

## Waldenström macroglobulinemia: 2017 update on diagnosis, risk stratification, and management

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**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:** Presence of IgM monoclonal protein associated with  $\geq 10\%$  clonal lymphoplasmacytic cells in bone marrow confirms the diagnosis. The L265P mutation in *MYD88* is detectable in more than 90% of patients.

**Risk Stratification:** Age, hemoglobin level, platelet count,  $\beta_2$  microglobulin, and monoclonal IgM concentrations are characteristics required for prognosis.

**Risk-Adapted Therapy:** Not all patients who fulfill WM criteria require therapy; these patients can be observed until symptoms develop. Rituximab-based therapy is used in virtually all U.S. patients with WM and can be combined with bendamustine, an alkylating agent, or a proteasome inhibitor. Purine nucleoside analogues are widely used in Europe. The preferred Mayo Clinic nonstudy therapeutic induction is rituximab and bendamustine. Potential for stem cell transplantation should be considered in induction therapy selection.

**Management of Refractory Disease:** Bortezomib, fludarabine, thalidomide, everolimus, ibrutinib, carfilzomib, lenalidomide, and bendamustine have all been shown to have activity in WM. Given WM's natural history, reduction of complications will be a priority for future treatment trials.

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### ■ Disease Overview

The World Health Organization defines Waldenström macroglobulinemia (WM) as a lymphoplasmacytic lymphoma associated with a monoclonal immunoglobulin M (IgM) protein [1]. The physical manifestations of the disorder are hepatomegaly (20%), splenomegaly (15%), and lymphadenopathy (15%) [2]. The most common presenting symptom is fatigue related to a normocytic anemia. The median hemoglobin value at diagnosis is 10 g/dL [3]. Many patients who fulfill the criteria of WM do not require immediate therapy because they are asymptomatic [4]. Virtually all patients have a preceding phase of IgM MGUS, but the clonal MGUS B cells already contain the molecular signature of a malignant clone. Phenotypically, the cells arise from CD25<sup>+</sup> CD22<sup>low</sup> activated B lymphocytes [5]. The 5- and 10-year PFS for IgM MGUS to WM is 90% and 81%, respectively [6].

The overall age-adjusted incidence of WM is 3.8 per million persons per year, with incidence increasing with age. As a comparison, the incidence of amyloidosis is 8 per million persons per year, and incidence of multiple myeloma is 65 per million persons per year [7]. The incidence of WM is twice as high in men than in women (5.4 vs. 2.7 per million, respectively). Incidence is higher in whites (4.1 per million per year) than in blacks (1.8 per million per year) (CME question 1), and the incidence in white patients has increased in the past 20 years [7]. 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 [8]. A study of monoclonal immunoglobulins showed that the M protein isotype in black and white patients was 2% and 16% IgM, 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 [9]. Median age at diagnosis is 63 years for blacks and 73 for whites [10], with blacks having a shorter survival than whites with WM.

Survival of WM is improving. The SEER database contained 5,784 patients with WM. Median OS from 1991 to 2000 and 2001 to 2010 improved from 6 to 8 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 a profound impact on survival. The hazard ratio for death for WM patients age 80 or greater was 6.99, compared to a reference group less than age 50 [11].

The presence of the monoclonal IgM protein adds a unique dimension to the disorder because it can result in hyperviscosity syndrome [12], peripheral neuropathy [13], hemolytic anemia [14], and immune complex vasculitis [15]. The 10-year survival rate is now 66% [16]. In a

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**TABLE I.** Definitions of IgM-Related Phenomenon in Macroglobulinemia

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

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

population-based study of 1,555 patients with WM and lymphoplasmacytic lymphoma, 5-year relative survival improved significantly over time from 57% in 1980 to 78% in 2005. Survival improvements were seen in all age groups, although increasing age was associated with inferior survival [17].

The management of peripheral neuropathy associated with IgM monoclonal protein (chronic inflammatory demyelinating polyneuropathy [CIDP]) remains frustrating for clinicians. Amyloidosis needs to be excluded when an IgM monoclonal protein is seen with neuropathy, particularly if the light-chain isotype is  $\lambda$ . The mechanism of the neuropathy is thought to be demyelination due to direct binding of the antibody to myelin-associated glycoprotein. The treatment of IgM-associated peripheral neuropathy can be similar to that of WM. In one study [18], four of five patients treated with fludarabine and rituximab showed a major hematologic response, with markedly improved neurologic symptoms and electrophysiologic findings. No relapses were reported during a follow-up of 12 to 45 months.

With the introduction of PET-CT imaging, extramedullary Waldenström has been recognized and carries with it a shorter PFS and OS. Rituximab appeared to have little impact in improving these adverse outcomes. Nucleoside analogues, however, did improve outcomes in this subgroup of extramedullary disease [19].

## ■ Diagnosis

In the original description of WM, Jan Gösta Waldenström [20] described two patients with oronasal bleeding, lymphadenopathy, anemia, thrombocytopenia, and an elevated sedimentation rate. The disorder is a lymphoplasmacytic lymphoma [1] with a monoclonal pentameric IgM protein [21]. Bone marrow and lymph nodes are infiltrated with pleomorphic B-lineage cells at different stages of maturation [22]. The bone marrow pattern is predominantly intertrabecular [1]. Many patients who fulfill all other criteria for the diagnosis have a presymptomatic phase and may not require therapy [23]. The cells express pan B-cell markers (e.g., CD19, CD20) and typically test negative for CD3 and CD103 [24]. The 6q genetic deletion is present in 42% of patients and is associated with an adverse prognosis [25]. Deletion of 6q and 11q and trisomy 4 had adverse effects on survival [26]. Whole-genome sequencing of lymphoplasmacytic cells from patients with WM has been reported [27]. A recurring sequence variant at position 38,182,641 in chromosome 3p22.2 was 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. Together, these studies demonstrate an important somatic variant in the malignant cells of WM and raise the future possibility of developing specific inhibitors. *MYD88* can be detected by polymerase chain reaction in the peripheral blood of untreated patients with WM [28]. *CXCR4* is mutated in 30% of patients with WM. In animal models, this mutation predicts resistance to ibrutinib and everolimus [29].

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 (MGUS). *MYD88* L265P also is seen in splenic marginal zone lymphoma (4%), IgM amyloidosis (71%) [30], mucosa-associated lymphatic tissue lymphoma (7%), and WM (67%–90%) (CME Question 5) [31]. *MYD88* L265P cannot be used to differentiate between WM and IgM MGUS, suggesting that the mutation is a precursor event but not the transforming event. *MYD88* mutations were observed in five of nine patients with IgM MGUS and in five of six patients with monoclonal protein levels exceeding 0.5 g/dL [32]. 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 [33]. Patients with mutated *MYD88* had significant differences in clinical presentation and a shorter survival compared with patients with unmutated *MYD88* [34].

Patients can present with markedly elevated IgM levels and infiltration of the bone marrow in excess of 30% yet still not require therapy because they have no symptoms [35]. 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 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 (CME Question 4) [36]. A classification scheme for WM is provided in Table I. Symptoms can be produced by the tumor mass or the monoclonal protein. The disease is incurable with current therapies.

IgM multiple myeloma is a distinct entity; although constituting only 1% of all multiple myeloma cases, it must be distinguished from WM. *MYD88* is not mutated in IgM myeloma [37]. Useful clues to the diagnosis of multiple myeloma include the presence of lytic bone lesions (rare in WM) and a translocation at t(11;14) (does not occur in WM). Patients with IgM multiple myeloma tend to have plasmacytic differentiation with high expression of CD138 and cytoplasmic immunoglobulin, whereas WM tends to express CD20 [38].

Monoclonal IgM proteins are found in 1 of 600 persons older than 50 years [39]. The overall age-standardized rate of WM is only 5.5 per 1 million persons per year [40]. Far more patients have IgM MGUS than have WM. However, all patients with IgM MGUS require lifelong monitoring because the risk of transformation into an overt lymphoplasmacytic lymphoma is approximately 2% per year and is somewhat higher when the immunoglobulin free light-chain ratio is abnormal [41,42]. Patients with IgM values greater than 3,000 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. The Box lists the recommended diagnostic tests for a patient with suspected WM.

Response in WM is defined by reduction in the M protein. If the M protein is not easily measurable by electrophoresis, then the

**TABLE II.** International Prognostic Scoring System for Waldenström Macroglobulinemia

Factor associated with prognosis		Value
Age, y		>65
Hemoglobin, g/dL		≤11.5
Platelet count, No./mcL		≤100,000
β <sub>2</sub> -Microglobulin, mg/L		>3
Monoclonal IgM, g/dL		>7
Risk stratum and survival		
Risk category	Score <sup>a</sup>	Median survival, mo
Low	0 or 1 (except age)	142.5
Intermediate	2 or age >65 y	98.6
High	>2	43.5

Abbreviation: IgM, immunoglobulin M.

<sup>a</sup> One point is assigned for each positive factor and the risk score is the sum of points.

Adapted from Morel et al. [49]. Used with permission.

quantitative IgM level can be used. Both IgM and M protein, measured by serum protein electrophoresis, correlate well with each other and with overall disease activity [43]. 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. An update of the criteria for response assessment recently was published [44]. 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, presumably because of its 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 [45,46].

### Risk stratification

Since WM is a distinct lymphoproliferative process with unique cell surface and genetic characteristics, the International Prognostic Index [47] and the Follicular Lymphoma International Prognostic Index [48] are not used to determine prognosis. Table II gives the currently accepted international staging system for WM [49].

The five criteria shown in Table II are not weighted equally. Age has a profound impact on prognosis. By definition, patients older than 65 years cannot be in a low-risk category. Although IgM protein levels are important prognostically, they do not enter into the staging system until the IgM level exceeds 7,000 mg/dL. Investigators have suggested that response rates to single-agent rituximab therapy decline when the IgM concentration exceeds 5,000 mg/dL [50]. In the largest study of single-agent rituximab therapy for WM, the IgM level did not affect response rate [51]. Lactate dehydrogenase is absent from the International Prognostic Scoring System for Waldenström Macroglobulinemia [52]. (CME Question 2) Elevations in the serum lactate dehydrogenase level, although having no impact on the outcome for patients of low or intermediate risk, are able to divide high-risk patients into two subgroups with significantly different outcomes [53,54].

The International Prognostic Scoring System for Waldenström Macroglobulinemia 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 [4]. The value of this scoring system has been validated in patients treated with rituximab [55]. Serial measurements of β<sub>2</sub> microglobulin are not contributory.

Because patients with WM have an indolent disease course and often are of an advanced age, nearly half of all patients succumb to diseases of the elderly, unrelated to WM. The impact of age on OS was investigated in 238 patients with WM [56]. Using the age cutoff of 65 years, the study showed that the poorest 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 [52]. In a competing risk survival analysis, 23% of deaths were unrelated to WM, and 40% of patients >75 years do not die of WM [57]. Patients with WM have greater overall risk of a second malignancy that is 1.69 times higher than expected ( $P = 0.002$ ) [58]. Compared with the general population, patients with WM appear to have a higher risk of large cell lymphoma, myelodysplasia, and brain cancer [59].

## Management

### Hyperviscosity syndrome

Hyperviscosity syndrome is seen in an ever-decreasing proportion of patients with WM because WM is being diagnosed earlier [60]. Symptomatic hyperviscosity is rare in patients with an IgM concentration less than 4,000 mg/dL, and viscosity measurements are not required in patients whose IgM levels are below that threshold [61]. The symptoms of hyperviscosity are primarily due to shear forces that rupture unsupported venous channels. As a consequence, the presentation generally includes epistaxis, gingival bleeding, and visual changes due to retinal hemorrhage. Central nervous system findings, including dizziness, light-headedness, and generalized fatigue, are nonspecific and should not be attributed automatically to hyperviscosity syndrome in the absence of other signs or symptoms. Reference serum viscosity is 1.8; water has a viscosity of 1. Hyperviscosity syndrome should not be suspected unless the serum viscosity exceeds 4 [62].

When hyperviscosity is present, plasma exchange is a validated treatment technique but should be considered a temporizing measure until systemic therapy successfully lowers the tumor mass and thereby reduces the IgM protein concentration in the serum [63,64]. Long-term plasma exchange is rarely required and is usually used in patients who have relapsed refractory disease, for whom adequate cytoreductive therapy no longer exists.

### Systemic chemotherapy to reduce tumor mass

Rituximab is a widely available treatment for the management of WM. Its lack of long-term toxicity, lack of impact on the mobilization of peripheral blood stem cells, and nonmyelosuppressive treatment profile have led to its incorporation in most therapeutic regimens for this disorder. Deep responses can be predicted by polymorphisms in *FCGR3A* [65].

However, rituximab alone is generally 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 virtually every other reported combination regimen [66]. A meta-analysis confirmed that a greater response was produced with combination therapy of 2+ drugs than with rituximab monotherapy (73% vs. 44%) [67].

An analysis of the impact of rituximab on depth of response and the impact of response depth on outcome has been reported [65]. No difference in PFS was seen when comparing patients achieving a complete response with those achieving a very good partial response.

Age, hemoglobin level, IgM level, platelet count, and  $\beta_2$  microglobulin level were not predictive of response depth. A complete or very good partial response was associated with significantly longer PFS.

Rituximab alone is inferior to single-agent chemotherapy with alkylating agents such as chlorambucil [68] and cladribine [69]. In one study [70], cladribine combined with rituximab in the treatment of newly diagnosed and previously treated patients with WM resulted in an overall response rate of 89.6%, with no difference between patient groups. No myelodysplasia or transformation to non-Hodgkin lymphoma was identified. Single-agent rituximab is used for patients who present with only a peripheral neuropathy related to the IgM anti-myelin-associated glycoprotein activity, with no concomitant evidence of symptomatic lymphoma [71].

Use of rituximab as a single agent is associated with the risk of "flare" for many patients [72]. In this phenomenon, the initiation of rituximab treatment results in a transient rise in the level of IgM, which can produce hyperviscosity that requires urgent plasma exchange. (CME question 6) This flare is seen infrequently when rituximab is combined with cytotoxic chemotherapy [73]. In some trials, rituximab is delayed until the second cycle to allow cytotoxic therapy to reduce IgM levels and reduce the risk of hyperviscosity associated with the introduction of rituximab.

The use of maintenance rituximab therapy is controversial. However, in a retrospective review comparing patients who were and were not selected for rituximab maintenance therapy [74], improved PFS and OS were seen in patients receiving maintenance therapy, independent of previous treatment status, although an increased number of infections was observed in patients with maintenance therapy. Nevertheless, caution is required when interpreting the findings of a retrospective study that lacks clearly defined criteria for maintenance and was performed without matched controls. At this time, insufficient evidence supports the use of maintenance rituximab [75].

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 [76]. Use of ofatumumab was authorized by the European Medicines Agency in April 2010 to treat patients with chronic lymphocytic leukemia that was refractory to fludarabine and alemtuzumab.

A phase III trial of chlorambucil vs. fludarabine in WM reported significantly improved PFS with fludarabine. OS was improved with fludarabine (median survival was not reached in the fludarabine arm vs. 69.8 months in the chlorambucil arm;  $P = 0.01$ ) [77].

Ten-year follow-up data are available on the use of single-agent fludarabine in the treatment of WM [78]. Durable responses have been seen with fludarabine, even as a single agent. In that study, 98 patients with no more than one risk factor had an 8-year survival estimate of 55%, compared with 33% among the 51 patients with two risk factors ( $P < 0.001$ ). By comparison, the 20 patients with more than two risk factors had an 8-year survival estimate of only 5% ( $P < 0.003$ ). In a separate study [79], 43 patients with untreated or previously treated WM received rituximab, fludarabine, and cyclophosphamide. Only  $\beta_2$  microglobulin levels were predictive of the frequency of response. Nineteen patients (44%) had long-term neutropenia. Three patients (7%) had development of myelodysplastic syndrome. The overall response rate was 79%, with complete remission in 21%. Event-free survival was 77 months [80]. The rituximab-fludarabine-cyclophosphamide treatment was active and led to rapid disease control, but myelodysplasia in 3 of 43 patients within a relatively short follow-up period, nonetheless, raises questions about long-term safety. In chronic lymphocytic leukemia, fludarabine was reported to be associated with an infection rate of 33% [81,82]. Fludarabine use has fallen significantly in the United States but remains a popular choice in the European Union. Fludarabine is not

recommended as a first-line regimen. [83]. The purine analogue, pentostatin, acts as an inhibitor of adenosine deaminase. It has been combined with rituximab and pentostatin in WM. Twenty-five patients (21 previously untreated) received this regimen for six 22-day cycles. Two-year PFS was 83.6% with no deaths at 2 years. Purine nucleoside analogues should not be forgotten in the salvage therapy of WM [84].

Today, most patients with WM are treated with combination chemotherapy. Cyclophosphamide, doxorubicin, vincristine, and prednisone plus rituximab (R-CHOP) treatment has been reported by two research groups as having at least a 90% response rate [85,86]. However, the value of adding doxorubicin in this disease is uncertain. Rituximab treatment combined with cyclophosphamide (orally) and dexamethasone has been reported, with a response rate of 83% and minimal toxicity [87]. Two-year PFS was 67%; 2-year disease-specific survival was 90%.

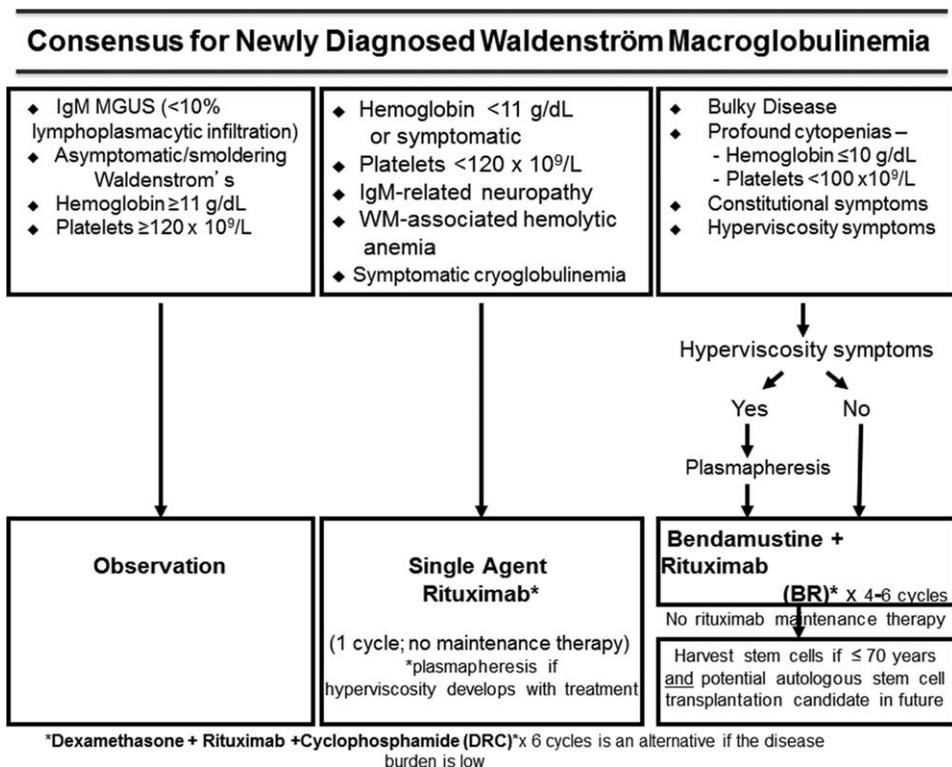
In an updated final analysis in 72 patients treated with rituximab cyclophosphamide and dexamethasone, the response rate on an intent-to-treat basis was 83%. Median PFS was 35 months. Median OS was 95 months [88]. This three-agent combination is currently an alternative regimen for first-line therapy if the disease burden is low, based on Mayo Clinic mSMART guidelines.

Stem cell transplantation has been shown to produce durable responses with a treatment-related mortality rate of 3.8% [89]. Good outcomes are seen with high-dose treatment; 5-year PFS and OS rates were 39.7% and 68.5%, respectively [89]. (CME question 3). The favorable outcome seen with high-dose therapy is related in part to the low proliferative rate of these malignant cells and the lack of such unfavorable cytogenetic abnormalities as  $-17p$  [90]. The biological factors of the disease make a single course of myeloablative therapy capable of producing deep, durable responses. A review of autologous and allogeneic transplants [91] concluded that autologous transplantation is an effective and potentially underutilized treatment in the management of WM. However, allogeneic transplantation should be considered an investigational therapy and used only in the context of a clinical trial or when other chemotherapeutic options have been exhausted.

Autologous stem cell transplantation has been reported to improve both OS and event-free survival in previously treated and untreated patients [92]. Among 158 patients, the median reported survival was 9.2 years. Patients with no prior therapy receiving stem cell transplantation as part of induction had a median survival of 13.8 years. Use of stem cell transplantation as part of the planned initial therapy of transplant-eligible patients with WM was emphasized in the study. Elevated lactate dehydrogenase was a poor prognostic factor in a multivariable analysis. In a recent review, a suggested algorithm considered autologous stem cell transplant for relapsed chemosensitive disease with a low prognostic index score and a remission duration of less than 2 years with induction therapy. The response rate reported is 90%; the relapse-free survival rate is 65% at 3 years [93] (CME Question 3).

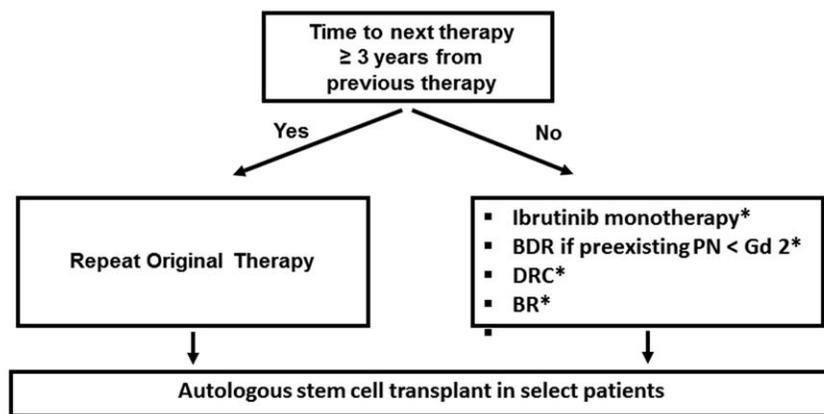
The introduction of novel agents for multiple myeloma has provided benefits for patients with WM. Rituximab combined with thalidomide [94] produced a 72% response rate, and rituximab combined with lenalidomide [95] produced a 50% response rate, although lenalidomide aggravated anemia in a large proportion of patients. Thalidomide and lenalidomide have activity, although the subclinical neuropathy [96] that exists in patients with WM predisposes them to enhanced neurotoxicity from thalidomide.

Bortezomib has been shown to have high levels of activity in the management of relapsed WM in schedules of twice weekly in two of three weeks [97,98] and of once weekly in four of five weeks [99], with response rates ranging from 81% to 96%. In newly diagnosed patients, weekly treatment with bortezomib and rituximab resulted in a better-than-minimal response in 23 of 26 patients and a 1-year



**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. <sup>a</sup>Avoid chlorambucil and nucleoside analogs in potential candidates for stem cell transplantation. <sup>b</sup>Administer plasmapheresis if hyperviscosity occurs with treatment. <sup>c</sup>Collect stem cells after completion of the 6 cycles in patients eligible for transplantation. [https://nebula.wsimg.com/22ce67ff555ac9dbe66843c682f456b9?AccessKeyId = A0994494BBBCBE4A0363&disposition = 0&alloworigin = 1](https://nebula.wsimg.com/22ce67ff555ac9dbe66843c682f456b9?AccessKeyId=A0994494BBBCBE4A0363&disposition=0&alloworigin=1).

### Waldenström Macroglobulinemia Consensus for Off-Study Salvage Therapy



DRC = Dexamethasone + Rituximab + Cyclophosphamide; BR = Bendamustine + Rituximab; BDR = Bortezomib (weekly), Dexamethasone + Rituximab; PN= peripheral neuropathy  
\* If not previously used.

**Figure 2.** Mayo Clinic Consensus for Salvage Therapy in Waldenström Macroglobulinemia. [https://nebula.wsimg.com/22ce67ff555ac9dbe66843c682f456b9?AccessKeyId = A0994494BBBCBE4A0363&disposition = 0&alloworigin = 1](https://nebula.wsimg.com/22ce67ff555ac9dbe66843c682f456b9?AccessKeyId=A0994494BBBCBE4A0363&disposition=0&alloworigin=1).

event-free survival rate of 79% [100]. 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 3-year OS was 81%. Peripheral neuropathy was seen in 46% [101]. Bortezomib-

### BOX. 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-Hour 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  $\beta_2$  microglobulin 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
- Cytogenetic studies with optional fluorescence in situ hybridization; *MYD88* mutational analysis required
- Computed tomography of abdomen and pelvis to detect organomegaly and lymphadenopathy (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 >4,000 mg/dL
- On the basis of clinical presentation, analysis involves Coombs test (cold autoantibody) and cryoglobulin or tissue stains for amyloid deposits
- Of myeloma patients, 1% have IgM, and their disorder behaves like other multiple myeloma [38]
- Hepatitis B and C screening is necessary if rituximab therapy is planned

rituximab–dexamethasone is a reasonable choice for front-line therapy, but attention to early neurotoxicity is required to avoid permanent impairment.

In view of the high neuropathy rates, the less neurotoxic proteasome 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% [102]. The oral proteasome inhibitor, ixazomib, would be expected to be active in WM, and a trial is recruiting.

The mammalian target of rapamycin (mTOR) inhibitor, everolimus, has been shown to produce a response rate of 70% in previously treated WM, although mouth sores and pulmonary toxicity occurred in 8% and 6% of patients, respectively [103]. Everolimus (as a single agent) was used to treat 33 patients with newly diagnosed WM [104]. Twenty-two patients were evaluable for response. The best overall response rate was 66.7%; 14 had partial responses, eight had minor responses, and 11 had stable disease. Everolimus can be administered orally, but oral ulcerations occurred in seven patients (21%). The median PFS of previously treated patients is 21 months [105]. Everolimus has been combined with bortezomib and rituximab followed by everolimus maintenance. A minor response or better was reported in 89%, PR or better 53%. Median PFS was 21 months. Grade 3 or 4 toxicity occurring in over 10% was hematologic only [106]. The Akt inhibitor, perifosine, has shown a response rate of 35% but is associated with high levels of gastrointestinal toxicity [107]. Histone deacetylase inhibitors also have shown activity in WM [108]. As a single agent, panobinostat resulted in a minimal response or better in 47%. The median PFS was 6.6 months [109].

In the 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 [110]. 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, four 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, lower frequency of infection, lower incidence of neuropathy, and reduced stomatitis. Bendamustine rituximab is clearly an active regimen [110]. Bendamustine also has been used as a salvage therapy in patients with relapsed or refractory multiple myeloma [111]. Twenty-four patients received the agent (90 mg/m<sup>2</sup>) 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 fludarabine or cladribine. 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 was approximately 80% and 60%, respectively [112]. Rituximab-bendamustine is the Mayo Clinic preferred induction regimen for newly diagnosed WM due to its ease of use and low rates of nonhematologic adverse events.

## ■ Ibrutinib

Sixty-three previously treated patients received 420 mg of the BTK inhibitor ibrutinib. The major response rate was 73.0%, including minor responses was 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 [113]. The median time to response was four weeks. Median IgM fell from 3,610 to 1,340. Median Hb rose from 10.5 to 12.6. Diarrhea, bleeding, and atrial fibrillation (10.7%) were seen as nonhematologic toxicities [114]. Unmutated MYD 88 patients have a lower response rate (none >50%) to ibrutinib [115]. This drug is FDA approved to be used in any line of therapy for WM.

Figure 1 shows the Mayo Clinic algorithm for the recommended management of patients with newly diagnosed WM. Figure 2 illustrates treatment recommendations for patients with relapsing WM, based on consensus criteria developed by the WM treatment and research group at Mayo Clinic [116]. The National Comprehensive Cancer Network has recently published its consensus recommendations on diagnosis and therapy of WM [117]. Recent consensus reviews on WM are available [75,83,118–120].

## ■ Conclusion

When WM is diagnosed before the development of symptoms, patients may be safely observed and monitored. However, patients with symptoms require chemotherapy. A nonstudy Mayo Clinic–preferred option is rituximab and bendamustine. Stem cell transplantation is highly active in WM. Because this disorder is associated with long-term survival, the clinician should focus on methods to minimize the toxicity associated with therapy and avoid late complications.

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