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- Master a simplified approach to staging and prognosis of Waldenström macroglobulinemia

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ANNUAL CLINICAL UPDATES IN HEMATOLOGICAL MALIGNANCIES:
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Waldenström Macroglobulinemia: 2012 update on diagnosis, risk stratification, and management

Morie A. Gertz

Disease Overview: **Waldenström macroglobulinemia (WM) is a lymphoplasmacytic lymphoma with immunoglobulin M (IgM) monoclonal protein. Clinical features include anemia, thrombocytopenia, hepatosplenomegaly, and lymphadenopathy.**
Diagnosis: **Presence of IgM monoclonal protein associated with $\geq$10% clonal lymphoplasmacytic cells in bone marrow confirms the diagnosis.**
Risk Stratification: **Age, hemoglobin level, platelet count, β_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 US patients with WM and can be combined with alkylating agent or purine nucleoside analog (or both). The preferred Mayo Clinic nonstudy therapeutic induction is rituximab, cyclophosphamide, and dexamethasone. Future stem-cell transplantation should be considered in induction therapy selection.**
Management of Refractory Disease: **Bortezomib, thalidomide, 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.** © **2012 Wiley Periodicals, Inc.**

Disease Overview

The World Health Organization defines Waldenström macroglobulinemia (WM) as a lymphoplasmacytic lymphoma associated with a monoclonal immunoglobulin M (IgM) protein [1]. The clinical manifestations of the disorder are hepatomegaly (20%), splenomegaly (15%), and lymphadenopathy (15%) [2]. The most common presenting symptom is fatigue related to a normochromic or normocytic anemia. The median hemoglobin value at diagnosis is 10 g/dL [3]. The majority of patients who fulfill the criteria of WM do not require immediate therapy because many cases are detected before symptoms occur [4].

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 40 per million persons per year [5]. The incidence of WM is twice as high in men than 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), and the incidence in white patients has increased in the past 20 years [5]. 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 to white patients and have a lower risk of transformation [6]. Unlike in other low-grade lymphoproliferative disorders, the presence of the monoclonal IgM protein adds a unique dimension to the disorder because it can result in hyperviscosity syndrome [7], peripheral neuropathy [8], hemolytic anemia [9], and immune complex vasculitis [10].

The management of peripheral neuropathy associated with IgM monoclonal protein remains frustrating for clinicians. The majority of affected patients do not fulfill criteria for WM. Amyloidosis needs to be excluded when an IgM monoclonal protein is seen with neuropathy, particularly if the light-chain isotype is λ. 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 [11], four of five patients treated with fludarabine and rituximab showed a major hematologic response, with markedly improved symptoms and electrophysiologic findings. No relapses were reported during a follow-up of 12–45 months.

When comparing patients with neuropathy associated with WM and patients with IgM monoclonal gammopathy of undetermined significance, the clinical presentations are similar. There are no differences in symptom duration, chief concern, or motor, sensory, or reflex abnormalities. Autonomic neuropathy generally is not seen with either syndrome, and the degree of axonal loss seen on nerve biopsies also is similar. Both syndromes likely have the same underlying pathophysiology. A review of 345 symptomatic patients [12] seen before and after January 1, 2000, did not show an improvement in overall survival when stratifying patients by treatment date, which suggests that the introduction of novel agents may not be having a profound impact on outcomes. This held true for overall survival and for deaths directly caused by complications of WM. The possibility of survival differences beyond 10 years cannot be excluded [13].

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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 (e.g., cold agglutinin hemolytic anemia, type II cryoglobulin, neuropathy, and amyloidosis)	+	−	±	+
Macroglobulinemia	+	+	+	±

Abbreviations: IgM, immunoglobulin M; MGUS, monoclonal gammopathy of undetermined significance.

Diagnosis

In the original description of WM, Waldenström [14] described two patients with oronasal bleeding, lymphadenopathy, anemia, thrombocytopenia, and an elevated sedimentation rate. The disorder is a lymphoplasmacytic lymphoma with a monoclonal pentameric IgM protein [15]. Bone marrow and lymph nodes are infiltrated with pleomorphic B-lineage cells at different stages of maturation [16]. The bone marrow pattern is predominantly intertrabecular and is considered lymphoplasmacytic lymphoma by the World Health Organization [1]. Most patients who fulfill all other criteria for the diagnosis have a presymptomatic phase and may not require therapy [17]. The cells express pan B-cell markers (e.g., *CD19* and *CD20*) and typically test negative for *CD3* and *CD103* [18]. The 6q genetic deletion is present in 42% of patients and is associated with an adverse prognosis [19]. Fluorescent in situ hybridization analysis for 20q12 changes was performed in nine patients with WM [20]. Four of nine patients in the study had lesions of 20q12 or 20qter at diagnosis. The authors concluded that chromosomal breakage at 20q13 is a nonrandom genetic change that could have a role in the neoplastic process of WM. Whole-genome sequencing of lymphoplasmacytic cells from 30 patients with WM has been reported [21]. 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 possibility of specific inhibitors.

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 [22]. 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 [23]. 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.

It is often difficult to distinguish WM from splenic marginal zone lymphoma because of their overlapping clinical characteristics. However, *CD138* expression may be useful in establishing the diagnosis. Differences between the two entities regarding the intensity and the percentage of $CD138^+$ cells are significant and correlated with the serum IgM level [24]. Bone marrow findings also can help distinguish splenic marginal zone lymphoma from WM. Comparison of bone marrow from 122 patients with WM and 98 patients with splenic marginal zone lymphoma, 17 of whom had monoclonal IgM in the serum, showed that patients with splenic marginal zone lymphoma had a higher percentage of sinusoidal infiltration (70%) and a more frequent nodular pattern, whereas patients with WM tended to have interstitial distribution of disease in the bone marrow [25].

IgM multiple myeloma is also a distinct entity; although constituting only 1% of all multiple myeloma cases, it 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 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*. Immunoglobulin localization is on the cell surface, whereas in myeloma, immunoglobulin is cytoplasmic.

The monoclonal IgM proteins are found in 1 of 600 patients older than 50 years [26]. The overall age-standardized rate of WM is only 5.5 per 1 million persons per year [27]. Far more patients have IgM monoclonal gammopathy of undetermined significance than have WM. However, all patients with IgM monoclonal gammopathy of undetermined significance require lifelong monitoring because the risk of transformation into an overt lymphoplasmacytic lymphoma is ~2% per year and is somewhat higher when the immunoglobulin free light-chain ratio is abnormal [28,29]. Yet 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. Box 1 [30] 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, then the quantitative IgM level can be used. 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. The immunoglobulin free light-chain assay also has been evaluated prospectively in WM. The involved serum-free light chain is a useful marker of tumor measurement and shows earlier response and progression than the intact IgM immunoglobulin, presumably because of its shorter half-life in the serum. Whether free light-chain measurements in serum should be a standard part of the evaluation of patients with WM requires further study; currently, it is not recommended [31].

Risk Stratification

Because WM is a distinct lymphoproliferative process with unique cell surface and genetic characteristics, the International Prognostic Index [32] and the Follicular Lymphoma International Prognostic Index [33] are not used in determining prognosis. Table II gives the currently accepted international staging system for WM [34].

The five criteria given in Table II are not weighted equally. First, age has a profound impact on prognosis. By definition, patients older than 65 years cannot be in a low-

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-Hr urine collection for protein electrophoresis; monoclonal light chains are detected in the urine of 40–80% of patients tested
- Immunoglobulin free light-chain assay
- Serum β_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
- 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 [30]

TABLE II. International Prognostic Scoring System for Waldenström's Macroglobulinemia

Factor associated with prognosis		Value
Age (years)		$>$65
Hemoglobin (g/dL)		$\leq$11.5
Platelet count (No./mcL)		$\leq$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.
Adapted from Morel et al (34). Used with permission.
[a]One point is assigned for each positive factor and the risk score is the sum of points.

risk category. Second, although IgM protein levels are important prognostically, they do not enter into the staging system until the IgM level exceeds 7,000 mg/dL, which is present in only some patients at diagnosis. Investigators have suggested that response rates to single-agent rituximab therapy decline when the IgM concentration exceeds 5,000 mg/dL [35]. In the largest study of single-agent rituximab therapy for WM, the IgM level did not affect response rate [36]. Third, lactate dehydrogenase is absent from the International Prognostic Scoring System for Waldenström's Macroglobulinemia [37]. Recently, investigators, in an attempt to refine the staging system, determined that 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 [38,39]. The role of the immunoglobulin free light-chain assay remains to be defined [40].

The International Prognostic Scoring System for Waldenström's 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 [41].

Because patients with WM have an indolent disease course and often are of an advanced age, nearly half of patients succumb to diseases of the elderly population, unrelated to WM. The impact of age on overall survival was investigated in 238 patients with WM [42]. 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 [37].

Management

Hyperviscosity syndrome

Hyperviscosity syndrome is seen in an ever-decreasing proportion of patients with WM because WM is being diagnosed earlier [43]. Symptomatic hyperviscosity is rare in patients with an IgM concentration less than 4,000 mg/dL, and viscosity measurement is not required in patients whose IgM levels fail to exceed 4,000 mg/dL [44]. The symptoms of hyperviscosity are due primarily to shear forces that rupture unsupported venous channels. As a consequence, the presentation generally includes epistaxis, gingival bleeding, and visual changes due to retinal hemorrhages. 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 is greater than 4.

When hyperviscosity is present, plasma exchange is a validated treatment technique but should be considered a temporizing measure until systemic chemotherapy successfully lowers the tumor mass and thereby reduces the IgM protein concentration in the serum [45]. Long-term plasma exchange rarely is required and usually is 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.

However, rituximab alone is generally a poor choice for patients in urgent 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 is no greater than 55% and is inferior to virtually every other reported combination regimen [46]. An analysis of the impact of rituximab on depth of response and the impact of response depth on outcome has been reported [47]. No difference in progression-free survival 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 β_2 microglobulin level were not predictive of a complete or very good partial response. A complete or very good partial response was associated with significantly longer progression-free survival.

Rituximab alone is inferior to single-agent alkylating agent chemotherapies such as chlorambucil [48] and single-agent cladribine [49]. In one study [50], 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 rituxi-

mab is commonly 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 [51].

Use of rituximab as a single agent contains the risk that many patients will have "flare" [52]. 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. This flare is seen infrequently when rituximab is combined with cytotoxic chemotherapy [53].

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 [54], improved progression-free and overall survival was seen in patients receiving maintenance therapy, independent of previous treatment status, although an increased number of infections were 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. Rituximab is not the only monoclonal antibody that has been used in WM. Alemtuzumab has also been used in previously treated and untreated patients [55]. Long-term follow-up of 28 patients included 1 with a complete response, 9 with partial responses, and 11 with minor responses. The median time to progression was 14.5 months. Infectious complications, including reactivation of cytomegalovirus, were observed; these were indirectly associated with three deaths. Late-onset autoimmune thrombocytopenia also was observed. Alemtuzumab is active against WM and may be considered as a salvage option, but clinicians should be mindful of the risk of serious infectious toxicity.

All available trials of chemotherapy in WM are single-arm, phase 2 studies, with the exception of a phase 3 trial of single-agent chlorambucil as continuous or pulse therapy [48]. In that trial, 46 patients were treated and 36 (78%) had an objective response. Patients needed greater than 6 months of therapy because responses were slow. This regimen was associated with a high risk of late myelodysplastic syndrome (3/46).

Ten-year follow-up data are available on the use of single-agent fludarabine in the treatment of WM [56]. 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 to 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 [57], 43 patients with untreated or previously treated WM received rituximab, fludarabine, and cyclophosphamide, the same regimen used to treat chronic lymphatic leukemia. Only β_2 microglobulin levels were predictive of the frequency of response. Nineteen patients (44%) had long-lasting neutropenia. Three patients (7%) had development of myelodysplastic syndrome. The overall response rate was 79%, with complete remission in 21%. 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.

Today, the majority of 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 [58,59]. Rituximab treatment combined with cyclophosphamide (orally) and dexamethasone has been reported, with a response rate of 83% and minimal toxicity [60]. Two-year progression-free survival was 67%; 2-year disease-specific survival was 90%. This three-agent combination is currently the nonstudy standard for symptomatic patients with a new diagnosis of WM at Mayo Clinic.

Rituximab has been combined with fludarabine in treatment of WM [61,62] and is capable of producing high response rates but also has been reported to predispose to late myelodysplasia [63] and large-cell lymphoma transformation [64]. One study described 176 patients treated with fludarabine, with a median follow-up of 41 months [63]. Nineteen patients (10.8%) with treatment-related myelodysplasia were identified; median survival after diagnosis of myelodysplasia was 11 months. Fludarabine combination chemotherapy is associated with a moderate risk of treatment-related myelodysplasia. The risk increases with the inclusion of mitoxantrone. In addition, fludarabine impedes the adequate mobilization of stem cells [65], and therefore its use is undesirable in patients who could be a candidate for stem-cell transplantation.

Stem-cell transplantation has been shown to produce durable responses with a low treatment-related mortality rate of 3.8% [66]. Good outcomes are seen with high-dose treatment; 5-year progression-free and overall survival rates were 39.7 and 68.5%, respectively [66]. 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 $-17p$ [67]. 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 [68] concluded that autologous transplantation is an effective and potentially underused 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 overall and event-free survival in previously treated and untreated patients [69]. 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.

The introduction of novel agents for multiple myeloma has provided benefits for patients with WM. Rituximab combined with thalidomide [70] produced a 72% response rate, and rituximab combined with lenalidomide [71] produced a 50% response rate, although lenalidomide aggravated anemia in a large proportion of patients. Thalidomide and lenalidomide have activity, although the subclinical neuropathy [72] 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 2 of 3 weeks [73,74], and of once weekly in 4 of 5 weeks [75], 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 event-free survival rate of 79% [76]. Most importantly, no grade 3 or 4 neuropathy was seen with the weekly bortezomib schedule. Recently, 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

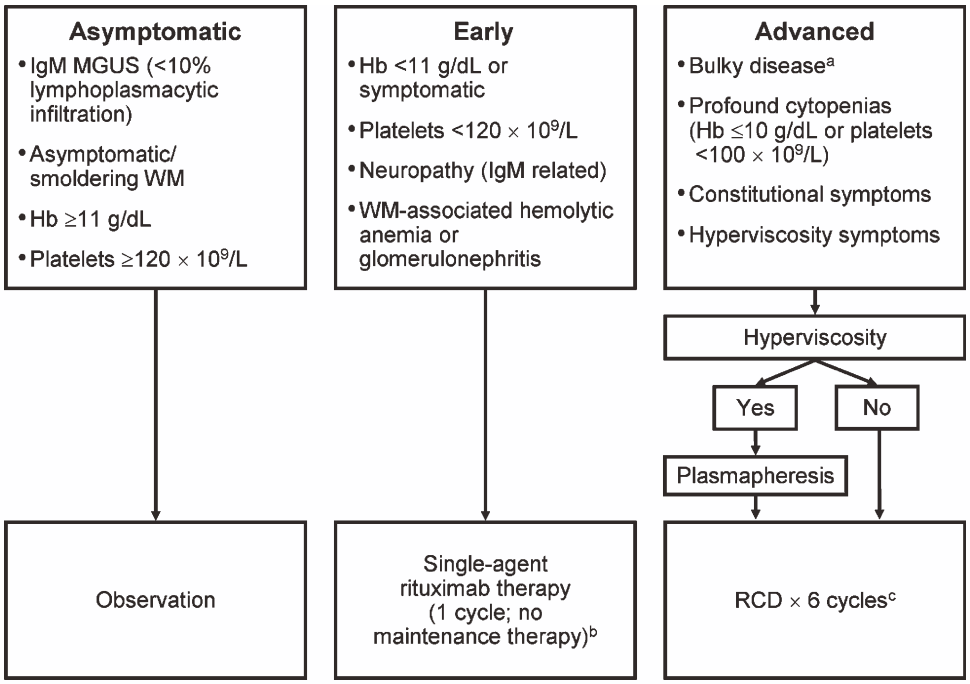

Figure 1. Mayo Clinic Consensus for Newly Diagnosed Waldenström Macroglobulinemia (WM). Hb indicates hemoglobin; IgM, immunoglobulin M; MGUS, monoclonal gammopathy of undetermined significance; RCD, rituximab, cyclophosphamide, and dexamethasone. [a]Avoid chlorambucil and nucleoside analogs in potential candidates for stem-cell transplantation. [b]Administer plasmapheresis if hyperviscosity occurs with treatment. [c]Collect stem cells after completion of the six cycles in patients eligible for transplantation. (Adapted from Fonseca R, Hayman S. Waldenström macroglobulinaemia. Br J Haematol. 2007 Sep;138[6]:700-20. Epub 2007 Aug 2. Used with permission of Mayo Foundation for Medical Education and Research.)

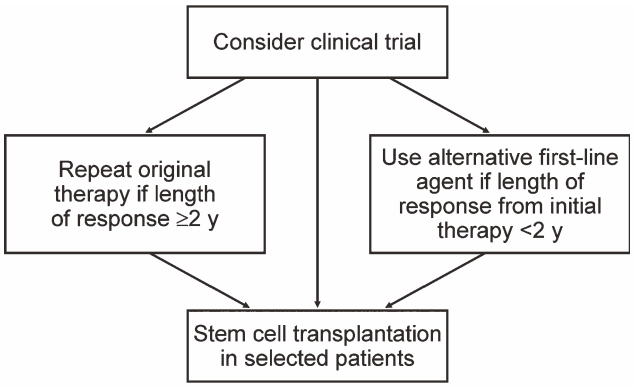

Figure 2. Mayo Clinic Consensus for Salvage Therapy in Waldenström Macroglobulinemia. (Adapted from Ansell et al. [83]. Used with permission of Mayo Foundation for Medical Education and Research.)

patients, respectively [77]. Everolimus (as a single agent) was used to treat 33 patients with newly diagnosed WM [78]. Twenty-two patients were evaluable for response. The best overall response rate was 66.7%; 14 had partial responses, 8 had minor responses, and 11 had stable disease. Everolimus can be administered orally, but oral ulcerations occurred in 7 patients (21%). Relapse-free and overall survival data were not available. The Akt inhibitor perifosine has shown a response rate of 35% but is associated with high levels of gastrointestinal toxicity [79]. Histone deacetylase inhibitors also have shown activity in WM [80].

In the prospective randomized study of bendamustine plus rituximab compared to 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 [81]. In both groups, the response rate was 95%, but median progression-free survival was significantly prolonged with bendamustine. The median progression-free survival for R-CHOP was 36 months in contrast to not being reached with bendamustine and rituximab ($P < 0.0001$). 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 infections, lower incidence of neuropathy, and reduced stomatitis. The role of bendamustine continues to be undefined in WM treatment, but it is clearly an active regimen [81]. Bendamustine also has been used as a salvage therapy in patients with relapsed or refractory multiple myeloma [82]. Twenty-four patients received the agent (90 mg/m^2) plus rituximab on 2 consecutive days. Each cycle was 4 weeks, with a median of five treatment cycles. The overall response rate was 83% (20/24). The median progression-free survival was 13.2 months. Prolonged myelosuppression was more common in patients who previously had received fludarabine or cladribine.

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 [83].

Conclusion

When macroglobulinemia 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, cyclophosphamide, and dexamethasone. 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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