National Comprehensive Cancer Network®

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

# Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma

## NCCN Evidence Blocks™

Version 1.2020 — December 12, 2019

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# Waldenström Macroglobulinemia/ Lymphoplasmacytic Lymphoma
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‡ Hematology
Þ Internal medicine
† Medical oncology
¥ Patient advocacy
¶ Surgery/Surgical oncology
* Discussion section writing committee

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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/member_institutions.aspx.

**NCCN Categories of Evidence and Consensus:** All recommendations are category 2A unless otherwise indicated.

See NCCN Categories of Evidence and Consensus.

**NCCN Categories of Preference:** All recommendations are considered appropriate.

See NCCN Categories of Preference.

**NCCN Guidelines for Patients® available at www.nccn.org/patients**

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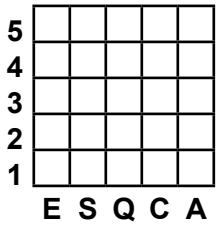
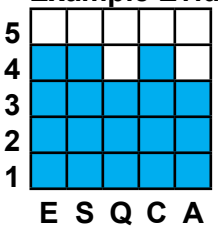
## NCCN EVIDENCE BLOCKS CATEGORIES AND DEFINITIONS




**E = Efficacy of Regimen/Agent**
**S = Safety of Regimen/Agent**
**Q = Quality of Evidence**
**C = Consistency of Evidence**
**A = Affordability of Regimen/Agent**

**Example Evidence Block**




**E = 4**
**S = 4**
**Q = 3**
**C = 4**
**A = 3**

### Efficacy of Regimen/Agent

| | |
|---|---|
| **5** | **Highly effective:** Cure likely and often provides long-term survival advantage |
| **4** | **Very effective:** Cure unlikely but sometimes provides long-term survival advantage |
| **3** | **Moderately effective:** Modest impact on survival, but often provides control of disease |
| **2** | **Minimally effective:** No, or unknown impact on survival, but sometimes provides control of disease |
| **1** | **Palliative:** Provides symptomatic benefit only |

### Safety of Regimen/Agent

| | |
|---|---|
| **5** | **Usually no meaningful toxicity:** Uncommon or minimal toxicities; no interference with activities of daily living (ADLs) |
| **4** | **Occasionally toxic:** Rare significant toxicities or low-grade toxicities only; little interference with ADLs |
| **3** | **Mildly toxic:** Mild toxicity that interferes with ADLs |
| **2** | **Moderately toxic:** Significant toxicities often occur but life threatening/fatal toxicity is uncommon; interference with ADLs is frequent |
| **1** | **Highly toxic:** Significant toxicities or life threatening/fatal toxicity occurs often; interference with ADLs is usual and severe |

**Note: For significant chronic or long-term toxicities, score decreased by 1**

### Quality of Evidence

| | |
|---|---|
| **5** | **High quality:** Multiple well-designed randomized trials and/or meta-analyses |
| **4** | **Good quality:** One or more well-designed randomized trials |
| **3** | **Average quality:** Low quality randomized trial(s) or well-designed non-randomized trial(s) |
| **2** | **Low quality:** Case reports or extensive clinical experience |
| **1** | **Poor quality:** Little or no evidence |

### Consistency of Evidence

| | |
|---|---|
| **5** | **Highly consistent:** Multiple trials with similar outcomes |
| **4** | **Mainly consistent:** Multiple trials with some variability in outcome |
| **3** | **May be consistent:** Few trials or only trials with few patients, whether randomized or not, with some variability in outcome |
| **2** | **Inconsistent:** Meaningful differences in direction of outcome between quality trials |
| **1** | **Anecdotal evidence only:** Evidence in humans based upon anecdotal experience |

### Affordability of Regimen/Agent (includes drug cost, supportive care, infusions, toxicity monitoring, management of toxicity)

| | |
|---|---|
| **5** | **Very inexpensive** |
| **4** | **Inexpensive** |
| **3** | **Moderately expensive** |
| **2** | **Expensive** |
| **1** | **Very expensive** |

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## DIAGNOSIS

**Essential[b,c]**
- 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[a]

**Essential**
- History and physical exam
- CBC, differential, platelet count
- Liver function tests (LFTs) as clinically indicated
- Peripheral blood smear
- Serum BUN/creatinine, electrolytes, albumin, calcium, serum uric acid, serum LDH, and beta-2 microglobulin
- Creatinine clearance (calculated or measured directly)
- Serum quantitative immunoglobulins, serum protein electrophoresis (SPEP), serum immunofixation electrophoresis (SIFE)
- Unilateral bone marrow aspirate and biopsy, including immunohistochemistry (IHC) and/or multi-parameter flow cytometry
- Chest/abdominal/pelvic CT with contrast when possible
- MYD88,[d] L265P AS-PCR testing of bone marrow

**Useful in Certain Circumstances**
- Serum viscosity
- CXCR4 gene mutation testing for patients being considered for ibrutinib[e]
- Hepatitis C testing[f]
- Hepatitis B testing, if rituximab planned
- Cryocrit[f,g]
- Consider coagulation testing if symptoms present (excess bruising or bleeding) or if clinically indicated
  - von Willebrand disease (VWD) testing only if clinical bleeding, bruising is present
- Cold agglutinins
- Neurology consult[h]
- Anti-MAG antibodies/anti-GM1[h]
- Nerve conduction study (NCS)/electromyogram (EMG)[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)
- 24-h urine for total protein, urine protein electrophoresis (UPEP), and urine immunofixation electrophoresis (UIFE)
- Amyloid tissue subtyping with mass spectrometry, if indicated

## INDICATIONS FOR TREATMENT

**Symptoms[i] related to:**
- Hyperviscosity
- Neuropathy
- Organomegaly
- Amyloidosis
- Cold agglutinin disease
- Cryoglobulinemia
- Anemia and other cytopenias associated with disease
- Bulky adenopathy

→ See Primary Treatment (WM/LPL-2)

[a] Frailty assessment should be considered in older adults. See NCCN Guidelines for Older Adult Oncology.
[b] See WHO Criteria for Lymphoplasmacytic Lymphoma and Waldenström Macroglobulinemia (WM/LPL-A).
[c] Lymphoplasmacytic lymphoma (LPL) does encompass IgG, IgA, serum free light chain alone, 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. It is important to differentiate from IgM MGUS or IgM multiple myeloma.
[d] MYD88 wild-type occurs in <10% of patients and should not be used to exclude diagnosis of WM if other criteria are met.
[e] Studies have shown that mutations in this gene are found in up to 40% of patients with WM/LPL and can impact ibrutinib response.
[f] Consider in patients with suspected cryoglobulinemia.
[g] If cryocrit positive, then repeat testing of initial serum IgM, and obtain all subsequent serum IgM levels under warm conditions.
[h] In patients presenting with suspected disease related to peripheral neuropathy, rule out amyloidosis in patients presenting with nephrotic syndrome or unexplained cardiac problems.
[i] Confirm symptoms are not related to or caused by comorbidities.

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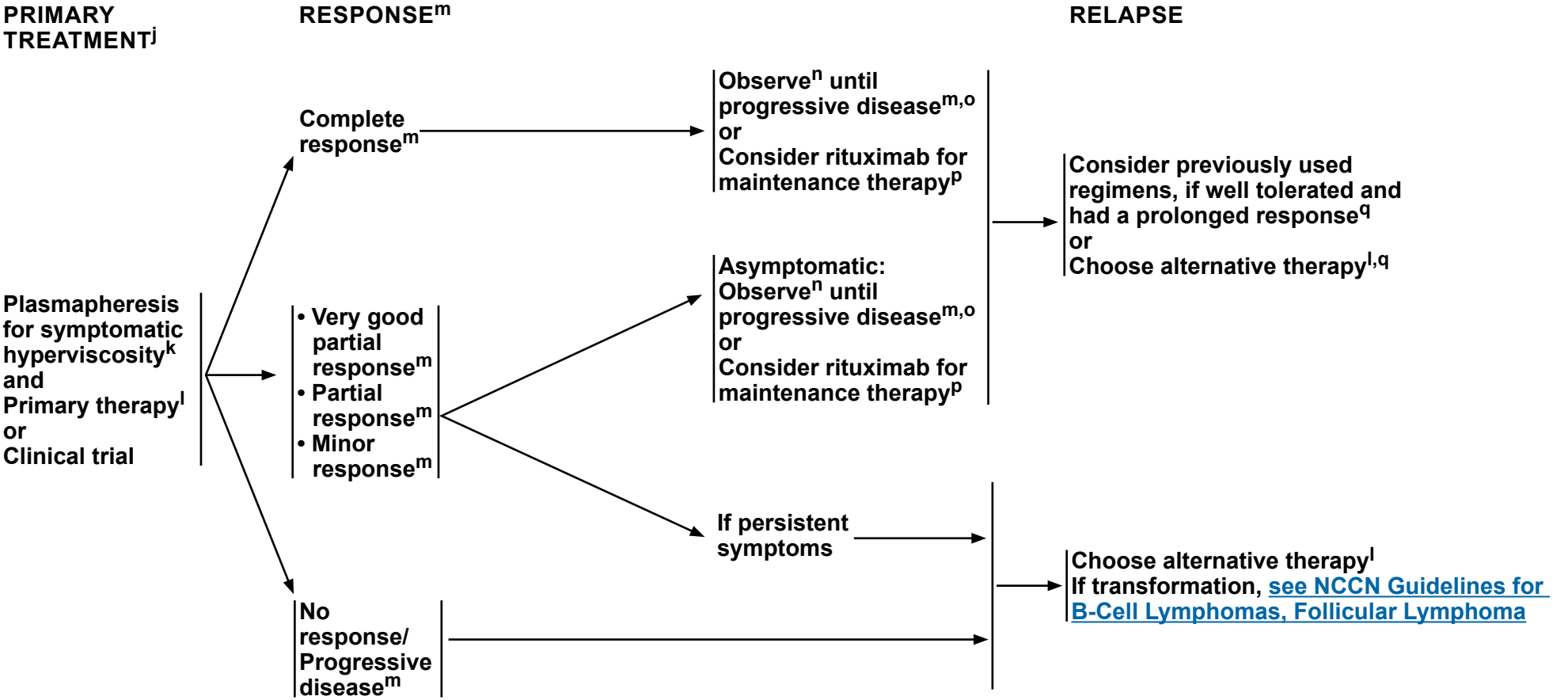
**All recommendations are category 2A unless otherwise indicated.**
**Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.**




[j] Intent of therapy should be based on palliation of symptoms, not necessarily levels of IgM unless the patient is exhibiting evidence of symptomatic hyperviscosity.

[k] Plasmapheresis should be performed for patients with symptomatic hyperviscosity, and before treatment with rituximab-containing regimen in patients with IgM ≥4000 mg/dL. IgM should be monitored closely in these patients thereafter and plasmapheresis should be considered again if symptomatic hyperviscosity recurs 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.

[l] See Waldenström Macroglobulinemia/Lymphoplasmacytic Lymphoma Therapy (WM/LPL-B).

[m] See Response Criteria for WM/LPL (WM/LPL-C).

[n] See NCCN Guidelines for Survivorship.

[o] IgM every 3 months for 2 years, then every 4–6 months for additional 3 years, then every 6–12 months. Progression based on IgM levels alone, without symptoms, should not be reason to retreat.

[p] Only for those who responded to rituximab-containing regimens.

[q] Caution should be used when re-treating with myelosuppressive regimens due to cumulative toxicities.

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## WHO CRITERIA FOR LYMPHOPLASMACYTIC LYMPHOMA AND WALDENSTRÖM 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**

Reproduced with permission from Swerdlow SH, Campo E, Harris NL, et al. World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissues, revised 4th edition. IARC, Lyon 2017.

- **Waldenström macroglobulinemia:**
  - **Lymphoplasmacytic lymphoma with bone marrow involvement and IgM monoclonal gammopathy of any concentration**

Adapted with permission. Owen RG, Treon SP, Al-Katib A, et al. Clinicopathological Definition of Waldenstrom's Macroglobulinemia: Consensus Panel Recommendations from the Second International Workshop on Waldenstom's Macroglobulinemia. Semin Oncol. 2003;30(2):110-115.

## WALDENSTRÖM MACROGLOBULINEMIA INTERNATIONAL WORKSHOP CRITERIA

**Proposed Criteria for the Diagnosis of Waldenström 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 macroglobulinemia and does not exclude diagnosis.**

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

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## WALDENSTRÖM MACROGLOBULINEMIA/LYMPHOPLASMACYTIC LYMPHOMA THERAPY
**(Order of regimens is alphabetical and does not indicate preference)**

### Primary Therapy[1]

**Preferred Regimens**
- **Bendamustine/rituximab[2,3,8]**
- **Bortezomib/dexamethasone/rituximab[3,4,5,6,7,8]**
- **Ibrutinib[13] ± rituximab[3] (category 1)**
- **Rituximab/cyclophosphamide/dexamethasone[3,8]**

**Other Recommended Regimens**
- **Bendamustine[8]**
- **Bortezomib ± rituximab[3,4,5,6,7,8]**
- **Bortezomib/dexamethasone[5,6,7,8]**
- **Carfilzomib[9]/rituximab/dexamethasone[3,5,8]**
- **Cladribine ± rituximab[3,5,10,11]**
- **Cyclophosphamide/doxorubicin/vincristine/prednisone/ rituximab[3,6,8,12]**
- **Fludarabine ± rituximab[3,5,8,10,11]**
- **Fludarabine/cyclophosphamide/rituximab[2,3,5,8,10,11]**
- **Ixazomib/rituximab/dexamethasone[3]**
- **Rituximab[3,8]**
- **Rituximab/cyclophosphamide/prednisone[3,8]**

See Evidence Blocks on WM/LPL-B (EB-1)

[1] See NCCN Guidelines for Older Adult Oncology.
[2] Pneumocystis jiroveci pneumonia (PJP) prophylaxis should be considered for patients receiving bendamustine/rituximab or fludarabine/cyclophosphamide/rituximab.
[3] In patients with symptomatic hyperviscosity, plasmapheresis should first be performed; plasmapheresis should also be considered before treatment with rituximab or ofatumumab for asymptomatic Waldenström macroglobulinemia patients with an IgM ≥4,000 mg/dL or who are symptomatic 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.
[4] Consider for patients presenting with symptomatic hyperviscosity, or in whom rapid IgM reduction is required.
[5] Herpes zoster prophylaxis should be considered for patients receiving these regimens.
[6] These regimens are associated with treatment-related neuropathy and should be avoided in patients with disease-related neuropathy. See Discussion.
[7] Subcutaneous bortezomib is the preferred method of administration.
[8] Serial serum IgA and IgG levels should be carefully monitored as these can be depleted with these therapies.
[9] Can potentially cause cardiac and pulmonary toxicity, especially in elderly patients.
[10] May be associated with disease transformation and/or development of MDS/AML in Waldenström macroglobulinemia patients.
[11] Avoid in patients who are potential autologous stem cell transplant candidates.
[12] Vincristine 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.
[13] Lower overall and absence of major responses observed in MYD88 wild-type patients.

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Continued
References

## EVIDENCE BLOCKS FOR PRIMARY THERAPY

| Preferred Regimens | |
|---|---|
| Bendamustine/rituximab |  |
| Bortezomib/dexamethasone/ rituximab |  |
| Ibrutinib |  |
| Ibrutinib/rituximab |  |
| Rituximab/cyclophosphamide/ dexamethasone |  |

| Other Recommended Regimens | |
|---|---|
| Bendamustine |  |
| Bortezomib |  |
| Bortezomib/rituximab |  |
| Bortezomib/dexamethasone |  |
| Carfilzomib/rituximab/ dexamethasone |  |
| Cladribine |  |
| Cladribine/rituximab |  |
| Cyclophosphamide/ doxorubicin/vincristine/ prednisone/rituximab |  |
| Fludarabine |  |
| Fludarabine/rituximab |  |
| Fludarabine/ cyclophosphamide/rituximab |  |
| Ixazomib/rituximab/ dexamethasone |  |
| Rituximab |  |
| Rituximab/cyclophosphamide/ prednisone |  |

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## WALDENSTRÖM MACROGLOBULINEMIA/LYMPHOPLASMACYTIC LYMPHOMA THERAPY
**(Order of regimens is alphabetical and does not indicate preference)**

### Therapy for Previously Treated WM/LPL[1]

**Preferred Regimens**
- Bendamustine/rituximab[2,3,8]
- Bortezomib/dexamethasone/rituximab[3,4,5,6,7,8]
- Ibrutinib[13] ± rituximab[3]
- Rituximab/cyclophosphamide/dexamethasone[3,8]

**Other Recommended Regimens**
- Bendamustine[8]
- Bortezomib ± rituximab[3,4,5,6,7,8]
- Bortezomib/dexamethasone[5,6,7,8]
- Cladribine ± rituximab[3,5,8,10,11]
- Cyclophosphamide/doxorubicin/vincristine/prednisone/rituximab[3,6,8,12]
- Everolimus
- Fludarabine ± rituximab[3,5,8,10,11]
- Fludarabine/cyclophosphamide/rituximab[2,3,5,8,10,11]
- Rituximab[3,8]
- Rituximab/cyclophosphamide/prednisone[3,8]

See Evidence Blocks on WM/LPL-B (EB-2)

**Useful In Certain Circumstances**
- Ofatumumab (for rituximab-intolerant individuals)[3,8,14]

**Stem Cell Transplant**
- In selected cases stem cell transplantation may be appropriate with either:
  - Autologous stem cell transplant
  - Allogeneic stem cell transplant (ablative or nonablative)[15]

[1] See NCCN Guidelines for Older Adult Oncology.
[2] Pneumocystis jiroveci pneumonia (PJP) prophylaxis should be considered for patients receiving bendamustine/rituximab or fludarabine/cyclophosphamide/rituximab.
[3] In patients with symptomatic hyperviscosity, plasmapheresis should first be performed; plasmapheresis should also be considered before treatment with rituximab or ofatumumab for asymptomatic Waldenström macroglobulinemia patients with an IgM ≥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.
[4] Consider for patients presenting with symptomatic hyperviscosity, or in whom rapid IgM reduction is required.
[5] Herpes zoster prophylaxis should be considered for patients receiving these regimens.
[6] These regimens are associated with treatment-related neuropathy and should be avoided in patients with disease-related neuropathy. See Discussion.
[7] Subcutaneous bortezomib is the preferred method of administration.
[8] Serial serum IgA and IgG levels should be carefully monitored as these can be depleted with these therapies.
[10] May be associated with disease transformation and/or development of MDS/AML in Waldenström macroglobulinemia patients.
[11] Avoid in patients who are potential autologous stem cell transplant candidates.
[12] Vincristine 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.
[13] Lower overall and absence of major responses observed in MYD88 wild-type patients.
[14] Ofatumumab may be used for rituximab-intolerant individuals as a single agent or in combination therapy.
[15] Should ideally be undertaken in the context of a clinical trial.

References

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## EVIDENCE BLOCKS FOR PREVIOUSLY TREATED WM/LPL

| Preferred Regimens | |
|---|---|
| Bendamustine/rituximab |  |
| Bortezomib/dexamethasone/ rituximab |  |
| Ibrutinib |  |
| Ibrutinib/rituximab |  |
| Rituximab/ cyclophosphamide/ dexamethasone |  |

| Other Recommended Regimens | |
|---|---|
| Bendamustine |  |
| Bortezomib |  |
| Bortezomib/rituximab |  |
| Bortezomib/dexamethasone |  |
| Cladribine |  |
| Cladribine/rituximab |  |
| Cyclophosphamide/ doxorubicin/vincristine/ prednisone/rituximab |  |
| Everolimus |  |
| Fludarabine |  |
| Fludarabine/rituximab |  |
| Fludarabine/ cyclophosphamide/rituximab |  |
| Rituximab |  |
| Rituximab/ cyclophosphamide/ prednisone |  |

| Useful in Certain Circumstances | |
|---|---|
| Ofatumumab (for rituximab-intolerant individuals) |  |

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**Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.**
**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.**

## 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.[2] 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[3]** | **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.[4] 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.[4] 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[3]** | **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.** |

[1] Reproduced with permission. Treon S. How I Treat Waldentrom Macroglobulinemia. 2015;126(6):721-732.
[2] Varghese AM, Rawstron AC, Ashcroft AJ, et al. Assessment of bone marrow response in Waldenström's macroglobulinemia. Clin Lymph Myeloma 2009;9:53-55.
[3] Require two consecutive assessments made at any time before the institution of any new therapy.
[4] CT scan may include chest/abdomen/pelvis with contrast.

**Note: For more information regarding the categories and definitions used for the NCCN Evidence Blocks™, see page EB-1.**
**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.**

| 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 indicated.

| NCCN Categories of Preference | |
|---|---|
| **Preferred intervention** | Interventions that are based on superior efficacy, safety, and evidence; and, when appropriate, affordability. |
| **Other recommended intervention** | Other interventions that may be somewhat less efficacious, more toxic, or based on less mature data; or significantly less affordable for similar outcomes. |
| **Useful in certain circumstances** | Other interventions that may be used for selected patient populations (defined with recommendation). |

All recommendations are considered appropriate.

## Table of Contents

This discussion is being updated to correspond with the updated algorithm. Last updated 09/14/18

## Overview

Waldenström macroglobulinemia (WM) is a B-cell disorder characterized primarily by bone marrow infiltration with lymphoplasmacytic cells, along with immunoglobulin M (IgM) monoclonal gammopathy.[1] This condition is defined as "lymphoplasmacytic lymphoma" (LPL) by the Revised European-American Lymphoma (REAL) and WHO classification systems.[2,3] WM is a rare disorder with approximately 1000 to 1500 new cases diagnosed every year in the United States.[4]

### Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines® for Waldenström Macroglobulinemia, an electronic search of the PubMed database was performed to obtain key literature in WM/LPL published between 4/08/15 and 02/14/18, using the following search terms: Waldenström macroglobulinemia OR lymphoplasmacytic lymphoma. The PubMed database was chosen as it remains the most widely used resource for medical literature and indexes peer-reviewed biomedical literature.[5]

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 potential relevance of the PubMed search 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 at www.NCCN.org.

## 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.[6,7]

## Workup

***Essential Studies***

History and physical (H&P) exam are essential components of initial evaluation. The essential laboratory studies include complete blood count (CBC) with differential, examination of peripheral blood smear, and comprehensive metabolic panel to access kidney and liver functions. 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), serum quantitative immunoglobulins, and serum immunofixation electrophoresis (SIFE) are used to identify and quantify the M-protein (IgM). While detection of a monoclonal IgM protein in the serum is a diagnostic criterion for WM, this monoclonal

IgM may be found clinically either in the setting of clinical WM, IgM monoclonal gammopathy of undetermined significance (IgM MGUS), or IgM multiple myeloma. It is important to make this distinction during diagnosis.

Beta-2 microglobulin and the WM International Prognostic Scoring System (IPSS) are useful for prognostication of WM.[8,9] Their use in making treatment-related decisions remains to be clarified.[8]

Bone marrow is almost always involved in WM; therefore; a unilateral bone marrow aspirate and biopsy should be evaluated by immunohistochemistry and/or flow cytometry to confirm excess lymphoplasmacytoid cells and should be evaluated by bone marrow immunohistochemistry and/or bone marrow flow cytometry. The bone marrow aspirate should be tested for *MYD88* (L265P) gene mutation. Whole genome sequencing of bone marrow LPL cells has identified *MYD88* (L265P) as a commonly recurring mutation in patients with WM.[10-12] *MYD88* (L265P) mutations are present in greater than 90% of patients with WM.[10] The NCCN Panel recommends allele-specific polymerase chain reaction (AS-PCR) for *MYD88* (L265P) as a helpful test in differentiating WM from non-IgM LPL, B-cell lymphomas, and plasma cell myeloma.

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.

***Studies Useful Under Certain Circumstances***

IgM 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. Many 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, lower levels of serum viscosity can cause retinal changes and hemorrhages in patients that may necessitate intervention.[13]

In about less than 10% of patients with WM, monoclonal IgM may present with cold agglutinin activity.[14] This means that the monoclonal IgM interact with specific red cell antigens below physiological temperatures, 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 will be symptomatic in ≤5% of the cases. The presence of cold agglutinins or cryoglobulins may affect determination of IgM levels; therefore, testing for cold agglutinins and cryoglobulins should be performed at diagnosis.[15]

When suspected, cryocrit, a test for cryoglobulins, should be obtained. The presence of cryoglobulins may render falsely low serum IgM levels. In such situations, maintaining the serum sample in a warm bath will provide a more reliable serum IgM level measurement.[16]

Patients with WM and peripheral neuropathy may harbor antibodies against myelin-associated glycoprotein (MAG) or other glycoproteins or lipids.[15,17] Testing for serum auto-antibodies to MAG and ganglioside M1 can be considered, as well as a fat pad biopsy or aspirate 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. Nerve conduction studies (NCS) or electromyography (EMG) may be helpful in determining if neuropathy is related to the monoclonal process or other causes.

High von Willebrand factor levels have been associated with worse prognosis in patients with WM.[18] If unexplained clinical bleeding or bruising is present, the NCCN Panel recommends von Willebrand disease (VWD) testing, as acquired VWD has been identified in some cases of WM.

Patients with WM, particularly those with cryoglobulinemia, have been associated with having underlying hepatitis C; therefore, liver function tests and hepatitis C serology should be obtained as well.[19-21]

Retinal examination is recommended if hyperviscosity is suspected or IgM levels are ≥3.0 g/dL.[22]

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, as it has been associated with risk of re-activation of hepatitis B. 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.

WM patients may have recurrent mutations in the *CXCR4* gene. Studies have shown that mutations in this gene are found in up to 40% of patients with WM/LPL and can impact ibrutinib response.[23-26] Given that certain *CXCR4* mutations can confer resistance to ibrutinib,[27,28] the NCCN Panel recommends consideration of *CXCR4* gene mutation testing for patients being initiated on ibrutinib 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.[8] Importantly, high IgM level per se should not be considered a criterion for initiation of therapy in the absence of other aforementioned indications.

Treatment of WM is discussed in detail in several reviews.[15,29-33] Since WM is a rare disease, there are very few randomized trials and limited data comparing different treatment approaches. Therefore, the treatment for WM has been largely adopted from data derived from phase II or retrospective studies.

According to the NCCN Panel, for patients requiring immediate disease control, such as those with symptomatic hyperviscosity, initial plasmapheresis is recommended.[34] After plasmapheresis, systemic treatment should be initiated as soon as possible.

Agents that limit future treatment options should be avoided during initial therapy. Exposure to continuous oral alkylator therapy or nucleoside analogs should be avoided prior to stem cell harvest if an autologous stem cell transplant (SCT) is being considered. Nucleoside analogs are associated with increased risk of disease transformation, development of myelodysplastic syndromes (MDS), and secondary acute myeloid leukemia (AML) in patients with WM treated with nucleoside analog–containing therapy.[35,36] Exposure to nucleoside analogs should therefore be limited, particularly in younger patients who may be potential stem cell candidates.

Herpes zoster prophylaxis should be considered for patients receiving proteasome inhibitor-based regimens.

All treatment options for WM/LPL are listed alphabetically in the NCCN Guidelines. In the 2018 version, the NCCN Panel has categorized WM

therapy regimens as: “preferred regimens,” “other recommended regimens,” and regimens “useful under certain circumstances.” The purpose of classifying regimens is to provide guidance on treatment selection considering the relative efficacy, toxicity, and other factors that play into treatment selection such as pre-existing comorbidities (eg, peripheral neuropathy, rituximab intolerance). The NCCN Panel Members strongly encourage treatment in the context of a clinical trial when possible.

### Preferred Regimens for Primary Therapy

The NCCN Panel prefers rituximab-based regimens as initial therapy for patients with WM.

#### *Bendamustine/Rituximab*

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. The Study Group Indolent Lymphomas (StiL) examined the activity of bendamustine plus rituximab (BR) versus cyclophosphamide, doxorubicin, vincristine, prednisone plus rituximab (CHOP-R) in a large, randomized, multicenter phase III trial of previously untreated patients with indolent non-Hodgkin’s lymphoma (NHL).[37] Included in this study were 41 patients with WM/LPL, 40 of whom were available for response assessment.[38] After a median follow-up of 45 months, the median progression-free survival (PFS) was significantly longer with BR treatment, 69.5 months versus 28.5 months with CHOP-R.[39] 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 as primary therapy for WM.[39]

Pneumocystis jiroveci pneumonia (PJP) prophylaxis should be considered for patients receiving bendamustine/rituximab.

#### *Bortezomib/Dexamethasone/Rituximab*

Bortezomib has shown to have high levels of activity in the management of WM as a single agent,[40] in combination with rituximab,[41] or in combination with rituximab and dexamethasone.[42,43]

The study by Waldenström Macroglobulinemia Clinical Trials Group (WMCTG) reported an overall response rate (ORR) of 96%, including 83% of patients 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.[42] 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. However, grade 3 peripheral neuropathy was observed in 30% of patients in the study that utilized twice-a-week bortezomib administration. The development of peripheral neuropathy led to premature discontinuation of bortezomib in 61% of patients in this study, underscoring the difficulties encountered with the use of this agent in this patient population.

In another multicenter phase II trial, the activity of a bortezomib/dexamethasone/rituximab regimen was evaluated in 59 newly diagnosed symptomatic patients with WM.[44] The ORR was 85% (3% complete response [CR], 7% VGPR, and 58% PR). In 11% of patients, an increase of IgM (≥25%) was observed after administration of rituximab. After 32 months of follow-up, median PFS was 42 months and 3-year overall survival (OS) was 81%. Peripheral neuropathy was observed in 46% (grade ≥3 in 7%) of patients; 8% discontinued bortezomib due to neuropathy.[44] The high rate of peripheral neuropathy could be attributed to the intravenous administration of

bortezomib in the trial. Administering bortezomib subcutaneously and once weekly reduces the risk of peripheral neuropathy.

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. For patients who are intolerant to rituximab, subcutaneous bortezomib with dexamethasone can be considered as an alternate option (see *Other Recommended Regimens for Primary Therapy*).

***Rituximab/Cyclophosphamide/Dexamethasone***

Another alternative to bortezomib-containing therapy is a cyclophosphamide-based regimen along with rituximab and a corticosteroid. In a prospective study of untreated WM patients (n = 72), treatment with rituximab/cyclophosphamide/dexamethasone (R-CD) resulted in an ORR of 83% that included a 7% CR and a 67% PR. The 2-year PFS was 67% for all evaluable patients and 80% for responders. 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.[45] The 8-year OS based on the IPSS risk status for WM was 100%, 55%, and 27% for low-, intermediate-, or high-risk disease, respectively ($P$ = .005).[46]

In a retrospective analysis of outcomes after treatment with R-CD in 50 patients with untreated WM, the ORR was 96% and the median PFS was 34 months. The response rate and duration of response were independent of *MYD88* mutation status.[47]

### Other Recommended Regimens for Primary Therapy

***Bendamustine***

Based on the durable responses seen in previously treated WM, as monotherapy in rituximab-intolerant individuals,[48] bendamustine has been included as an option for primary therapy for WM.

***Bortezomib***

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.[40] Bortezomib was administered using the standard schedule until the patients demonstrated progressive disease or were two cycles beyond best response.[40] The ORR 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.

***Bortezomib/rituximab***

A phase II study of weekly bortezomib plus rituximab in newly diagnosed patients with WM reported an ORR of 88%, including a major response in 65% of patients. The estimated 1-year PFS in this study was 79%.[41]

***Bortezomib/Dexamethasone***

While bortezomib/dexamethasone/rituximab is an active regimen and induces long-lasting responses in patients with newly diagnosed WM, bortezomib/dexamethasone without rituximab may be effective as initial therapy. Therefore, it is included as an option under *Other Recommended Regimens for Primary Therapy*.

***Carfilzomib/Rituximab/Dexamethasone***

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.[49] The study enrolled 31 patients and reported an ORR of 87.1% (35% achieved VGPR/CR).[49] The response rate seen in this study is comparable to those seen in studies using bortezomib-based regimens with an ORR of 85% to 96%.[42,44] 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 ≥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 1 patient (3.2%). IgA and IgG depletion were commonly observed and necessitated truncation of therapy and/or intravenous immunoglobulin use in several patients.[49] No significant peripheral neuropathy was observed in this study. The NCCN Panel recommends serial monitoring of serum IgA and IgG levels while on carfilzomib-based therapy.

***Cladribine Alone or with Rituximab***

Cladribine, a nucleoside analogue, has been studied alone or in combination with rituximab and found to induce good ORRs with prolonged survivals.[50-52] In a phase II trial of cladribine with rituximab in 29 patients with newly diagnosed or previously treated WM, reported ORRs and CR rates were 90% and 24%, respectively.[52]

***Cyclophosphamide/Doxorubicin/Vincristine/Prednisone/Rituximab***

R-CHOP is a stem cell–sparing regimen reported to be active and tolerated by patients with WM.[53-56] It has been reported as having at least a 90% response rate in patients with WM.[53,56,57] In a randomized study involving 69 patients, most of whom had WM, the addition of rituximab to CHOP resulted in a higher ORR (94% vs. 67%) and median time to progression (63 vs. 22 months) in comparison to patients treated with CHOP alone.[56] The addition of vincristine to cyclophosphamide-containing regimens is associated with risk of neuropathy in patients with WM.[42] According to the NCCN Panel, since vincristine is associated with a high risk of peripheral neuropathy in patients with WM/LPL alternative regimens without vincristine (eg, cyclophosphamide/dexamethasone/rituximab), it may be considered if cyclophosphamide-based therapy is being considered.

***Fludarabine Alone or with Rituximab***

Like cladribine, fludarabine is a nucleoside analogue and has been studied alone or in combination with rituximab and/or cyclophosphamide in patients with newly diagnosed WM. 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 OS (not reached in the fludarabine arm vs. 69.8 months [95% CI, 61.6–79.8 months; $P = .014$] in the chlorambucil arm).[58]

A prospective, multicenter trial evaluated treatment with fludarabine with rituximab in patients with WM (n = 43) who had received <2 prior therapies, of whom 63% had received no prior therapy. The ORR was 95%. The reported median time to progression for all patients was 51.2 months and was longer for untreated patients ($P = .017$) and those achieving at least a VGPR ($P = .049$). After a median follow-up of 40.3 months, 3 cases with transformation to aggressive lymphoma and 3 cases with MDS/AML were reported.[59]

***Fludarabine/Cyclophosphamide/Rituximab***

Another multicenter, prospective trial treated previously untreated or pretreated chemotherapy patients with WM (n = 43) with the fludarabine, cyclophosphamide, and rituximab (FCR) regimen.[60] 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. There is a risk of PJP associated with FCR treatment, including late onset of PJP.[61] Therefore, the NCCN Panel recommends PJP prophylaxis for those treated with the FCR regimen.

***Ibrutinib***

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.[62]

The FDA now approves ibrutinib, a small-molecule irreversible inhibitor of BTK, as single-agent therapy for patients with WM until disease progression or unacceptable toxicity.

A phase II trial of ibrutinib in patients with symptomatic WM (n = 63) who received at least one prior treatment reported an ORR of 90.1% (10 with a VGPR, 36 with a PR, 11 with a minor response, none with a CR) and a median time to response of 4 weeks.[28] The study also investigated the effect of *MYD88* and *CXCR4* mutations on patient outcomes. A major response was seen in approximately 60% of patients with mutated *MYD88* and *CXCR4* mutations. At 2 years, the PFS and OS were 69.1% and 95.2%, respectively. Treatment-related toxic effects of grade 3 or higher included neutropenia (in 14% of patients) and thrombocytopenia (in 13% of patients), more commonly in heavily pretreated patients.[28]

The NCCN Panel has listed ibrutinib in the algorithm under *Other Recommended Regimens* for *Primary Therapy* and as one of the *Preferred Regimens* for *Therapy for Previously Treated WM/LPL*.

***Rituximab***

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%.[36,63,64] 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.[65,66] 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)[67] 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.[42] Rituximab may be regarded as a reasonable choice for treating patients with IgM anti-MAG antibody-related neuropathies.[68]

***Rituximab/Cyclophosphamide/Prednisone***

The use of cyclophosphamide/prednisone/rituximab (CP-R) has been shown to be analogous to the more intense cyclophosphamide-based regimens with lesser treatment-related complications.[53] A single institutional retrospective study examined the outcomes of symptomatic patients with WM who received CHOP-R (n = 23), CVP-R (cyclophosphamide/vincristine/prednisone plus rituximab; n = 16), or CP-R (n = 19). Baseline characteristics were similar for all three cohorts

except for serum IgM levels, which were higher in patients treated with CHOP-R ($P \leq .015$). The ORR and CR to the three regimens were: CHOP-R (ORR, 96%; CR, 17%); CVP-R (ORR 88%; CR 12%); and CP-R (ORR, 95%; CR, 0%). A higher incidence for neutropenic fever and treatment-related neuropathy were reported for CHOP-R and CVP-R versus CP-R ($P < .03$).[53]

### Assessment of Response to Primary Treatment

Consensus-based uniform response criteria for WM have been developed by the International Workshops on WM.[29,69] Response to therapy in WM is defined by reduction in the IgM protein. According to the updated summary of response categories from the Sixth International Workshop on WM,[70] a minor response is an IgM reduction of at least 25%; a PR is defined as ≥50% reduction in IgM immunoglobulin; a VGPR is ≥90% reduction in IgM immunoglobulin; and a CR is immunofixation negativity in the serum. Stable disease is defined as a <25% reduction and <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 WM[70] 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.[15,65,66] On the other hand, bortezomib and everolimus can suppress IgM levels independent of killing tumor cells in certain patients.[71-73] One study 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.[74] 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 IgM) to initial therapies are often delayed and may result in underestimation of response.

If primary therapy is not working and there is significant enlargement of the spleen, splenectomy may be considered. There is anecdotal evidence in the literature showing that splenectomy may result in complete remission in patients with WM.[75-77]

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.[78]

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.[79-81]

### 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.[82] 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 OS (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.[82] An increased number of infectious events was observed among patients receiving maintenance therapy with rituximab, but events 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.[83] 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 24 months or more. Otherwise, use of an alternate single agent or combination is recommended.

For patients with remissions lasting less than 24 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. In addition, 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.

Bendamustine-based therapy is effective in relapsed/refractory WM because it produces high response rates and durable responses both as monotherapy and bendamustine combination with rituximab (BR). A phase II study of patients with relapsed/refractory WM, who received bendamustine-based therapy, reported an ORR of 83.3%.[48] The median PFS in patients with refractory WM/LPL was 13.2 months.[48] Another study evaluated the efficacy of BR and R-CD. Of the 160 patients, 60 received BR (43 with relapsed/refractory WM) and 100 received R-CD (50 had relapsed/refractory WM). In patients with relapsed/refractory WM, ORR with BR was 95% versus 87% with R-CD, $P = .45$; median PFS with BR was 58 versus 32 months with DRC (2-year PFS was 66% vs. 53%; $P = .08$).[84] Bendamustine in combination with rituximab is listed as one of the preferred options for relapsed/refractory disease and single-agent bendamustine is listed under *Other Recommended Regimens* in the algorithm.

The use of bortezomib as therapy for relapsed disease is associated with an ORR of 60% when administered as a single agent, and of 70% to 80% when in combination with rituximab[40,71,72,85,86, 87] with or without dexamethasone.[88] 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. Bortezomib/dexamethasone/rituximab is listed as one of the preferred options for relapsed/refractory disease, and single-agent bortezomib or bortezomib in combination with rituximab or dexamethasone is listed under *Other Recommended Regimens* in the algorithm.

Treatment with single-agent rituximab has been reported to produce response rates of 50% to 70%.[63,66,89] Other rituximab-containing chemotherapy regimens include: R-CD, CP-R, and CHOP-R. The NCCN Panel has listed R-CD in the algorithm under *Preferred Regimens*, and single-agent rituximab, CP-R, and CHOP-R are listed in the algorithm under *Other Recommended Regimens* for *Therapy for Previously Treated WM/LPL*.

Nucleoside analogs have shown efficacy in relapsed/refractory WM/LPL either alone or in combination with rituximab.[52,59,60] All cladribine- and fludarabine- containing regimens have been listed in the algorithm under *Other Recommended Regimens* for *Therapy for Previously Treated WM/LPL*.

In addition, the NCCN Panel has included newer agents as therapy options for previously treated disease, such as everolimus,[90,91] ibrutinib,[28,62] and ofatumumab for patients who are intolerant to

rituximab, either as a single agent[92] or in combination therapy.[48] Ibrutinib (discussed under *Other Recommended Regimens for Primary Therapy*) has been included in the algorithm as a "preferred" single agent for relapsed/refractory WM/LPL.

Everolimus, an inhibitor of mTOR, is a potentially effective drug in treating WM, with high single-agent activity but substantial toxicity. With a different mechanism of action it offers an alternate 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.[91] The response rate (minor response or better) was 73% with a PR rate of 50% and a minor response rate of 23%.[93] 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.[93] 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.[73] Everolimus is listed in the algorithm under *Other Recommended Regimens* for *Therapy for Previously Treated WM/LPL*.

*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.[94,95] In cells expressing low levels of CD20, it induces complement-dependent cytotoxicity in vitro that is more potent compared with rituximab.[74,94] Two studies have addressed the role of ofatumumab in patients with WM, including patients who were intolerant to rituximab.[48,92] These studies demonstrated that ofatumumab could be successfully administered, either as a single agent or as combination therapy with meaningful 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. Therefore, it is listed as an agent that is "useful in certain circumstances."

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.

SCT is also an option for relapsed WM in selected patients.[96] 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,[97] but in the context of a clinical trial.

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