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REVIEW ARTICLE

Waldenström macroglobulinemia: a review of pathogenesis, current treatment, and future prospects

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Abstract
Waldenström macroglobulinemia (WM) is a chronic B-cell lymphoproliferative disorder characterized by lymphoplasmacytic cell overgrowth in the bone marrow and increased secretion of IgM immunoglobulins into the serum. Patients with WM have a variety of clinical outcomes, including long-term survival but inevitable recurrence. Recent advances in disease knowledge, including molecular and genetic principles with the discovery of MYD88 and CXCR4 mutations, have rapidly increased patient-tolerable treatment options. WM patients may benefit from chemotherapy regimens that include rituximab-based regimens, alkylating drugs, proteasome inhibitors, monoclonal antibodies, and drugs targeting Bruton tyrosine kinase inhibitors. In light of these advancements, patients can now receive treatment customized to their specific clinical characteristics, focusing on enhancing the depth and durability of their response while limiting the adverse effects. Despite the rapidly developing therapeutic armament against WM, a lack of high-quality evidence from extensive phase 3 trials remains a significant challenge in the research. We believe clinical outcomes will keep improving when new medicines are introduced while preserving efficacy and minimizing toxicity.

Keywords Waldemström macroglobulinemia · Lymphoplasmacytic lymphoma · Rituximab · Alkylating agents · Proteasome inhibitors · BTK inhibitors

Introduction

Waldenström macroglobulinemia (WM) is a chronic B-cell lymphoproliferative disorder characterized by an accumulation of lymphoplasmacytic cells within the bone marrow and hypersecretion of IgM immunoglobulins into serum belonging to the non-Hodgkin B lymphoma category. WM represents 1 to 2% of hematologic malignancies with an age-adjusted incidence of 3.8 cases per million person-years [1]. In a population-based study, an age-adjusted incidence rate of 0.92 and 0.30 per 100,000 person-year for males and females was reported, along with age- and sex-adjusted incidence of 0.57 per 100,000 person-years [2]. In the USA, approximately 1000 to 1500 new cases are diagnosed yearly, predominantly among advanced age males and Caucasians than in younger age females and non-Caucasians. At diagnosis, the median age is 70 years. More than 80% of WM patients are white, and about 20% are of Ashkenazi Jewish descent. Along with ethnicity, familial history also plays a role, as about 20% of the patients have a positive family history of hematologic malignancy in first-degree relatives [3]. Overall and age-stratified hazard ratio (HR) of death depicts a 10% decrease in hazard of death for each 5-year increase in the year of diagnosis [4].Monoclonal IgM MGUS is among the precursor condition of WM [5]. This review summarizes WM pathogenesis, current treatment, and future prospects.

Pathogenesis

In WM, the underlying pathologic diagnosis is lymphoplasmacytic lymphoma. The characteristic immunophenotypic profile for lymphoplasmacytic cells includes the expression of the pan B-cell antigens CD19, CD20, CD22, and CD79, as well as the expression of the chain-restricted surface IgM [6]. As a result of the identification of mutations in the MYD88 and CXCR4 genes, as well as a crucial actionable

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target on Bruton's tyrosine kinase (BTK), innovative treatments are being tested [7].

Next-generation sequencing (NGS) has identified somatic mutations in MYD88 in 95–97%, CXCR4 in 30–40%, ARID1A (17%), and CD79B in 8–15% of WM patients [8, 9]. MYD88L265P, pro-survival "gain of function," is caused by a somatic point mutation of the MYD88 protein in which the amino acid leucine changes to proline at position 265 [10]. Patients with MYD88-mutated WM frequently have copy number changes that affect both chromosome 6q and non-chromosome 6q regions. The alterations found on chromosome 6q have been linked to regulatory genes for NFKB, Bruton tyrosine kinase (BTK), BCL2, and apoptotic signaling [11]. MYD88 is a toll-like receptor 4 (TLR-4) and interleukin-1 and -2 receptor adaptor protein (IL-1R and IL-2R). After binding, MYD88 is either activated by these receptors directly or indirectly through interactions with TIR domain-containing adaptor protein (TIRAP) and Bruton tyrosine kinase (BTK), which activates the NF-B pathway [10, 12]. MYD88 wild-type patients have a higher risk of disease transformation and a lower overall survival (OS) rate [13].

It has been demonstrated that the G-protein coupled receptor CXCR4 is essential for cytokine release and chemotaxis [14]. CXCR4 knockdown, CXCR4 inhibitor, and Gi protein inhibitor treatments were all shown to inhibit WM cell migration and adhesions in response to stromal-derived factor (SDF-1), indicating the critical role that CXCR4 plays in WM cell homing [15]. Additionally, it was discovered that WM cells express VLA-4, a different chemokine receptor, which directly interacts with CXCR4 to activate the AKT and MAPK pathways, preventing the cell from dying and going into apoptosis [15].

CXRC4 mutations have inferior outcome compared to CXCR4 wild-type mutation. Progression-free survival, depth of response, and time to major response are all affected by MYD88 and CXCR4 mutation status. [16] These mutation statuses improved our understanding of its pathophysiology and guided WM treatment, leading to the development of BTK and CXCR4 inhibitors.

Clinical presentation

At the time of initial diagnosis, only 15–30% of patients with WM present with extramedullary diseases, such as lymphadenopathy or hepatosplenomegaly [1]. In the initial stages, patients exhibit non-specific B symptoms, such as fatigue, fever, weight loss, and excessive sweating at night. In the later stages of the disease, patients may develop anemia, thrombocytopenia, neutropenia, bone marrow infiltration, and IgM paraprotein. IgM paraprotein-mediated symptoms comprise hyperviscosity syndrome, neuropathy, cryoglobulinemia, and cold agglutinin hemolytic anemia [17]. Patients with hyperviscosity syndrome often demonstrate fatigue, dizziness, mucocutaneous bleeding, retinal abnormalities, high output cardiac failure, and rarely altered mental status or stroke. A funduscopic examination reveals retinal hemorrhage, dilated and tortuous retinal veins, and papilledema resulting from retinal vein thrombosis. Cell infiltration and IgM paraprotein effects on the kidney, gastrointestinal tract, and skin are rare, accounting for 4%, 4%, and 3% of cases, respectively [18]. Cryoglobulinemia in association with WM is also relatively common, ranging from 8 to 18% of cases; however, < 5% have symptoms or complications [19]. This is indicated by the Raynaud phenomenon/acrocyanosis, peripheral neuropathy, purpura, skin ulceration, necrosis, arthralgia, or glomerulonephritis-related hematuria.

Some monoclonal proteins from WM patients possess antigen-binding activity directed to autogenous or foreign antigens. Autoimmune hemolytic anemia (AIHA), most commonly cold agglutinin disease, is associated with WM. These monoclonal IgM autoantibodies include cold agglutinins, mixed cryoglobulins, and anti-neuronal components.

IgM neuropathy is seen in up to 46% of cases and is typically indolently progressive, distal, symmetric, and predominantly sensory peripheral neuropathy [20]. IgM MGUS patients have serum IgM protein < 3g/dl, bone marrow containing less than 10% lymphoplasmacytic cells, and are completely asymptomatic. Smoldering WM has IgM protein ≥ 3 g/dl and/or bone marrow containing bone marrow ≥ 10% lymphoplasmacytic cells. Smoldering WM patients are also asymptomatic. Symptoms of underlying lymphoproliferative disorder like anemia, hepatosplenomegaly, hyperviscosit,y and constitutional symptoms along with monoclonal IgM protein and bone marrow containing > 10% lymphoplasmacytic cells distinguish IgM MGUS and smoldering WM from active illnesses requiring therapy.

Initial investigations

At diagnosis, complete blood count, liver function tests, ß2 microglobulin, lactate dehydrogenase (LDH), serum protein electrophoresis, immunofixation, quantifying IgM, IgG, and IgA by densitometry, serum-free light chain assay, plasma viscosity, and ophthalmic examination for signs of hyperviscosity are recommended. Before initiating treatment, computerized tomography (CT) imaging of the neck, chest, abdomen, and pelvis, along with serology for viral infections (hepatitis B, C, and HIV), bone marrow biopsy, and trephine biopsy, should be obtained. If high-grade transformation is suspected, then positron emission tomography, computed tomography (PET-CT), and a biopsy of suspected areas of transformation should be performed [21].

Diagnostic criteria

The diagnosis of newly suspected WM patients depends on clinical and pathological criteria, such as bone marrow (BM) biopsy and multiparametric flow cytometry and molecular studies. Diagnostic bone marrow biopsy findings include infiltration of ≥ 10% clonal lymph plasmacytoid cells with an intertrabecular pattern and the presence of serum monoclonal IgM regardless of M-protein size [22].

The plasmacytic component includes CD138+, CD38+, and CD45-. The MYD88 and L265P gene mutation have been identified in over 90% of patients with WM and can help differentiate WM from B-cell (including IgM-secreting) disorders, such as mucosa-associated lymphoid tissue lymphoma, splenic marginal zone lymphoma, nodal marginal zone lymphoma, IgM-secreting multiple myeloma, and chronic lymphocytic leukemia [9, 23].

Risk stratification and prognosis

The revised International Prognostic Scoring System for WM (ISSWM) is based on age (≤ 65 vs 66–75 vs ≥76 years), b2-microglobulin ≥ 4 mg/L, serum albumin < 3.5 gr/dl, and LDH ≥ 250 IU/L (ULN < 225) to stratify patients in five different prognostic groups and identify a very low-risk as well as a very high-risk group [24]. Table 1 depicts the ISSWM classification for prognosis scoring.

A significant proportion of WM patients are asymptomatic at presentation and can be safely observed at 3–6-month intervals [25]. Indications for initiation of treatment include constitutional symptoms, symptomatic or bulky lymphadenopathy or splenomegaly, cytopenia secondary to marrow infiltration, hyperviscosity syndrome, and IgM-related syndromes, including cryoglobulinemia, amyloidosis, peripheral neuropathy, and cold agglutinin disease [26].

Table 1 The Revised International Prognostic Scoring System for Waldenström macroglobulinemia (ISSWM) classification

Revised ISSWM categories				
Stage	**Score**	**3-year WM-related mortality**	**5-year OS**	**10-year OS**
Very low	0	0%	95%	84%
Low	1	10%	86%	59%
Intermediate	2	14%	78%	37%
High	3	38%	47%	19%
Very high	4-5	48%	36%	9%

Management

There is no cure for WM, but treatment goals are to control disease symptoms and prevent end-organ damage while maximizing the quality of life [27]. Drug therapies are reserved for patients with symptomatic diseases, and treatment is determined by age, the severity of symptoms, comorbidities, and preferences. They should also consider other factors specific to medical goals, such as rapid disease control, the risk of treatment-related neuropathy, immunosuppression, secondary malignancies, and future autologous stem cell transplantation.

Management of hyperviscosity

Hyperviscosity syndrome results from elevated IgM levels, leading to decreased blood flow with compromised microcirculation. The severity of the symptoms is noted to be directly related to the increased levels of serum viscosity [28]. Plasmapheresis should be started in patients who demonstrate hyperviscosity-related symptoms such as headaches, blurry vision, papilledema, chest pain, or ischemic changes to remove IgM from the serum. Red blood cell transfusion is avoided as it can further increase blood viscosity and worsen the symptoms [29]. Plasmapheresis can temporarily relieve symptoms, and patients should receive systemic treatment to prevent the symptoms from recurring.

Systemic treatment

Various drugs and drug combinations have demonstrated clinical benefits in prospective trials, but few have been compared directly in randomized trials. In addition, individual trials have used different protocols and response criteria, making it difficult to compare these agents or regimens based on response rates alone. Frontline treatments include solely rituximab or rituximab combined with alkylators (bendamustine and cyclophosphamide), proteasome inhibitors (bortezomib and carfilzomib), nucleoside analogs (fludarabine and cladribine), and ibrutinib. An alternative frontline regimen, ibrutinib, everolimus, or stem cell transplantation, can be considered in the salvage setting.

Rituximab (monotherapy): limited and extended duration and ofatumumab therapy

Rituximab is an anti-CD20 monoclonal antibody, based on clinical trials that showed an overall response rate (ORR) of 44% with standard treatment (375 mg/m^2 intravenously

for 4 weeks) and 65.5% with prolonged treatment (two sessions of treatment with four 375 mg/m^2/week infusions at weeks 1–4 and 12–16) [30, 31]. In a phase II trial by Gertz et al., rituximab 375 mg/m^2 was given to sixty-nine patients weekly over the course of four consecutive weeks. Results of the trial showed that 19 (27.5%) patients showed an objective response, whereas a total of 17 (24.6%) patients showed a minor response. The ORR in the trial was 52.2% (90% CI [41.6%, 62.2%]) [32]. In a follow-up study, Dimopoulos et al. assessed 17 treatment-naive patients and found that extended rituximab treatment resulted in an ORR of 35% [33].

Treon et al. evaluated extended rituximab therapy in 29 WM patients, and the results showed that patients with serum IgM levels of < 6000 mg/dl were more likely to show a favorable response to therapy [31]. In a phase II study by Ghobrial et al., 72 patients received treatment with Rituximab (375 mg/m^2 weekly for 4 weeks). Serum IgM levels were measured at five separate time points, and an IgM flare in up to 54% of patients was observed. Trial results show that most of the patients with IgM flare experienced a reduction in IgM levels within 4 months after the initiation of therapy, suggesting that a response to rituximab may develop slowly [34]. Furman et al. enrolled fifteen WM patients and treated them with ofatumumab, an anti-CD20 fully human monoclonal antibody that binds to a different epitope from the rituximab binding site. Trial results show that of the 14 patients with measurable IgM levels, 3 achieved a partial response (PR), whereas 3 achieved a minor response (ORR = 43%) at 8 weeks to 5 months after the start of therapy. These results suggest that ofatumumab shows clinical activity in patients with WM, including those patients who relapse after initial therapy with Rituximab [35]. Table 2 summarizes the clinical trials utilizing Rituximab and Ofatumumab therapy in WM patients.

Rituximab with alkylating agents

Combination therapies with rituximab have been shown to reduce IgM levels rapidly compared to monotherapy. Alkylating agents are effective for symptom relief and extending survival time. In a phase II trial by Dimopoulos et al., 72 treatment-naive patients received rituximab + cyclophosphamide + dexamethasone (DRC). They reported an ORR of 83% (95% CI 73–91), CR of 7%, partial response (PR) of 67%, 2-year PFS of 67%, and 2-year OS of 81%, at a median follow-up of 23.4 months. Neutropenia of grade 3 or 4 only occurred in seven cases; thrombocytopenia was essentially non-existent. This study summarized that the DRC regimen is effective for symptomatic patients with untreated WM, is well-tolerated, simple to give, and convenient [36].

Treon et al. evaluated 24 relapsed/refractory WM patients who received rituximab (375 mg/m^2 IV on either day 1 or day 2) and bendamustine (90 mg/m^2 IV on days 1 and 2). Bendamustine was administered either alone (n = 4) or in combination with ofatumumab (n = 2) to six rituximab-intolerant subjects. Each cycle lasted 4 weeks, with five being the median number of treatment cycles. They reported ORR 83.3%, very good partial response (VGPR) in 5 patients, and PR in 20 patients [37].

Paludo et al. studied bendamustine + rituximab (BR) and DRC in both treatment-naive and relapsed/refractory settings in relation to MYD88 mutation status. Sixty patients

Table 2 Rituximab and ofatumumab therapy in Waldenström macroglobulinemia

Study, year	Regimen	No. of patients	Treatment response (%)	Survival rates	Median follow-up (months)
Dimopoulos et al., 2002	Rituximab 375 mg/m^2 IV for 4 weeks, repeat 4-week courses in patients without disease progression 3 months after treatment	27	PR 12 44% ORR 44%	PFS 33.3%	15.7
Gertz et al., 2004	Rituximab 375 mg/m^2 IV infusion weekly for 4 consecutive weeks	69	MR 17 (24.6%) ORR 52.2%		
Dimopoulos et al., 2002	Rituximab extended duration 375 mg/m^2 IV for 4 weeks, repeat 4-week courses in patients with no disease progression	17	PR 6 (35%) ORR 35%		> 22–40
Treon et al., 2005	Rituximab extended duration two sets of four (375 mg/m^2/week) infusions at weeks 1–4 and 12–16	29	PR 14 (48.3%) MR 5 (17.2%) ORR 65.5%		29
Furman et al., 2011	Ofatumumab 300 mg week 1 and 1000 mg weeks 2–4	15	PR 3 MR 3 ORR 43%		

Abbreviations: *ORR*, overall response rate; *PFS*, progression-free survival; *MR*, minor response; *OS*, overall survival; *IV*, intravenous

received BR, and 43 of them had RRWM. One hundred patients received DRC, while 50 of them had RRWM. In the treatment-naive setting, ORR with BR was 93% versus 96% with DRC ($p = 0.55$). Two-year PFS in BR and DRC arms was 88% and 61%, respectively ($p = 0.07$). In the salvage setting, ORR in the BR arm was 95% versus 87% in the DRC arm ($p = 0.45$). The median PFS was 58 vs. 32 months with BR and DRC, respectively, and the 2-year PFS was 66% vs. 53% with BR and DRC, respectively ($p = 0.08$). The response to BR and DRC was unaffected by MYD88 mutation status in patients. Adverse events were comparable in both settings [38].

Tedeschi A et al. evaluated rituximab and bendamustine in 71 RRWM patients with a median age of 72 years who had received an average of the prior two lines of treatment (range 1–5). Rituximab 375 mg/m^2 was administered on day 1 and bendamustine on days 1 and 2, with doses ranging from 50 to 90 mg/m^2. They reported an ORR of 80.2% and a major response rate of 74.6%. After a median follow-up of 19 months, the median progression-free survival (PFS) was not reached (range 3–54). Grade 3/4 neutropenia was the most common toxicity. No patient developed lymphoma, acute myeloid leukemia, or myelodysplastic syndrome. The BR salvage regimen was discovered to be well-tolerated and effective with quick disease control [39].

Ioakimidis et al. evaluated the WM patients who received CHOP-R (cyclophosphamide/doxorubicin/vincristine/prednisone plus rituximab; $n = 23$), CVP-R (cyclophosphamide/vincristine/prednisone plus rituximab; $n = 16$), or CP-R (cyclophosphamide/prednisone plus rituximab; $n = 19$). They reported ORR of 96%, 88%, and 95% in CHOP-R, CVP-R, and CP-R, respectively, and CR of 17%, 12%, and 0 in CHOP-R, CVP-R, and CP-R, respectively. While the results were not statistically significant, WM patients receiving CHOP-R and CVP-R had a significantly higher incidence of treatment-related neuropathy and febrile neutropenia than CP-R patients. While reducing treatment-related complications in patients with WM, using CP-R may offer therapeutic responses comparable to more intense cyclophosphamide-based regimens [40]**.** Table 3 summarizes the clinical trials utilizing rituximab in combination with alkylating agents in WM.

An overview of how alkylating agents in WM patients' treatment outcomes are impacted by their MYD88 and CXCR4 mutation status can be seen through a prospective analysis using bendamustine and rituximab (BR). The results showed that PFS was shorter in patients with the MYD88 wild-type and did not affect the overall response rate (ORR) [41]. The retrospective analysis found that PFS and time to the next therapy (TINT) were lower in MYD88 wild-type patients [8, 38]. In another retrospective analysis of rituximab, cyclophosphamide, and dexamethasone (RCyD), MYD88 wild-type patients had a shorter PFS and time to next treatment (TINT), but there was no effect of MYD88 status on the overall response rate (ORR) [8, 38].

In a European study, Buske et al. evaluated response rates, PFS and OS, and safety in 204 treatment-naive patients who were assigned randomly to dexamethasone, rituximab, and cyclophosphamide (DRC) or bortezomib-DRC (B-DRC) for six cycles for a median follow-up of 27.5 months. The estimated 24-month PFS was 80.6% (95% CI, 69.5–88.0) for B-DRC and 72.8% (95% CI, 61.3–81.3) for DRC ($p = .32$). B-DRC and DRC had major responses in 80.6% against 69.9% of patients at the end of treatment, and complete/very good partial responses in 17.2% versus 9.6% of patients. With a median of 3.0 (95% CI, 2.8–3.2) months as opposed to 5.5 (95% CI, 2.9–5.8) months for DRC, the median time to first response was shorter for B-DRC. Peripheral neuropathy grade 3 was reported in two patients who were treated with B-DRC and in none with DRC [42]

As the first-line therapy for patients with indolent (WM is a rare indolent B lymphoproliferative disorder) and mantle-cell lymphomas, Rummel et al. compared bendamustine plus rituximab with CHOP plus rituximab (R-CHOP). Eighty-one German centers participated in a prospective, multicenter, randomized, open-label, non-inferiority trial between September 1, 2003, and August 31, 2008. Patients were randomly assigned to receive CHOP, which consisted of cycles every 3 weeks of cyclophosphamide 750 mg/m [2], doxorubicin 50 mg/m [2], and vincristine 1.4 mg/m [2] on day 1, as well as prednisone 100 mg/day for 5 days, or intravenous bendamustine (90 mg/m [2] on days 1 and 2 of a 4-week cycle). Rituximab 375 mg/m [2] was administered to patients in both groups on the first day of each cycle, and their PFS was analyzed. Two hundred seventy-four patients were assigned to bendamustine plus rituximab (261 assessed) and 275 to R-CHOP (253 assessed). At a median follow-up of 45 months, median PFS was significantly longer in the bendamustine plus rituximab group than in the R-CHOP group (69.5 months [26.1 to not yet reached] vs 31.2 months [15.2–65.7]; hazard ratio 0.58, 95% CI 0.44–0.74; $p < 0.0001$). Bendamustine plus rituximab was better tolerated than R-CHOP, with lower rates of alopecia, peripheral neuropathy, and stomatitis except erythematous skin reactions which were more common in patients in the bendamustine plus rituximab group than in those in the R-CHOP group [43].

Bendamustine plus rituximab is considered a preferred first-line treatment approach. Both as a monotherapy and combined with CD20-directed monoclonal antibodies, bendamustine is effective and causes long-lasting responses in previously treated WM. Patients who had previously taken nucleoside analogs had a higher incidence of prolonged myelosuppression [37].

Table 3 Rituximab in combination with alkylating agents in Waldenström macroglobulinemia

Study, year	Regimen	No. of pts	Treatment response	Survival rate	Median follow-up (months)
Dimopoulos et al., 2007	DRC Dexamethasone 20 mg, followed by rituximab 375 mg/m^2 intravenously On days 1–5, oral cyclophosphamide 100 mg/m^2 bid was administered (total dose, 1000 mg/m^2). After six DRC doses repeated every 21 days, patients without progressive illness were monitored without intervention	72 (Newly diagnosed)	ORR: 83% (95% CI, 73 to 91%) CR 7% PR 67% MR 9%	2-year PFS 67% and 80% 2-year OS was 81%	23.4
Treon et al., 2011	Rituximab (375 mg/m^2 on either day 1 or day 2) and bendamustine (90 mg/m^2 on days 1 and 2). Bendamustine was administered either alone ($n = 4$) or in combination with ofatumumab ($n = 2$) to six rituximab-intolerant subjects	30 (RR)	ORR 83.3% 5 VGPR and 20 PR	PFS 13.2 months	
Paludo et al., 2018 []	60 consecutive patients underwent BR (43 had relapsed/refractory WM), and one hundred patients received (DRC)	160	**Treatment-naive setting** ORR with BR: 93% ORR with DRC: 96% **In a salvage setting** ORR with BR: 95% ORR with DRC: 87%	**Treatment-naive setting** PFS with BR: 88% PFS with DRC: 61% **In a salvage setting** PFS with BR was 58 versus 32 months with DRC (2-year PFS was 66 versus 53%	
Tedeschi et al., 2015 []	Rituximab 375 mg/m (2) on day 1 and bendamustine on days 1 and 2 (dosage ranging from 50 to 90 mg/m^2)	71	Overall and major response rates were 80.2% and 74.6%	PFS was not achieved (range 3–54)	19
Ioakimidis et al., 2009 []	CHOP-R ($n = 23$), CVP-R ($n = 16$), or CP-R ($n = 19$)	CHOP-R ($n = 23$), CVP-R ($n = 16$), or CP-R ($n = 19$)	CHOP-R: ORR, 96%, CR 17% CVP-R: ORR 88%, CR 12% CP-R: ORR, 95%, CR, 0%		
Rummel et al., 2013	Bendamustine plus rituximab with CHOP plus rituximab (R-CHOP). Cyclophosphamide 750 mg/m(2), doxorubicin 50 mg/m(2), and vincristine 1.4 mg/m(2) prednisone 100 mg/day bendamustine (90 mg/m(2). Rituximab 375 mg/m(2) both groups	549	-	PFS (69.5 months [26.1 to not yet reached] vs 31.2 months [15.2–65.7])	45 months
Buske et al., 2023	DRC or bortezomib-DRC B-DRC for six cycles	204	Major responses in 80.6% versus 69.9% CR/VGPR 17.2% versus 9.6% of patients	24-month PFS was 80.6% (95% CI, 69.5 to 88.0) for B-DRC 72.8% (95% CI, 61.3 to 81.3) for DRC ($p = .32$)	27.5 months

Abbreviations: *DRC*, rituximab+ cyclophosphamide+ dexamethasone; *BR*, bendamustine + rituximab; *ORR*, overall response rate; *RR*, relapsed refractory; *CR*, complete response; *PR*, partial response; *VGPR*, very good partial response; *MR*, minor response; *PFS*, progression-free survival; *OS*, overall survival; *CHOP-R*, cyclophosphamide/doxorubicin/vincristine/prednisone plus rituximab; *CVP-R*, cyclophosphamide/vincristine/prednisone plus rituximab; *CP-R*, cyclophosphamide/prednisone plus rituximab.

Nucleoside analog-based regimens

Purine nucleoside analogs and alkylating drugs such as fludarabine were first investigated in patients with the recurrent or refractory disease following alkylating agents for WM. In the late 1990s, fludarabine was a monotherapy for first-line treatment, with response rates ranging from 36 to 94%. The recent phase III research found that fludarabine monotherapy outperformed chlorambucil in progression-free survival, length of response, and OS [44]. Combinations of fludarabine with rituximab and alkylating medications have been investigated, and the results indicate that the responses are of greater quality and last longer when administered in combination.

In a phase II trial by Laszlo et al., 29 patients with newly diagnosed or previously treated WM, combination therapy with subcutaneous cladribine (0.1 mg/kg days 1–5) and intravenous rituximab (375 mg/m^2 on day 1) demonstrated overall and complete response rates of 90% and 24%, respectively [45]. The median response time was 4 months. The most common side effects were neutropenia and anemia; ten cases of severe (grade 3/4) neutropenia and one case of severe (grade 3/4) anemia were identified.

In a prospective, multicenter Italian study by Tedeschi et al., 43 patients with symptomatic WM responded effectively to a combination of fludarabine (25 mg/m^2), cyclophosphamide (250 mg/m^2), and rituximab (375 mg/m^2) administered every 28 days for up to six cycles. The median time to achieve a 25% and 50% reduction in serum monoclonal protein was 2 and 3 months, and the median event-free survival was 50 months with ORR 79% [46].

In a prospective, multicenter trial by Treon et al., 43 patients with WM who had only undergone one or two prior treatments were given six cycles of fludarabine (25 mg/m^2 per day for 5 days) and eight weekly rituximab (375 mg/m^2 per week) infusions. The ORR was 95%, and the median response and progression times were 19 and 51 months, respectively [47]. After a median of 40.3 months of follow-up, three patients developed myelodysplastic syndrome/acute myeloid leukemia (MDS/AML), and three others developed aggressive lymphoma. The most prevalent adverse severe events were neutropenia (27 patients), pneumonia (six patients), and thrombocytopenia (seven patients). Since three of the initial 21 patients developed herpes zoster, prophylaxis with acyclovir or famciclovir was administered to subsequent patients until 1 year after treatment was discontinued.

Although nucleoside analogs (such as fludarabine or cladribine) are effective in treating WM, they can potentially harm stem cells and lead to the developing of a more aggressive form of lymphoma. The results of a study by Leleu et al., involving 439 patients with WM who were followed for a median of 5 years, found that patients who received nucleoside analog-based therapy had a higher rate of transformation to aggressive lymphoma (Richter syndrome), myelodysplasia, or acute leukemia (6.2% versus 0.4%, respectively) [48]. Patients eligible for stem cell transplantation do not get these medicines as an initial treatment because they risk damaging stem cells. The chief hazards of nucleoside analog-containing regimens are myelosuppression and immunosuppression, which can lead to infections, with a mortality rate of up to 5% due to treatment-related complications [49].

Nucleoside analogs (fludarabine or cladribine) are effective treatment regimen for WM. Nucleoside analogs increase the risk of second malignancy and should be avoided as a primary treatment. Table 4 summarizes the clinical trials utilizing nucleoside analog-based therapy in WM.

Proteasome inhibitor therapy

Proteosome inhibitor (PI) therapies have also been used in WM treatment, involving first-generation PI bortezomib or second-generation carfilzomib in combination with rituximab and dexamethasone [50, 51].

Treon et al. evaluated bortezomib, dexamethasone, and rituximab (BDR) in 23 treatment-naive WM patients. Following a median of 7 cycles of treatment in 23 patients, ORR was 96%, major response rate (MRR) 83% with CR in 3 patients, near-complete response (NCR) in 2 patients, VGPR defined by > 90% reduction in IgM in 3 patients with 11 partial responses (PR) and 3 minor responses

Table 4 Nucleoside analog-based regimens in Waldenström macroglobulinemia

Study, year	Regimen	No. of pts	Treatment response	Survival rate	Median follow-up (months)
Laszlo et al., 2010	Rituximab plus cladribine	29	ORR 90% CR – 24%	-	-
Tedeschi et al., 2011	Fludarabine plus cyclophosphamide and rituximab	43	ORR – 79%	Event-free survival 50 months	
Treon et al., 2009	Fludarabine plus rituximab	43	ORR – 95%	-	40.3

Abbreviations: *ORR*, overall response rate; *CR*, complete response

(MR). There was a statistically significant decline in bone marrow involvement from 55 to 10% ($p < 0.001$), serum IgM level decreased from 1115 to 4830 mg/dl ($p < 0.001$), and hematocrit improved from 38.2 to 29.8% ($p = 0.002$). At a median follow-up of 22.8 months of treatment, 18 patients remained free of disease progression [52].

A phase II trial by Ghobrial et al. in 2010 involved patients who had at least one previous therapy to be eligible for the study. Thirty-seven patients with RRWM were given 6 cycles of 1.6 mg/m^2 of weekly intravenous bortezomib on days 1, 8, and 15 every 28 days, with rituximab 375 mg/m^2 weekly on cycles 1 and 4. Following a median of 16 months of treatments, 18 patients experienced disease progression, out of which 3 deaths occurred. The median PFS was 15.6 months, the median OS was not achieved, and the median duration of response was 19.5 months [53].

In a phase II trial involving both untreated or previously treated 27 WM patients, Chen et al. used intravenous bortezomib monotherapy at 1.3 mg/m^2 on a 21-day cycle every 1, 4, 8, and 11 days for a median of 6 cycles [54]. CR was seen in 0% of patients, PR was seen in 26% of patients, stable disease in 70%, and progressive disease in 4% of patients. The median PFS was 16.3 months, and the total response rate was 26%. Twenty-one patients had at least a 25% decrease in IgM, while 12 patients had a 50% IgM reduction. Bortezomib had good efficacy in WM, but peripheral neuropathy was dose-limiting as 20 patients (74%) suffered new or worsening peripheral neuropathy.

Buske et al. conducted a recent trial comparing two treatment groups of naive WM patients: one with dexamethasone, rituximab, and cyclophosphamide with bortezomib and the other without. They found a statistically significant 7.8% increase in 24-month PFS in the group with bortezomib [42]. In addition, within 3 cycles of the regimen, the group with bortezomib exhibited a significantly higher major response (by 24.5%) compared to the group without this proteasome agent [42].

Another PI, ixazomib, has also been used alongside dexamethasone and rituximab in treatment-naive WM patients in a phase II study reported by Castillo et al. [55] An ORR of 96% and MRR of 77% during a median follow-up time of 52 months were noted. In addition, with a median PFS of 40 months, VGPR was seen in 19%, PR in 58%, and stable disease in 4%.

In contrast with trials involving the use of bortezomib, trials involving the use of carfilzomib are far scarcer. One completed phase II trial on intravenous carfilzomib in combination therapy with dexamethasone and rituximab over 6–8 cycles demonstrated an ORR of 87.1% in 31 treatment-naive patients [56]. They reported CR of 87% and VGPR of 35%, and 20 patients remained progression-free within a median follow-up of 15.4 months.

Bortezomib combination therapy shows efficacy for the treatment of WM with a rapidly decrease in IgM level. Peripheral neuropathy is a major dose-limiting factor. Carfilzomib could offer a treatment with less neuropathy. Further studies are needed to compare the efiicacy of PIs in the treatment of WM. Table 5 summarizes the clinical trials utilizing protostome inhibitor therapy in treatment-naive and relapsed refractory WM patients.

Bruton tyrosine kinase inhibitors: ibrutinib

Ibrutinib is approved as first-line therapy for treatment-naive patients. Due to the paucity of randomized controlled studies, there needs to be a clear standard of care, and most recommendations are based on phase II research findings.

Treon et al. evaluated 63 symptomatic patients in a multicenter trial of ibrutinib monotherapy in previously treated WM patients. Forty percent were resistant to their previous therapy and were administered 420 mg/day of ibrutinib [16]. With a median follow-up duration of 59 months, the overall and major response rates were 90.5% and 79.5%, respectively. There was a statistically significant reduction in median serum IgM levels from 3520 to 821 mg/dl, bone marrow disease involvement reduction from 60 to 20%, and an increase in hemoglobin level from 10.3 to 14.3 g/dl ($p < .001$). Patients who had MYD88 mutation with wild-type CXCR4 had better MRR (97.2 vs. 68.2%, $p < 0.001$), better VGPR (47.2 vs. 9.1%, $p < 0.01$), and short interval to major response (1.8 months vs. 4.7 months, $p = 0.02$) as compared to MYD88, CXCR4 mutation. Based on these findings, the FDA has approved ibrutinib for treating patients with WM.

Ilhan et al. used off-label ibrutinib monotherapy or rituximab in a multicenter retrospective cohort analysis. In five patients, the WM IPSS score was determined as moderate and was evaluated as high in eleven patients. At the time of WM diagnosis, the presence of MYD88 mutations was confirmed in eight patients. Before therapy, nine of the sixteen patients (56.3%) had a serum IgM level of 3000 mg/dl or higher. The median follow-up for the subset who received ibrutinib as salvage therapy was 29 months, while the median treatment duration for the entire cohort was 12.5 months. After therapy, only three patients (18.8%) had a serum IgM level of 3000 mg/dl or higher. Four patients had a complete response, four had a very good response, and six had a partial response, with an overall response rate of 83.3% [57].

Castillo et al. analyzed 229 WM patients previously treated with ibrutinib monotherapy. Seventy-two patients were on trial, and 157 were no longer receiving treatment. The median time to commencement of ibrutinib for patients on and off trial was 3.1 years (95% CI 2–4.9) and 3.5 years (95% CI 2.3–5.1), respectively. Patients in the ON trial were younger (66 years versus 68 years; $p = 0.04$) and had higher

Table 5 Proteosome inhibitor therapy in treatment naïve and relapsed refractory Waldenström macroglobulinemia

Study, year	Treatment regimen	No. of pts	Treatment response	Survival rate	Median follow-up duration (months)
Treon et al., 2009	Bortezomib, dexamethasone, rituximab 4 cycles of induction therapy with 1.3 mg/m^2 intravenous bortezomib, 40 mg dexamethasone on days 1, 4, 8, and 11, along with rituximab 375 mg/m^2 on day 11. 4 cycles of maintenance therapy were then given 3 months apart leading to a median of 7 cycles of treatment	23 treatment-naive	ORR 96%	18 patients with the progression-free disease, progression-free survival rate not specified.	22.8
Ghobrial et. al., 2010	Bortezomib + rituximab 6 cycles of 1.6 mg/m^2 intravenous bortezomib weekly on days 1, 8, and 15 every 28 days, along with rituximab 375 mg/m^2 weekly on cycles 1 and 4. Patients with progressive disease following two cycles were taken off therapy, while patients with stable or responsive disease continued for a total of 6 cycles. No maintenance therapy was given	37 RRWM	CR/nCR 5%, PR 17%, MR 30%	Median PFS of 15.6 months, with estimated 12-month and 18-month PFS of 57% and 45%, respectively. Median OS was not reached	16
Chen et al., 2007	Bortezomib monotherapy A median of 6 cycles of 1.3 mg/m^2 intravenous bortezomib on days 1, 4, 8, and 11 every 28 days	27 RRWM	CR 0%, PR 26%, progression in 4%, stable disease in 70% of patients	Median PFS of 16.3 months	Every 3 months until relapse or death
Treon et al., 2014	Carfilzomib, dexamethasone, rituximab 20 mg/m^2 intravenous carfilzomib cycle 1 and 36 mg/m^2 for cycles 2–6, along with 20 mg dexamethasone on days 1, 2, 8, and 9. 375 mg/m^2 rituximab was also given on day 2 every 9 weeks for 8 cycles	31 treatment-naive	ORR 87.1%, CR 87%, VGPR 35%	20 patients with progression-free disease, PFS survival rate undefined	15.4
Buske et al., 2023	2 groups of patients, one with dexamethasone, rituximab, cyclophosphamide with bortezomib, and the other without 6 cycles were given.	204 treatment-naive	CR/VGPR increased to 32.6% for the group with bortezomib	24-month PFS of 80.6% for the group with bortezomib, and 72.8% without	27.5
Castillo et al., 2020	Ixazomib, dexamethasone, and rituximab 12 cycles of 4 mg ixazomib and 20 mg dexamethasone on days 1, 8, and 15, and 375 mg/m^2 rituximab day 1	26 treatment-naive	ORR 96%, 19% VGPR, 58% PR, 4% stable disease	Median PFS of 40 months	52

Abbreviations: Bortezomib, dexamethasone, rituximab (BDR); relapsed refractory Waldenström macroglobulinemia (RRWM); overall response rate (ORR); complete response (CR); near complete response (nCR); very good partial response (VGPR); partial response (PR); minimal response (MR); overall survival (OS); progression-free survival (PFS)

median serum 2-microglobulin levels (4.0 versus 3.4 mg/dl; $p = 0.02$). In contrast, individuals participating in the study were more likely to have bone marrow involvement of 60% or more (65%) and to be male (76%) than patients not participating. Off-therapy patients had 4-year PFS and OS rates of 83% and 81%, respectively. ON trial patients had 4-year PFS and OS rates of 72% and 63%, respectively (log-rank $p = 0.14$). There was a statistically significant difference of 34% and 44% ($p = 0.10$) between the discontinuation rates of ibrutinib in the ON and OFF trials [58]. CXCR4 mutations impacted the response and survival results of ibrutinib monotherapy. CXCR4 mutations have been identified in 68 (38%) of 180 people receiving ibrutinib therapy in a clinical trial. In multivariate models, those with $CXCR4^{NS}$ had a lower likelihood of a significant response (odds ratio 0.25, 95% confidence interval [CI] 012–053) and a shorter PFS (hazard ratio 402, 95% CI 195–802) than individuals without these mutations [16].

A phase III randomized trial (iNNOVATE study) compared ibrutinib in combination with rituximab (IR) to rituximab monotherapy + placebo in patients with treatment-naive or relapsed WM. In the treatment-naive cohort, IR significantly increased PFS from 59 to 84% compared to placebo-rituximab (hazard ratio 0.34; 95% CI: 0.12–0.95) [59]. The improvement in PFS was observed regardless of the MYD88L265P and CXCR4 genotypes of the patients. The 30-month PFS was 80% in both CXCR4MUT and CXCR4WT groups, indicating that the addition of rituximab may overcome the ibrutinib resistance in the CXCR4MUT genotype. The combination of ibrutinib and rituximab lowered the rate of IgM flare compared to the placebo-rituximab group (8% vs. 47%), most likely due to a reduction in cytokines associated with concurrent ibrutinib therapy.

Buske et al. conducted a retrospective review and identified 483 patients with WM to evaluate adherence to ibrutinib treatment. Twenty-three patients received ibrutinib (mean age 71.8 years, with 47.8% female patients). The average duration of follow-up for patients was 321.5 days. According to Kaplan-Meier's estimates, 77.1% (95% CI: 34.5–93.9%) of patients were still taking ibrutinib after 1 year. The mean proportion of days covered was 77.4% (95% CI 68.7–86.1%), and non-adherence to ibrutinib was 42.9% (95% CI: 19.8–65.9%) [60]. Table 6 summarizes the clinical trials utilizing Bruton tyrosine kinase inhibitors in WM patients. Ibrutinib is approved as first-line treatment as first-line therapy. Ibrutinib is also reserved for elderly, frail patients who are not candidates for systemic chemotherapy and can take the medicine orally.

Second- and next-generation BTK inhibitors

AU003 study was the first-in-human, multicenter, phase 1/2 trial of zanubrutinib carried out in patients with B-cell malignancies at 24 sites in 6 countries. Seventy-seven patients (24 treatment-naive and 53 relapsed refractory) with WM and no prior BTK inhibitor exposure were enrolled between September 2014 and March 2018. Seventy three of these patients received an initial daily dose of 320 mg. The median follow-up was 36 months for relapsed refractory patients and 23.5 months for treatment-naive patients. The majority were male, and the median age was 67 years. Upon protocol amendment, 4 relapsed refractory, and 8 treatment-naive patients who initially received 320 mg once daily were switched to 160 mg twice daily. At the data cutoff date of August 31, 2019, 56 patients (19/24 treatment-naive, 37/53 relapsed refractory) continued the study, while 21 (5/24 treatment-naive, 17/53 53 relapsed refractory) discontinued the study. Seventy-three patients were evaluable for efficacy (another 4 had baseline IgM concentration of ˂ 5 g/L). Serum IgM levels decreased with increasing treatment duration. Hemoglobin concentrations increased with time on treatment, demonstrating a median maximal improvement of 35 g/L, a 32.7% improvement over baseline. They reported a VGPR of 45.2%, MRR of 95.9%, and ORR of 82.2% [61].

Table 6 Bruton tyrosine kinase inhibitors in the treatment of Waldenström macroglobulinemia

Study, year	Regimen	No. of patients	Treatment response	Survival rates	Median follow-up
Ilhan et al., 2022	Ibrutinib as salvage therapy or rituximab	16	CR: 4 patients VGPR: 4 patients PR: 6 patients	ORR: 83.3%	29 months
Castillo et al., 2020	Ibrutinib monotherapy	229		4-year PFS: 72% 4-year OS: 63%	3.1–3.5 years
Treon et al., 2020	Ibrutinib at 420 mg/dl	63	ORR: 90.5% MRR: 79.4%	5-year overall survival rate: 87%	59 months
Buske et al., 2022	Ibrutinib in combination with rituximab (IR) with rituximab monotherapy plus a placebo	Treatment-naive cohort (n = 68)		30-month PFS of 84% compared to 59% in the placebo-rituximab arm	

Abbreviations: *CR*, complete response; *VGPR*, very good partial response; *PR*, partial response; *ORR*, overall response rate; *PFS*, progression-free survival; *OS*, overall survival; *MRR*, minimal response rate

JapicCTI-173646 is a phase 2, open-label, and single-arm design at 19 sites in Japan. In total, 30 patients were assessed for eligibility from November 2018 to February 2019; 27 (18 treatment-naive and 9 relapsed refractory) were enrolled in 2 cohorts and treated with tirabrutinib 480 mg once daily. Primary eligibility criteria for both cohorts were age ≥ 20 years, monoclonal gammopathy with serum IgM levels of > 500 mg/dl, and ECOG performance score of 0 or 1. In addition, cohort A had inclusion criteria of either symptomatic WM or serum IgM levels of > 4000 mg/dl. The median follow-up was 6.5 and 8.3 months for cohorts A and B, respectively. The median age was 71 years. The primary endpoint was the major response rate. MYD88L265P mutation made up 96.2% of the cohort. Both cohorts experienced a decrease in serum IgM levels. The most significant reductions in individual serum IgM levels were greater than 50% in 92.6% of the patients. They reported a VGPR of 11.1%, an MRR of 88.9%, and an ORR of 96.3% [62].

A phase 2 trial in Chinese patients is a pivotal, single-arm, open-label, and multicenter study of Zanubrutinib by An et al. The study was conducted in China, starting on August 31, 2017, and the last patient visit in this study occurred on January 11, 2021. Forty-four patients were enrolled, and most (75%) were intermediate or high risk as per IPSS for WM. Patients inducted in the study were all confirmed relapsed refractory WM, with approximately 16% being MYD88WT type. Eligible patients were aged ≥ 18 years, had at least one prior line of a standard chemotherapy-containing regimen, and met at least one of the criteria for treatment per a consensus panel from the 7th IWWM and an ECOG performance status score between 0 and 2. The median follow-up was 33 months. The maximal reduction from baseline in the level of serum IgM was 21.7 g/L, and the median reduction from baseline was 83.8%. The median maximal improvement from baseline was 31 g/L, and the median percentage improvement was 32.2%. Those patients who achieved resolution of one or more manifestations of WM-related disease were 83.7%. They reported VGPR 32.6%, MRR 95.9%, and ORR [63].

A phase 3 trial (ASPEN study) compared the efficacy and safety of ibrutinib with zanubrutinib. Between January 2017 and July 2018, 201 patients (164 RRWM and 37 were treatment-naive, i.e., TN) with MYD88L265P WM from 58 study sites were enrolled in cohort 1. Patients were randomly assigned 1:1 to treatment with either ibrutinib or zanubrutinib, and 199 received ≥ 1 dose of study treatment. Randomization was stratified by CXC4WHIM mutation status and several prior lines of therapy. The primary endpoint was the proportion of patients achieving CR or VGPR by an independent review. More patients randomized to zanubrutinib than ibrutinib were > 75 years old (33% vs. 22%, respectively), and approximately, 85% were in the intermediate- or high-risk prognostic category. No patient achieved a CR. VGPRs were higher among zanubrutinib than ibrutinib arm (28% and 19%, $p = .09$) as assessed by IRC. According to investigator-assessed rates, VGPR was 28% vs. 17% in the zanubrutinib and ibrutinib arms, respectively ($p = .04$). Concordance rates between IRC- and investigator-assessed best responses were 94% and 95% for zanubrutinib and ibrutinib arms. Median times to achieve a VGPR were skewed towards zanubrutinib than ibrutinib in treatment-naive patients and were 5.6 and 22.1 months ($P = .35$), respectively. Relapsed refractory patients took 4.7 and 5.1 months ($P = .17$), respectively. The median IgM levels were reduced by 79% and 72% for zanubrutinib and ibrutinib patients. The median maximal hemoglobin concentrations increased by 27 g/L and 2 8g/L among zanubrutinib and ibrutinib patients, respectively [64]. This trial showed higher VGPR rates, greater IgM reduction, and established zanubrutinib as highly effective for treating WM patients with less cardiovascular toxicity compared to ibrutinib.

In cohort 2 of the ASPEN study, 28 patients were included based on MYD88 mutation status. Twenty-six patients had documented MYD88WT disease, and 2 had unknown mutation status. Twenty-three had relapsed refractory disease, and 5 were treatment-naive. According to IPSS for WM, most were in the intermediate-risk (39%) and high-risk (43%) prognostic category. At baseline, 54% of the patients were anemic (Hb ≤ 110 g/L). The median age was 72 years. The median times from initial diagnosis to initiation of zanubrutinib were 1.5 years (range, 0.1 to 12.4) for TN patients and 4 years (range, 0.5 to 20.3) for relapsed refractory patients. The median duration of treatment was 16.4 months, and the median follow-up was 17.9 months. No patient achieved a CR. Among the 26 patients with MYD88WT status, VGPR, major response, and the overall response were achieved in 7 (27%), 13 (50%), and 21 (81%) patients, respectively. At 18-month follow-up, PFS and OS were 68% and 88%, respectively. The concordance rate between IRC- and the investigator-assessed best response was 88%. Following IWWM-6 consensus criteria and IgM reductions, the concordance rate for IRC- and the assessed best response was 92%. From baseline, the median maximal reduction in serum IgM levels was 56% (25th, 75th percentile: 86%, 37%), while the median maximal increase in Hb concentration was 19% (25th, 75th percentile: 11%, 24%) [65]. This study concluded that zanubrutinib monotherapy could provide better response in MYD88WT disease WM patients.

Acalabrutinib is a next-generation BTK inhibitor. A single-arm, multicenter, phase 2 trial was completed in 19 European and 8 US academic centers. Eligible patients were aged ≥ 18 years, either had R/R disease or were TN and had an ECOG performance status score of 2 or less. One hundred twenty-two patients were assessed for eligibility, but 106 were enrolled and received acalabrutinib.

Six patients received acalabrutinib 200 mg per oral daily; however, a protocol amendment was made as of March 13, 2015, and these patients were switched to 100 mg twice daily. All subsequent patients received 100 mg twice daily. At the data cutoff, the median duration of follow-up was 27.4 months. An ORR of 93% was reported in both TN and R/R patients. On the other hand, MRR was 79% and 78% in TN and R/R patients, respectively. Response by MYD88 mutation status was assessed in 50 patients (36 MYD88L265P/14 MYD88WT). ORR was 94% and 79%, while MRR was 78% and 57% in MYD88L265P and MYD88WT patients, respectively. Rapid reductions in IgM were associated with clinically useful improvement in Hb levels in R/R patients. There was a 57% reduction in IgM levels and an improvement of 12% in Hb levels in R/R patients. Similar figures were also obtained for TN patients [66]. Based on this study, acalabrutinib monotherapy is active in both TN and RR settings.

Second- and next-generation BTK inhibitors have shown promising results in both TN and RR settings. Zanubrutinib induces IgM reduction and showed better response in MYD88WT WM patients. Table 7 summarizes the clinical trials utilizing second- and next-generation BTK inhibitors in WM patients.

BCL2 inhibitor

BCL2 inhibitor venetoclax was used in the phase 2 multicenter study. The dose given was 200 mg oral which was increased to a maximum of 800 mg daily for up to 2 years. Thirty-two patients were studied; all had either refractory or relapsed WM. All patients were MYD88 L265P–mutated, and 17 patients carried CXCR4 mutations. Previous exposure to BTK is associated with a longer response time (4.5 vs. 1.4 months). The median time for a minor response was 1.9 months and 5.1 months for a major response. The ORR

Table 7 Second- and next-generation BTK inhibitors in Waldenström macroglobulinemia

Study, year	Regimen	No. of pts	Treatment response (%)	Survival rate (%)	Median follow-up (months)
Tam et al., 2020	Ibrutinib 420 mg once daily vs zanubrutinib 160 mg twice daily in 28-day cycle until progression or intolerance	201[a]	(Zanubrutinib vs Ibrutinib) VGPR 28 vs 19[b] MRR 77 vs 78 ORR 94 vs 93	(Zanubrutinib vs Ibrutinib) PFS 15 vs 16 OS 97 vs 93	18 and 18.5
Dimopoulou et al., 2020	Zanubrutinib 160 mg twice daily in 28-day cycle until progression or intolerance	28	VGPR 27 MRR 50 ORR 81	PFS (18-mo) 68 OS (18-mo) 88	17.9
Gang et al., 2021	Zanubrutinib 160 mg orally twice daily until disease progression or unacceptable toxicity	44	VGPR 32.6 MRR 69.8 ORR 76.7	PFS and OS were 60.5% and 87.8%, respectively	33
Trotman et al., 2020	Zanubrutinib 160 mg twice daily or 320 mg once daily	77	VGPR 45.2 MRR 95.9 ORR 82.2	PFS was 80.5% (24 and 36 mo.) OS was 94.1% and 84.8% at 24 and 36 mo., respectively)	36
Sekiguchi et al., 2020	Tirabrutinib 480 mg once daily	27	VGPR 11.1 MRR 88.9 ORR 96.3	No events were observed during the study period	6.5 and 8.3 in cohort A and B, respectively
Owen et al., 2020	Acalabrutinib 100 mg twice daily orally in 28 days cycle	106	ORR: 93% in both TN and R/R MRR: 79% and 78% in TN and R/R, respectively	PFS: 90% in TN and 82 % in R/R OS: 92% in TN and 89 % in R/R	

[a]R/R patients were never dosed (1 ibrutinib patient had CNS lymphoma and 1 zanubrutinib patient had acute kidney injury)

[b]Two R/R, ibrutinib-treated patients assessed as having VGPRs by the independent review were assigned the best response of PR and MR by their investigators

Abbreviations: *VGPR*, very good partial response; *MRR*, minimal response rate; *ORR*, overall response rate; *PFS*, progression-free survival; *OS*, overall survival; *R/R*, relapsed/refractory; *TN*, treatment-naive

was 84%, the MRR was 81%, and the VGPR was 19%. The median PFS was 30 months. The only significant side effect reported was neutropenia, including an episode of febrile neutropenia, which was well-managed. The laboratory reported tumor lysis without any clinical symptoms or signs in one patient. Venetoclax was reported as a safe and effective drug [67].

A clinical trial was conducted to check the safety and efficacy of ibrutinib and venetoclax (NCT04273139). It was started in July 2020 when a combination of ibrutinib and venetoclax was given to patients with previously untreated WM. In the first cycle, only ibrutinib was given. In the second cycle, venetoclax was given in progressively increasing doses up to a maximum of 400 mg/day. In the third cycle, the combination was given, and the aim was to continue with the combination for up to cycle 24. The study had to be prematurely terminated due to increased cardiac toxicities. There were 9% reported cases of ventricular arrhythmias. Initially, in January 2022, the study was suspended temporarily after a few patients developed ventricular arrhythmias/cardiac arrest. All patients were advised to undergo monitoring with ECG, echocardiography, and stress test. During the stress test, another patient developed a ventricular arrhythmia, and therefore, the study was completely stopped in April 2022.

CXCR-4 therapy

Approximately 40% of WM patients have a CXCR4 activating mutation, leading to a more rapid disease progression. CXCR4Mut has an impact on BTK-inhibitor response and suboptimal treatment outcomes. Recent research has identified the endogenous human peptide EPI-X4 as a natural CXCR4 antagonist that inhibits CXCL12-mediated receptor internalization and lowers cancer cell motility and invasion along a CXCL12 gradient [68]. These results indicate that developing EPI-X4 molecules may offer a promising strategy for reducing growth and enhancing CXCR4 signaling in WM.

A phase 1 clinical trial by Treon et al. used ulocuplumab, a CXCR4-antagonist, in combination with ibrutinib for treating CXCR4Mut in WM. Ibrutinib began at 420 mg/day with cycle one and continued until intolerance or disease progression. Ulocuplumab was administered using a dose-escalation approach from cycles 1 to 6. Thirteen symptomatic patients were enrolled in the study, nine of whom had never received any treatment. At optimal response, the median serum immunoglobulin M concentration declined from 5574 to 1114 mg/dl, bone marrow disease decreased from 65 to 10%, and hemoglobin increased from 10.1 to 14.2 g/dl (p =.001). With a median follow-up of 22.4 months, the estimated 2-year PFS was 90% [69]. The most frequent adverse events of grade 2 severity were reversible thrombocytopenia, dermatitis, and skin infections.

Mavorixafor, an oral CXCR4 antagonist, is being studied in combination with ibrutinib in WM patients with tumors expressing MYD88 and CXCR4 mutations (NCT04274738). The study's primary goal is to determine a pharmacologically active dose of mavorixafor in combination with ibrutinib based on pooled safety, pharmacokinetics, pharmacodynamics, and clinical response data for a randomized trial. The study's results promote the development of CXCR4-antagonists for CXCR4Mut WM and demonstrate the feasibility of combining a CXCR4-antagonist with ibrutinib. CXCR-4-related therapy is still in early phases of studies to evaluate its role in the treatment of WM. Table 8 summarizes the clinical trials utilizing venetoclax and CXCR-4 therapy in WM patients.

Hematopoietic stem cell transplantation (HSCT)

In treating WM, the role of HSCT, either autologous or allogeneic, is not rampant. Although published evidence is limited, HSCT has generally been used in WM patients with refractory disease or those with a high risk of disease progression [70].

Table 8 Venetoclax and CXCR-4 therapy

Study, year	Drug name	Number of patients	Median time to minor response	Median time to major response	Treatment response	Survival rate
Castillo et al., 2022	Venetoclax 200 mg oral escalated to 800 mg	32	1.9 months	5.1 months	OR 84% MRR 81% VGPR 19%	PFS 30 months OS 100% at the end of 30 months
Treon et al., 2021	Ibrutinib + venetoclax	50 treatment-naive pts with MYD88 gene mutation				
Treon et al., 2021	Ulocuplumab + ibrutinib	13		Median follow-up of 22.4 months		PFS 90%

Abbreviations: *OR*, overall response; *MRR*, minimal response rate; *VGPR*, very good partial response; *PFS*, progression-free survival; *OS*, overall survival

A Center for International Blood and Marrow Transplant Research (CIBMTR) analysis of 36 patients who underwent HSCT was reported by Anagnostopoulos et al., in which 10 patients received high-dose chemotherapy followed by autologous HSCT. In comparison, the other 26 patients underwent allogeneic HSCT. At 3 years, PFS was 65% (95% CI 32–91%) in the autologous group and 31% (95% CI 14–50%) in the allogeneic group. OS at 3 years was 70% (95% CI 40–93%) in the autologous cohort and 46% (95% CI 27–65%) in the allogeneic cohort. Non-relapse mortality was 11% (95% CI 0–36%) in the autologous cohort and 40% (95% C0, 23–59%) in the allogeneic cohort. At 3-year follow-up, the relapse rate was 24% (95% CI 4–54%) in the autologous cohort and 29% (95% CI 14–48%) in the allogeneic cohort. They concluded that autologous HSCT is a feasible option for patients with adverse prognostic factors, but allogeneic HSCT had higher non-relapse mortality compared to autologous HSCT [70].

A British Society of Blood and Marrow Transplantation study provided results from 9 autologous HSCT recipients who received high-dose chemotherapy with total body irradiation. It showed a reassuring 4-year OS and PFS of 73% and 43%, respectively. No transplant-related mortality was reported. In 9 allogeneic HSCT patients who received conditioning with total body irradiation, BEAM, or FLU-MEL, 4-year OS and PFS were 56% and 44%, respectively, with 44% transplant-related mortality [71].

The French study included 54 cases of WM undergoing transplant in 18 institutions. Thirty-two patients received autologous HSCT. At a median follow-up of 45 months, the relapse rate was 56%, event-free survival was 25%, and OS at 1, 3, and 5 years of 87%, 77%, and 58%, respectively. In 11 myeloablative allogeneic HSCT recipients, event-free survival was 48%, relapse was 36%, transplant-related mortality was 36%, and OS at 1, 3, and 5 years of 64%, 54%, and 54%, respectively, at a median follow-up of 68 months. In 11 reduced intensity conditioning allogeneic HSCT recipients, event-free survival was 68%, relapse was 0, transplant-related mortality was 27%, and OS at 1, 3, and 5 years of 82%, 68%, and 68%, respectively, at a median follow-up of 22 months [72].

The European group of blood and marrow transplantation lymphoma working party reported results from 158 autologous HSCT WM recipients. At 1 year, non-relapse mortality was 3.8%. At 5 years, PFS and OS were 39.7% and 68.5%, respectively, with a relapse rate of 52.1% [73].

At presentation, most of the patients of MW are of advanced age; however, SCT is a reserved treatment option for young WM patients with no significant associated comorbidity. Most of the studies evaluating the role of SCT in WM are old. More evidence is needed to establish the feasibility and safety of high-dose chemotherapy and autologous SCT in elderly patients [70].

Outlook

Significant progress has been made over the years in understanding and management of WM, leading to improved patient outcomes. However, challenges remain, and ongoing research continues to investigate novel therapeutic strategies to improve the treatment of WM. The introduction of targeted therapies has significantly changed the landscape of WM treatment. Mutations in the MYD88 and CXCR4 genes have led to the creation of drugs that disrupt the corresponding signaling cascades. Ibrutinib and other BTK inhibitors have demonstrated remarkable efficacy, but resistance to BTK inhibitors remains a concern. To overcome resistance, researchers are investigating novel agents that target alternative signaling pathways, such as proteasome inhibitors, PI3K inhibitors, and SYK inhibitors.

Immunotherapy has emerged as a promising avenue for the treatment of various malignancies, and its potential in WM is being actively investigated. Monoclonal antibodies, such as rituximab and ofatumumab, have shown efficacy in combination with chemotherapy or as maintenance therapy. Furthermore, the advent of chimeric antigen receptor (CAR) T-cell therapy has opened new possibilities for the treatment of WM. Additionally, immune checkpoint inhibitors, such as pembrolizumab and nivolumab, are being explored in combination with other therapies to enhance anti-tumor immune responses.

Advancements in molecular profiling techniques have enabled the identification of distinct genetic and molecular subtypes in WM, leading to personalized medicine approaches. Biomarkers such as MYD88 and CXCR4 mutations are being used to guide treatment decisions and predict responses to therapies. Research is ongoing to further elucidate the molecular mechanisms underlying WM.

Given the complexity and heterogeneity of WM, combination therapies are being explored to optimize treatment outcomes. Combinations of targeted therapies, immunotherapies, and chemotherapy regimens are being evaluated in clinical trials to determine their efficacy and potential synergistic effects. Additionally, treatment sequencing is an important aspect to consider, especially in the era of rapidly evolving therapeutic options. Research is focused on identifying optimal treatment sequences that maximize response rates, minimize toxicity, and improve long-term outcomes.

Recommendations

(i) Asymptomatic WM patients can be observed for months and years with blood counts and monoclonal blood protein levels. Symptomatic patients or

patients with hyperviscosity related symptoms need treatment with plasmapheresis followed by chemotherapy.

(ii) Various drugs and combinations showed benefit in trials, but there are limited randomized clinical trials for head-to-head comparison.

(iii) Rituximab is currently used as a first-line treatment in newly diagnosed WM as monotherapy or combination therapy. Rituximab monotherapy can cause IgM flare with resultant hyperviscosity and is generally not used in high IgM levels (> 4000 mg/dl). Rituximab monotherapy response rates are also lower than rituximab combination therapy. Rituximab monotherapy is not routinely used for WM. Rituximab and bendamustin combination therapy is used as preferred first-line therapy in treatment-naive WM patients.

(iv) Nucleoside analogs (fludarabine or cladribine) are effective for treating WM, but they increase the risk of second malignancy. Nucleoside analogs should be avoided as a primary treatment.

(v) Bortezomib combination therapy with rituximab shows efficacy for the treatment of WM with a rapid decrease in IgM levels. However, peripheral neuropathy is a major dose-limiting factor. Carfilzomib could be used as a peripheral neuropathy sparing agent.

(vi) Ibrutinib (BTK Inhibitor) is approved as first-line therapy for treatment-naive patients. Ibrutinib is reserved for elderly, frail patients who are not candidates for systemic chemotherapy and can take orally until disease progression.

(vii) Second-generation BTK inhibitor (zanubrutinib) and next-generation BTK inhibitor (acalabrutinib) have shown promising results. Further studies are warranted before their routine use.

(viii) Relapsed WM patients are usually retreated with the same therapy if they relapsed more than 3 years after completing initial therapy. If patients relapse less than 3 years following initial therapy, they are treated using alternative therapy.

(ix) The role of autologous stem cell transplant following high-dose chemotherapy needs further evaluation and is currently limited.

Conclusion

With the introduction of targeted therapies, immunotherapies, and personalized medicine techniques, the landscape of WM treatment has undergone significant changes recently. Although these developments have improved patient outcomes, issues like disease heterogeneity and acquired resistance still exist. Future treatment options for WM include refining targeted therapies, investigating immunotherapeutic approaches, utilizing biomarkers for personalized treatment, and optimizing treatment sequencing and combination strategies. The prognosis for patients with WM will be improved through continued research efforts, including strong clinical trials and translational studies.

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Data availability The authors declare that data supporting the findings of this study are available within the article

Declarations

Informed consent Not applicable.

Conflict of interest Faiz Anwer Reports personalities from Bristol Myers Squibb as a speaker and feeds from Janssen pharmaceutical as an advisory board member; these fevers are unrelated to the submitted work. Without receiving direct funding, served as the local principal investigator for Allogene Therapeutics, Celgene, GlaxoSmithKline, and Bristol Myers Squibb; has a consulting on an advisory role for Seattle genetics, Incyte Corporation speakers Bureau, Company: Insight Corporation; receives travel and accommodations expenses from Seattle genetics, insight; receives on the radio from insight, complaining: Seattle genetics; and received research funding from Seattle Genetics, company: Calgene, Acetylon pharmaceuticals, Millennium, Astellas Pharma and AbbVie; and reports no other potential conflicts of interest for this work. The other authors declare no competing interests.

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