and 3.5 years in patients with double mutations (both MYD88 and CXCR4 mutations).

In the sub-study of iNNOVATE phase 3 trial involving rituximab refractory patients who were treated with ibrutinib[59], the 18-month PFS rate (94% vs 86%) and MRR (82% vs 71%) were higher in patients with $MYD88^{L265P}/CXCR4^{WT}$ compared to $MYD88^{L265P}/CXCR4^{WHIM}$. Ibrutinib monotherapy in the frontline setting [60] has also shown MRR of 94% in patients with $MYD88^{MUT}/CXCR4^{WT}$ vs 71% in $MYD88^{MUT}/CXCR4^{WHIM}$ in addition to a longer time to MR in patients with coexisting CXCR4 mutation (7.3 vs 1.8 months) compared to those without.

Ibrutinib in combination with rituximab in the randomized (main) portion of the iNNOVATE trial was associated with an improved MRR (77% vs 33%, $p < 0.0001$), ORR (95% vs 48%,$p<0.0001$) and PFS (NR vs 20.3months) when compared to rituximab monotherapy [61].The five-year follow up confirmed an ongoing PFS benefit with the combination therapy (54% vs 28%), irrespective of the IPSS-WM stratification or genotype [62]. However, the superiority of IR doublet to ibrutinib monotherapy is not known given the lack of a head-to-head comparative study. Interestingly, the iNNOVATE trial demonstrated a noticeable decline in the rate of infusion-related reactions (IRR) when rituximab was paired with ibrutinib, perhaps a reflection of ibrutinib related suppression of IRR-inducing cytokines.

Ibrutinib has CNS penetration and may be used in the treatment of Bing Neel Syndrome. [63] However, the risk of atrial fibrillation, hypertension and bleeding are major limitations with prolonged ibrutinib use[64], along with the risk of withdrawal and rebound increase in IgM from abrupt discontinuation [65]. BTK^{Cys481} alteration at the site where

Table 4
Efficacy and toxicity of BTK inhibitors

Trial Phase	Agent	Setting	Size	ORR (%)	MRR	PFS	Major Toxicities
2[58]	Ibrutinib	R/R	63	91	79.4	69% at 2y	Cytopenias, Atrial arrythmia
3[59]	Ibrutinib	R/R	31	90	71	86% at 18m	Cytopenia, infection Hypertension
3 [66, 111]	Zanubrutinib vs. Ibrutinib Zanubrutinib vs. Ibrutinib	TN R/R	37 164	95 89 94 94	74 67 78 80	78% at 18 m 94% at 18 m 86% at 18 m 82% at 18 m	Zanubrutinib: Diarrhea, neutropenia, infection Ibrutinib: Atrial fibrillation, diarrhea, contusion, hypertension, peripheral edema, muscle spasms, neutropenia, infection
2[112]	Acalabrutinib	TN R/R MYD88+ vs WT	14 92	93 93 94 79	79 80 81 64	90% at 2 y 82% at 2 y	Neutropenia, Infection, headache
2 [113]	Tirabrutinib	TN R/R	18 9	94.4 100	89 in both cohorts	NR*	Rash Neutropenia Lymphopenia
1/2[99]	Pirtobrutinib	R/R	26 (19-efficacy analysis)	68	47	NR*	Fatigue, diarrhea, contusion, bruising, rash

* NR-Not reached.

ibrutinib covalently attaches to the BTK enzyme may be acquired with continuous ibrutinib use, with resultant sustained activation of ERK1/2 pathway and emergence of resistance. [65] The patients with baseline CXCR4 mutations are more predisposed to acquiring resistance. Over the past few years other selective BTK inhibitors have been introduced, and a few such as pirtobrutinib that bind non-covalently can potentially overcome BTK^{Cys481} mutation associated resistance. The ASPEN study compared the efficacy of zanubrutinib to ibrutinib [66] and showed similar MRR (78% vs 77%) and PFS, but a more favorable toxicity profile of zanubrutinib was noted in this randomized, phase 3 trial. The very good partial response (VGPR) rates were numerically higher with zanubrutinib, and it has been approved in August 2021 for WM by the US Food and Drug Administration, based on the ASPEN study results. In a separate non-randomized arm of ASPEN, comprising $MYD88^{WT}$ patients only, zanubrutinib, unlike its predecessor, ibrutinib led to an impressive 50% MRR, including 27% VGPR rate [67]. At 18 months follow up, the median PFS and OS were not reached for patients with $MYD88^{WT}$ genotype, attesting to its ongoing efficacy. Acalabrutinib, another second generation irreversible BTK inihibitor has demonstrated an ORR of 93% in both treatment-naïve [95% CI [66–100]] and R/R [95% CI(86–98)] patients with WM at a median follow up of 27.4 months, when used as a single agent[68] In a small, multicenter open label phase 2 trial of tirabrutinib (ONO/GS4059) involving both treatment-naïve ($n = 18$) and RR WM ($n = 9$) patient populations, [69] the MMR and ORR were 88.9% and 96.3%, respectively, in the entire cohort.

Proteasome inhibitors (PI)

Bortezomib is the most studied PI, either alone or in combination with rituximab and/or dexamethasone[70] for the management of WM. Bortezomib has shown an ORR of 78–85%[71–73] as a single agent, 81–90% in combination with rituximab[74–76]. Bortezomib in combination with rituximab and dexamethasone in treatment-naïve patients with WM showed an ORR of 96%, median time to response (TTR) of 1.4 months, median time to progression (TTP) of 5.5 years, and an estimated 5-year PFS in WMCTG 05–180. [77, 78] Reversible neurotoxicity was the most common side effect. Another phase-2 European study showed an ORR of 85%, OS at 7 years of 66% and median PFS of 43 months [79]. Second generation PI, carfilzomib, in combination with rituximab and dexamethasone has demonstrated an ORR of 87.1%, independent of MYD88/CXCR4 mutational status. [80] Long term follow up from this study after 8 cycles of maintenance with KRD has shown a median PFS of 46 months (2–63 months) and in patients who had achieved at least a VGPR the median PFS had not been attained at last follow up. [81] Ixazomib, an oral PI, in combination with rituximab and dexamethasone showed ORR of 88–96% in two phase 2 trials [82, 83] but the median PFS was not reached in either study, due to short follow up (19.5–22 months). The presence of CXCR4 mutation resulted in a longer time to response (8 weeks vs 12 weeks, $p = 0.03$) [83]. Oprozomib, another oral PI, showed promising results in patients with RR WM in a phase Ib/2 dose escalation study[84], although gastrointestinal toxicity was a major limitation with its use. PIs in general have shown a rapid onset of action with durable responses (Table 5). The recently reported phase 2 ECWM1 study enrolled 204 patients with treatment-naïve WM who were randomly assigned to DRC (control) or bortezomib plus DRC regimen. Although VGPR rates were higher (19% vs. 11% for DRC), bortezomib-DRC failed to show any incremental benefit of adding bortezomib to the triplet backbone. Median PFS was not reached with the experimental arm, but 50 months with DRC ($p = 0.32$).

Additional options

A few other novel agents (Table 6) that have been evaluated in phase II trials, with evidence of clinical benefit in WM in salvage setting include AKT inhibitor perifosine[85], serine/threonine kinase inhibitor enzastaurin[86], HDAC inhibitor, panobinostat[87] and PI3K-inhibitor idelalisib. [88, 89] Monotherapy with an oral mTOR inhibitor, everolimus [90] showed at least a minor response in upto 73% of patients with RRWM, that improved to 91% in combination with bortezomib and rituximab. [91] However mucositis, diarrhea and myelosuppression limit its use. Bcl-2 inhibition with venetoclax [92] has shown promising activity, with a VGPR rate of 19% as fixed-duration salvage therapy. The VGPR rates (13% vs 27%, $p = 0.33$) were impacted by prior BTKi exposure, but not by CXCR4 status. The median PFS was 30 months, with a steep drop observed in the PFS following completion of therapy at 2 years, questioning the durability of response in the absence of continued BCL2 inhibition.

Role of stem cell transplantation (SCT)

Although there are data to suggest that patients with a high tumor burden benefit from early SCT [93], in the era of novel therapies, it is not standard practice. Autologous SCT may be considered in transplant

Table 5
Efficacy and Safety of Proteasome Inhibitors in WM.

Trial Phase	Agent	Setting	Size	ORR (%)	MRR (%)	PFS (median)	Major Toxicities
2[114]	Bortezomib	TN R/R	27	26%	44	16.3mo	Peripheral neuropathy Leukopenia
2[115]	Bortezomib	TN R/R	27	85	48	7.9m*	Neutropenia Dizziness
2[116]	Bortezomib + Rituximab	TN	26	92	66	NR	Cytopenia Fatigue
2[76]	Bortezomib + Rituximab	R/R	37	81	51	16 (mo)	Cytopenia
2[79]	Bortezomib Rituximab Dexamethasone	TN	59	85	68	43mo	Peripheral neuropathy Neutropenia,
2 [117]	Bortezomib, Dexamethasone, Rituximab (BDR)	TN	23	96	83	78% at 2 years	Thrombocytopenia
2[118]	Carfilzomib, rituximab and dexamethasone (CaRD)	TN RR	31	81	67	46 m	Lipase elevation Reversible neutropenia Cardiomyopathy
2[119]	Ixazomib, Rituximab, Dexamethasone (IRD)	TN	26	96	77	40mo	Infusion reaction
1/2[82]	I xazomib, Rituximab, Dexamethasone (IRD)	R/R	59	88	74	NR	6 patients died 1 PMLE
Ib/2[120] ongoing	Oprazomib	R/R	36	56% CFZ naïve 67% in BTZ refractory	NA	NA	Cytopenia, Diarrhea, nausea, vomiting and constipation noted in WM subgroup

* Median time to progression, NA- Not available, NR-Not reached.

Table 6
Efficacy and Safety of Other Novel Agents in RR WM

Trial Phase	Agent	Size	ORR (%)	MRR (%)	PFS (median)*	Major Toxicities
2 [121]	Everolimus	50	70	42	NR	Cytopenias, diarrhea, mucositis dyspnea and pleural effusion
2 [122, 123]	Perifosine	37	36	11	12.6 m	Anemia, leukopenia, dose dependent arthritis
2[124]	Enzastaurin	42	38	5	44% at 1y	Cytopenias, infection, fatigue
Phase I/II [125]	Everolimus, Bortezomib, Rituximab or Everolimus Rituximab X 6 cycles followed by Everolimus maintenance	46	87	50	18 months	No dose limiting toxicity in Phase 1 fatigue anemia neutropenia diarrhea
2[126]	Panobinostat	36	47	22	6.6 m	Cytopenia, fatigue
2[127]	Venetoclax	32	84	81	80% at 2 y	Cytopenias, rarely TLS

* unless otherwise stated NR- Not reached,.

eligible patients with high risk [94] and chemo-sensitive disease [95] after first relapse due to impressive PFS and OS; however due to availability of more options currently, it is reasonable to defer this approach until after a trial of a BTK inhibitor [94]. Allogeneic SCT is not a widely acceptable approach due to substantial morbidity and mortality.

Supportive care

Plasmapheresis can be used as an adjunct therapy in patients with symptomatic hyperviscosity, cryoglobulinemia, or prophylactically, when IgM flare-associated precipitation of hyperviscosity syndrome is anticipated in the setting of rituximab monotherapy use (IgM levels $\geq$ 4 g/dl). [96] In our practice, rituximab monotherapy use has fallen out of favor in the face of multiple effective combination therapies utilizing rituximab backbone. The duration of plasmapheresis is dependent on the time it takes for the hyperviscosity symptoms to resolve, but this approach is considered a temporizing measure, with the goal to commence cytoreductive shortly after the initiation of plasmapheresis.

Ongoing or recently reported clinical trials

A combination of zanubrutinib and PD1 antibody (BGB A 317) in an ongoing phase 1 dose escalation study showed good response, however severe hemolysis and transfusion reaction was reported [97].

Non-covalent BTK inhibitors like ARK 531[98] and pirtobrutinib [99] have shown promising results, with evidence of activity even among patients that become resistant to the first generation (covalent) BTK inhibitors. Other important studies include trials targeting CXCR4 with ulocuplumab (a CXCR4 antibody, that has now been withdrawn despite preliminary data demonstrating clinical efficacy) in combination with ibrutinib (NCT03225716) or the ongoing study mavorixafor (an oral inhibitor of CXCR4) in combination with ibrutinib (NCT04274738), the RAINBOW (NCT04061512) study (DCR vs IR) and a phase 2 study evaluating VCR against FCR (NCT01592981). Additionally, the results of a few more trials pairing ibrutinib with a) venetoclax (NCT04273139), b) subcutaneous bortezomib-rituximab (NCT04273139/ECWM2), c) carfilzomib (ECWM-3/CZAR1, phase 3 against ibrutinib) and d) ixazomib (a Mayo Clinic study, NCT03506373) would shed light on the value of combining using newer ibrutinib based combinations.

In summary, the management of WM continues to evolve, with a remarkable progress witnessed over the past decade. Although not disease-defining in WM, *MYD88* ^{L265P} mutations, present in most patients with WM, as well as the non-L265P type encountered in a small subset, can aid in differentiating WM from other low-grade lymphomas and IgM multiple myeloma. The mutations in the C-terminal domain of CXCR4 are typically encountered in patients with concurrent *MYD88* mutation and adversely impact BTK inhibitor-based treatments, with lower response rates and resultant shorter PFS in comparison to those with wild-type CXCR4. While BTK inhibitors have certain advantages, including a preferred route of administration, the requirement for indefinite use until progression or intolerable toxicity is a major limitation for this class of drugs in comparison to the fixed duration regimens [100]. Furthermore, the knowledge about the patient's MYD88 mutation status along with CXCR4 mutation status (if feasible) is a prerequisite for BTK inhibitor based regimens, particularly when considering ibrutinib monotherapy as its activity in the patients harboring MYD88^{WT} signature is unimpressive and mutated CXCR4 delays response to therapy. Acalabrutinib is currently commercially available for indications other than WM in US and may be considered an off-label alternative particularly in responders who are intolerant of ibrutinib. Zanubrutinib may also be considered over ibrutinib in the elderly patient population that is predisposed to developing cumulative toxicities such as treatment emergent atrial fibrillation or hypertension. The FDA has recently approved the use of zanubrutinib in WM based on the ASPEN study data. Bendamustine and rituximab (BR) is our preferred regimen for the treatment naïve patients with active WM, given its substantial activity, irrespective of the MYD88 signature, and the fixed duration (4–6 cycles) of therapy. Although ibrutinib, with or without rituximab, is approved in both the previously untreated and RR patient populations, we typically use a BTK inhibitor in the first salvage setting in patients with MYD88^{L265P} mutation, and zanubrutinib is our BTK inhibitor of choice, given its superior toxicity profile over ibrutinib. Trials exploring the feasibility of using BTK inhibitors in combination with other agents for a finite duration are underway and have the potential to change our current practice.

CRediT authorship contribution statement

Gayathri Ravi: Writing – review & editing, Writing – original draft.
Prashant Kapoor: Writing – review & editing, Writing – original draft.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Our conflicts of interest (COI) are outlined below: *Prashant Kapoor: Sanofi:* Consultancy, Research Funding; *Celgene:* Honoraria; *Cellectar:* Consultancy; *Janssen:* Research Funding, Honoraria; *Amgen:* Research Funding; *GlaxoSmithKline:* Research Funding; *Takeda:* Honoraria, Research Funding, *Karyopharm* Honoraria, Beigene Honoraria; *AbbVie*, Research Funding, Honoraria, Regeneron: Research Funding Gayathri Ravi: No COI to disclose.

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