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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Waldenström's Macroglobulinemia / Lymphoplasmacytic Lymphoma

Version 1.2017— January 31, 2017

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Waldenström’s Macroglobulinemia/ Lymphoplasmacytic Lymphoma

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Clinical Trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

To find clinical trials online at NCCN Member Institutions, [click here: nccn.org/clinical_trials/physician.html](#).

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 1.2017 Updates

Waldenström's Macroglobulinemia/ Lymphoplasmacytic Lymphoma

Updates in Version 1.2017 of the NCCN Guidelines for Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma from Version 2.2016 include:

[WM/LPL-1](#)

- **Diagnosis, modified the second bullet "Adequate *tissue biopsy* for immunophenotyping to establish diagnosis."**
- **Workup, essential:**
 - ▶ **Clarified chest/abdominal/pelvic CT is done "with contrast when possible."**
 - ▶ **Added "CXCR4 gene testing for patients being considered for ibrutinib" with a footnote.**
 - ◊ **The new footnote states "Studies have shown that mutations in this gene are found in up to 40% of patients with WM/LPL and can impact ibrutinib response."**
 - ▶ **Added a new bullet "Consider coagulation testing if symptoms present (excess bruising or bleeding) or as a part of workup in the preoperative testing.**
 - ◊ **Added "von Willebrand disease (WVD) testing only if clinical bleeding, bruising is present"**

[WM/LPL-2](#)

- **Added a column heading for "Response."**
- **Modified footnote "i" "Plasmapheresis should be performed for patients with symptomatic hyperviscosity, and before treatment with rituximab-containing regimen in patients with IgM \geq 5000 mg/dL. IgM should be monitored closely in these patients thereafter and plasmapheresis should be considered again if symptomatic hyperviscosity occurs or if IgM \geq 4000 mg/dL while on rituximab-containing therapy. *RBC transfusion, if indicated, should be done after plasmapheresis to prevent added hyperviscosity load.*"**
- **Footnote "k" added "Response assessment may include CT scan with contrast. [See Response Criteria for WM/LPL \(WM/LPL-C\)](#)"**
- **Changed relapse from <12 mo to <24 mo prior to "Choose an alternative therapy."**
- **Changed relapse from \geq 12 mo to \geq 24 mo prior to "May use previous treatment or consider alternative therapy."**

[WM/LPL-B \(2 of 2\)](#)

- **Updated reference: Treon SP. How I treat Waldenstrom macroglobulinemia. *Blood* 2015;126:721-732.**

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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 tissue biopsy for 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 with contrast when possible
- MYD88, L265P AS-PCR testing of bone marrow^d
- CXCR4 testing for patients being considered for ibrutinib^e

Useful in certain circumstances

- Hepatitis C testing^f
- Hepatitis B testing, if rituximab planned
- Cryocrit^{f,9}
- Consider coagulation testing if symptoms present (excess bruising or bleeding) or as a part of workup in the preoperative testing
 - ▶ von Willebrand disease (WVD) testing only if clinical bleeding, bruising is present
- Cold agglutinins
- Neurology consult^h
- Anti-MAG antibodies/anti-GM1^h
- Electromyogram^h
- Fat pad biopsy and/or congo red staining of bone marrow for amyloid^h
- 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 \(WM/LPL-2\)](#)

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

^bLymphoplasmacytic lymphoma (LPL) does encompass IgG, IgA, and non-secretory subtypes though makes up <5% of all LPLs. The treatment of 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.

^dNon-L265P MYD88 mutations can rarely be found in patients with Waldenström's macroglobulinemia. Consider Sanger sequencing to establish MYD88 status

if MYD88 L265P mutation is not detected in an adequate tumor-containing sample. Treon SP, Xu L, Henter ZR. MYD88 mutations and ibrutinib responses in Waldenström's macroglobulinemia. N Engl J Med 2015;373(6):584-6.

^eStudies have shown that mutations in this gene are found in up to 40% of patients with WM/LPL and can impact ibrutinib response.

^fConsider in patients with suspected cryoglobulinemia.

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

^hIn patients presenting with suspected disease related to peripheral neuropathy.

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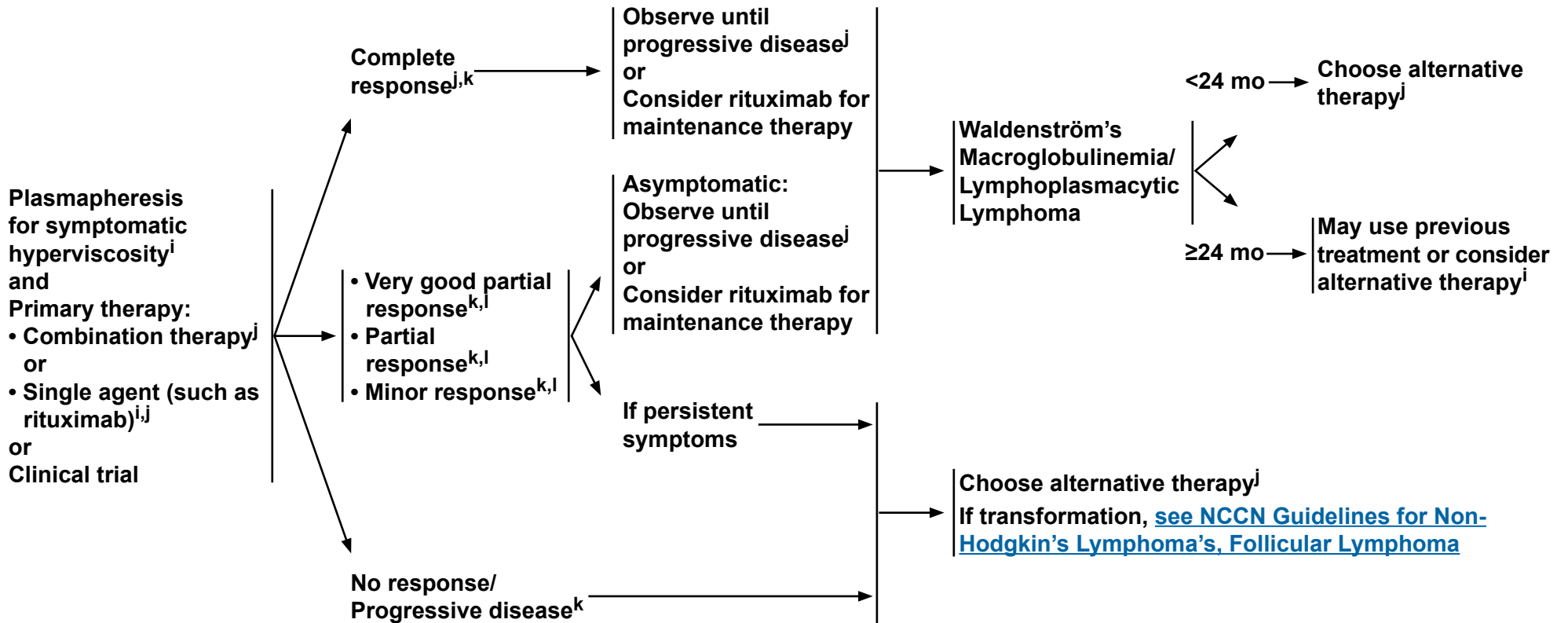
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Waldenström's Macroglobulinemia/ Lymphoplasmacytic Lymphoma

PRIMARY TREATMENT

RESPONSE^k

RELAPSE



ⁱPlasmapheresis 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 should be considered again if symptomatic hyperviscosity occurs or if IgM is ≥4000 mg/dL while on rituximab-containing therapy. RBC transfusion, if indicated, should be done after plasmapheresis to prevent added hyperviscosity load.

^jSee [Suggested Treatment Regimens \(WM/LPL-B\)](#).

^kResponse assessment may include CT scan with contrast. See [Response Criteria for WM/LPL \(WM/LPL-C\)](#).

^lIntent of therapy should be based on palliation of symptoms, not necessarily levels of IgM unless the patient is exhibiting evidence of symptomatic hyperviscosity.

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Waldenström's Macroglobulinemia/ Lymphoplasmacytic Lymphoma

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.

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

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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}
- Carfilzomib/rituximab/dexamethasone^{1,3,5}
- Cyclophosphamide/doxorubicin/vincristine/prednisone/rituximab^{1,4,6}
- Ibrutinib⁷
- 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^{1,3,8,9}
- Chlorambucil^{7,8}
- Fludarabine ± rituximab^{1,3,8,9}
- Fludarabine/cyclophosphamide/rituximab^{1,3,8,9}

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 $\geq 4,000$ 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 should be considered for patients receiving these regimens.

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

⁵Serial serum IgA and IgG levels should be carefully monitored as these can be depleted with carfilzomib-based therapy.

⁶Vincristine is associated with a high risk of peripheral neuropathy in patients with WM/LPL. Consider alternative regimens without vincristine (eg, cyclophosphamide, dexamethasone, rituximab) if cyclophosphamide-based therapy is being considered.

⁷Lower overall and absence of major responses observed in MYD88 wild-type patients. Treon SP, Xu L, Henter ZR. MYD88 mutations and ibrutinib responses in Waldenström's macroglobulinemia. N Engl J Med 2015;373(6):584-6.

Previously Treated WM/LPL:

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^{1,4,6}
- Everolimus
- Ibrutinib
- Ofatumumab (for rituximab-intolerant individuals)^{1,10}
- 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^{1,3,8,9}
- Chlorambucil^{8,9}
- Fludarabine ± rituximab^{1,3,8,9}
- Fludarabine/cyclophosphamide/rituximab^{1,3,8,9}

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 nonablative)¹¹

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

⁸May be associated with disease transformation and/or development of MDS/AML in Waldenström's macroglobulinemia patients.

⁹Avoid in patients who are potential autologous stem cell transplant candidates.

¹⁰Ofatumumab may be used for rituximab-intolerant individuals as a single agent or in combination therapy.

¹¹Should ideally be undertaken in the context of a clinical trial.

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Waldenström's Macroglobulinemia/ Lymphoplasmacytic Lymphoma

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

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**NCCN Guidelines Version 1.2017**
**Waldenström's Macroglobulinemia/
Lymphoplasmacytic Lymphoma****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, and thalidomide, and can 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 Response³	CR	IgM in normal range, and disappearance of monoclonal protein by immunofixation; no histologic 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 Disease³	PD	A ≥25% increase in serum IgM by protein confirmed by a second measurement or progression of clinically significant findings due to disease (ie, 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, et al. Report from the Sixth International Workshop on Waldenström's Macroglobulinemia. Clin Lymph Myeloma Leukemia 2011;11:69-73.²Varghese AM, et al. Assessment of bone marrow response in Waldenström's macroglobulinemia. Clin Lymph Myeloma 2009;9:53-5.³Require two consecutive assessments made at any time before the institution of any new therapy.**Note: All recommendations are category 2A unless otherwise indicated.****Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**

Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 09/16/2015

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.

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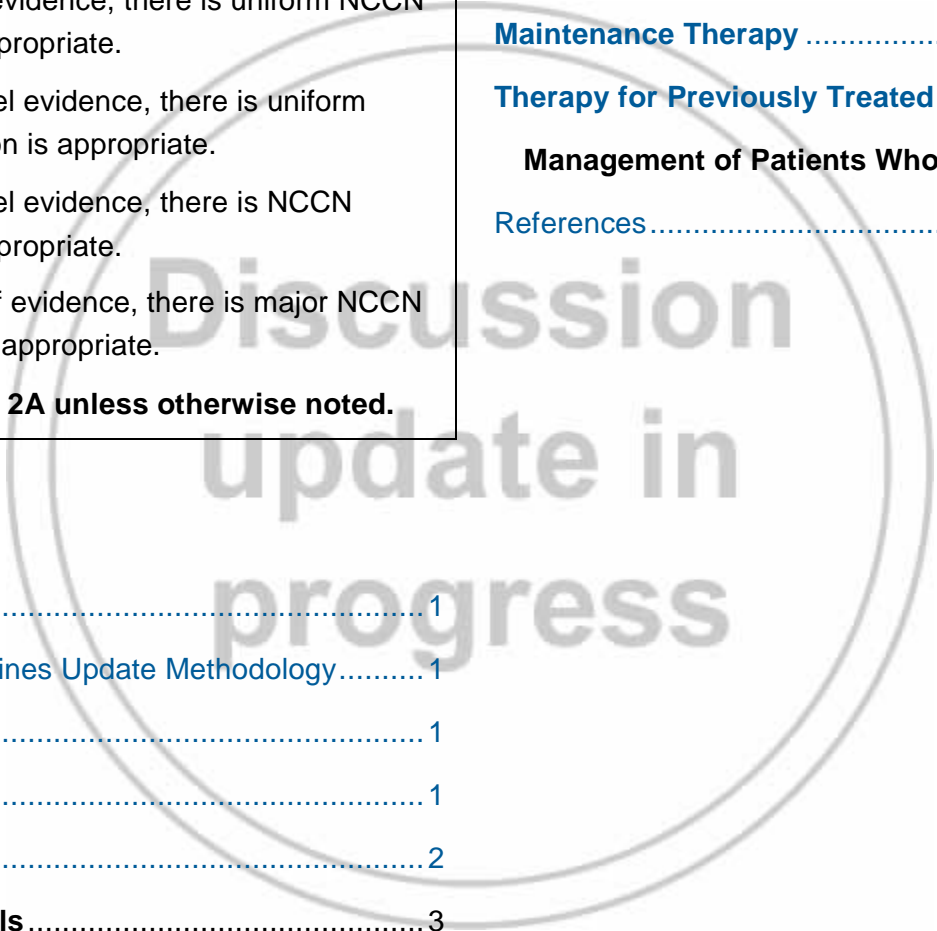
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Overview

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 WHO classification systems.^{2,3}

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for Waldenström's Macroglobulinemia, an electronic search of the PubMed database was performed to obtain key literature in WM/LPL published between 4/08/14 and 04/14/15, using the following search terms: Waldenström's macroglobulinemia OR lymphoplasmacytic lymphoma. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.⁴

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Practice Guideline; Randomized Controlled Trial; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 16 citations and their potential relevance was examined. The data from key PubMed articles as well as articles from additional sources deemed as relevant to these Guidelines have been included in this version of the Discussion section. Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN [webpage](#).

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% to 20% of cases may express CD5, CD10, or CD23.^{5,6}

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, quantitative immunoglobulins, and immunofixation are used to identify and quantify the M-protein (IgM).

Immunoglobulin M is a pentamer and a common cause of hyperviscosity. Therefore, evaluation of characteristic clinical signs and symptoms of serum viscosity should be done at the time of diagnosis. Most patients with WM 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 that may necessitate

intervention.⁷ The serum IgM should be obtained under warm bath conditions for those patients suspected to have cryoglobulinemia.

In about less than 10% of patients with WM, monoclonal IgM may present with cold agglutinin activity.⁸ This means that the monoclonal IgM 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 patients with WM, 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.⁹

Beta-2 microglobulin and the WM International Prognostic Scoring System are useful in prognostication of WM.^{10,11} Their use in making treatment-related decisions remains to be clarified.¹⁰

Bone marrow is almost always involved in WM; therefore, a unilateral bone marrow aspirate and biopsy are done to confirm excess lymphoplasmacytoid cells. CT 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.^{9,12} Testing for serum auto-antibodies to MAG and ganglioside M1 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. Retinal examination should be done if hyperviscosity is suspected or IgM levels are greater than or equal to 3.0 g/dL.¹³

Whole genome sequencing of bone marrow LPL cells has identified MYD88 (L265P) as a commonly recurring mutation in patients with WM.¹⁴⁻¹⁶ MYD88 (L265P) mutations are present in greater than 90% of patients with WM.¹⁴ The NCCN Panel recommends allele-specific polymerase chain reaction (AS-PCR) for MYD88 (L265P) as an essential test in differentiating WM from non-IgM LPL, B-cell lymphomas, and plasma cell myeloma. If MYD88 (L265P) mutation is not detected by AS-PCR in an adequate tumor-containing sample, the NCCN Panel recommends considering the Sanger sequencing to establish MYD88 status, since non-L265P MYD88 mutations can rarely be found in patients with WM.¹⁷

Patients with WM, particularly those with cryoglobulinemia, have been associated with underlying hepatitis C; therefore, liver function tests and hepatitis C serology should be obtained as well.¹⁸⁻²⁰ The U.S. Food and Drug Administration (FDA) recommends that patients at high risk for 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 Regimens

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 of treatment include hyperviscosity; neuropathy; symptomatic adenopathy or organomegaly; amyloidosis; cryoglobulinemia; cold agglutinin disease; and presence of cytopenia.¹⁰

Treatment of WM is discussed in detail in several reviews.^{9,21} According to the NCCN Panel, 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 chemotherapy options include oral alkylator (eg, chlorambucil); nucleoside analogs (cladribine or fludarabine); rituximab as single agent; or rituximab in combination with cyclophosphamide, bortezomib, nucleoside analogues, thalidomide, or bendamustine.

Agents that limit future treatment options should be avoided during initial therapy. Exposure to continuous oral alkylator therapy or nucleoside analogs should be avoided if a stem cell transplant (SCT) is being considered. Nucleoside analogs are associated with increased risk of disease transformation, myelodysplasia, and acute myelogenous leukemia.²²

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 patients with WM. Single-agent rituximab is active in patients with WM; however, the response rates of single-agent rituximab utilizing either standard or extended dosing vary between 25% and 45%.²³⁻²⁵ Transient increases in IgM titers (also called the IgM flare) have been reported in 40% to 50% of patients after initiation of rituximab therapy, including in circumstances where rituximab has been used in combination therapy.^{26,27} 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 4,000 mg/dL or higher)²⁸ before 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.²⁹ Rituximab may be regarded as a reasonable choice for treating patients with IgM anti-MAG antibody-related neuropathies.³⁰

Bortezomib has shown to have high levels of activity in the management of WM as a single agent,³¹ in combination with rituximab,³² or in combination with rituximab and dexamethasone.^{29,33}

In a phase II study, bortezomib was administered to 27 patients with WM, 44% of whom were previously untreated and 56% of whom were previously treated.³¹ Bortezomib was administered using the standard schedule until the patients demonstrated progressive disease or were two cycles beyond best response.³¹ 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 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 (PFS) in this study was 79%.³²

Rituximab in combination with corticosteroids and bortezomib has been studied and found to be active in patients with WM. The study by Waldenström's Macroglobulinemia Clinical Trials Group (WMCTG)

reported an overall response rate of 96%, including 83% achieving partial response (PR) with the combination of bortezomib (using a twice-a-week schedule), along with rituximab and dexamethasone in newly diagnosed patients with WM.²⁹ 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 (VGPR) or better. Grade 3 peripheral neuropathy was observed in 30% of patients in the study that utilized twice-a-week bortezomib administration.

In another multicenter phase II trial, the activity of a bortezomib/dexamethasone/rituximab regimen, with weekly administration of bortezomib, was evaluated in 59 newly diagnosed symptomatic patients with WM.³⁴ The overall response rate was 85% (3% complete response [CR], 7% VGPR, and 58% PR). In 11% of patients, an increase of IgM ($\geq 25\%$) was observed after administration of rituximab. After 32 months of follow-up, median PFS was 42 months and a 3-year survival was seen in 81% of patients. Peripheral neuropathy was observed in 46% (grade ≥ 3 in 7%) of patients; 8% discontinued bortezomib due to neuropathy.³⁴

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, the NCCN Panel recommends prophylaxis against herpes zoster. For patients who are intolerant to rituximab, bortezomib with dexamethasone can be considered as an alternate option.

As a neuropathy-sparing treatment option, a recent prospective phase II study examined the carfilzomib, rituximab, and dexamethasone (CaRD) regimen in newly diagnosed symptomatic patients with WM/LPL.³⁵ The study enrolled a total of 31 patients and reported an

overall response rate of 87.1% (35% achieved VGPR/CR).³⁵ The response rate seen in this study is comparable to the response rate seen in studies using bortezomib-based regimens that showed an overall response rate of 85% to 96%.^{29,34} The study also found that the response to this regimen was not impacted by MYD88 (L265P) mutation status. Rituximab-associated IgM flare (increase of IgM $\geq 25\%$) was observed in 22.7% of patients. With a median follow-up of 15.4 months, 64% remained progression-free. Treatment-related toxicities (grade >2) reported in the study included asymptomatic hyperlipasemia (41.9%), reversible neutropenia (12.9%), and cardiomyopathy in one patient (3.2%). IgA and IgG depletion was commonly observed and necessitated truncation of therapy and/or intravenous immunoglobulin use in several patients.³⁵ No significant peripheral neuropathy was observed in this study. Another 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 an overall response and CR in 78% and 7% of patients with WM, respectively.³⁶ The 2-year PFS 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 patients with WM.³⁷⁻⁴⁰ It has been reported as having at least a 90% response rate in patients with WM.^{37,40,41} 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% vs. 67%) and median time to progression (63 vs. 22 months) in comparison

to patients treated with CHOP alone.⁴⁰ A retrospective study examined the outcomes of patients with symptomatic WM who received CHOP-R; cyclophosphamide, vincristine, prednisone plus rituximab (CVP-R); or cyclophosphamide, prednisone plus rituximab (CP-R).³⁷ 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 patients with WM.²⁹ 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.³⁷

The use of thalidomide in combination with rituximab represents an alternative choice non-toxic to stem cells in the management of patients with WM. This regimen is associated with an overall response rate of 70% and a median PFS of 3 years.⁴² Lower start doses of thalidomide (ie, 50–100 mg/d) may decrease risk of neuropathy in patients with WM. Lenalidomide may lead to abrupt declines in hematocrit in these patients and should be avoided.⁴³

Based on the above data, the suggested primary treatment regimens that 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; CaRD; thalidomide and rituximab; bortezomib, dexamethasone, and rituximab; and bortezomib and dexamethasone^{23-25,29,32,36-40} 35 Response rates of 70% to 90% have been reported with rituximab-based combination therapies.^{19,20}

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.⁴⁴⁻⁴⁹ However, nucleoside analogues can cause immunosuppressive complications.⁵⁰ 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 patients with WM treated with nucleoside analog-containing therapy.²³ 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%.⁵¹ Chlorambucil treatment also carries with it long-term complications such as myelodysplasia and acute leukemia from therapy-induced chromosomal breakage.⁵² 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.

A recent phase III trial showed that monotherapy with fludarabine was more effective than chlorambucil in terms of PFS (36.3 vs. 27.1 months; $P = .012$), duration of response (38.3 vs. 19.9 months; $P < .001$), and overall survival (not reached in the fludarabine arm vs. 69.8 months [95% CI, 61.6–79.8 months; $P = .014$] in the chlorambucil arm).⁵³

In a multicenter, prospective, clinical trial, 43 patients with WM who were previously untreated or pretreated with chemotherapy were treated with the fludarabine, cyclophosphamide, and rituximab (FCR)

regimen.⁴⁹ Most of the patients in this study (65%) received FCR as first-line treatment, 28% of patients had relapsed disease, and 7% had disease that was refractory to a previous line of treatment. The results demonstrated that FCR produces rapid response rates of 79%, with high rates of CR and VGPR. However, the potential risk for secondary malignancies and rate of myelosuppression with the FCR regimen is high.

The Study Group Indolent Lymphomas (StIL) examined the activity of bendamustine plus rituximab (BR) versus CHOP-R in a large, randomized, multicenter phase III trial of previously untreated patients with indolent non-Hodgkin's lymphoma (NHL).⁵⁴ Included in this study were 41 patients with WM/LPL, 40 of whom were available for response assessment.⁵⁵ After a median follow-up of 45 months, the median PFS was significantly longer with BR treatment, 69.5 months versus 28.5 months with CHOP-R.⁵⁶ 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.⁵⁶

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

Assessment of Response to Primary Treatment

Consensus-based uniform response criteria for WM have been developed by the International Workshops on WM.^{21,57} 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,⁵⁸ a minor response is an M-spike reduction of at

least 25%; a PR is defined as greater than or equal to 50% reduction in M protein; a VGPR is greater than or equal 90% reduction in M protein; and a CR is immunofixation negativity in the serum. Stable disease is defined as a less than 25% reduction and less than 25% increase of serum IgM by electrophoresis 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 electrophoresis confirmed by a second measurement. The updated summary of response categories and criteria from the Sixth International Workshop on WM⁵⁸ has been included in the NCCN Guidelines (see Table 1 in the algorithm).

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 that 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.^{9,26,27}

On the other hand, bortezomib and everolimus can suppress IgM levels independent of killing tumor cells in certain patients.⁵⁹⁻⁶¹ 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.⁶²

Therefore, in circumstances whereby 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.

Follow-up After Primary Treatment

After primary therapy, the NCCN Panel recommends assessing the response to treatment using consensus panel criteria outlined in the algorithm (Table 1). The goal of treatment is symptom relief and reducing the risk of organ damage. When assessing responses, it is important to recognize that with some agents, responses (reduction of M-protein) to initial therapies are often delayed and may result in underestimation of response.

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 therapy with rituximab.⁶³

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 initially involve a course of plasmapheresis, particularly in patients with a more aggressive course of progressing peripheral neuropathy attributed to the IgM paraprotein. Typically a course of 2 to 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 should be considered. Post-plasmapheresis, IgM levels will return to baseline in 4 to 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, 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. When patients are undergoing plasmapheresis, or are on therapy, treatment directed at symptomatic improvement can also be considered with gabapentin, pre-gabapentin, and duloxetine.⁶⁴⁻⁶⁶

Maintenance Therapy

The use of maintenance rituximab was recently reported in a study that examined the outcome of 248 rituximab-naïve patients with WM who responded to rituximab-containing regimens.⁶⁷ Eighty-six patients (35%) received maintenance 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 rituximab as maintenance therapy. Categorical responses improved in 16 out of 162 (10%) patients overall and 36 out of 86 (41.8%) patients receiving maintenance rituximab, respectively, following primary therapy ($P < .0001$). Both PFS (56.3 vs. 28.6 months; $P = .0001$) and overall survival (not reached vs. 116 months; $P = .0095$) were longer in patients who received rituximab as maintenance therapy. Improved PFS 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 hematocrit was higher ($P = .001$) for patients receiving rituximab as maintenance therapy.⁶⁷ An increased number of infectious events were observed among patients receiving maintenance therapy with rituximab, but were mainly less than or equal to grade 2 ($P = .008$). The findings of

this observational study suggest improved clinical outcomes following maintenance therapy with rituximab in patients with WM who respond to induction with a rituximab-containing regimen. A prospective study aimed at clarifying the role of rituximab as maintenance therapy in patients with WM is underway by the German STiL group.

The NCCN Panel recommends considering maintenance rituximab in patients who have had either a CR to primary therapy or in patients who are asymptomatic and achieved either a very good, partial, or minor response.

Therapy for Previously Treated WM

Many patients inevitably experience relapse after initial therapy and require further treatment. According to the NCCN Guidelines, administering the same regimen used for primary treatment is reasonable as 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 an alkylator or nucleoside analogs, in patients who are candidates for autologous SCT; 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 consideration in patients with previously treated WM.

The use of bortezomib as therapy for relapsed disease is associated with an overall response rate of 60% when administered as a single

agent, and of 70% to 80% when in combination with rituximab^{31,59,60,68,69,70} with or without dexamethasone.⁷¹ Grade 3 peripheral neuropathy may occur in 30% of patients using the twice-a-week dosing schedule of bortezomib and in 10% of 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 because it produces high response rates and durable responses both as monotherapy and in combination with rituximab. A phase II study of patients with relapsed/refractory WM, who received bendamustine-based therapy, reported an overall response rate of 83.3%.⁷² The median PFS in patients with refractory WM/LPL was 13.2 months.⁷²

In addition, the NCCN Panel has included newer agents as therapy options for previously treated disease such as everolimus,^{73,74} alemtuzumab,⁷⁵⁻⁷⁷ ibrutinib,^{78,79} and ofatumumab for patients who are intolerant to rituximab, either as a single agent⁸⁰ or in combination therapy.⁷²

Everolimus, an inhibitor of mTOR, is a potentially effective drug in treating WM, with high single-agent activity and manageable toxicity. It is therefore a new therapeutic strategy for patients 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 60 patients with relapsed or relapsed/refractory WM.⁷⁴ The response rate (minor response or better) was 73% with a PR rate of 50% and a minor response rate of 23%.⁸¹ The median PFS was 21 months. Grade 3- or 4-related toxicities

were reported in 67% of patients. Dose reductions due to toxicity were made in 62% of patients. The most commonly reported hematologic toxicities with everolimus treatment were cytopenias. Pulmonary toxicity was seen in 5% of patients.⁸¹ The study reported that the patients who achieved a PR responded after a median of two months of treatment. Discordance between serum IgM levels and underlying bone marrow disease burden is common in patients with WM treated with everolimus, and clinicians should consider repeating a bone marrow biopsy when clinically indicated to assess treatment response.⁶¹

Alemtuzumab is a fully humanized human IgG1 monoclonal antibody that targets CD52 and has established efficacy in the treatment of other lymphomas.^{82,83} In patients with WM, CD52 is widely expressed in lymphoplasmacytic cells in bone marrow.⁸⁴ High response rates with alemtuzumab have been reported in another series of heavily pretreated patients with WM.⁷⁶ In a multicenter phase II study, the activity of alemtuzumab was examined in 28 patients with symptomatic WM/LPL.⁷⁷ 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 in 4 patients, contributing to the death of 1 patient.

Signaling pathways from the B-cell antigen receptor and Bruton's tyrosine kinase (BTK) play a crucial role in mediating growth and survival of B-cell malignancies, including WM. In preclinical studies, ibrutinib, a small-molecule irreversible inhibitor of BTK was found to prevent the binding of MYD88 to BTK in L256P-expressing WM cells. A multicenter phase I study of ibrutinib included patients with NHL, chronic

lymphocytic leukemia (CLL), or WM who had at least one previous therapy.⁷⁸ Objective responses were observed across all histologies, including three of four patients with WM.⁷⁸

In a phase II trial, 63 patients with relapsed/refractory WM received ibrutinib until progressive disease or unacceptable toxicity.⁷⁹ The study also investigated the effect of MYD88 and CXCR4 mutations on patient outcomes. Treatment with ibrutinib decreased the median serum IgM levels from 3520 mg/dL to 880 mg/dL; the median hemoglobin levels were increased from 10.5 g/dL to 13.8 g/dL; and bone marrow involvement decreased from 60% to 25% ($P < .01$ for all comparisons). The median time to any response seen in the study was 4 weeks. The overall response rate was 90.5%, and the major response rate was 73.0%. The response rates were highest among patients with MYD88 (L265P) and those without CXCR4 mutations. Among all the patients, the estimated 2-year PFS rate was 69.1% and overall survival rate was 95.2%. Treatment-related toxic effects of grade 3 or higher included neutropenia (in 14% of patients) and thrombocytopenia (in 13% of patients), more common in heavily pretreated patients.⁷⁹

SCT is also an option for relapsed WM in selected patients.⁸⁵ SCT options listed in the NCCN Guidelines for WM/LPL are for high-dose therapy with autologous stem cell rescue. According to the NCCN Panel, myeloablative or non-myeloablative allogeneic SCT may be considered,⁸⁶ but preferably in the context of a clinical trial.

Management of Patients Who Are 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.^{87,88} In cells expressing low levels of CD20, it induces complement-dependent cytotoxicity in vitro that is more potent compared with rituximab.^{74, 87} Two studies have

addressed the role of ofatumumab in patients with WM, including patients who were intolerant to rituximab.^{72,80} These studies demonstrated that ofatumumab could be successfully administered, either as a 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 patients who are intolerant to rituximab, either as single-agent or 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 treatment options for WM/LPL 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 a clinical trial when possible.

Discussion
update in
progress

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Discussion
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