

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Waldenström's Macroglobulinemia / Lymphoplasmacytic Lymphoma

Version 2.2013
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Waldenström's Macroglobulinemia/ Lymphoplasmacytic Lymphoma

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NCCN Categories of Evidence and Consensus: All recommendations are Category 2A unless otherwise specified.

See [NCCN Categories of Evidence and Consensus](#)

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NCCN Guidelines Version 2.2013 Updates Waldenström's Macroglobulinemia/ Lymphoplasmacytic Lymphoma

Updates in version 2.2013 NCCN Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma Guidelines from the 1.2013 include:

[Discussion](#)

- The discussion section has been updated to reflect the changes in the algorithm.

Updates in version 1.2013 NCCN Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma Guidelines from the 1.2012 include:

[WMLPL-1](#)

- Under workup: changed CBC, differential, platelets to “CBC, differential, platelet count.”

[WMLPL-B](#)

- Under salvage therapy, added the following footnote to Ofatumumab (for rituximab intolerant individuals): “Ofatumumab may be used for rituximab intolerant individuals as a single agent or in combination therapy.”
- Changed footnote 4 to read: “These regimens are associated with treatment-related neuropathy and should be avoided in patients with disease-related neuropathy. See Discussion.”

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NCCN Guidelines Version 2.2013 Waldenström's Macroglobulinemia/ Lymphoplasmacytic Lymphoma

DIAGNOSIS

Essential^{a,b}

- Hematopathology review of all slides with at least one paraffin block representative of the tumor. Rebiopsy if consult material is nondiagnostic.
- Adequate immunophenotyping to establish diagnosis
 - Typical immunophenotype: CD19+, CD20+, sIgM+; CD5, CD10, CD23 may be positive in 10-20% of cases and does not exclude diagnosis

WORKUP

Essential

- H&P
- CBC differential, platelet count
- Comprehensive panel
- Quantitative immunoglobulins/Immunofixation
- Serum protein electrophoresis (SPEP)
- Beta-2 microglobulin
- Serum viscosity^c
- Unilateral aspirate and biopsy
- Chest/abdominal/pelvic CT

Useful in certain circumstances

- Hepatitis C testing^d
- Hepatitis B testing, if rituximab planned
- Cryocrit^{d,e}
- Cold agglutinins
- Neurology consult^f
- Anti-MAG antibodies/anti-GM1^f
- Electromyelogram^f
- Fat pad biopsy and/or congo red staining of bone marrow for amyloid^f
- Retinal exam (if IgM ≥ 3.0 g/dL or if hyperviscosity is suspected)

INDICATIONS FOR TREATMENT

Symptoms related to:

- Hyperviscosity
- Neuropathy
- Organomegaly
- Amyloidosis
- Cold agglutinin disease
- Cryoglobulinemia
- Cytopenias associated with disease
- Bulky adenopathy

[See Primary Treatment \(WMLPL-2\)](#)

^aSee WHO Criteria for Lymphoplasmacytic Lymphoma and Waldenström's Macroglobulinemia (WMLPL-A).

^bLymphoplasmacytic lymphoma (LPL) does encompass IgG, IgA, and non secretory subtypes though make up <5% of all LPLs. The treatment non-IgM LPLs parallels that of IgM secreting LPLs, but these are less likely to have either hyperviscosity associated with them, or autoimmune related neuropathy.

^cMost patients with serum viscosity of less than 4 cP will not have symptoms of hyperviscosity.

^dConsider in patients with suspected cryoglobulinemia.

^eIf cryocrit positive, then repeat testing of initial serum IgM, and obtain all subsequent serum IgM levels under warm conditions.

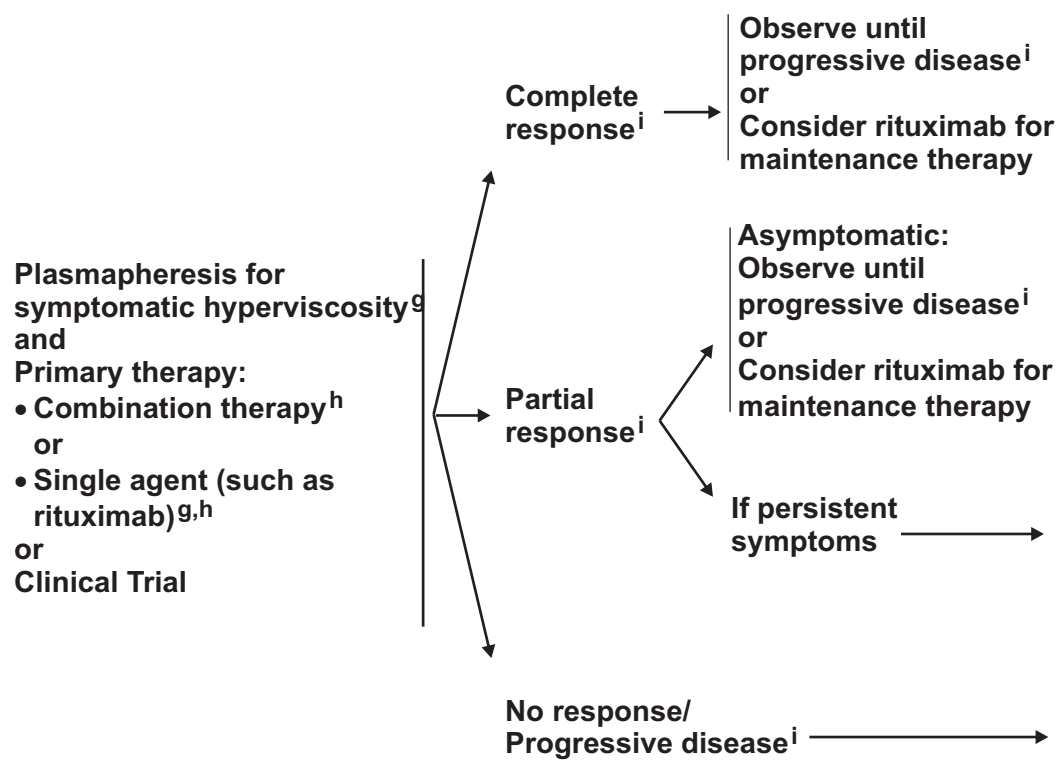
^fIn patients presenting with suspected disease related peripheral neuropathy.

Note: All recommendations are category 2A unless otherwise indicated.

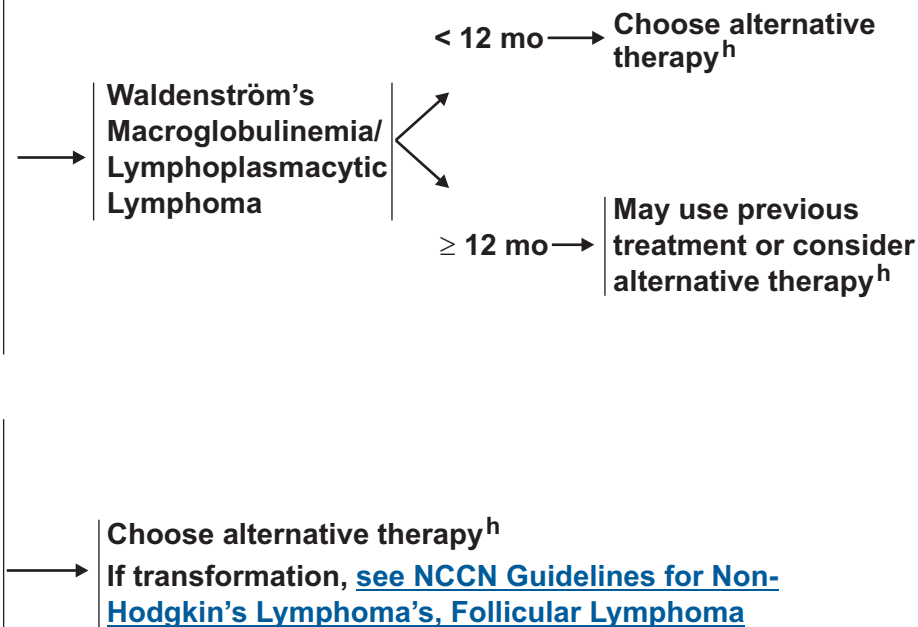
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PRIMARY TREATMENT



RELAPSE



^gPlasmapheresis should be performed for patients with symptomatic hyperviscosity, and before treatment with rituximab containing regimen in patients with IgM ≥ 5000 mg/dL. IgM should be monitored closely in these patients thereafter and plasmapheresis considered again if symptomatic hyperviscosity occurs or if IgM ≥ 5000 mg/dL while on rituximab containing therapy.

^h[See Suggested Treatment Regimens \(WMLPL-B\).](#)

ⁱ[See Response Criteria for WM/LPL \(WMLPL-C\).](#)

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WHO CRITERIA FOR LYMPHOPLASMACYTIC LYMPHOMA AND WALDENSTRÖM'S MACROGLOBULINEMIA

- **Lymphoplasmacytic lymphoma:**
 - Neoplasm of small B lymphocytes, plasmacytoid lymphocytes, and plasma cells
 - Usually involving bone marrow and sometimes lymph nodes and spleen
 - Does not fulfill criteria of any other small B-cell lymphoid neoplasm that may also have plasmacytic differentiation
- **Waldenström's Macroglobulinemia:**
 - Lymphoplasmacytic lymphoma with bone marrow involvement and IgM monoclonal gammopathy of any concentration

From Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW (Eds): World Health Organization Classification of Tumours of the Haematopoietic and Lymphoid Tissues. IARC Press: Lyon 2008.

WALDENSTRÖM'S MACROGLOBULINEMIA INTERNATIONAL WORKSHOP CRITERIA**Proposed Criteria for the Diagnosis of Waldenström's Macroglobulinemia**

- IgM monoclonal gammopathy of any concentration
- Bone marrow infiltration by small lymphocytes, plasmacytoid cells, and plasma cells
- Diffuse, interstitial, or nodular pattern of bone marrow infiltration
- CD19+, CD20+, sIgM+; CD5, CD10, CD23 can be expressed in some cases of Waldenström's Macroglobulinemia and does not exclude diagnosis.

Reprinted with permission from Elsevier. Owen RG. Developing diagnostic criteria in Waldenstrom's macroglobulinemia. Semin Oncol. 2003;30:196-200.

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SUGGESTED TREATMENT REGIMENS

(Order of regimens is alphabetical and does not indicate preference)

Primary Therapy:

Non-stem cell toxic

- Bortezomib ± rituximab^{1,2,3,4}
- Bortezomib/dexamethasone^{3,4}
- Bortezomib/dexamethasone/rituximab^{1,2,3,4}
- Cyclophosphamide/doxorubicin/vincristine/prednisone/rituximab^{1,4}
- Rituximab¹
- Rituximab/cyclophosphamide/prednisone¹
- Rituximab/cyclophosphamide/dexamethasone¹
- Thalidomide ± rituximab^{1,4}

Possible stem cell toxicity and/or risk of transformation (or unknown)

- Bendamustine ± rituximab¹
- Cladribine ± rituximab^{1,5,6}
- Chlorambucil^{5,6}
- Fludarabine ± rituximab^{1,5,6}
- Fludarabine/cyclophosphamide/rituximab^{1,5,6}

¹In patients with symptomatic hyperviscosity plasmapheresis should first be performed; plasmapheresis should also be considered before treatment with rituximab or ofatumumab for asymptomatic Waldenström's Macroglobulinemia patients with an IgM ≥ 5,000 mg/dL to avoid aggravation of serum viscosity on the basis of rituximab related IgM flare. Rituximab or ofatumumab may also be held in patients with elevated serum IgM levels for initial treatment cycles.

²Consider particularly for patients presenting with symptomatic hyperviscosity, or in whom rapid IgM reduction is required.

³Herpes zoster prophylaxis for patients treated with bortezomib.

⁴These regimens are associated with treatment-related neuropathy and should be avoided in patients with disease-related neuropathy. See Discussion.

Salvage Therapy:

Non-stem cell toxic

- Alemtuzumab
- Bortezomib ± rituximab^{1,2,3,4}
- Bortezomib/dexamethasone^{3,4}
- Bortezomib/dexamethasone/rituximab^{1,2,3,4}
- Cyclophosphamide/doxorubicin/vincristine/prednisone/rituximab^{1,4}
- Everolimus
- Ofatumumab (for rituximab intolerant individuals)^{1,7}
- Rituximab¹
- Rituximab/cyclophosphamide/prednisone¹
- Rituximab/cyclophosphamide/dexamethasone¹
- Thalidomide ± rituximab^{1,4}

Possible stem cell toxicity and/or risk of transformation (or unknown)

- Bendamustine ± rituximab¹
- Cladribine ± rituximab^{1,5,6}
- Chlorambucil^{5,6}
- Fludarabine ± rituximab^{1,5,6}
- Fludarabine/cyclophosphamide/rituximab^{1,5,6}

Stem cell transplant

- In selected cases stem cell transplantation may be appropriate with either:
 - High dose therapy with stem cell rescue
 - Allogeneic stem cell transplant (ablative or non-ablative)⁸

⁵May be associated with disease transformation and/or development of MDS/AML in Waldenström's Macroglobulinemia patients.

⁶Avoid in patients who are potential autologous stem cell transplant candidates.

⁷Ofatumumab may be used for rituximab intolerant individuals as a single agent or in combination therapy.

⁸Should ideally be undertaken in the context of a clinical trial.

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[See Suggested References](#)
[\(WMLPL, 2 of 2\)](#)

WMLPL-B
(1 of 2)

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RESPONSE CRITERIA FOR WM/LPL^{1,2}

Response categories and criteria for progressive disease in WM based on consensus recommendations are summarized in Table 1. An important concern with the use of IgM as a surrogate marker of disease is that it can fluctuate, independent of tumor cell killing, particularly with newer biologically targeted agents such as rituximab, bortezomib, and everolimus. Rituximab induces a spike or flare in serum IgM levels which can occur when used as monotherapy and in combination with other agents including cyclophosphamide, nucleoside analogues, thalidomide, and last for several weeks to months, whereas bortezomib and everolimus can suppress IgM levels independent of tumor cell killing in certain patients. Moreover, Varghese et al showed that in patients treated with selective B-cell depleting agents such as rituximab and alemtuzumab, residual IgM producing plasma cells are spared and continue to persist, thus potentially skewing the relative response and assessment to treatment. Therefore, in circumstances where the serum IgM levels appear out of context with the clinical progress of the patient, a bone marrow biopsy should be considered in order to clarify the patient's underlying disease burden.

Table 1. Summary of Updated Response Criteria adopted at the 6th International Workshop on Waldenström's Macroglobulinemia.

Complete Response	CR	IgM in normal range, and disappearance of monoclonal protein by immunofixation; no histological evidence of bone marrow involvement, and resolution of any adenopathy / organomegaly (if present at baseline), along with no signs or symptoms attributable to WM. Reconfirmation of the CR status is required by repeat immunofixation studies.
Very Good Partial Response	VGPR	A ≥90% reduction of serum IgM and decrease in adenopathy/organomegaly (if present at baseline) on physical examination or on CT scan. No new symptoms or signs of active disease.
Partial Response	PR	A ≥50% reduction of serum IgM and decrease in adenopathy/organomegaly (if present at baseline) on physical examination or on CT scan. No new symptoms or signs of active disease.
Minor Response	MR	A ≥25% but < 50% reduction of serum IgM. No new symptoms or signs of active disease.
Stable Disease	SD	A <25% reduction and <25% increase of serum IgM without progression of adenopathy/organomegaly, cytopenias or clinically significant symptoms due to disease and/or signs of WM.
Progressive Disease	PD	A ≥25% increase in serum IgM by protein confirmed by a second measurement or progression of clinically significant findings due to disease (i.e. anemia, thrombocytopenia, leukopenia, bulky adenopathy/organomegaly) or symptoms (unexplained recurrent fever ≥38.4°C, drenching night sweats, ≥10% body weight loss, or hyperviscosity, neuropathy, symptomatic cryoglobulinemia or amyloidosis) attributable to WM.

¹Treon SP, Merlini G, Morra E, et al. Report from the Sixth International Workshop on Waldenström's Macroglobulinemia. Clin Lymph Myeloma Leukemia 2011; 11:69-73.

²Varghese AM, Rawstron AC, Ashcroft AJ, et al. Assessment of bone marrow response in Waldenström's macroglobulinemia. Clin Lymph Myeloma 2009; 9:53-5.

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Discussion

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Overview

Waldenström's macroglobulinemia (WM) is a B-cell disorder characterized primarily by bone marrow infiltration with lymphoplasmacytic cells, along with demonstration of an IgM monoclonal gammopathy.¹ This condition is considered to be lymphoplasmacytic lymphoma (LPL) as defined by the Revised European-American Lymphoma (REAL) and World Health Organization (WHO) classification systems.^{2,3}

Diagnosis

Key to the diagnosis of WM/LPL is the demonstration of bone marrow infiltration by a lymphoplasmacytic cell population manifested by small lymphocytes with evidence of plasmacytoid/plasma cell differentiation. The bone marrow infiltration should be supported by immunophenotypic studies (flow cytometry and/or immunohistochemistry) showing the

following profile: sIgM+, CD19+, CD20+, CD22+.¹ According to the current WHO classification, the lymphocytes in WM are typically negative for CD5, CD10, and CD23.³ However, this should not exclude diagnosis as exceptions occur. About 10- 20% of cases may express CD5, CD10, or CD23.^{4,5}

Workup

To establish the diagnosis of WM, it is necessary to demonstrate IgM monoclonal protein in the serum, along with histologic evidence of lymphoplasmacytic cells in the bone marrow.¹ Serum protein electrophoresis (SPEP), quantitative immunoglobulins, and immunofixation is used to identify and quantify the M-protein (which is IgM).

Immunoglobulin M is a pentamer and a common cause of hyperviscosity. Therefore, evaluation for characteristic clinical signs and symptoms of serum viscosity should be done at the time of diagnosis. Most WM patients will exhibit an elevated serum viscosity level, that is, more than 1.8 centipoise (cP). Patients typically become symptomatic at serum viscosity levels of more than 4.0 cP. However, in some patients, serum viscosity as low as 3.0 cP can cause retinal changes and hemorrhages in patients which may necessitate intervention.⁶ The serum IgM should be obtained under warm bath conditions for those patients suspected to have cryoglobulinemia.

In about less than 10% of WM patients, monoclonal IgM may present with cold agglutinin activity.⁷ This means that the monoclonal IgMs interact with specific red cell antigens at temperatures below physiological, producing chronic hemolytic anemia. The cold agglutinin titers are >1:1000 in most cases. In up to 20% of WM patients, the monoclonal IgM may behave as a cryoglobulin (type I), but is symptomatic in 5% or less of the cases. The presence of cold

agglutinins or cryoglobulins may affect determination of IgM levels and, therefore, testing for cold agglutinins and cryoglobulins should be performed at diagnosis.⁸

Beta-2 microglobulin and the WM IPSS score are useful in prognostication of WM.^{9, 10} Their use in making treatment-related decisions remains to be clarified.⁹

Since bone marrow is almost always involved in WM, a unilateral bone marrow aspirate and biopsy is done to confirm excess lymphoplasmacytoid cells. Computed tomographic scans of the chest, abdomen, and pelvis at time of diagnosis are useful to properly stage the patient and can assess adenopathy, splenomegaly, and other extramedullary disease sites in patients who are symptomatic.

Patients with WM and peripheral neuropathy may harbor antibodies against myelin-associated glycoprotein (MAG) or other glycoproteins or lipids.^{8, 11} Testing for serum auto-antibodies to MAG and ganglioside M1 (GM1) can be considered, as well as a fat pad biopsy and/or congo red staining of the bone marrow to evaluate for the presence of amyloid in patients with peripheral neuropathy. Referral for neurologic consultation should be considered for these patients. Electromyography may be helpful in determining the type of neuropathy.

Waldenström's macroglobulinemia patients, particularly those with cryoglobulinemia, have been associated with underlying hepatitis C; therefore, liver function tests and hepatitis C serology should be obtained as well.¹²⁻¹⁴ The U.S. FDA recommends that patients at high risk of hepatitis B infection be screened before initiation of rituximab therapy. Hepatitis B carriers should be closely monitored for clinical and laboratory signs and symptoms of active hepatitis B virus infection during rituximab therapy and for several months following therapy.

Primary Treatment

According to the NCCN WM/LPL Panel, treatment should be initiated for patients with a diagnosis of WM/LPL only in those who are symptomatic. The indicative symptoms for treatment include hyperviscosity; neuropathy; symptomatic adenopathy or organomegaly; amyloidosis; cryoglobulinemia; cold agglutinin disease; and presence of cytopenia.⁹

Treatment of WM is discussed in detail in several reviews.^{8, 15} For patients requiring immediate disease control, such as those with symptomatic hyperviscosity, initial plasmapheresis is recommended. After plasmapheresis, treatment should be initiated as soon as possible. The primary treatment options include oral alkylators (eg, chlorambucil); nucleoside analogs (cladribine or fludarabine); rituximab as single agent; or rituximab in combination with cyclophosphamide, bortezomib, nucleoside analogues, thalidomide, or bendamustine.

Exposure to continuous oral alkylator therapy or nucleoside analogs should be avoided if a stem cell transplant is being considered. Nucleoside analogs are associated with increased risk of disease transformation, myelodysplasia, and acute myelogenous leukemia.¹⁶

Primary Treatment Regimens Not Toxic to Stem Cells

Rituximab, a monoclonal antibody that targets the B-lymphocyte antigen CD20, has been used successfully in the treatment of WM, because CD20 is expressed on lymphoplasmacytic cells in WM patients. Single agent rituximab is active in patients with WM; however, the response rates to single agent rituximab utilizing either standard or extended dosing vary between 25% and 45%.¹⁷⁻¹⁹ Transient increases in IgM titers (also called the IgM flare) have been reported in 40-50% of patients after initiation of rituximab therapy, including in circumstances when rituximab has been used in combination therapy.^{20, 21} The



rituximab related IgM flare may lead to symptomatic hyperviscosity, as well as worsening of IgM-related neuropathy, cryoglobulinemia, and other IgM-related complications. These levels may persist for months and do not indicate treatment failure, but may necessitate plasmapheresis to reduce hyperviscosity. Prophylactic plasmapheresis can be considered in patients with high IgM levels (typically 5,000 mg/dL or higher) prior to rituximab exposure to minimize risk of symptomatic hyperviscosity. The risk of IgM flare may be decreased in patients receiving rituximab in combination therapy with bortezomib and dexamethasone.²² Rituximab may be regarded as a reasonable choice for treating patients with IgM anti-MAG antibody-related neuropathies.²³

Bortezomib has shown to have high levels of activity in the management of WM as single agent,²⁴ in combination with rituximab,²⁵ or in combination with rituximab and dexamethasone,^{22, 26}

In a phase II study, bortezomib was administered to 27 WM patients, 44% of whom were previously untreated and 56% were previously treated.²⁴ Bortezomib was administered using the standard schedule until the patients demonstrated progressive disease or were two cycles beyond best response.²⁴ The overall response rate in this study was 78%, with major responses observed in 44% of patients. Sensory neuropathy occurred in 20 patients after two to four cycles of therapy. Among the 20 patients who developed a neuropathy, it resolved in 14 patients and improved by one grade in one patient at 2 to 13 months.

A phase II study of weekly bortezomib plus rituximab in newly diagnosed patients with WM reported an overall response rate of 88%, including a major response in 65% of patients. The estimated 1 year progression free survival in this study was 79%.²⁵

Rituximab in combination with corticosteroids and bortezomib has been studied and found to be active in WM patients. The study by Waldenström's Macroglobulinemia Clinical Trials Group (WMCTG), reported an overall response rate of 96%, including 83% achieving partial response with the combination of bortezomib (using a twice-a-week schedule) along with rituximab and dexamethasone in newly diagnosed patients with WM.²² With a median follow-up of 2 years, 80% of patients remained free of disease progression, including all patients achieving a very good partial response or better. Grade 3 peripheral neuropathy was observed in 30% of patients in the study that utilized twice-a-week bortezomib administration. For rituximab intolerant individuals, bortezomib with dexamethasone can be considered as an alternate option.

Sensory neuropathy is a primary toxicity observed with bortezomib-based regimens. Therefore, evaluation of patients for the development of bortezomib-related peripheral or autonomic neuropathy is important. To avoid reactivation of herpes zoster, prophylaxis against herpes zoster is recommended.

An alternative to bortezomib-containing therapy is a cyclophosphamide-based regimen along with rituximab and a corticosteroid. A study by Dimopoulos et al reported that the combination of rituximab, cyclophosphamide, dexamethasone (R-CD) induces overall and complete responses in 78% and 7% of WM patients, respectively.²⁷ The 2-year progression-free survival in responders was found to be 80%. The R-CD regimen was well tolerated, with 9% of patients experiencing grade 3 or 4 neutropenia and approximately 20% of patients experiencing some form of toxicity related to rituximab.

Cyclophosphamide, doxorubicin, vincristine, prednisone plus rituximab (CHOP-R) is a stem cell sparing regimen reported to be active and

tolerated by WM patients.²⁸⁻³¹ It has been reported as having at least a 90% response rate in patients with WM.^{28, 31, 32} In a randomized study involving 69 patients, most of whom had WM, the addition of rituximab to CHOP resulted in a higher overall response rate (94% versus 67%) and median time to progression (63 versus 22 months) in comparison to patients treated with CHOP alone.³¹ A retrospective study examined the outcomes of symptomatic WM patients who received CHOP-R, cyclophosphamide, vincristine, prednisone plus rituximab (CVP-R) or CP-R.²⁸ Baseline characteristics for all 3 cohorts were similar for age, prior therapies, bone marrow involvement, hematocrit, platelet count, and serum beta-2 microglobulin, though serum IgM levels were higher in patients treated with CHOP-R. The overall response rates to therapy were comparable among all three treatment groups: CHOP-R (96%); CVP-R (88%); and CP-R (95%). The addition of vincristine to cyclophosphamide containing regimens is associated with risk of neuropathy in WM patients.²² Treatment-related adverse effects including neuropathy from vincristine, febrile neutropenia, and hospitalization were higher in patients treated with CHOP-R and CVP-R compared to CP-R.²⁸

The use of thalidomide in combination with rituximab represents an alternative choice non-toxic to stem cells in the management of WM patients. This regimen is associated with an overall response rate of 70%, and a median progression-free survival of 3 years.³³ Lower start doses of thalidomide (i.e. 50-100 mg per day) may decrease risk of neuropathy in WM patients. Lenalidomide may lead to abrupt declines in hematocrit in WM patients and should be avoided.³⁴

Based on the above data, the suggested primary treatment regimens which are stem cell sparing listed in the NCCN Guidelines for WM/LPL include: rituximab single agent; R-CD; CP-R; CHOP-R; bortezomib and rituximab; thalidomide and rituximab; bortezomib, dexamethasone, and

rituximab; and bortezomib and dexamethasone.^{17-19, 22, 25, 27-31} Response rates of 70-90% have been reported with rituximab based combination therapies.^{13, 14}

Primary Treatment Regimens with Potential or Unknown Toxicity to Stem Cells

Nucleoside analogues such as cladribine and fludarabine, alone or in combination with rituximab and/or cyclophosphamide, have been studied in previously untreated WM and found to induce good overall response rates with prolonged survivals.³⁵⁻⁴⁰ However, nucleoside analogues can cause immunosuppressive complications.⁴¹ In addition, there are reports indicating that nucleoside analogs increase incidence of disease transformation and development of myelodysplastic syndromes and secondary acute myelogenous leukemia in WM patients treated with nucleoside analog-containing therapy.¹⁷ Exposure to nucleoside analogs should therefore be limited, particularly in younger patients who may be potential stem cell candidates.

The alkylating agent, chlorambucil as a single agent has shown response rates varying between 31% and 92%.⁴² Chlorambucil treatment also carries with it long term complications such as myelodysplasia and acute leukemia from therapy-induced chromosomal breakage.⁴³ In addition, chlorambucil may cause stem cell damage. Although chlorambucil is a treatment that has proven efficacy in WM, due to the availability of newer combination therapies, it is now reserved for patients with limited therapeutic options.

In a multicenter, prospective clinical, 43 patients with WM who were previously untreated or pretreated with chemotherapy were treated with fludarabine, cyclophosphamide, and rituximab (FCR) regimen.⁴⁰ Most of patients in this study (65%) received FCR as first-line treatment, 28% of patients were in relapse, and 7% had disease that was refractory to a

previous line of treatment. The results demonstrate that FCR produces rapid responses (OR rate of 79%), with high rates of complete response and very good partial response. However the potential risk of secondary malignancies and rate of myelosuppression with FCR regimen was high.

The Study Group for Lymphomas (Stil) recently examined the activity of bendamustine plus rituximab (BR) versus CHOP-R in a large cohort of previously untreated patients with indolent non-Hodgkin's lymphoma.⁴⁴ Included in this study were 42 patients with WM/LPL, 40 of whom were available for response assessment.⁴⁵ The overall response rate with BR in this study was similar to CHOP-R (96% versus 94%, respectively). With a median follow-up of 26 months, progressive disease was documented in 2 of 23 patients treated with BR, while 7 of 17 patients treated with CHOP-R progressed. BR was associated with a lower incidence of grade 3 or 4 neutropenia, infectious complications, and alopecia in this study. These results suggest that BR may be a preferable option to CHOP-R in the frontline therapy of WM.

Based on the above data, primary treatment regimens potentially toxic to stem cells listed in the NCCN Guidelines include: nucleoside analogues (claridribine or fludarabine) alone or with rituximab and/or cyclophosphamide; chlorambucil; bendamustine alone or in combination with rituximab.

Follow-up after Primary Treatment

Assessment of Response

Consensus-based uniform response criteria for WM have been developed by the International Workshops on WM.^{15, 46} Response to therapy in WM is defined by reduction in the M protein. According to the updated summary of response categories from the sixth International

Workshop on WM, a minor response is an M-spike reduction of at least 25%; a partial response is defined as greater than or equal to 50% reduction in M protein; a very good partial response is greater than or equal 90% reduction in M protein; and a complete response is immunofixation negativity in the serum. Stable disease is defined as a less than 25% reduction and less than 25% increase of serum IgM without progression of adenopathy/organomegaly, cytopenias, or clinically significant symptoms due to disease and/or signs of WM. Progressive disease is defined as a 25% increase in serum IgM by protein. confirmed by a second measurement.

An important concern with the use of IgM as a surrogate marker of disease is that it can fluctuate independent of tumor cell killing, particularly with newer biologically targeted agents such as rituximab, bortezomib, and everolimus. Rituximab induces a spike or flare in serum IgM levels which can occur when used as monotherapy and in combination with other agents including cyclophosphamide, nucleoside analogues, and thalidomide, and lasts for several weeks to months.^{8, 20, 21} On the other hand, bortezomib and everolimus can suppress IgM levels independent of killing tumor cells in certain patients.⁴⁷⁻⁴⁹ The study by Varghese et al showed that residual IgM producing plasma cells are spared and continue to persist in patients treated with selective B-cell depleting agents such as rituximab and alemtuzumab, thus potentially skewing the relative response and assessment to treatment.⁵⁰ Therefore, in circumstances where the serum IgM levels appear to be out of context with the clinical progress of the patient, a bone marrow biopsy should be considered in order to clarify the patient's underlying disease burden.

The updated summary of response categories and criteria from the sixth International Workshop on WM⁵¹ have been included in the NCCN Guidelines (see Table 1 in the algorithms). After primary therapy, the

NCCN panel recommends assessing the response to treatment using consensus panel criteria outlined in Table 1. Subsequent management options for patients with WM/LPL outlined in the NCCN Guidelines are based on the response assessment after therapy.

For patients showing a response to primary treatment, the follow-up options could include either observation until the disease progresses or the use of maintenance rituximab therapy.⁵²

For those patients who do not show any response to primary therapy or if symptoms persist, an alternate regimen may be used.

Treatment of IgM related Peripheral Neuropathy

The treatment of IgM related neuropathy may involve initially a course of plasmapheresis, particularly in patients with more aggressive course of progressing peripheral neuropathy attributed to the IgM paraprotein. Typically a course of 2-3 months of weekly plasmapheresis may be required before any impact on symptomatic neuropathy may be seen. Plasmapheresis, however, should not be used as a permanent modality, and consolidation with chemotherapy considered. Post-plasmapheresis, IgM levels will return to baseline in 4-6 weeks.

Chemotherapy with rituximab is commonly used, with improvements in sensory function accompanying reduction in anti-neuronal antibody titers observed in several studies, including a placebo controlled trial. The use of single agent rituximab can be considered as the first intervention in patients with mild, slowly progressive neuropathy. In patients with moderate to severe IgM related neuropathy or where the course of the IgM neuropathy appears aggressive, the use of CP-R or R-CD may be preferable in order to achieve more robust paraprotein reductions. Patients who experience a rituximab related flare may also have a flare in their IgM related neuropathic symptoms. While patients

are undergoing plasmapheresis, or are on therapy, treatment directed at symptomatic improvement can also be considered with gabapentin, pre-gabapentin, and duloxetine.⁵³⁻⁵⁵

Maintenance Therapy

The use of maintenance rituximab was recently reported in a study which examined the outcome of 248 rituximab-naïve WM patients who responded to a rituximab-containing regimens.⁵⁶ Eighty-six patients (35%) received maintenance rituximab (M-rituximab). No differences in baseline characteristics and post-induction categorical responses between cohorts were observed. The median number of rituximab infusions during induction was 6 for both cohorts, with 8 infusions over a 2-year period for patients receiving M-rituximab. Categorical responses improved in 16/162 (10%) patients overall and 36/86 (41.8%) of M-rituximab patients respectively, following induction therapy ($P < .0001$). Both progression-free (56.3 versus 28.6 months; $P = .0001$) and overall survival (Not reached versus 116 months; $P = .0095$) were longer in patients who received M-rituximab. Improved progression-free survival was evident despite previous treatment status or induction with rituximab alone or in combination therapy ($P \leq .0001$). Best serum IgM response was lower ($P < .0001$) and haematocrit higher ($P = .001$) for patients receiving M-Rituximab.⁵⁶ An increased number of infectious events were observed among patients receiving M-rituximab, but were mainly $\leq$ grade 2 ($P = .008$). The findings of this observational study suggest improved clinical outcomes following M-rituximab in WM patients who respond to induction with a rituximab-containing regimen. A prospective study aimed at clarifying the role of M-rituximab therapy in WM patients is underway by the German STiL group.

The NCCN panel recommends considering maintenance rituximab in patients who have had either a complete response to primary therapy or in patients who are asymptomatic and achieved a partial response.

Salvage Therapy

According to the NCCN Guidelines, administering the same regimen used for primary treatment is reasonable as second-line or salvage therapy for relapsed disease if a patient achieved a response that lasted for at least 12 months or more; otherwise, use of an alternate single agent or combination is recommended.

For patients with remissions lasting less than 12 months or who show progressive disease/resistance to a first-line regimen, second-line treatment may include agents of a different class of drugs, either alone or in combination. Also, it is important to avoid exposure to stem cell damaging agents, such as alkylators or nucleoside analogs, in patients who are candidates for autologous stem cell transplantation; regimens that are not toxic to stem cells must be offered, especially if stem cells have not previously been harvested. All regimens listed under primary treatment options are effective options for salvage therapy.

The use of bortezomib as salvage therapy is associated with an overall response rate of 60% when administered as single agent, and 70-80% in combination with rituximab^{24, 47, 48, 57, 58, 59} with or without dexamethasone.⁶⁰ Grade 3 peripheral neuropathy may occur in 30% patients using the twice-a-week dosing schedule of bortezomib and 10% in those patients receiving once-a-week dosing. Therefore, evaluation of patients for the development of bortezomib-related peripheral or autonomic neuropathy is important. Prophylaxis against herpes zoster should be strongly considered with bortezomib and steroid combinations.

Bendamustine-based therapy is effective in relapsed/refractory WM since it produces high response rates and durable responses both as monotherapy and in combination with rituximab. A phase II study of previously treated WM patients who received bendamustine-based therapy reported overall response rate of 83.3%.⁶¹ The median PFS in a mostly refractory population of WM/LPL patients was 13.2 months.⁶¹

In addition, the NCCN Panel has included newer agents as salvage therapy options such as everolimus,^{62, 63} alemtuzumab,⁶⁴⁻⁶⁶ and ofatumumab for rituximab-intolerant patients, either as single agent⁶⁷ or in combination therapy.⁶¹

Everolimus, an inhibitor on mTOR, is a potentially effective drug in WM with high single-agent activity and manageable toxicity and therefore offers a new therapeutic strategy for patient with relapsed/refractory WM. Preclinical data show increased activity of the mTOR pathway in WM and significant cytotoxicity seen in WM cell lines in response to the mTOR inhibitor. Based on these studies, a phase II trial of single-agent everolimus was initiated in 50 patients with relapsed or relapsed/refractory WM.⁶³ In this study, the overall response rate to everolimus measured by paraprotein reduction alone was 70%. The estimated PFS at 6 and 12 months was 75% and 62%, respectively. Common toxicities reported were mostly hematological with cytopenias. Pulmonary toxicity was reported in 10% of patients. Discordance between serum IgM levels and underlying bone marrow disease burden is common in WM patients treated with everolimus, and clinicians should consider repeating a bone marrow biopsy when clinically indicated to assess treatment response.⁴⁹

Alemtuzumab is a fully humanized human IgG1 monoclonal antibody that targets CD52 and has established efficacy in the treatment of other lymphomas.^{68, 69} In patients with WM, CD52 is widely expressed on



lymphoplasmacytic cells in the bone marrow.⁷⁰ High response rates with alemtuzumab have been reported in another series of heavily pretreated WM patients.⁶⁵ In a multicenter phase II study, the activity of alemtuzumab was examined in 28 symptomatic LPL/WM patients.⁶⁶ Twenty-three of these patients were previously treated. The overall response rate in this study was 76%, with major responses in 32% of patients, and the median time to progression was 14.5 months. Hematologic and infectious complications, including CMV reactivation, were more common in previously treated patients and were indirectly associated with 3 deaths. Long-term follow-up revealed late-onset autoimmune thrombocytopenia (AITP) in 4 patients which contributed to 1 death.

Stem cell transplantation (SCT) is also an option for the salvage therapy of WM in selected patients.⁷¹ SCT options listed in the NCCN Guidelines for WM/LPL are for high dose therapy with autologous stem cell rescue. The use of myeloablative or non-myeloablative allogeneic SCT should preferably be considered in the context of a clinical trial.

Management of Patients intolerant to Rituximab

Ofatumumab is a human monoclonal antibody (IgG1) that binds specifically to a distinct epitope encompassing both the small and large extracellular loops of the CD20 molecule.^{72, 73} In cells expressing low levels of CD20 it induces complement-dependent cytotoxicity in vitro, that is more potent compared with rituximab.^{74, 72} Two studies recently addressed the role of ofatumumab in patients with WM, including patients who were intolerant to rituximab.^{61, 67} These studies demonstrated that ofatumumab could be successfully administered, either as single agent or as combination therapy, in patients with WM who were intolerant to rituximab, and were associated with responses. Therefore, according to the NCCN Panel ofatumumab may be considered in rituximab intolerant patients, either as single agent or as

combination therapy. There is a risk of IgM flare with ofatumumab, as with rituximab; therefore, similar precautions as with rituximab should be considered when using ofatumumab in those patients who have evidence of hyperviscosity or who have elevated IgM levels.

All WM/LPL treatment options are listed alphabetically in the NCCN Guidelines and do not indicate or imply preference. The NCCN panel members strongly encourage treatment in the context of clinical trial when possible.

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