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Waldenström Macroglobulinemia: 2025 Update on Diagnosis, Risk Stratification, and Management

Morie A. Gertz

Division of Hematology, Mayo Clinic, Rochester, Minnesota, USA

Correspondence: Morie A. Gertz (gertz.morie@mayo.edu)

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ABSTRACT

Disease Overview: Waldenström macroglobulinemia (WM) is a lymphoplasmacytic lymphoma with immunoglobulin M (IgM) monoclonal protein. Clinical features include anemia, thrombocytopenia, hepatosplenomegaly, lymphadenopathy, and rarely hyperviscosity.

Diagnosis: The presence of IgM monoclonal protein associated with ≥ 10% clonal lymphoplasmacytic cells in bone marrow confirms the diagnosis. The L265P mutation in *MYD88* is detectable in more than 90% of patients and is found in most IgM MGUS patients. MYD88 is not required for the diagnosis.

Risk Stratification: Age, albumin, hemoglobin level, platelet count, β_2 microglobulin, Lactate dehydrogenase (LDH), and monoclonal IgM concentrations are characteristics that are predictive of outcomes.

Risk-Adapted Therapy: Not all patients who fulfill WM criteria require therapy; these patients can be observed until symptoms develop. Rituximab-monotherapy is inferior to combination regimens. Recommended first-line therapy can be chemoimmunotherapy or a covalent Bruton tyrosine kinase inhibitor. The preferred Mayo Clinic induction is either rituximab and bendamustine (without rituximab maintenance) or zanubrutinib.

Management of Refractory Disease: Bortezomib, cyclophosphamide, fludarabine, thalidomide, everolimus, pirtobrutinib, carfilzomib, lenalidomide, bendamustine, and venetoclax have all been shown to have activity in relapsed WM. Given WM's natural history, the reduction of therapy toxicity is an important part of treatment selection. Most patients succumb to causes unrelated to macroglobulinemia.

1 | Patient

A 55-year-old male was found to have an immunoglobulin M (IgM) monoclonal gammopathy in January 2008. He was observed until November 2013, when his IgM level climbed to 9135 mg/dL. He was treated with rituximab, bortezomib, and dexamethasone for 4 months. Treatment was interrupted due to neuropathy, but the IgM level fell to 1150 mg/dL. He was observed until April 2018. At the time of symptomatic progression, his IgM was 11,500 mg/dL, and he was found to have acquired von Willebrand disease. He was treated with a single agent rituximab, which failed to produce a minor response. He received bendamustine and rituximab, with a response of less than 1 year. In 2021, he was placed on an experimental trial of oprozomib, with a response of 3 years duration. At relapse in August 2024, he was placed on a trial of ixazomib and ibrutinib.

Abbreviations: BTK, Bruton tyrosine kinase; IgM, immunoglobulin M; MGUS, monoclonal gammopathy of undetermined significance; mTOR, mammalian target of rapamycin; OS, overall survival; PFS, progression-free survival; R-CHOP, cyclophosphamide,doxorubicin, vincristine,and prednisone plus rituximab; WM, Waldenström macroglobulinemia.

Ixazomib was poorly tolerated due to diarrhea, and he continued ibrutinib alone and has achieved a very good partial response.

Comment: This patient illustrates many common features of the disease. A smoldering phase lasted 5 years managed with surveillance only; multiple therapeutic interventions resulted in responses. Failure of a single agent rituximab is typical. Bortezomib neuropathy was severe but resolved completely. Acquired Von Willebrand's disease is seen in nearly 10% of patients with macroglobulinemia and is often associated with higher levels of IgM. Bleeding resolves with the reduction of the IgM level [1] Bleeding in macroglobulinemia is often multifactorial [2]. A durable response with a Bruton tyrosine kinase (BTK)i is expected in most patients.

2 | Disease Overview

The World Health Organization (WHO) defines Waldenström macroglobulinemia (WM) as a lymphoplasmacytic lymphoma associated with a monoclonal IgM protein. The physical manifestations of the disorder are hepatomegaly (20%), splenomegaly (15%), and lymphadenopathy (15%). The most common presenting symptom is fatigue related to a normocytic anemia. The median hemoglobin value at diagnosis is 10 g/dL. Many patients who fulfill the WHO criteria of WM do not require immediate therapy because they are asymptomatic (smoldering). Virtually all patients have a preceding phase of IgM monoclonal gammopathy of undetermined significance (MGUS), but the clonal MGUS B cells already contain the molecular signature of a malignant clone. Patients under the age of 70 have a median survival in excess of 10 years; those 70 to 79, approximately 7 years; and those 80 or older, approximately 4 years. In patients with Waldenstrom over age 65 at diagnosis, the most common cause of death is not cancer related. Clonal hematopoiesis is present in 14% of patients with macroglobulinemia. Clonal hematopoiesis was associated with an increased risk of progression from smoldering disease to active disease [3]. The key clinical features of the disease are represented in the graphical abstract. There is no threshold of IgM above which treatment should be initiated in the absence of symptoms.

The median age at the time of diagnosis is 71 years. The age-adjusted incidence rate is 0.42/100 000 person-years, with an age- and sex-adjusted incidence of 0.57 per 100 000 person-years, with a male-to-female ratio of 3.2:1. There is no evidence of a change in the incidence of WM over the past 50 years [4, 5]. The diagnosis is established in the US annually in approximately 1500 patients (1% of lymphoma).

WM incidence is higher in Whites (4.1 per million per year) than in Blacks (1.8 per million per year). Waldenström patients had a positive family history of lymphoplasmacytic lymphoma or WM in 4.3%, and a family history was associated with poorer survival than the non-familial forms. A study of monoclonal immunoglobulins showed that the M protein isotype was IgM in 2% and 16% of Black and White patients, respectively. The median M protein concentration for blacks was 0.44 g/dL, whereas it was 1.2 g/dL in whites. Black patients less commonly have IgM monoclonal gammopathy compared with White patients. The median age at diagnosis is 63 years for Blacks and 73 for Whites, with blacks having a shorter survival than Whites. Multiple genes are likely involved in the etiology of macroglobulinemia [6].

Survival of WM is improving [7]. The SEER database contained 5784 patients with WM. Median OS from 1991 to 2000 and 2001 to 2010 improved from six to eight years, respectively. Deaths in the 2001 to 2010 cohorts were reduced both from WM-related and non–WM-related causes. Age at diagnosis continues to have the greatest impact on survival. The hazard ratio for death for WM patients aged 80 or greater was 6.99, compared to a reference group aged less than 50. Twelve percent of macroglobulinemia patients are under the age of 50. The estimated average years of life lost for this group is 11.2. Nearly all young patients succumb to their disease [8].

The presence of a monoclonal IgM protein adds a unique dimension to the disorder because it can result in hyperviscosity syndrome, peripheral neuropathy, hemolytic anemia, and immune complex vasculitis. The 10-year survival rate is 66%. In a population-based study of Latin American patients with WM and lymphoplasmacytic lymphoma, the 5-year relative survival was 81%. Survival improvements were seen in all age groups, although increasing age was associated with inferior survival [9].

The management of peripheral neuropathy associated with IgM monoclonal protein remains frustrating for clinicians. The mechanism of the neuropathy is thought to be demyelination due to direct binding of the antibody to myelin-associated glycoprotein. The course is generally slowly progressive, often over a decade. Autonomic neuropathy and carpal tunnel syndrome are not features. The neuropathy is not painful. The treatment of IgM-associated peripheral neuropathy is similar to that of WM [10]. Overall improvement following rituximab treatment in IgM-associated neuropathy was seen in 54.5%. Six patients who were unchanged after the 1st treatment with rituximab improved after another rituximab cycle. Rituximab monotherapy retains a role in IgM-mediated neuropathy. In a double-blind, placebo-controlled trial, 54 patients with anti-MAG IgM chronic demyelinating neuropathy were randomized to receive either placebo or rituximab. The primary outcome of absolute improvement in ISS (INCAT sensory score) from baseline to 12 months was not achieved in the study, as no significant difference in the change in ISS was seen between rituximab and placebo groups. Ibrutinib was administered to three patients with anti-myelin–associated glycoprotein IgM neuropathy; all reported an early subjective benefit pointing to the possible efficacy of ibrutinib in this setting. Among 49 patients with peripheral neuropathy symptoms treated with a BTK inhibitor, 35 (71.4%) experienced resolution of symptoms, with the median time to resolution of 10.1 months [11].

2.1 | Diagnosis

In the original description of WM, Jan Gösta Waldenström described two patients with oronasal bleeding (hyperviscosity), lymphadenopathy, anemia, thrombocytopenia, and an elevated sedimentation rate. The disorder is a lymphoplasmacytic lymphoma with a monoclonal pentameric IgM protein. Bone marrow and lymph nodes are infiltrated with pleomorphic B-lineage

cells at different stages of maturation. The bone marrow pattern is predominantly intertrabecular. Many patients who fulfill all other criteria for the diagnosis have a presymptomatic phase and may not require therapy. The cells express pan B-cell markers (e.g., CD19, CD20) and typically test negative for CD3 and CD103. A recurring sequence variant at position 38 182 641 in chromosome 3p22.2 has been identified. A single-nucleotide change from T to C in the *MYD88* gene resulted in a leucine-to-proline change at amino acid position 265 (L265P). This mutation is seen in 93% of patients. CXCR4 mutations are seen in 29% [12]. Fifty-three percent of patients with hyperviscosity have mutations of CXCR4. This is an important somatic variant in the malignant cells of WM. MYD88 status does not predict survival 10.2 (mutant) versus 13.9 years (wild type) in patients treated with chemoimmunotherapy [13]. Others have reported a survival difference between those with mutant and those with wild-type MYD88. The estimated 10-year survival was 73% for MYD88WT versus 90% for mutated MYD88MUT. Median cause–specific survival in cyclophosphamide-treated patients was 166 months.

MYD88 can be detected by polymerase chain reaction in the peripheral blood of patients with WM [14]. *CXCR4* is mutated in 30% of patients with WM. In animal models, this mutation predicts resistance to ibrutinib and everolimus. CXCR4 mutation is associated with a shorter treatment-free survival with covalent BTK inhibitors [15]. In an analysis of patients participating in a phase 3 trial of BTK inhibitors, patients with mutations in CXCR4 or TP53 had a poorer prognosis after treatment with BTKi [16]

Distinguishing between WM and marginal zone lymphoma can be challenging. *MYD88* mutation L265P is specifically associated with WM and IgM monoclonal gammopathy of undetermined significance. *MYD88* L265P is also seen in splenic marginal zone lymphoma (4%), IgM amyloidosis (71%), mucosa-associated lymphatic tissue lymphoma (7%), and WM (67%–90%). *MYD88* L265P cannot be used to differentiate between WM and IgM MGUS. MYD88 mutations are seen in 64% of patients with IgM MGUS [17]. The mutation is not found in IgM multiple myeloma, and mutation expression is concordant with the extent of bone marrow involvement. Responses after chemotherapy are associated with declines in mutation expression [12].

Patients can present with markedly elevated IgM levels and infiltration of the bone marrow of more than 30% yet still not require therapy because they have no symptoms. Conversely, patients can have low levels of monoclonal IgM protein and minimal clonal marrow infiltration and still require therapy for complications associated with the IgM protein, including moderate or severe peripheral neuropathy, amyloid deposition, cold agglutinin hemolytic anemia, and type II mixed cryoglobulinemia—all a consequence of the antibody-binding specificity and protein folding of the IgM protein [18]. Only half of patients with a cryoglobulin have active manifestations when they are initially recognized. The primary indication for therapy in most patients is cutaneous ulcerations due to vasculitis [19]. A classification scheme for WM is provided in Table 1. Symptoms can be produced by the tumor mass or the monoclonal protein. The disease is incurable with current therapies. Therapy is most often needed for symptomatic anemia. However, a subset of patients has an inflammatory syndrome resulting in constitutional fatigue in the absence of anemia. Most of these patients can be identified by elevation of the C-reactive protein. Treatment results in symptomatic improvement in the majority of these patients [20].

A demyelinating peripheral neuropathy associated with monoclonal IgM proteins can be very frustrating to manage. The sensory neuropathy will progress often over a decade. The lack of involvement of the axon makes it painless, and autonomic features and carpal tunnel syndrome are not present. Much of the morbidity is associated with fall risk, although after a prolonged course, muscle wasting does occur. Measurement of anti-myelin–associated antibodies can be supportive in the diagnosis but is not specific. Skin biopsy, although not required, can reveal a decrease in nerve fiber density. Rituximab is often used as a first-line intervention for patients with sufficient symptoms to justify an therapy [21]. In patients treated with BTKi, a major hematologic response was associated with peripheral neuropathy symptom resolution. This translates to improved quality of life and physical functioning [11].

IgM multiple myeloma is a distinct entity, constituting only 1% of all multiple myeloma cases, and must be distinguished from WM. Useful clues to the diagnosis of multiple myeloma include the presence of lytic bone lesions (rare in WM) and a translocation at chromosome 14 (does not occur in WM). Patients with

TABLE 1 | Definitions of IgM-related phenomena in macroglobulinemia.

	IgM monoclonal component	Symptoms of tumor mass/infiltration (adenopathy anemia)	Marrow infiltration >10%	IgM-mediated symptoms
MGUS	+	−	−	−
Smoldering macroglobulinemia	+	−	+	−
IgM-related disorder (e.g., cold agglutinin hemolytic anemia, type II cryoglobulin, neuropathy, amyloidosis)	+	−	±	+
Macroglobulinemia	+	+	+	±

Note: IgM, immunoglobulin M; MGUS, monoclonal gammopathy of undetermined significance; +, positive; −, negative; ±, equivocal.

IgM multiple myeloma tend to have plasmacytic differentiation with high expression of CD138 and cytoplasmic immunoglobulin, whereas WM expresses CD20. MYD88 mutations are not seen in IgM multiple myeloma [22].

Monoclonal IgM proteins are found in 1 of 600 persons older than 50 years. More patients have IgM MGUS than have WM. All patients with IgM MGUS require lifelong monitoring. Among patients with IgM MGUS, the presence of two adverse risk factors—namely, an abnormal serum-free light-chain ratio (ratio of kappa to lambda free light chains) and a high serum monoclonal protein (M protein) level (≥ 1.5 g per deciliter)—was associated with a risk of progression at 20 years of 55%. In a study of 176 IgM MGUS patients, a monoclonal protein peak of > 1 g/deciliter and the presence of an MYD88 mutation successfully predicted progression to symptomatic macroglobulinemia with hazard ratios of over 20 for both variables. The cumulative incidence of progression at 10 years was 38%. MYD88 wild type is also an independent predictor of transformation to large-cell lymphoma, which carries an inferior overall survival [23].

Patients with IgM values greater than 3000 mg/dL may have no symptoms, a normal hemoglobin value, and no clinically important increase in serum viscosity. In these instances, observation continues to be an appropriate option. Symptomatic hyperviscosity was only seen in 13% of Mayo Clinic patients with WM. Even among patients presenting with an IgM greater than 6000 mg/deciliter, the median time to initial therapy was 6.9 years [24]. In patients with smoldering macroglobulinemia, independent predictors of disease progression to symptomatic disease included IgM level greater than 4500 mg/dL, bone marrow infiltration with 70% or greater lymphoplasmacytic lymphoma, beta 2 microglobulin > 4 mg/L, and albumin < 3.5 g/dL. Wild-type MYD 88 is also an independent predictor of progression to symptomatic disease. The Box 1 lists the recommended diagnostic evaluation for a new patient with suspected WM. Imaging plays a minor role since the majority of patients have modest lymphadenopathy; however, there is a suggestion that the results from fluorodeoxyglucose (FDG) positron emission tomography (PET) are prognostic in patients with macroglobulinemia [25].

Response in WM is defined by reduction in the M protein. A minor response is an M-spike reduction of at least 25%. A partial response is defined as a 50% or greater reduction in M protein. A very good partial response is a 90% reduction in M protein, and a complete response is immunofixation negativity in the serum. There may be discrepancies between IgM levels and bone marrow response. The involved serum-free light chain is a useful marker of tumor burden and acts as a leading indicator of response and progression, before the intact IgM, related to the light chain's shorter half-life in the serum. The immunoglobulin-free light chain assay, which is quite valuable in myeloma, has not been well established in WM. It is not required for serial monitoring of patients with WM. The goal of therapy is disease control. There is no convincing evidence to suggest that response depth correlates well with outcomes. This puts into question the use of a very good partial response as a primary end point for trials [26]. Among 472 macroglobulinemia patients, survival after progression was not influenced by the time to progression. Progression within 24 months of treatment did not predict higher mortality. This is different from other lymphomas where this parameter is an important predictor of outcome [27].

BOX 1 | Diagnostic approach to suspected Waldenström macroglobulinemia.

- Serum protein electrophoresis.
- Serum immunofixation to validate the immunoglobulin M (IgM) heavy chain and the type of light chain.
- Quantitative test for immunoglobulin G, immunoglobulin A, and IgM.
- 24-h urine collection for protein electrophoresis; monoclonal light chains are detected in the urine of 40%–80% of patients tested.
- Immunoglobulin-free light chain assay (long-term value not established).
- Serum β_2 microglobulin and LDH evaluation for prognosis; part of the international staging system for Waldenström macroglobulinemia.
- Bone marrow biopsy; intertrabecular monoclonal lymphoplasmacytic infiltrate ranges from predominantly lymphocytic cells to overt plasma cells.
- Perform *MYD88*^{L265P} mutational analysis on bone marrow sample in all cases of WM by allele-specific polymerase-chain-reaction (AS-PCR) assay.
- *CXCR4* mutational analysis, if available.
- Computed tomography of abdomen and pelvis to detect organomegaly and lymphadenopathy or a combined 18F-FDG positron emission tomography (PET)/CT scan (a skeletal survey and radiographic imaging of the bones are unnecessary in the absence of symptoms; lytic bone lesions are unusual)
- Serum viscosity required when signs and symptoms of hyperviscosity syndrome are present or when IgM > 4000 mg/dL
- Ophthalmologic evaluation for hyperviscosity.
- Based on clinical presentation, analysis involves Coombs test (cold autoantibody), cryoglobulin, Von Willebrand Ag, Factor VIII C, or tissue stains for amyloid deposits.
- Of myeloma patients, 1% have IgM, and their disorder behaves like other multiple myeloma.
- Hepatitis B and C screening is necessary if rituximab therapy is planned.

2.1.1 | Risk Stratification

Since WM is a distinct lymphoproliferative process with unique cell surface and genetic characteristics, the International Prognostic Index and the Follicular Lymphoma International Prognostic Index are not used to determine prognosis. Table 2 gives the currently accepted staging systems for WM.

The five criteria shown in Table 2 are not weighted equally. Age has the greatest impact on prognosis. Patients older than 65 years cannot be in a low-risk category. Although IgM protein levels are important prognostically, they do not enter the staging

TABLE 2 | International prognostic scoring system for Waldenström macroglobulinemia.

For	Value
Age, years	> 65
Hemoglobin, g/dL	≤ 11.5
Platelet count, No./mcL	≤ 100 000
β_2-Microglobulin, mg/L	> 3
Monoclonal IgM, g/dL	> 7

Risk stratum and survival

Risk category	Score[a]	Median survival, mo
Low	0 or 1 (except age)	142.5
Intermediate	2 or age > 65 years	98.6
High	> 2	43.5

Abbreviation: IgM, immunoglobulin M.
[a]One point is assigned for each positive factor and the risk score is the sum of points.

TABLE 3 | New prognostic system for WM.

Parameter	Points assigned
Albumin < 35 g/L	1
Age 66–75 years	1
Age > 75	2
LDH>ULN	1
Point score	OS @ 5 years, %
0 low risk	93
1 low-intermediate	82
2 intermediate	69
≥ 3 high risk	55

system until the IgM level exceeds 7000 mg/dL. In the largest study of single-agent rituximab therapy for WM, the IgM level did not affect the response rate. Lactate dehydrogenase (LDH) is absent from the International Prognostic Scoring System for WM. In a revision of the prognostic scoring system age (≤ 65 vs. 66–75 versus ≥ 76 years), β2-microglobulin ≥ 4 mg/L, serum albumin < 3.5 g/dL, and LDH ≥ 250 IU/L (ULN < 225) were able to stratify patients into five different prognostic groups and identify a very-low risk as well as a very-high risk group with a 3-year WM-related death rate of 0%, 10%, 14%, 38%, and 48% ($p < 0.001$) and a 10-year survival rate of 84%, 59%, 37%, 19%, and 9% ($p < 0.001$). LDH is a predictor of early mortality in this disease. Age is the most powerful predictor of outcome. The 10-year survival of patients aged 45 years or younger is 86%.

A newly proposed staging system (Table 3) found age, LDH, and albumin were independently prognostic for survival. By assigning 1 point each for albumin less than 3.5 g/deciliter, 1 point for age 66 to 75, 2 points for age greater than 75, and 1 point for any elevation in LDH, patients could have from 0 to 4 points. Five-year overall survival ranged from 55% to 93% [28].

The International Prognostic Scoring System for WM is to be used only for patients who require treatment. The system should not be used to determine whether a patient requires intervention; this determination continues to be a clinical decision. Serial measurements of β_2 microglobulin are not useful in monitoring therapy. Both hemoglobin and beta-2 microglobulin levels at diagnosis are independent predictors of progression to active macroglobulinemia.

Because most patients with WM have an indolent disease course and often are elderly, nearly half of all patients succumb to diseases unrelated to WM. The impact of age on OS was investigated in 238 patients with WM. The shorter survival of patients older than 65 years at diagnosis was attributable to the higher number of non–WM-related deaths. Cause-specific survival has been introduced as an important outcome measure. This statistical technique censors patients who die of causes unrelated to the malignancy and accounts for the competing risks of death that these patients face. In a competing risk survival analysis, 23% of deaths were unrelated to WM, and 40% of patients > 75 years do not die of WM. Patients with WM have a greater overall risk of a second malignancy that is 1.69 times higher than expected ($p = 0.002$). Compared with the general population, patients with WM appear to have a higher risk of large cell lymphoma, myelodysplasia, and brain cancer. Therapy-related myeloid neoplasms occur in 2.7% of patients.

3 | Management

3.1 | Hyperviscosity Syndrome

Hyperviscosity syndrome is seen in a decreasing proportion of patients with WM because WM is being diagnosed earlier. Symptomatic hyperviscosity is rare in patients with an IgM concentration less than 4000 mg/dL, and viscosity measurements are not required in patients whose IgM levels are below that threshold. The symptoms of hyperviscosity are primarily due to shear forces that rupture unsupported venous channels. Therefore, the presentation generally includes epistaxis, gingival bleeding, and visual changes due to retinal hemorrhage [29]. Central nervous system findings, including dizziness, light-headedness, and generalized fatigue, are nonspecific and must be confirmed with measures of serum viscosity. The reference viscosity of normal serum is 1.8; water has a viscosity of 1. Hyperviscosity syndrome is not likely unless the serum viscosity exceeds 4. When hyperviscosity is present, plasma exchange should be considered a temporizing measure until systemic therapy successfully lowers the tumor mass and thereby reduces the IgM protein concentration in the serum. A single plasma exchange is often sufficient to relieve symptoms and allow initiation of systemic therapy. An increasing number of protocols using chemoimmunotherapy delay the initiation of rituximab until the 2nd or 3rd cycle of therapy to avoid rituximab flare-precipitation of hyperviscosity related to rituximab [30]. In patients with an IgM level greater than 3000 mg/dL on observation, a retinal examination by an eye care professional should be performed semiannually.

3.2 | Systemic Chemotherapy to Reduce Tumor Mass

3.2.1 | Rituximab

Rituximab is a widely available treatment for the management of WM. Its lack of long-term toxicity and nonmyelosuppressive treatment profile has led to its incorporation in most therapeutic regimens for this disorder. However, rituximab alone is a poor choice for patients in need of therapy. Including both minor (25%–50% reduction of M protein) and objective (> 50% reduction of IgM protein) responses, the response rate to rituximab (< 55%) is inferior to every other reported combination regimen [31]. A meta-analysis confirmed that a higher response rate was produced with the combination therapy of 2+ drugs than with rituximab monotherapy (73% vs. 44%). In a double-blind randomized placebo-controlled phase 3 trial, rituximab was the control arm. The median progression-free survival with rituximab was 20.3 months; partial response or better was observed in only 31%. The median time to next treatment was 18 months. Hemoglobin improvement was seen in only 43%. Rituximab monotherapy is generally only suited for IgM-associated symptoms such as type II cryoglobulinemia, MGUS-associated neuropathy, and cold agglutinin disease.

The use of rituximab is associated with the risk of "flare" for many patients. In this phenomenon, the initiation of rituximab treatment results in a transient rise in the level of IgM, which can produce an increase in serum viscosity. This flare is seen less frequently when rituximab is combined with cytotoxic chemotherapy.

The use of maintenance rituximab therapy has been controversial. In a trial of patients treated with bendamustine and rituximab initially followed by randomization to observation or rituximab, an improvement in progression-free survival was not observed [32].

Rituximab is not the only monoclonal antibody that has been used in WM. Ofatumumab, an anti-CD20 monoclonal human antibody, has shown activity in WM. In a trial of 37 Waldenström patients receiving ofatumumab, 15 (41%) achieved a partial response, seven (19%) a minor response. All 37 patients had at least one adverse event [33]. The addition of pembrolizumab does not appear to add to rituximab, with an overall response rate of 50% at 24 weeks and a median progression-free survival of 13.6 months inferior to other published combination regimens [34].

3.3 | Rituximab Cyclophosphamide Dexamethasone RCd

Rituximab treatment combined with cyclophosphamide (orally) and dexamethasone has been reported with a response rate of 84% and minimal toxicity. Two-year PFS was 67%; two-year disease-specific survival was 90%. In an updated final analysis in 72 patients treated with rituximab, cyclophosphamide, and dexamethasone, the response rate on an intent-to-treat basis was 83%. The median PFS was 35 months. The median OS was 95 months. This three-agent combination is currently an alternative regimen for first-line therapy if the disease burden is low, based on Mayo Clinic mSMART guidelines [35].

Table selected outcomes with RCd:

Regimen	ND/RR	Response rate > MR, %	Response rate > PR	Response rate > VGPR	PFS, months	Reference
RCd	19/0	89.5	89.5	42.1	69.4% @ 5 years	[36]
RCVP	54/0	84	80	37	79 months	[37]
RCd	50/50	96/87	87/68	17/4	34/32	[38]

3.4 | Proteosome Inhibition

Bortezomib has been shown to have high levels of activity in the management of relapsed WM in schedules of twice weekly, two of three weeks, with response rates ranging from 81% to 96%. CXCR4 mutation does not lower the response rate to bortezomib. In newly diagnosed patients, weekly treatment with bortezomib and rituximab resulted in a better-than-minimal response in 23 of 26 patients and a one-year event-free survival rate of 79%. Most importantly, no grade 3 or 4 neuropathy was seen with the weekly bortezomib schedule. The European Myeloma Network reported outcomes of bortezomib, rituximab, and dexamethasone in previously untreated symptomatic patients. Rituximab was delayed to cycles 2 and 5 to reduce the risk of flare. No patient required plasma exchange for flare. The response rate was 85%, the median PFS was 42 months, and the three-year OS was 81%. Peripheral neuropathy was seen in 46%. Bortezomib-rituximab-dexamethasone is a reasonable choice for front-line therapy, but attention to early neurotoxicity is required. Bortezomib also has reported activity in cold agglutinin disease with an overall response rate of 32%.

In view of the high neuropathy rates, the less neurotoxic proteosome inhibitor, carfilzomib, was combined with rituximab and dexamethasone in patients not previously treated with the combination of rituximab and bortezomib. The overall response rate was 87%, with 36% having at least a very good partial response. At 2 years, 65% were progression-free. The peripheral neuropathy rate and cardiomyopathy rates were both 3%. The oral proteosome inhibitor, ixazomib, was combined with dexamethasone and rituximab, 26 patients were enrolled with an overall response rate of 96%, and a major response rate of 77%. The median time to response was 8 weeks. Fifty-nine previously treated patients received ixazomib, subcutaneous rituximab, and dexamethasone. After 8 cycles overall response rate was 71% with 14% very good partial response. Median response duration was 36 months. At 2 years, progression-free and overall survival were 56% and 88%, respectively. Proteosome inhibitiors are an important treatment option for the management of macroglobulinemia.

Selected Outcomes with Proteosome Inhibitors:

Regimen	ND/RR	Response rate > MR, %	Response rate > PR, %	Response rate > VGPR, %	PFS, months	Reference
Bortezomib DRC	102/0	80.6	57	32.6	80.6% @ 24 months	[39]
BCd19;Bd18;other 6	44/0	93.2	81.8	36.3	36.0	[40]
VCd	19/0	89.5	73.7	26.3	33	[36]
Carfilzomib	6/0	100	67	17	Not reported	[41]
Ixazomib ibrutinib	9/12	90.4	76.2	23.8	22.9	[42]

3.5 | Bendamustine

In a prospective randomized study of bendamustine plus rituximab compared with R-CHOP in low-grade lymphoma, a subset analysis identified 41 patients with WM, of whom 22 received bendamustine and rituximab, and 19 received R-CHOP. In both groups, the response rate was 95%, but median PFS was significantly prolonged with bendamustine. The median PFS for R-CHOP was 36 months in contrast to not being reached with bendamustine and rituximab ($p < 0.001$). At the time of analysis, 4 relapses were identified (18%) in the bendamustine and rituximab group and 11 relapses (58%) in the R-CHOP group. Bendamustine and rituximab treatment was better tolerated, with no alopecia, less hematotoxicity, a lower frequency of infection, a lower incidence of neuropathy, and reduced stomatitis [43]. Twenty-four previously treated patients received bendamustine (90 mg/m^2) plus rituximab on two consecutive days. Each cycle was 4 weeks, with a median of five treatment cycles. The overall response rate was 83% (20/24). The median PFS was 13.2 months. Prolonged myelosuppression was more common in patients who previously had received a nucleoside analog. In a cohort of 71 patients, with a median age of 72, all with relapsed/refractory WM (median two prior lines of therapy), R-bendamustine produced a PR of 74.6% and PR + MR of 80.2%. One- and three-year PFS were approximately 80% and 60%, respectively. The risk of progression appears to be lower in patients treated with bendamustine-rituximab or bortezomib-dexamethasone-rituximab when compared with cyclophosphamide-dexamethasone-rituximab. At Mayo Clinic, 60 patients receiving rituximab-bendamustine were compared with 100 patients receiving rituximab-cyclophosphamidecyclophosphamide-dexamethasone. Two-year PFS was 88 vs. 61%, favoring bendamustine, with outcomes independent of MYD88 status. A total of 69 patients received bendamustine plus rituximab. The overall response rate at 18 months was 97%. The progression-free survival at 2 years was 87%. MYD88 and CXCR4 mutations had no impact on response rate or PFS. One patient developed myelodysplastic syndrome 6 months after bendamustine initiation (1.4%). In one trial of 69 patients treated with R-bendamustine, two developed acute myelogenous leukemia (2.9%) [44].

In an East German lymphoma Study group trial, 293 patients received bendamustine rituximab. The overall response rate was 91.4%. The 5-year survival is estimated to be 78%; two therapy-related myeloid neoplasms were seen (0.7%). Median progression-free survival was 65.3 months. There was no difference between those receiving maintenance rituximab and those that did not. As a result of this large trial, Mayo Clinic does not recommend rituximab maintenance therapy.

Rituximab-bendamustine is one of the Mayo Clinic preferred induction regimen for newly diagnosed WM due to its ease of use and low rates of non-hematologic adverse events. It also has the advantage of time-limited therapy usually less than 6 months and there is no risk of IgM flare. In older patients and those with extensive bone marrow infiltration initiating bendamustine at 90 mg/m^2 but for only 1 day q28 is recommended to avoid excessive myelosuppression in this population. In the presence of central nervous system infiltration so-called Bing Neel syndrome BTKi is preferred as it is known to cross the blood–brain barrier. Ibrutinib shows rapid and durable symptomatic and radiologic responses in patients with central nervous system infiltration with lymphoplasmacytic lymphoma. A patient with Bing Neel syndrome was treated with tirabrutinib and within 2 months of treatment lower extremity muscle strength had normalized and T2 weighted magnetic resonance imaging showed improvement in contrast enhancement in the spinal cord. Tirabrutinib shows promise as a therapeutic option for Bing Neel syndrome [45]. Complete symptomatic recovery and long-term control is observed in only a minority of patients [46].

Bendamustine-based therapies:

Regimen	ND/RR	≥25%↓ IgM, %	≥50%↓ IgM, %	≥90%↓ IgM, %	PFS, months	Reference
BR	69/0	97	96	56	66.6 @ 5 years	[44]
BR	57/0	93	88	51	60.5	[37]
BR bortezomib	0/38	84.6	81.6	50	78.8 @ 30 months	[47]
BR	139/111	97.8/83.8	91.4/73.9	47.5/24.3	60/42 @ 5 years	[48]

3.6 | BTK Inhibitors

Sixty-three previously treated patients received 420 mg of the BTK inhibitor ibrutinib. The major response rate was 73.0%,

including minor responses of 90.5%. Two-year PFS and OS survival rates were 69.1% and 95.2%, respectively. Neutropenia and thrombocytopenia were the most common adverse events. The median time to response was 4 weeks. Median IgM fell from 3610 to 1340. Median Hb rose from 10.5 to 12.6. Diarrhea, bleeding, and atrial fibrillation (10.7%) were seen as non-hematologic toxicities. Ibrutinib should be given indefinitely as rapid IgM increases have been reported on its cessation. Following discontinuation of ibrutinib, a rapid increase in serum IgM was observed in 60% of patients. Ten patients acutely developed hyperviscosity [49]. Unmutated MYD 88 patients have a lower response rate to ibrutinib.

In an open-label sub-study of Ibrutinib that was multi-center and phase 3, 31 patients, all of whom were rituximab refractory with a median age of 67, were enrolled. Overall response rate was 71%, progression-free survival at 18 months was 86%, and overall survival was 97%. A trial of 30 patients who were newly diagnosed and received ibrutinib achieved a major response rate of 80% with no difference between patients with wild-type or mutated MYD88. Atrial arrhythmias were seen in 10%. In treatment-naïve patients overall (MR + PR) and major (≥ PR) responses for all patients were 100% and 83%, respectively. It does not appear that a deep response is critical with ibrutinib. Comparing patients with a greater than very good partial response at 6 months versus others, no significant differences in progression-free survival were observed.

Outside of a clinical trial setting ("real world") 80 patients received ibrutinib therapy, achieving an overall response rate of 91% with an 18-month progression-free survival of 82%; 21% of patients discontinued therapy due to treatment-related toxicity. Atrial fibrillation was seen in 11%. IgM rebound was seen in 36% of patients following ibrutinib discontinuation [50]. The standard dose of ibrutinib is 420 mg per day; however, when dose reductions are instituted to manage adverse effects, outcomes do not appear to be compromised. In a trial where dose reductions were required in 27%, the response was preserved in spite of the dose reduction [51].

In newly diagnosed and relapsed Waldenström, a phase 3 trial randomized patients to ibrutinib with rituximab vs. rituximab placebo. At 30 months, the progression-free survival rate was 82% with ibrutinib–rituximab versus 28% with placebo–rituximab (hazard ratio for progression or death, 0.20; $p < 0.001$). The benefit in the ibrutinib–rituximab group over that in the placebo–rituximab group was independent of the MYD88 or CXCR4 genotype. More patients had sustained increases in hemoglobin levels with ibrutinib–rituximab than with placebo–rituximab (73% vs. 41%, $p < 0.001$). Events of grade 3 or higher that occurred more frequently with ibrutinib–rituximab than with placebo–rituximab included atrial fibrillation (12% vs. 1%) and hypertension (13% vs. 4%). When treating macroglobulinemia with ibrutinib, the administered dose is important. Patients with a dose intensity lower than 97% had a shorter progression-free survival. Holding ibrutinib for longer than 1 week is associated with a 4-fold increased risk of progression. When initiated, ibrutinib therapy should be considered indefinite, and compliance should be emphasized to optimize outcomes. Following discontinuation of ibrutinib, a rapid increase in serum IgM level was observed in 60% of patients. Adverse events associated with stopping ibrutinib include fever, body aches, night sweats, arthralgias, chills, and headache.

Acalabrutinib was developed to be more potent and selective than ibrutinib. Acalabrutinib is rapidly absorbed, has a short half-life, and lacks irreversible targeting to alternative kinases including the epidermal growth factor receptor, interleukin-2-inducible T-cell kinase, and T cell X chromosome kinase. Acalabrutinib is approved for the treatment of chronic lymphatic leukemia and mantle cell lymphoma. In a trial of 106 patients with WM, a response was achieved in 93%. Grade 3/4 atrial fibrillation occurred in only 1 patient.

Zanubrutinib is a second-generation BTKi. At a dose of 160 mg twice daily 77 patients achieved an overall response rate of 95.9% with a ≥ VGPR rate at 24 months of 43.8% [52]. Three year progression-free survival was 80.5%. However, the incidence and severity of toxicities was lower with zanubrutinib compared with ibrutinib. Atrial fibrillation was seen in only 2% of zanubrutinib patients compared with 15% of those receiving ibrutinib. In both arms 84% and 85% of patients were progression-free at 18 months with ibrutinib and zanubrutinib, respectively.

Tirabrutinib is a 2nd-generation irreversible BTKi. Of 27 enrolled patients the major response rate was 93%, including 1 complete and 5 very good partial responses. The progression-free and overall survival rates a 24 months were 92.6% and 100%. One patient experienced grade 2 atrial fibrillation. Treatment-related skin adverse events were observed in 14 patients (52%). Pirtobrutinib is a highly selective reversible BTKi. It is active in patients previously treated with covalent BTKi and represents a potential salvage therapy in patients failing a covalent BTKi (ORR 69%),

Selected outocimes with BTKi.

Regimen	ND/RR	≥25%↓ IgM, %	≥50%↓ IgM, %	≥90%↓ IgM, %	PFS, months	Reference
Ibrutinib	0/49	91.8	87.7	28.5	76.7 @ 2 years	[53]
Ibrutinib	0/17	100	64.7	6	18.4	[54]
Ibrutinib-R	34/41	92	78	30	6 8 @ 54 months	[55]
Acalabrutinib	14/92	93/93	79/80	0/9	90/82 @ 24 months	[56]
Zanubrutinib	102/0	98	61.7	16.6	78.3% @ 42 months	[57]
Tirabrutinib	18/9	94.4/100	88.9/88.9			[58]
Pirtobrutinib	0/19	68	47			[59]

A multi-center global case series of 347 symptomatic patients compared the use of rituximab bendamustine to ibrutinib. Deeper responses were obtained with rituximab bendamustine. Overall survival and progression-free survival were not different between the 2 groups. Both are rational options for the treatment of macroglobulinemia [60]. A systematic review and meta-analysis comparing bendamustine rituximab, bortezomib dexamethasone cyclophosphamide rituximab, and ibrutinib rituximab reported 2-year progression-free survival of 89%, 81%, and 82%, respectively. Bendamustine rituximab yielded a higher response rate but this was marginal suggesting all options are reasonable for induction [61]. A retrospective review of rituximab cyclophosphamide dexamethasone, bortezomib rituximab dexamethasone, and rituximab bendamustine demonstrated an overall response rates of 78%, 84%, and 98%, respectively. R bendamustine showed a longer progression-free survival of 5.2 years compared with 4.3 and 1.8 for the other regimens. The results were unaffected by the patient's MYD88 signature [62]. Often the decision rests on the patient's desire for oral versus parenteral therapy or indefinite versus time-limited therapy. A survey of 330 patients with macroglobulinemia found progression-free survival the most important attribute for making a treatment decision. Patient's preferred fixed duration treatment at the hospital over continuous daily oral therapy at home [63].

3.7 | Venetoclax

Since macroglobulinemia cells highly express Bcl-2, long-term therapy is a logical approach for this disorder. Waldenstrom macroglobulinemia cells devoid of BTKC481S or CXCR4WHIM-like mutations acquire resistance to ibrutinib [64] through upregulation of Bcl-2 and AKT, resulting in vulnerability to venetoclax treatment. In a phase 2 clinical trial, venetoclax (at a maximum target dose of 800 mg daily) demonstrated an ORR and MRR of 87% and 80%, respectively [65]. When ibrutinib and venetoclax were combined, deep and durable responses were seen, but a higher than expected occurrence of ventricular arrhythmias resulted in early termination of the trial [66]. CD19-directed car T therapy is currently being explored in macroglobulinemia. Three patients were treated; all responded, and all 3 developed recurrent disease from 3 to 26 months after infusion [67, 68].

Figure 1 shows the Mayo Clinic algorithm for the recommended management of patients with newly diagnosed WM. Figures 2 and 3 illustrate treatment recommendations for patients with relapsing WM, based on consensus criteria developed by the WM treatment and research group at Mayo Clinic. Unlike other low-grade lymphomas, early disease progression within 24 months does not impact mortality. Survival after progression is not

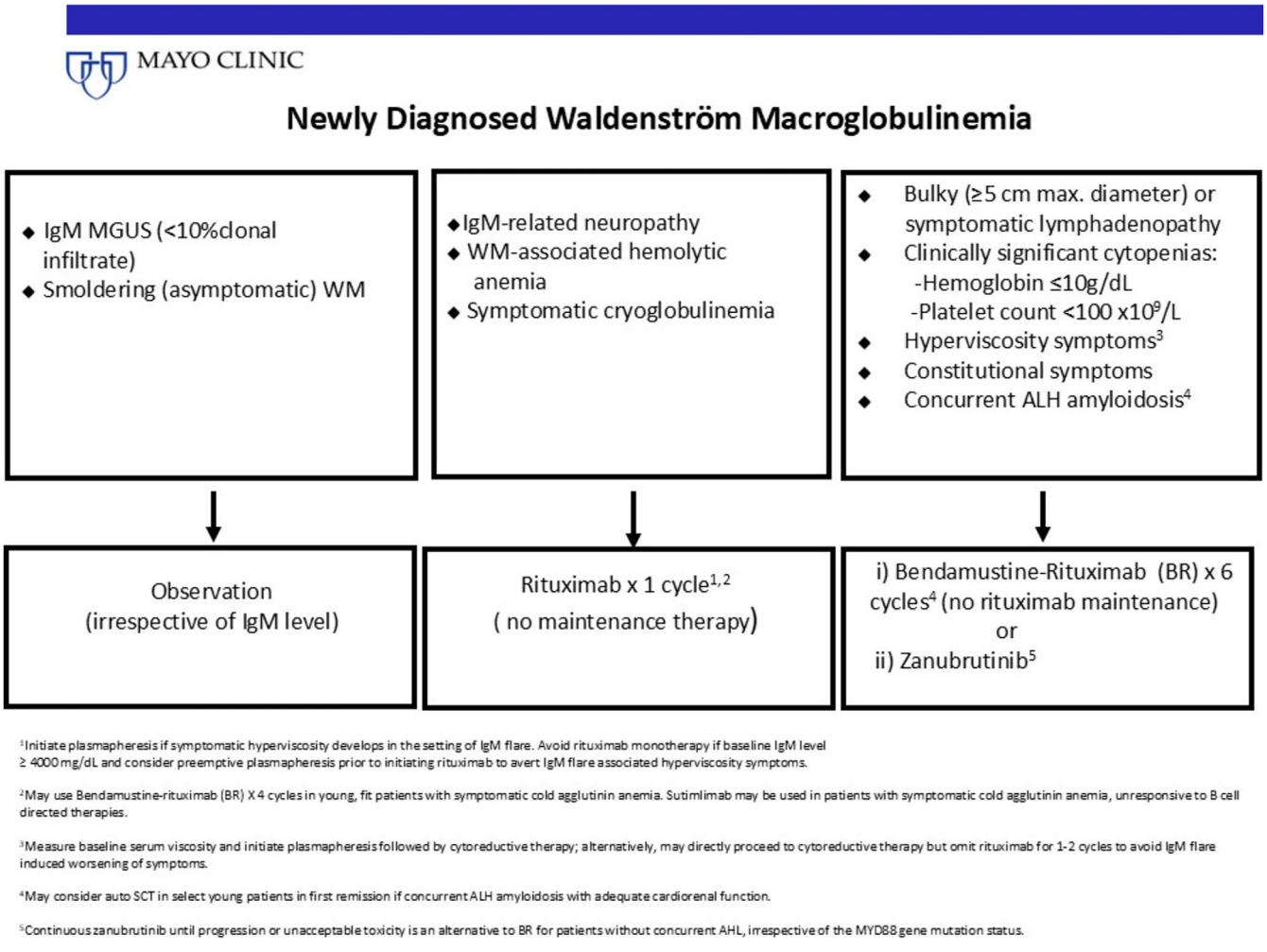

FIGURE 1 | Mayo Clinic consensus for newly diagnosed Waldenström macroglobulinemia (WM). Hb indicates hemoglobin; IgM, immunoglobulin M; MGUS, monoclonal gammopathy of undetermined significance; RCD, rituximab, cyclophosphamide, and dexamethasone. (https://www.msmart.org/wm-treatment-guidelines).

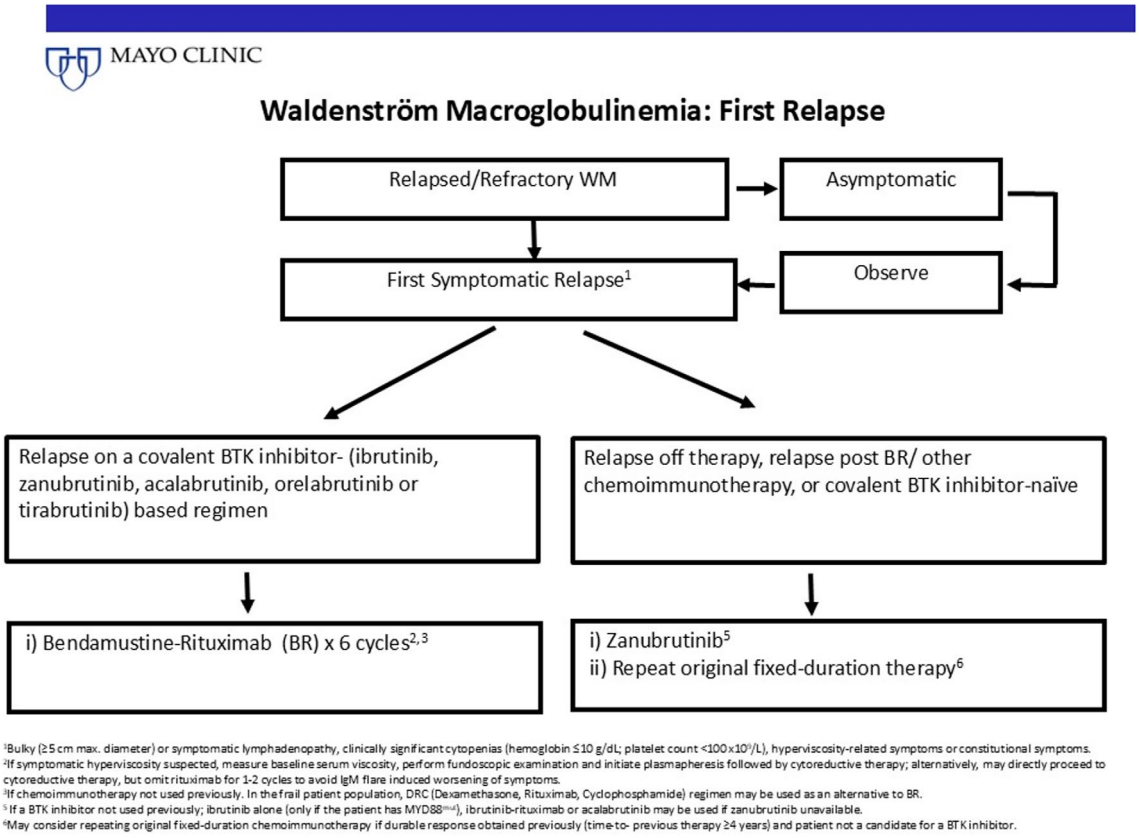

FIGURE 2 | Mayo Clinic consensus for first relapse therapy in Waldenström macroglobulinemia. (https://www.msmart.org/wm-treatment-guidelines).

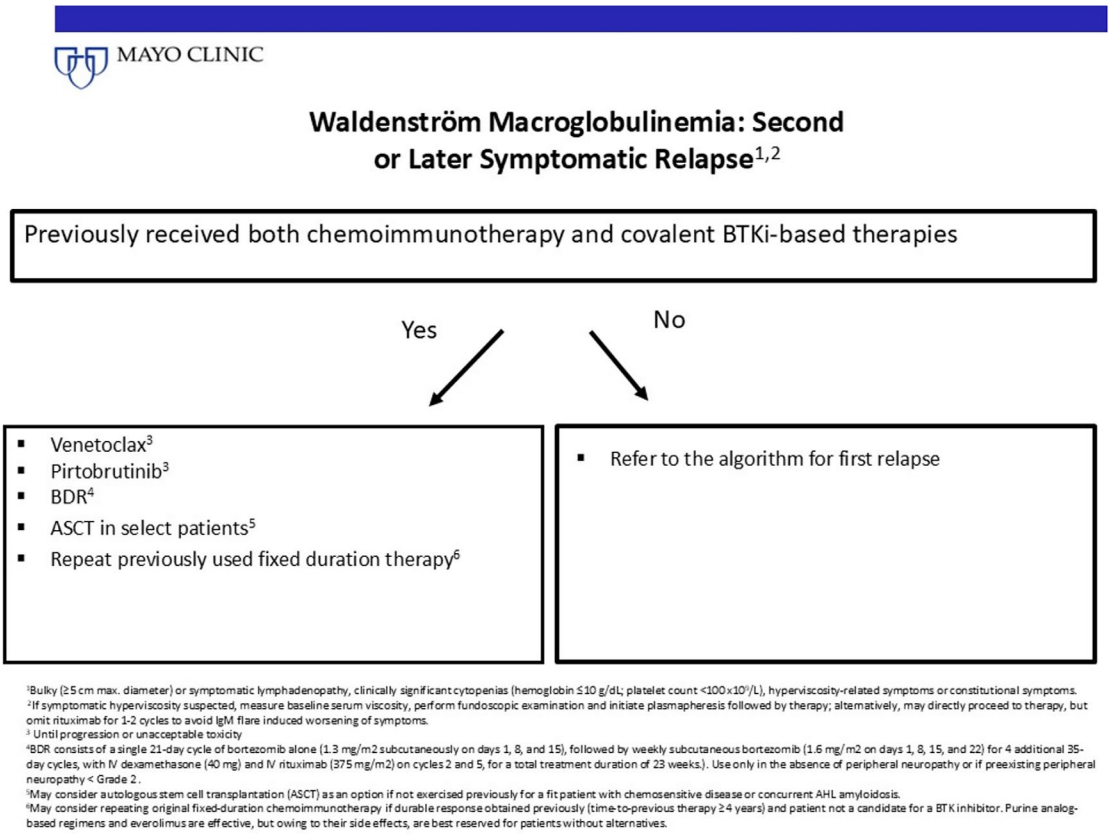

FIGURE 3 | Mayo Clinic consensus for second or later symptomatic relapse Therapy in Waldenström macroglobulinemia. (https://www.msmart.org/wm-treatment-guidelines).

influenced by time to progression, regardless of treatment. The National Comprehensive Cancer Network has recently published its consensus recommendations on the diagnosis and therapy of WM. (NCCN Guidelines for Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma V.1.2022) Recent consensus reviews on WM are available.

4 | Conclusion

When WM is diagnosed before the development of symptoms, patients may be safely observed and monitored. However, patients with symptoms require chemotherapy. Nonstudy Mayo Clinic–preferred options are rituximab and bendamustine or zanubrutinib. The clinician should focus on methods to minimize the toxicity associated with therapy and avoid late complications.

Conflicts of Interest

Dr. Gertz has received honoraria from Celgene Corporation (Summit, NJ), Millennium: The Takeda Oncology Company (Cambridge, MA), The Binding Site Group Ltd. (Birmingham, UK), Onyx (San Francisco, CA), Novartis (Basel, Switzerland), Ionis (Carlsbad, CA), Amgen (Thousand Oaks, CA); Prothena (San Francisco, CA) Sandoz (Princeton, NJ), AbbVie (North Chicago, IL), Alnylam (Cambridge, MA), Prothena (South San Francisco, CA), Janssen (Beerse, Belgium), Spectrum (Henderson, NV), Apellis (Louisville, KY), Medscape (New York, NY), Physicians Education Resource (Cranbury NJ), Research to Practice (Miami, FL), Teva (Petah Tikva, Israel), Astra Zeneca.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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