Clinical Trials: NCCN believes that the best management for any cancer patient 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.
Updates in version 1.2014 of the NCCN Guidelines for Waldenström’s Macroglobulinemia/Lymphoplasmacytic Lymphoma from the 2.2013 version include:

**WMLPL-1**

• Work up section, added “MYD88 L265P AS-PCR testing of bone marrow” to list of test that are useful in certain circumstances.

**WMLPL-2**

• Added “Very good partial response” (VGPR) and “Minor response” (MR) with “Partial response.”
• Added a footnote to the branches for complete response and partial response (including VGPR and MR). The new footnote states “Intent of therapy should be based on palliation of symptoms, not necessarily levels of IgM unless the patient is exhibiting evidence of symptomatic hyperviscosity.”

**WMLPL-B**

• Suggested treatment regimens: added “ibrutinib” as a non-stem cell toxic, salvage therapy option.

**WMLPL-C**

• Response criteria for WM/LPL, added a footnote to complete response and progressive disease stating “Require two consecutive assessments made at any time before the institution of any new therapy.”
## Diagnosis

### Workup

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

**Useful in certain circumstances**
- Hepatitis C testing
- Hepatitis B testing, if rituximab planned
- Cryocrit
- Cold agglutinins
- Neurology consult
- Anti-MAG antibodies/anti-GM1
- Electromyelogram
- Fat pad biopsy and/or congo red staining of bone marrow for amyloid
- MYD88 L265P AS-PCR testing of bone marrow
- 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

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

Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Plasmapheresis 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 ≥5000 mg/dL while on rituximab-containing therapy.

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.

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

Plasmapheresis should be performed for symptomatic hyperviscosity and 
Primary therapy:
• Combination therapy or
• Single agent (such as rituximab) orClinical Trial

Complete response or Partial response or Minor response

Asymptomatic: Observe until progressive disease or Consider rituximab for maintenance therapy

If persistent symptoms

No response/Progressive disease

Waldenström’s Macroglobulinemia/ Lymphoplasmacytic Lymphoma

<12 mo Choose alternative therapy

≥12 mo May use previous treatment or consider alternative therapy

Choose alternative therapy

If transformation, see NCCN Guidelines for Non- Hodgkin’s Lymphoma’s, Follicular Lymphoma

<12 mo Choose alternative therapy

≥12 mo May use previous treatment or consider alternative therapy

Choose alternative therapy

If transformation, see NCCN Guidelines for Non- Hodgkin’s Lymphoma’s, Follicular Lymphoma

Plasmapheresis 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 ≥5000 mg/dL while on rituximab-containing therapy.

See Suggested Treatment Regimens (WMLPL-B).

See Response Criteria for WM/LPL (WMLPL-C).

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


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.

NCCN Guidelines Version 1.2014
Waldenström’s Macroglobulinemia/
Lymphoplasmacytic Lymphoma

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

Primary Therapy:
Non-stem cell toxic
• Bortezomib ± rituximab¹,²,³,⁴
• Bortezomib/dexamethasone³,⁴
• Bortezomib/dexamethasone/rituximab¹,²,³,⁴
• Cyclophosphamide/doxorubicin/vincristine/prednisone/rituximab¹,⁴
• Rituximab¹
• Rituximab/cyclophosphamide/prednisone¹
• Rituximab/cyclophosphamide/dexamethasone¹
• Thalidomide ± rituximab¹,⁴

Possible stem cell toxicity and/or risk of transformation (or unknown)
• Bendamustine ± rituximab¹
• Cladribine ± rituximab¹,⁵,⁶
• Chlorambucil⁵,⁶
• Fludarabine ± rituximab¹,⁵,⁶
• Fludarabine/cyclophosphamide/rituximab¹,⁵,⁶

Salvage Therapy:
Non-stem cell toxic
• Alemtuzumab
• Bortezomib ± rituximab¹,²,³,⁴
• Bortezomib/dexamethasone³,⁴
• Bortezomib/dexamethasone/rituximab¹,²,³,⁴
• Cyclophosphamide/doxorubicin/vincristine/prednisone/rituximab¹,⁴
• Everolimus
• Ibrutinib
• Ofatumumab (for rituximab-intolerant individuals)¹,⁷
• Rituximab¹
• Rituximab/cyclophosphamide/prednisone¹
• Rituximab/cyclophosphamide/dexamethasone¹
• Thalidomide ± rituximab¹,⁴

Possible stem cell toxicity and/or risk of transformation (or unknown)
• Bendamustine ± rituximab¹
• Cladribine ± rituximab¹,⁵,⁶
• Chlorambucil⁵,⁶
• Fludarabine ± rituximab¹,⁵,⁶
• Fludarabine/cyclophosphamide/rituximab¹,⁵,⁶

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

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

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

³Herpes zoster prophylaxis for patients treated with bortezomib.

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

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

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

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

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


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

<table>
<thead>
<tr>
<th>Response Category</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete Response</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td>CR</td>
</tr>
<tr>
<td><strong>Very Good Partial Response</strong></td>
<td>VGPR</td>
</tr>
<tr>
<td><strong>Partial Response</strong></td>
<td>PR</td>
</tr>
<tr>
<td><strong>Minor Response</strong></td>
<td>MR</td>
</tr>
<tr>
<td><strong>Stable Disease</strong></td>
<td>SD</td>
</tr>
<tr>
<td><strong>Progressive Disease</strong>&lt;sup&gt;3&lt;/sup&gt;</td>
<td>PD</td>
</tr>
</tbody>
</table>

<sup>3</sup>Require 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 cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.
Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

Treatment of IgM related Peripheral Neuropathy .................................................. MS-7
Maintenance Therapy ................................................................................................ MS-7
Salvage Therapy ........................................................................................................ MS-8
Management of Patients intolerant to Rituximab ................................................ MS-9
References ................................................................................................................. MS-11
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 gammapathy.\textsuperscript{1} This condition is considered to be lymphoplasmacytic lymphoma (LPL) as defined by the Revised European-American Lymphoma (REAL) and World Health Organization (WHO) classification systems.\textsuperscript{2,3}

Diagnosis

Key to the diagnosis of WM/LPL is the demonstration of bone marrow infiltration by a lymphoplasmacytic cell population manifested by small lymphocytes with evidence of plasmacytoid/plasma cell differentiation. The bone marrow infiltration should be supported by immunophenotypic studies (flow cytometry and/or immunohistochemistry) showing the following profile: sIgM+, CD19+, CD20+, CD22+.\textsuperscript{1} According to the current WHO classification, the lymphocytes in WM are typically negative for CD5, CD10, and CD23.\textsuperscript{3} However, this should not exclude diagnosis as exceptions occur. About 10-20% of cases may express CD5, CD10, or CD23.\textsuperscript{4,5}

Workup

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

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

In about less than 10% of WM patients, monoclonal IgM may present with cold agglutinin activity.\textsuperscript{7} This means that the monoclonal IgMs interact with specific red cell antigens at temperatures below physiological, producing chronic hemolytic anemia. The cold agglutinin titers are >1:1000 in most cases. In up to 20% of WM patients, the monoclonal IgM may behave as a cryoglobulin (type I), but is symptomatic in 5% or less of the cases. The presence of cold agglutinins or cryoglobulins may affect determination of IgM levels and, therefore, testing for cold agglutinins and cryoglobulins should be performed at diagnosis.\textsuperscript{8}

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

Since bone marrow is almost always involved in WM, a unilateral bone marrow aspirate and biopsy is done to confirm excess lymphoplasmacytoid cells. Computed tomographic scans of the chest, abdomen, and pelvis at time of diagnosis are useful to properly stage the patient and can assess adenopathy, splenomegaly, and other extramedullary disease sites in patients who are symptomatic.
Patients with WM and peripheral neuropathy may harbor antibodies against myelin-associated glycoprotein (MAG) or other glycoproteins or lipids. Testing for serum auto-antibodies to MAG and ganglioside M1 (GM1) can be considered, as well as a fat pad biopsy and/or congo red staining of the bone marrow to evaluate for the presence of amyloid in patients with peripheral neuropathy. Referral for neurologic consultation should be considered for these patients. Electromyography may be helpful in determining the type of neuropathy. Retinal examination should be done if hyperviscosity is suspected or IgM levels are greater than or equal to 3.0 g/dL.

Whole genome sequencing of bone marrow LPL cells has identified MYD88 (L265P) as a commonly recurring mutation in patients with Waldenström’s macroglobulinemia. The NCCN panel recommend allele-specific polymerase chain reaction (AS-PCR) for MYD88 (L265P) as useful test in differentiating WM from non-IgM LPL, B-cell lymphomas and plasma cell myeloma.

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

**Primary Treatment**

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

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

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 is being considered. Nucleoside analogs are associated with increased risk of disease transformation, myelodysplasia, and acute myelogenous leukemia.

**Primary Treatment Regimens Not Toxic to Stem Cells**

Rituximab, a monoclonal antibody that targets the B-lymphocyte antigen CD20, has been used successfully in the treatment of WM, because CD20 is expressed on lymphoplasmacytic cells in WM patients. Single agent rituximab is active in patients with WM; however, the response rates to single agent rituximab utilizing either standard or extended dosing vary between 25% and 45%. Transient increases in IgM titers (also called the IgM flare) have been reported in 40-50% of patients after initiation of rituximab therapy, including in circumstances when rituximab has been used in combination therapy. The rituximab related IgM flare may lead to symptomatic hyperviscosity, as well as worsening of IgM-related neuropathy, cryoglobulinemia, and other
IgM-related complications. These levels may persist for months and do not indicate treatment failure, but may necessitate plasmapheresis to reduce hyperviscosity. Prophylactic plasmapheresis can be considered in patients with high IgM levels (typically 5,000 mg/dL or higher) prior to rituximab exposure to minimize risk of symptomatic hyperviscosity. The risk of IgM flare may be decreased in patients receiving rituximab in combination therapy with bortezomib and dexamethasone.\textsuperscript{25} Rituximab may be regarded as a reasonable choice for treating patients with IgM anti-MAG antibody-related neuropathies.\textsuperscript{26}

Bortezomib has shown to have high levels of activity in the management of WM as single agent,\textsuperscript{27} in combination with rituximab,\textsuperscript{28} or in combination with rituximab and dexamethasone.\textsuperscript{25,29} In a phase II study, bortezomib was administered to 27 WM patients, 44\% of whom were previously untreated and 56\% were previously treated.\textsuperscript{27} Bortezomib was administered using the standard schedule until the patients demonstrated progressive disease or were two cycles beyond best response.\textsuperscript{27} The overall response rate in this study was 78\%, with major responses observed in 44\% of patients. Sensory neuropathy occurred in 20 patients after two to four cycles of therapy. Among the 20 patients who developed a neuropathy, it resolved in 14 patients and improved by one grade in one patient at 2 to 13 months.

A phase II study of weekly bortezomib plus rituximab in newly diagnosed patients with WM reported an overall response rate of 96\%, including 83\% achieving partial response with the combination of bortezomib (using a twice-a-week schedule) along with rituximab and dexamethasone in newly diagnosed patients with WM.\textsuperscript{25} With a median follow-up of 2 years, 80\% of patients remained free of disease progression, including all patients achieving a very good partial response or better. Grade 3 peripheral neuropathy was observed in 30\% of patients in the study that utilized twice-a-week bortezomib administration. For rituximab intolerant individuals, bortezomib with dexamethasone can be considered as an alternate option.

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

An alternative to bortezomib-containing therapy is a cyclophosphamide-based regimen along with rituximab and a corticosteroid. A study by Dimopoulos et al reported that the combination of rituximab, cyclophosphamide, dexamethasone (R-CD) induces overall and complete responses in 78\% and 7\% of WM patients, respectively.\textsuperscript{30} The 2-year progression-free survival in responders was found to be 80\%. The R-CD regimen was well tolerated, with 9\% of patients experiencing grade 3 or 4 neutropenia and approximately 20\% of patients experiencing some form of toxicity related to rituximab.

Cyclophosphamide, doxorubicin, vincristine, prednisone plus rituximab (CHOP-R) is a stem cell sparing regimen reported to be active and tolerated by WM patients.\textsuperscript{31-34} It has been reported as having at least a 90\% response rate in patients with WM.\textsuperscript{31,34,35} In a randomized study involving 69 patients, most of whom had WM, the addition of rituximab
to CHOP resulted in a higher overall response rate (94% versus 67%) and median time to progression (63 versus 22 months) in comparison to patients treated with CHOP alone. A retrospective study examined the outcomes of symptomatic WM patients who received CHOP-R, cyclophosphamide, vincristine, prednisone plus rituximab (CVP-R) or CP-R. Baseline characteristics for all 3 cohorts were similar for age, prior therapies, bone marrow involvement, hematocrit, platelet count, and serum beta-2 microglobulin, though serum IgM levels were higher in patients treated with CHOP-R. The overall response rates to therapy were comparable among all three treatment groups: CHOP-R (96%); CVP-R (88%); and CP-R (95%). The addition of vincristine to cyclophosphamide containing regimens is associated with risk of neuropathy in WM patients. 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.

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

Based on the above data, the suggested primary treatment regimens which are stem cell sparing listed in the NCCN Guidelines for WM/LPL include: rituximab single agent; R-CD; CP-R; CHOP-R; bortezomib and rituximab; thalidomide and rituximab; bortezomib, dexamethasone, and rituximab; and bortezomib and dexamethasone Response rates of 70-90% have been reported with rituximab based combination therapies.

Primary Treatment Regimens with Potential or Unknown Toxicity to Stem Cells

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

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

In a multicenter, prospective clinical, 43 patients with WM who were previously untreated or pretreated with chemotherapy were treated with fludarabine, cyclophosphamide, and rituximab (FCR) regimen. Most of patients in this study (65%) received FCR as first-line treatment, 28% of patients were in relapse, and 7% had disease that was refractory to a previous line of treatment. The results demonstrate that FCR produces rapid responses (OR rate of 79%), with high rates of complete response and very good partial response. However the potential risk of secondary
malignancies and rate of myelosuppression with FCR regimen was high.

The Study Group for Lymphomas (Stil) 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. Included in this study were 41 patients with WM/LPL, 40 of whom were available for response assessment.

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 R_CHOP. BR was associated with a lower incidence of grade 3 or 4 neutropenia, infectious complications, and alopecia in this study. These results suggest that BR may be a preferable option to CHOP-R in the frontline therapy of WM.

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

**Follow-up after Primary Treatment**

**Assessment of Response**

Consensus-based uniform response criteria for WM have been developed by the International Workshops on WM. Response to therapy in WM is defined by reduction in the M protein. According to the updated summary of response categories from the sixth International Workshop on WM, a minor response is an M-spike reduction of at least 25%; a partial response is defined as greater than or equal to 50% reduction in M protein; a very good partial response is greater than or equal 90% reduction in M protein; and a complete response is immunofixation negativity in the serum. Stable disease is defined as a less than 25% reduction and less than 25% increase of serum IgM 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.

An important concern with the use of IgM as a surrogate marker of disease is that it can fluctuate independent of tumor cell killing, particularly with newer biologically targeted agents such as rituximab, bortezomib, and everolimus. Rituximab induces a spike or flare in serum IgM levels which can occur when used as monotherapy and in combination with other agents including cyclophosphamide, nucleoside analogues, and thalidomide, and lasts for several weeks to months. On the other hand, bortezomib and everolimus can suppress IgM levels independent of killing tumor cells in certain patients. 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. Therefore, in circumstances where the serum IgM levels appear to be out of context with the clinical progress of the patient, a bone marrow biopsy should be considered in order to clarify the patient's underlying disease burden.

The updated summary of response categories and criteria from the sixth International Workshop on WM have been included in the NCCN Guidelines (see Table 1 in the algorithms). After primary therapy, the NCCN panel recommends assessing the response to treatment using consensus panel criteria outlined in Table 1. 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 rituximab therapy.56

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

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

Chemotherapy with rituximab is commonly used, with improvements in
sensory function accompanying reduction in anti-neuronal antibody
titers observed in several studies, including a placebo controlled trial.
The use of single agent rituximab can be considered as the first
intervention in patients with mild, slowly progressive neuropathy. In
patients with moderate to severe IgM related neuropathy or where the
course of the IgM neuropathy appears aggressive, the use of CP-R or
R-CD may be preferable in order to achieve more robust paraprotein
reductions. Patients who experience a rituximab related flare may also
have a flare in their IgM related neuropathic symptoms. While patients
are undergoing plasmapheresis, or are on therapy, treatment directed at
symptomatic improvement can also be considered with gabapentin, pre-
gabapentin, and duloxetine.57-59

Maintenance Therapy
The use of maintenance rituximab was recently reported in a study
which examined the outcome of 248 rituximab-naïve WM patients who
responded to a rituximab-containing regimens.60 Eighty-six patients
(35%) received maintenance rituximab (M-rituximab). No differences in
baseline characteristics and post-induction categorical responses
between cohorts were observed. The median number of rituximab
infusions during induction was 6 for both cohorts, with 8 infusions over a
2-year period for patients receiving M-rituximab. Categorical responses
improved in 16 out of 162 (10%) patients overall and 36 out of 86
(41.8%) of M-rituximab patients respectively, following induction therapy
(P< .0001). Both PFS (56.3 versus 28.6 months; P=.0001) and overall
survival (Not reached versus 116 months; P=.0095) were longer in
patients who received M-rituximab. Improved PFS was evident despite
previous treatment status or induction with rituximab alone or in
combination therapy (P ≤ .0001). Best serum IgM response was lower
(P< .0001) and haematocrit higher (P=.001) for patients receiving M-
Rituximab.60 An increased number of infectious events were observed
among patients receiving M-rituximab, but were mainly ≤ grade 2 (P=
.008). The findings of this observational study suggest improved clinical
outcomes following M-rituximab in WM patients who respond to
induction with a rituximab-containing regimen. A prospective study
aimed at clarifying the role of M-rituximab therapy in WM patients is
underway by the German STiL group.
The NCCN panel recommends considering maintenance rituximab in patients who have had either a complete response to primary therapy or in patients who are asymptomatic and achieved either a very good, partial, or minor response.

**Salvage Therapy**

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 second-line or salvage therapy for relapsed disease if a patient achieved a response that lasted for at least 12 months or more; otherwise, use of an alternate single agent or combination is recommended.

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

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

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

In addition, the NCCN Panel has included newer agents as salvage therapy options such as everolimus, alemtuzumab, ibrutinib, and ofatumumab for rituximab-intolerant patients, either as single agent or in combination therapy.

Everolimus, an inhibitor on mTOR, is a potentially effective drug in WM with high single-agent activity and manageable toxicity and therefore offers a new therapeutic strategy for patient with relapsed/refractory WM. Preclinical data show increased activity of the mTOR pathway in WM and significant cytotoxicity seen in WM cell lines in response to the mTOR inhibitor. Based on these studies, a phase II trial of single-agent everolimus was initiated in 60 patients with relapsed or relapsed/refractory WM. The overall response rate was 73% with a partial response rate of 50% and a minor response rate of 23%. The estimated PFS at 12 and 24 months was 62% (95% CI: 51-75%) and 48% (95% CI: 37-63%), respectively. Grade 3 or 4 related toxicities were reported in 67% of patients. Dose reduction due to toxicity were made in 62% of patients. The most commonly reported hematological toxicities with everolimus treatment were cytopenias. Pulmonary toxicity was seen in 5% of patients.
The study reported that the patients who achieved a partial response responded after a median of two months of treatment. Discordance between serum IgM levels and underlying bone marrow disease burden is common in WM patients treated with everolimus, and clinicians should consider repeating a bone marrow biopsy when clinically indicated to assess treatment response.

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

Signaling pathways from the B-cell antigen receptor and Bruton tyrosine kinase (BTK) play a crucial role in mediating of 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 multi-center phase I study of ibrutinib included patients with NHL, CLL, or WM who had failed at least one previous therapy. Objective responses were observed across all histologies, including three of four patients with WM.

In an ongoing phase II trial, 63 patients with relapsed/refractory WM received ibrutinib for up to 2 years until progressive disease or unacceptable toxicity. The results were presented at the 2013 ASH annual meeting, after a median follow-up at 9 months (9 cycles). The overall response rate (minor response or better, using consensus criteria adapted from the 3rd International Workshop on WM) was found to be 83%. Six patients had a very good partial response, 34 achieved a PR, and 12 achieved a minor response (MR), with a major response rate (PR or better) of 64%. Ten patients showed stable disease. After 9 cycles, fifty-five patients (87.3%) are still continuing ibrutinib treatment. The most commonly reported treatment related adverse events (grade 2 or higher) were anemia, neutropenia; thrombocytopenia; bleeding; and pneumonic infection, and tachyarrhythmia. Stem cell transplantation (SCT) is also an option for the salvage therapy of WM in selected patients. SCT options listed in the NCCN Guidelines for WM/LPL are for high dose therapy with autologous stem cell rescue. The use of myeloablative or non-myeloablative allogeneic SCT should preferably be considered in the context of a clinical trial.

Management of Patients intolerant to Rituximab

Ofatumumab is a human monoclonal antibody (IgG1) that binds specifically to a distinct epitope encompassing both the small and large extracellular loops of the CD20 molecule. In cells expressing low levels of CD20 it induces complement-dependent cytotoxicity in vitro, that is more potent compared with rituximab. Two studies recently addressed the role of ofatumumab in patients with WM, including patients who were intolerant to rituximab. These studies demonstrated that ofatumumab could be successfully administered, either as single agent or as combination therapy, in patients with WM who were intolerant to rituximab, and were associated with responses.
Therefore, according to the NCCN Panel ofatumumab may be considered in rituximab intolerant patients, either as single agent or as combination therapy. There is a risk of IgM flare with ofatumumab, as with rituximab; therefore, similar precautions as with rituximab should be considered when using ofatumumab in those patients who have evidence of hyperviscosity or who have elevated IgM levels.

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


