Diagnosis and Management of Waldenström Macroglobulinemia
Mayo Stratification of Macroglobulinemia and Risk-Adapted Therapy (mSMART) Guidelines 2016

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Supplemental content

IMPORTANCE Waldenström macroglobulinemia (WM), an IgM-associated lymphoplasmacytic lymphoma, has witnessed several practice-altering advances in recent years. With availability of a wider array of therapies, the management strategies have become increasingly complex. Our multidisciplinary team appraised studies published or presented up to December 2015 to provide consensus recommendations for a risk-adapted approach to WM, using a grading system.

OBSERVATIONS Waldenström macroglobulinemia remains a rare, incurable cancer, with a heterogeneous disease course. The major classes of effective agents in WM include monoclonal antibodies, alkylating agents, purine analogs, proteasome inhibitors, immunomodulatory drugs, and mammalian target of rapamycin inhibitors. However, the highest-quality evidence from rigorously conducted randomized clinical trials remains scant.

CONCLUSIONS AND RELEVANCE Recognizing the paucity of data, we advocate participation in clinical trials, if available, at every stage of WM. Specific indications exist for initiation of therapy. Outside clinical trials, based on the synthesis of available evidence, we recommend bendamustine-rituximab as primary therapy for bulky disease, profound hematologic compromise, or constitutional symptoms attributable to WM. Dexamethasone-rituximab-cyclophosphamide is an alternative, particularly for nonbulky WM. Routine rituximab maintenance should be avoided. Plasma exchange should be promptly initiated before cytoreduction for hyperviscosity-related symptoms. Stem cell harvest for future use may be considered in first remission for patients 70 years or younger who are potential candidates for autologous stem cell transplantation. At relapse, retreatment with the original therapy is reasonable in patients with prior durable responses (time to next therapy ≥3 years) and good tolerability to previous regimen. Ibrutinib is efficacious in patients with relapsed or refractory disease harboring *MYD88* L265P mutation. In the absence of neuropathy, a bortezomib-rituximab–based option is reasonable for relapsed or refractory disease. In select patients with chemosensitive disease, autologous stem cell transplantation should be considered at first or second relapse. Everolimus and purine analogs are suitable options for refractory or multiply relapsed WM. Our recommendations are periodically updated as new, clinically relevant information emerges.

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Table 1. Classification System for Levels of Evidence and Grades of Recommendations

Category	Type of Evidence
Level of Evidence	
1	Evidence obtained from meta-analysis of multiple, well-designed, controlled studies. Randomized trials with low false-positive and low false-negative errors (high power)
2	Evidence obtained from at least 1 well-designed experimental study. Randomized trials with high false-positive and/or false-negative errors (low power)
3	Evidence obtained from well-designed, quasi experimental studies such as nonrandomized, controlled single-group, pre-post, cohort, time, or matched case-control series
4	Evidence from well-designed, nonexperimental studies, such as comparative and correlational descriptive and case studies
5	Evidence from case reports and clinical examples
Grade of Recommendation	
A	Evidence of type 1 or consistent findings from multiple studies of type 2, 3, or 4
B	Evidence of type 2, 3, or 4, and findings are generally consistent
C	Evidence of type 2, 3, or 4, but findings are inconsistent
D	Minimal or no systematic empirical evidence

Herein, the Mayo Clinic Cancer Center Myeloma, Amyloidosis and Dysproteinemia and Lymphoma Disease-Oriented Groups, the multidisciplinary panels of experts with a collective experience of treating hundreds of Waldenström macroglobulinemia (WM) cases, update their evidence-based recommendations for the management of WM. Important advances have led to a broader understanding of the biology of this rare cancer since our initial risk stratification–based approach was published in 2010.[1] Clinical and observational studies published or presented through December 2015 are reviewed to provide consensus recommendations for clinicians as patients with WM are infrequently encountered in practice. The guidelines are formulated using a grading system of evidence and grades of recommendations (**Table 1**). In the absence of adequate data or a clear superiority vis-à-vis a particular approach, we used expert consensus to formalize recommendations (eAppendix 1 in the Supplement).

Waldenström macroglobulinemia, a distinct, low-grade B-cell lymphoproliferative disorder (LPD), was initially chronicled more than 70 years ago in Jan Waldenström's 2 landmark cases, and accounts for 1% to 2% of LPDs.[2] It is predominantly a disease of elderly white men, with an overall age-adjusted incidence of 3.8/million-persons/y.[3] Besides racial disparity, the epidemiologic estimates suggest genetic susceptibility and strong familial aggregation (eAppendix 1 in the Supplement). In the Surveillance, Epidemiology, and End Results data analysis (N = 4304), the median overall survival (OS) was 74 months, with a striking improvement for patients whose disease was diagnosed since 2000 (84 vs 64 months for years prior).[4,5]

Diagnosis

In practice, it is important to adhere strictly to the diagnostic criteria and to exclude other LPDs before establishing the diagnosis of WM. Central to its diagnosis is the detection of IgM monoclonal protein of any size and at least 10% lymphoplasmacytic lymphoma cells in the marrow (Mayo criteria) (eTable 1 in the Supplement).[1,6,7]

The immunophenotypic hallmark of lymphocytes is a pan–B-cell profile, with expression of surface IgM, CD19, CD20, CD22, and CD79a antigens.[7] Paired tumor/normal whole-genome sequencing was instrumental in the detection of a highly recurrent somatic mutation (leucine265proline) involving the myeloid differentiation primary response 88 (*MYD88*) gene in almost all (>90%) patients with WM.[8] Another set of recently discovered nonsense and frameshift somatic mutations affecting *CXCR4* are similar to those present in WHIM (warts, hypogammaglobulinemia, infections, and myelokathexis) syndrome, and are harbored by nearly one-third of patients with WM.[9] Data regarding the prognostic and therapeutic implications of these mutations are beginning to unravel, and require confirmation (eAppendix 2 in the Supplement).[9-12]

A focused history and physical examination (eTable 2 in the Supplement) is required in all patients.

Recommendations

- In cases of suspected, histopathologically difficult-to-interpret lymphoplasmacytic lymphoma, MYD88 mutation status should be assessed by allele-specific polymerase chain reaction assay (level 3, grade A)
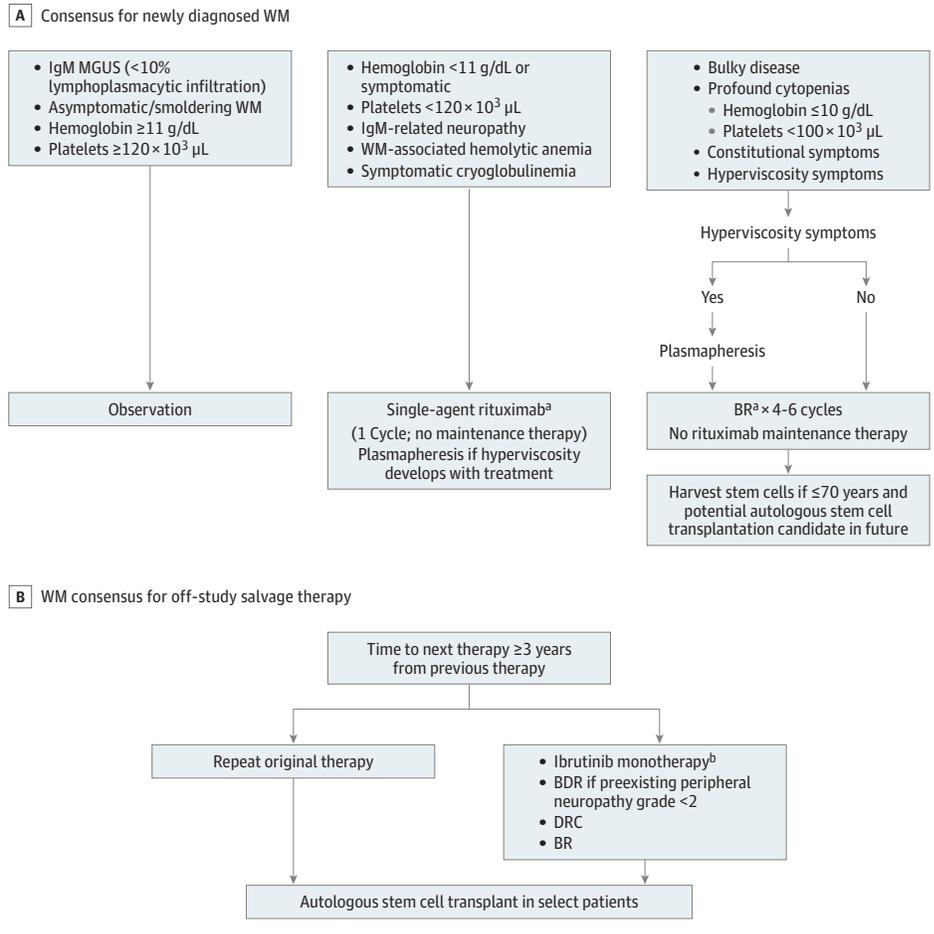
Risk Stratification and Response Assessment

Waldenström macroglobulinemia has a heterogeneous disease course.[13-16] With the median age of 69 years at presentation, and accompanying comorbidities in a substantial proportion of patients, its management can be challenging. The median disease-specific survival of 10-11 years attests to its indolent course.[14,17] The International Prognostic Scoring System was developed through a collaborative analysis of treatment-naive symptomatic patients with WM (eTable 2 in the Supplement).[16] Although used for patient stratification in trials, and externally validated, its value in treatment decision making remains unproven.

- Virtually all patients with symptomatic WM transition from precursor conditions: IgM monoclonal gammopathy of undetermined significance (MGUS) and smoldering WM (SWM). However, SWM (eTable 1 in the Supplement) is infrequently recognized (eAppendix 3 in the Supplement). The temptation to manage an increased size of the monoclonal protein with immediate therapy should be resisted. We endorse the specific indications, developed at the Second International Workshop on WM, to initiate therapy.[18] Acknowledging the paucity of level I evidence, we approach patients by categorizing them into 3 groups (**Figure**, A) with distinct, risk-adapted strategies, discussed herein. We consistently use the Sixth International Workshop Response Criteria for WM (eTable 3 in the Supplement) for response assessment.

Recommendations

- Patients with IgM MGUS or SWM with preserved marrow function should be managed with a "wait and watch" approach (level 3, grade B)
- Patients with IgM MGUS require lifelong active surveillance (history, physical and laboratory tests) with follow-up at 6 months initially, and then annually, if stable. Patients with SWM require lifelong active surveillance, every 4 months for the first 3 years, every

Figure. Consensus for Waldenström Macroglobulinemia (WM)

A Consensus for newly diagnosed WM

- IgM MGUS (<10% lymphoplasmacytic infiltration)
- Asymptomatic/smoldering WM
- Hemoglobin ≥11 g/dL
- Platelets ≥120 × 10³ µL

→ Observation

- Hemoglobin <11 g/dL or symptomatic
- Platelets <120 × 10³ µL
- IgM-related neuropathy
- WM-associated hemolytic anemia
- Symptomatic cryoglobulinemia

→ Single-agent rituximab[a]
(1 Cycle; no maintenance therapy)
Plasmapheresis if hyperviscosity develops with treatment

- Bulky disease
- Profound cytopenias
  - Hemoglobin ≤10 g/dL
  - Platelets <100 × 10³ µL
- Constitutional symptoms
- Hyperviscosity symptoms

Hyperviscosity symptoms

Yes → Plasmapheresis / No

→ BR[a] × 4-6 cycles
No rituximab maintenance therapy

→ Harvest stem cells if ≤70 years and potential autologous stem cell transplantation candidate in future

B WM consensus for off-study salvage therapy

Time to next therapy ≥3 years from previous therapy

→ Repeat original therapy

- Ibrutinib monotherapy[b]
- BDR if preexisting peripheral neuropathy grade <2
- DRC
- BR

→ Autologous stem cell transplant in select patients

BDR indicates bortezomib (weekly) + dexamethasone + rituximab; BR, bendamustine + rituximab; DRC, dexamethasone-rituximab-cyclophosphamide; MGUS, monoclonal gammopathy of undetermined significance.

To convert hemoglobin from grams per deciliter to grams per liter, multiply by 10; to convert platelet count from thousands per microliter to billions per liter, multiply by 1.0.

[a] Six cycles of DRC is an alternative if the disease burden is low.

[b] If not previously used.

6 months for the subsequent 2, and, if stable, annually thereafter, with a focus on the emergence of symptoms consistent with disease progression, immunoglobulin light-chain (AL) amyloidosis or second cancers (level 3, grade B)

- Without a distinct symptomatology suggestive of an LPD, the family members of patients affected with WM should not be screened (level 3, grade B)
- Selection of therapy should not be based on familial predisposition (eAppendix 1 in the Supplement) of patients with WM (level 3, grade B)
- Specific indications for initiation of therapy (Table 2) for WM exist (level 3, grade B)

Initial Therapy

The overarching goals of therapy for WM are to achieve symptomatic relief and reduce further organ damage without compromising the quality of life. As WM cells of treatment-naive patients uniformly express CD20, rituximab, a generally well-tolerated chimeric anti-CD20 antibody, has become a backbone to which several other agents have been successfully integrated.[20-29] Rituximab monotherapy is associated with a median progression-free survival (PFS) of 16 to 29 months, and an overall response rate (ORR) of 25% to 40% from a single 4-week cycle and 65% with an extended course of 2 4-week cycles administered 8 weeks apart.[23,28] The responses may be delayed (median, 7 months).[28] For patients requiring urgent therapy, rituximab is considered inferior to combination therapies. Ofatumumab, a human anti-CD20 antibody, has been successfully used in patients intolerant to rituximab.[30] Literature, to date, is devoid of comparative trials involving single-agent rituximab, and our risk-adapted approach considers its use only in low-risk, symptomatic WM (Figure, A).

Recommendations

- Rituximab is indicated in WM with symptomatic mild to moderate anemia, symptomatic cryoglobulinemia (in combination with steroids), or hemolytic anemia unresponsive to corticosteroids (level 3, grade B)
- Rituximab monotherapy is contraindicated in patients with symptomatic hyperviscosity, and, without preemptive plasmapheresis, is best avoided in patients with very high serum IgM (level 3, grade A)
- To avoid underestimation of the magnitude of response to rituximab monotherapy, a lag period to attain maximal response should be taken into account (level 3, grade A)

Table 2. Key Waldenström Macroglobulinemia (WM) Recommendations and Their Rationale

Area	Key Recommendations	Rationale
Diagnosis	Histopathologically difficult-to-interpret suspected cases of lymphoplasmacytic lymphoma warrant *MYD88* mutation status assessment by AS-PCR assay (level 3, grade A)	*MYD88* L265P is detected in 93% of patients with WM with AS-PCR but is either rare in other B-cell disorders (eg, splenic marginal zone lymphoma [10%], CLL [4%]) or absent (multiple myeloma and IgG MGUS)
IgM MGUS/ SWM	A "wait and watch" approach is recommended for patients with IgM MGUS, or SWM with relatively preserved marrow function, with a focus on the emergence of symptoms consistent with disease progression, AL amyloidosis, or second cancers: (1) Patients with IgM MGUS require lifelong active surveillance with follow-up at 6 mo initially, and then annually, if stable (level 3, grade B) (2) Patients with SWM require lifelong active surveillance. Follow-up could involve assessment every 4 mo for the first 3 y, every 6 mo for the subsequent 2, and, if stable, annually thereafter (level 3, grade B)	Early intervention in an asymptomatic phase has not been shown to favorably affect outcome, and exposes patients to treatment-related toxic effects. Patients with diagnoses of precursor conditions, IgM MGUS or SWM, are at risk of progression until death. The cumulative probability of progression of IgM MGUS to WM, other non-Hodgkin lymphoma, and AL and CLL is 10% at 5 y, 18% at 10 y, and 24% at 15 y, with overall risk being approximately 1.5% per year. The cumulative probability of progression of SWM to symptomatic WM or a related condition is approximately 12% per year (6% at 1 y, 39% at 3 y, and 59% at 5 y) for the first 5 y and then 2% per year for the next 5 y (68% at 10 y)
Familial WM	• Without a distinct symptomatology suggestive of a lymphoproliferative disorder, avoid screening of family members of patients with WM (level 3, grade B) • Selection of therapy should not be based on familial predisposition of patients with WM (level 3, grade B)	• Although the relative risk of a first-degree relative developing a B-cell malignant neoplasm is increased, the absolute risk remains low • Prospective studies have yet to verify therapeutic advantage of altering approach on the basis of familial predisposition
Indications for therapy	• WM-related constitutional symptoms (high fever, drenching sweats or significant weight loss, severe fatigue),[a] symptomatic anemia, lymphadenopathy or hepatosplenomegaly, coexisting AL amyloidosis with organ dysfunction (level 3, grade B) • For patients with HVS, TPE should be promptly initiated prior to commencement of cytoreductive therapy (level 3, grade B)	• Alleviation of symptoms, improvement in quality of life and hematologic parameters, and arrest in organ damage has been observed with the institution of therapy • Due to a nonlinear correlation of serum viscosity with IgM, substantial viscosity reduction is feasible with small-volume TPE (a temporizing measure) with prompt relief of HVS
Frontline therapy for symptomatic WM	• Rituximab monotherapy is contraindicated in patients with HVS and, without preemptive plasmapheresis, is best avoided in patients with very high serum IgM levels (level 3, grade A) • Treatment with BR (4-6 cycles), particularly for bulky WM when expeditious disease control is desired (level 2, grade B) • Treatment with DRC is an alternative when the disease burden is low (level 3, grade B) • On completion of primary therapy, responders should be observed periodically until disease progression or reemergence of WM-related symptoms (level 3, grade B) • Nonresponders to primary therapy with persistent symptoms or patients with refractory WM should be offered an alternative regimen (level 3, grade A)	• Due to the risk of flare,[b] rituximab (or ofatumumab) monotherapy is avoided in HVS or those patients who are predisposed to developing HVS from exceedingly high baseline IgM • High ORR (95%) and long PFS (approximately 70 mo) with BR in a small phase 3 trial attests to its efficacy, although follow-up is short • Updated phase 2 data (median follow-up, 8 y) show median PFS of 35 mo and median TTNT of 51 mo with DRC, a well-tolerated regimen • A substantially longer TTNT than PFS with the DRC trial and other studies indicates that symptoms may not reappear for a length of time after biochemical progression, and observation is reasonable in such patients until the development of symptoms • Based on lack of data in the primary setting, we currently do not recommend ibrutinib until progression as frontline therapy • Because symptom control is one of the major goals of treatment of this incurable disease, it is justifiable to switch to an alternative approach in nonresponders. However, a monitoring phase for patients who achieve only modest M-protein reductions is acceptable as the best response may not be attained until 12 mo or longer
Maintenance therapy	Rituximab maintenance therapy should not be routinely used currently outside clinical trials (level 3, grade D)	The role of rituximab maintenance therapy in WM is controversial. A single nonrandomized study demonstrated improved outcomes with rituximab maintenance, albeit at a cost of increased toxic effect. The results of an ongoing randomized clinical trial (rituximab maintenance vs observation after BR induction and rituximab consolidation) are awaited
Salvage setting systemic, non-ASCT approach; high-dose therapy with stem cell rescue	• Repeating previous therapy is an option in relapsing patients who had achieved durable remission (TTNT ≥3 y) without significant toxic effects to prior treatment (level 3, grade B) • Ibrutinib monotherapy is suitable for patients with MYD88 mutation, irrespective of the presence of CXCR4 mutation at first or second relapse (level 3, grade B) • A bortezomib-based combination is considered a suitable salvage regimen, provided that patients' underlying peripheral neuropathy, if present, is of grade ≤2 (level 3, grade B) • Everolimus or purine analogs are suitable for use in select patients with refractory or multiply relapsed disease (level 3, grade B) • ASCT should be considered for first or second relapse in transplant-eligible patients with chemosensitive disease, especially if the first remission duration is short (<2 y). Patients with refractory WM should not be offered ASCT (level 3, grade B)	• Because TTNT is often delayed, and the indications of retreatment can emerge ≥12 mo after the detection of biochemical progression, we recommend using a 3-y TTNT cutoff (equivalent of the median PFS of the DRC study) to determine whether the original therapy may be repeated at relapse. In the DRC study, among patients who received second-line treatment, 70% were retreated with a rituximab-based regimen and attained high response rates (82%) • CXCR4 mutations confer a degree of resistance to ibrutinib therapy. However, the efficacy of this agent is primarily determined by the MYD88 mutation status. Patients with the MYD88 mutation alone achieved a metabolic response rate of 92% vs 62% for patients with MYD88 plus CXCR4 mutations, and 0% for the MYD88 WT and CXCR4 WT • BR combination therapy produces an ORR >80% in the salvage setting, and the responses appear to be durable. Neuropathy is a major toxic effect associated with bortezomib therapy • Despite substantial efficacy, the unfavorable toxicity profile of everolimus makes it a difficult-to-use initial salvage therapy • A large European Bone Marrow Transplant Registry experience (N = 615) has demonstrated superior outcomes with early ASCT for patients responding to induction therapy compared with those with refractory disease

Abbreviations: AL, immunoglobulin light-chain; ASCT, autologous stem cell transplantation; AS-PCR, allele-specific polymerase chain reaction; BR, bendamustine and rituximab; CLL, chronic lymphocytic leukemia; DRC, dexamethasone-rituximab-cyclophosphamide; HVS, hypatomegaly; MGUS, monoclonal gammopathy of undetermined significance; MYD88, myeloid differentiation primary response 88; ORR, objective response rate; PFS, progression-free survival; SWM, smoldering WM; TPE, therapeutic plasma exchange; TTNT, time to next therapy; WT, wild type.

[a] After ruling out transformation to a lymphoma of higher histologic grade and other medical conditions that could potentially cause constitutional symptoms.

[b] Flare, a phenomenon associated with a 25% or greater increase in baseline monoclonal proteins, has the potential to exacerbate IgM-associated morbidity.[19]

- In patients with slowly progressing, mild IgM peripheral neuropathy (PN) with otherwise quiescent WM, we recommend conservative therapeutic strategies (level V, grade D)
- We recommend a trial of rituximab at 375 mg/m^2 intravenously once weekly for 4 weeks in patients with isolated IgM-related, subacute, progressive disabling sensorimotor PN (eAppendix 4 in the Supplement) with moderate to severe functional impairment (level 2, grade C)

Therapeutic plasma exchange facilitates rapid removal of circulating IgM pentamers on an emergent basis and plays an important adjunctive—albeit a temporary—role in ameliorating hyperviscosity-related symptoms until the cytoreductive therapy effectively decreases the disease burden and, in turn, its surrogate marker, the IgM protein (eAppendix 4 in the Supplement).[31]

The schedule and efficacy of a few commonly used regimens in WM are outlined in eTables 4 and 5 in the Supplement.

With the emergence of compelling phase 3 data from the Study Group Indolent Lymphomas (StiL) trial, bendamustine/rituximab (BR) has catapulted to a commonly used frontline regimen with manageable toxicity profile.[26] A subset analysis involving patients with WM (n = 41) compared BR (n = 22 of 261) to rituximab plus cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone (R-CHOP) (n = 19 of 253). While high ORR (approximately 95%) was evident with both regimens, better tolerability (lower rates of infections, hematologic toxic effects, PN, stomatitis, and alopecia) and, importantly, longer PFS (median 69.5 months; interquartile range, 36.6-73.0 months) was notable with BR.[26] However, a clear OS advantage with BR has not yet been demonstrated.

In a multicenter, phase 2 trial of 72 treatment-naive patients with WM, dexamethasone-rituximab-cyclophosphamide (DRC) proved to be safe and neuropathy sparing. An ORR of 83%, with low (9%) rates of grade 3 to 4 toxic effects, was noted (eTable 5 in the Supplement).[32] Importantly, therapy-related myelodysplastic syndrome has not been documented so far, and the majority of those requiring retreatment demonstrated a meaningful response (ORR, 82%) to rituximab-based salvage therapy.[33] Given the modest toxicity profile and stem cell–sparing effect, DRC was considered the initial regimen of choice in our guidelines previously.[1]

The caveats with the aforementioned regimens are that DRC was evaluated in a single-arm study and the StiL study did not compare BR with the most effective contemporaneous regimens for WM.[26,32] Furthermore, despite the high ORR, the suitability of R-CHOP as a frontline regimen is questioned, given the concerns of vinca alkaloid–associated neurotoxicity, potential for cardiotoxicity, and inferiority of the CHOP backbone to even older agents such as fludarabine phosphate.

A large phase 3 trial (WM1) has demonstrated superiority—including OS advantage—of oral fludarabine to chlorambucil in treatment-naive patients with advanced WM.[34] In contrast to the reports from prior retrospective studies, second cancers were more frequent with chlorambucil therapy (6-year cumulative incidence rate 20.6% vs 3.7% with fludarabine).[34] Notwithstanding the unavailability of oral fludarabine in the United States, and the limited practical applicability of the WM1 trial comparing monotherapies in the era of rituximab-based combinations, this study illustrates that the choice of initial therapy significantly affects OS.

Three small phase 2 studies have evaluated bortezomib-based combinations in the frontline setting, showing an ORR of 81% to 96%.[22,24,35] Although bortezomib, the first-in-class proteasome inhibitor, elicits rapid (median, 1.4-3 months) and durable responses, an underlying PN at diagnosis, as well as an increased predisposition for PN even with its absence at baseline, raises concern for the use of this neurotoxic agent in patients with WM. In the WMCTG 05-180 trial, a majority developed PN (overall, 69%; grade 3, 30%), resulting in premature discontinuation in 61% of patients.[35] To mitigate the risk of PN the bortezomib-dexamethasone-rituximab regimen was modified, transitioning patients from twice to once weekly intravenous administration of bortezomib beyond the first cycle.[22] Reduced frequency of administration decreased neurotoxic effects (grade 3, 0%-7%) and resultant discontinuation (approximately 8%) but compromised the response (major response rate, 65%-68%).[22,24] The ongoing R2W trial (NCT01592981), using a potentially less neurotoxic, subcutaneous route for bortezomib, compares bortezomib-containing and fludarabine-cyclophosphamide-rituximab regimens, and could help clarify any potential advantages of using rituximab-bortezomib combination over conventional chemoimmunotherapy. Newer proteasome inhibitors (eAppendix 4 in the Supplement) have the potential to overcome some of the bortezomib-associated challenges.

Trials assessing the irreversible Bruton tyrosine kinase inhibitor, ibrutinib, in the frontline setting are currently under way (NCT02165397).

A single retrospective study supports the use of rituximab maintenance in WM, but the results of the StiL NHL7-2008 trial addressing this important issue are awaited (eAppendix 4 in the Supplement).

Recommendations

- Therapeutic plasma exchange should be promptly initiated for hyperviscosity syndrome, prior to commencement of cytoreductive therapy (level 3, grade B)
- We consider 4 to 6 cycles of BR, with its tolerable toxicity profile and ability to induce durable responses, to be our primary regimen of choice for symptomatic treatment-naive patients with WM, particularly bulky disease when expeditious disease control is desired (level 2, grade B)
- Dexamethasone-rituximab-cyclophosphamide may be an alternative in patients with symptomatic WM when the disease burden is low (level 3, grade B).
- In the absence of prospective data, rituximab maintenance therapy should not be routinely used currently outside clinical trials (level 3, grade D)
- On completion of primary therapy, responders should be observed periodically until the disease progresses and WM-related symptoms reemerge (level 3, grade B)
- Nonresponders to primary therapy with persistent symptoms/patients with refractory disease should be offered an alternative regimen (level 3, grade A)

Subsequent Therapy

Waldenström macroglobulinemia remains an incurable disease with an inexorable propensity for relapse. A small proportion of patients have primary refractory disease. Management decisions for the pa-

tients with relapsed disease hinge on a multitude of factors, including the magnitude and durability of remission with prior therapy, patients' candidacy for autologous stem cell transplantation (ASCT), the type and number of prior regimens and their tolerability, the patients' preferences, the pace of relapse, the impact on future treatment options, and most importantly, the need to reinitiate therapy. The study involving DRC demonstrated substantially longer time to next therapy (TTNT; median, 51 months) than PFS (median, 36 months), underscoring that biochemical progression does not equate with the requirement to reintroduce therapy.[33] The indications for initiating treatment in relapsing patients are largely similar to those for the treatment-naive patients.

Similar to the frontline setting, comparative trials to determine the optimal approach are nonexistent. Retreatment with the initial therapy can be considered if the TTNT is at least 3 years from the commencement of previous therapy (Figure, B). Bendamustine, as monotherapy and in combination with rituximab and/or ofatumumab, has shown an ORR of 83% in relapsed-refractory WM but leads to prolonged myelosuppression in patients previously exposed to a nucleoside analog.[36,37] More recently, an Italian retrospective study of patients with relapsed-refractory WM (n = 71) reported an ORR of 80% with BR, with the median PFS not being reached after a median follow-up of 19 months. Transformation or therapy-related myelodysplastic syndrome/acute myeloid leukemia was not observed.[37]

The appropriate subset of patients with WM who should be offered ASCT, as well as its optimal timing, is unestablished, with indolent disease course, advanced age, and multiple comorbidities at presentation rendering a large proportion of candidates transplant ineligible. Moreover, its rarity hampers conduction of trials comparing ASCT with alternative approaches.

Despite the lack of data to support survival advantage with myeloablative therapy in WM, several studies have reported encouraging results suggesting long-term disease control with ASCT.[38,39] In the European Bone Marrow Transplant Registry series (n = 158), the disease chemosensitivity at ASCT affected outcome. The modest nonrelapse mortality rate (3.8%), with estimated 5-year PFS and OS rates of 40% and 69%, respectively, attest to the tolerability and efficacy of ASCT.[39]

In patients who are potentially ASCT eligible, particularly those presenting with active disease at age 70 years or younger, consideration should be given to stem cell harvest in first remission after a low tumor burden has been achieved. Without evidence supporting survival benefit, ASCT is best avoided as a primary consolidative approach outside a trial. Our preferred strategy is to use cryopreserved cells early in the relapsed setting in chemosensitive disease because the efficacy of ASCT is markedly reduced in heavily pretreated (≥3 lines of prior therapy)/refractory WM. Despite graft-vs-lymphoma effect and high complete response rates (62%-66%), the associated toxic effects and the prohibitively high 1-year treatment-related mortality rates of up to 44% limit the use of allogeneic transplantation (eAppendix 4 in the Supplement).[38]

A phase 1 trial of advanced B-cell malignant neoplasms demonstrated strong activity of ibrutinib in the WM cohort,[40] prompting a phase 2 study with relapsed-refractory disease (n = 63).[41,42] The convincing results of this trial led to ibrutinib's approval for WM in the United States and the European Union in 2015. Rapid reduction in IgM (median time to response, 1.2 months), in paral-

lel to the hematocrit increase, was evident. While *MYD88* L265P–Bruton tyrosine kinase complex promotes cell proliferation and makes cells susceptible to ibrutinib therapy, the presence of *CXCR4* WHIM confers resistance. Significant activity (ORR, 95.5%) was noted, with highest response rates witnessed in those harboring *MYD88* L265P and *CXCR4* wild-type (WT) genotype.[41,42] Although superior PFS and improved tolerability was noted in the less pretreated patients (as expected), data with ibrutinib for treatment-naive WM are currently unavailable. Importantly, complete responses have not been observed and the follow-up remains short. The estimated 2-year PFS and OS of 69% and 95%, respectively, are comparable to those of other salvage therapies. Notably, IgM-mediated PN improved or stabilized with ibrutinib treatment, and IgM flare was not observed. Clinicians should be mindful of the drug-drug interactions and toxic effects associated with ibrutinib treatment, including neutropenia, thrombocytopenia, postprocedural hemorrhage, epistaxis with concurrent fish oil use, and atrial fibrillation in patients with a history of arrhythmias. Despite these limitations, there is potential to further expand the use of this oral, stem cell–sparing agent as the results of ongoing trials of ibrutinib-based combinations unfold (NCT02165397).[43]

The purine analogs cladribine and fludarabine phosphate are effective against relapsed-refractory WM as single agents (ORR, 31%-55%)[44-46] as well as combination therapies[25,27,47] (ORR, 79%-96%; complete response, 12% with fludarabine-cyclophosphamide-rituximab and 25% with cladribine-rituximab). However, toxic effects, including stem cell toxicity, prolonged myelosuppression/immunosuppression with infections, and secondary malignant neoplasms/transformation have limited their use.[48]

The PI3K/AKT/mTOR pathway is another constitutively activated pathway regulating cell metabolism, proliferation, survival, and angiogenesis in WM.[49] Everolimus, an oral mTORC1 inhibitor,[50] can produce responses bearing a striking resemblance to those from ibrutinib treatment, with rapid IgM reduction (median time to response, 2 months; median duration of response, not reached) in the face of persistent marrow infiltration. However, everolimus causes mucositis, diarrhea, fatigue, and dose-dependent myelosuppression.

Recommendations

- With biochemical progression alone, patients can be observed until the reemergence of symptoms, unless there is historical evidence of hyperviscosity syndrome with a prior known symptomatic IgM threshold for an individual patient (level 3, grade B)
- The disease burden should be reexamined by imaging and marrow reevaluation (and reassessment of CD20 expression if rituximab integration is contemplated with therapy) prior to initiation of salvage therapy as certain therapies (purine analogs, ibrutinib, everolimus, or bortezomib-based therapies) (eAppendix 4 in the Supplement) demonstrate discordant IgM and marrow responses (level 3, grade B)
- Consideration to repeating previous therapy may be given in relapsing patients who had achieved durable responses without substantial toxic effects to prior treatment. Because TTNT is often delayed and can occur 12 or more months after biochemical

Table 3. Mayo Stratification of Risk-Adapted Therapy (mSMART): Comparison and Contrast With Other Published Guidelines

Categories	mSMART 2016	National Comprehensive Cancer Network Version 2.2016	Eighth International Workshop for WM	British Society of Haematology 2014	European Society of Medical Oncology/Japanese Society of Medical Oncology 2013
WM Definition: IgM gammopathy positive	≥10% BMLP infiltration	Any degree of BMLP infiltration	Any degree of BMLP infiltration	Any degree of BMLP infiltration	Any degree of BMLP infiltration
MYD88 mutational status assessment	With AS-PCR in (1) Suspected lymphoplasmacytic lymphoma cases that are histopathologically challenging to diagnose (2) In potential candidates for ibrutinib salvage therapy	Essential in all cases; Sanger sequencing if AS-PCR negative for *MYD88* L265P	Essential in all cases; methodology based on institutional preference	Not specified	Not specified
Choice of primary therapy	Risk-adapted approach: (1) rituximab monotherapy in unique scenarios (2) BR (3) DRC[a]	Lists 15 regimens categorized by their potential for stem cell toxic effects	6 Regimens: (1) ibrutinib (2) BR (3) DRC (4) bortezomib-based (5) carfilzomib-based (6) rituximab monotherapy[b]	6 Regimens: (1) DRC (2) BR (3) FR (4) FCR (5) Clad-R (6) chlorambucil in frail patients	Medically fit: rituximab-based chemotherapy (DRC, RCHOP, BR, R-bortezomib with or without dexamethasone); medically unfit: rituximab monotherapy
Rituximab maintenance therapy	Not recommended	Considered in patients responding to rituximab-based induction	Not recommended	Not recommended	Not recommended outside clinical trials
Optimal timing of stem cell harvest	Preferably first remission in potentially ASCT-eligible patients younger than 70 y	Sometime prior to administration of stem cell toxic therapies	Optimal timing not fully specified, but prior to administration of fludarabine	Not specified	Not specified
ASCT	Strong consideration for chemosensitive, transplant-eligible patients in first relapse taking into account the patient's preference	An option for salvage therapy (not specified whether this approach should be undertaken early or late in the disease course)	Conflicting statements; table indicates ideal in high-risk, early relapses, those who have received <3 lines of therapies or have chemosensitive WM. Text suggests considering in multiply relapsed, young patients, or in primary refractory disease	In younger fitter patients with aggressive disease (short progression-free survival or transformation) in the setting of chemosensitive disease and at least a partial response to reinduction	As salvage therapy in transplant-eligible patients with aggressive disease
Retreatment with prior therapy	TTNT of ≥36 mo from the prior therapy	Remission duration of ≥12 mo from previous therapy	Response duration of at least 24 mo[c]	In patients with "durable response" to initial therapy	Not typically recommended
Other salvage therapeutic options	Ibrutinib or BDR; Multiply relapsed/refractory: fludarabine-based or everolimus	19 Approaches listed, including alemtuzumab, everolimus, or rituximab monotherapy, and in select patients autologous or allogeneic transplant[d]	(1) Ibrutinib (2) fludarabine-based (3) everolimus (4) immunomodulatory drugs[d]	(1) DRC (2) BR (3) FR (4) FCR (5) Clad-R (6) bortezomib based (7) alemtuzumab in refractory WM (8) ASCT or allogeneic SCT in young patients with a short first remission (<2 y)	An alternative rituximab-based chemotherapeutic agent (class should be different from that used previously; classes include alkylators, nucleoside analogs, or bortezomib based)

Abbreviations: ASCT, autologous stem cell transplantation; AS-PCR, allele-specific polymerase chain reaction; BMLP, bone marrow lymphoplasmacytic; BR, bendamustine rituximab; Clad-R, cladribine rituximab; DRC, dexamethasone-rituximab-cyclophosphamide; FCR, fludarabine-cyclophosphamide-rituximab; FR, fludarabine-rituximab; RCHOP, rituximab + cyclophosphamide, doxorubicin, vincristine, and prednisone; TTNT, time to next therapy; WM, Waldenström macroglobulinemia.

[a] An alternative for nonbulky (absence of extensive lymphadenopathy/extramedullary) disease.

[b] In frail patients or those with IgM-mediated immunologic disorders.

[c] Retreatment with ibrutinib should be avoided.

[d] In the context of clinical trials.

progression, we recommend using a 3-year TTNT cutoff to determine whether the original therapy may be repeated at relapse (level 3, grade B)

- Ibrutinib monotherapy is a viable option for patients with MYD88 mutation (irrespective of *CXCR4* mutation) in their first or second relapse. *MYD88* mutation status should be assessed prior to ibrutinib use as it is not sufficiently effective in *MYD88*-WT cases (level 3, grade B)

- A bortezomib-based combination (eg, bortezomib-dexamethasone-rituximab) is a suitable salvage regimen, provided the underlying PN, if present, is grade 2 or less (level 3, grade B)

- Autologous stem cell transplantation should be considered for first or second relapse in transplant-eligible patients with chemosensitive disease, especially if the first remission duration is short (<2 years). Patients with refractory WM should not be offered ASCT (level 3, grade B)

• Everolimus or purine analogs are considered suitable in select patients with refractory or multiply relapsed disease (level 3, grade B) **Table 3** highlights our key differences from other published guidelines.

Future Directions

Substantial recent progress, particularly the seminal discoveries of MYD88 and CXCR4 mutations, has paved the way for an exciting era in WM treatment. Extensive evaluations are ongoing to determine the precise role of these mutations. Furthermore, the therapeutic armamentarium against WM is poised to expand as the efficacy of several new, potentially effective agents, including the second-generation BCR inhibitors, oral proteasome inhibitors (ixazomib and oprozomib), B-cell lymphoma 2 inhibitor (venetoclax), glycoengineered anti-CD20 antibody (obinutuzumab), and programmed cell death 1 inhibitors, is being examined. In particular, targeted therapies need to be developed for the *MYD88* WT patient population.

We periodically update our evidence- and consensus-driven recommendations at http://www.mSMART.org to present a coherent management approach as new clinically relevant data emerge.

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