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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Waldenström's Macroglobulinemia / Lymphoplasmacytic Lymphoma

Version 1.2012

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NCCN Guidelines Version 1.2012 Panel Members Waldenström's Macroglobulinemia/ Lymphoplasmacytic Lymphoma

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Clinical Trials: The 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

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NCCN Guidelines Version 1.2012 Updates Waldenström's Macroglobulinemia/ Lymphoplasmacytic Lymphoma

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

WMLPL-1

- Workup section: Retinal exam (if IgM ≥ 3.0 g/dL, added "or if hyperviscosity is suspected)."
- Footnote b is new to the page, "Lymphoplasmacytic lymphoma (LPL) does encompass IgG, IgA, and non secretory subtypes though make up <5% of all LPLs. The treatment non-IgM LPLs parallels that of IgM secreting LPLs, but these are less likely to have either hyperviscosity associated with them, or autoimmune related neuropathy."

WMLPL-2

- Added a footnote and link to Response Criteria for WM/LPL (WMLPL-C)

WMLPL-B

- Added "Order of regimens is alphabetical and does not indicate preference" to the page heading.
- Primary therapy, Non-stem cell toxic, added:
  - Cyclophosphamide/doxorubicin/vincristine/prednisone/rituximab regimen (category 2A).
  - Bortezomib/dexamethasone (category 2A)
- Primary therapy, Possible stem cell toxicity and/or risk of transformation (or unknown): Added Fludarabine/cyclophosphamide/rituximab regimen (category 2A).
- Salvage therapy, Non-stem cell toxic added:
  - Cyclophosphamide/doxorubicin/vincristine/prednisone/rituximab regimen (category 2A).
  - Bortezomib/dexamethasone (category 2A)
  - Ofatumumab (for rituximab intolerant individuals)
- Salvage therapy, Possible stem cell toxicity and/or risk of transformation (or unknown): Added Fludarabine/cyclophosphamide/rituximab regimen (category 2A).
- Modified footnote 1, "In 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."
- Footnote 4 is new to the page, "Bortezomib may be associated with increased risk of peripheral neuropathy in patients with WM/LPL. Avoid in patients with disease-related peripheral neuropathy (See Discussion)."

WMLPL-C

- This page is new to the Guidelines, "Response Criteria for WM/LPL."

Discussion

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

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DIAGNOSIS

Essential[a,b]

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

→

WORKUP

Essential

- H&P
- CBC differential, platelets
- Comprehensive panel
- Quantitative immunoglobulins/Immunofixation
- Serum protein electrophoresis (SPEP)
- Beta-2 microglobulin
- Serum vicosity[c]
- Unilateral aspirate and biopsy
- Chest/abdominal/pelvic CT

Useful in certain circumstances

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

→

INDICATIONS FOR TREATMENT

Symptoms related to:

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

→ See Primary Treatment (WMLPL-2)

[a] See WHO Criteria for Lymphoplasmacytic Lymphoma and Waldenström's Macroglobulinemia (WMLPL-A).

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

[c] Most patients with serum viscosity of less than 4 cP will not have symptoms of hyperviscosity.

[d] Consider in patients with suspected cryoglobulinemia.

[e] If cryocrit positive, then repeat testing of initial serum IgM, and obtain all subsequent serum IgM levels under warm conditions.

[f] In patients presenting with suspected disease related peripheral neuropathy.

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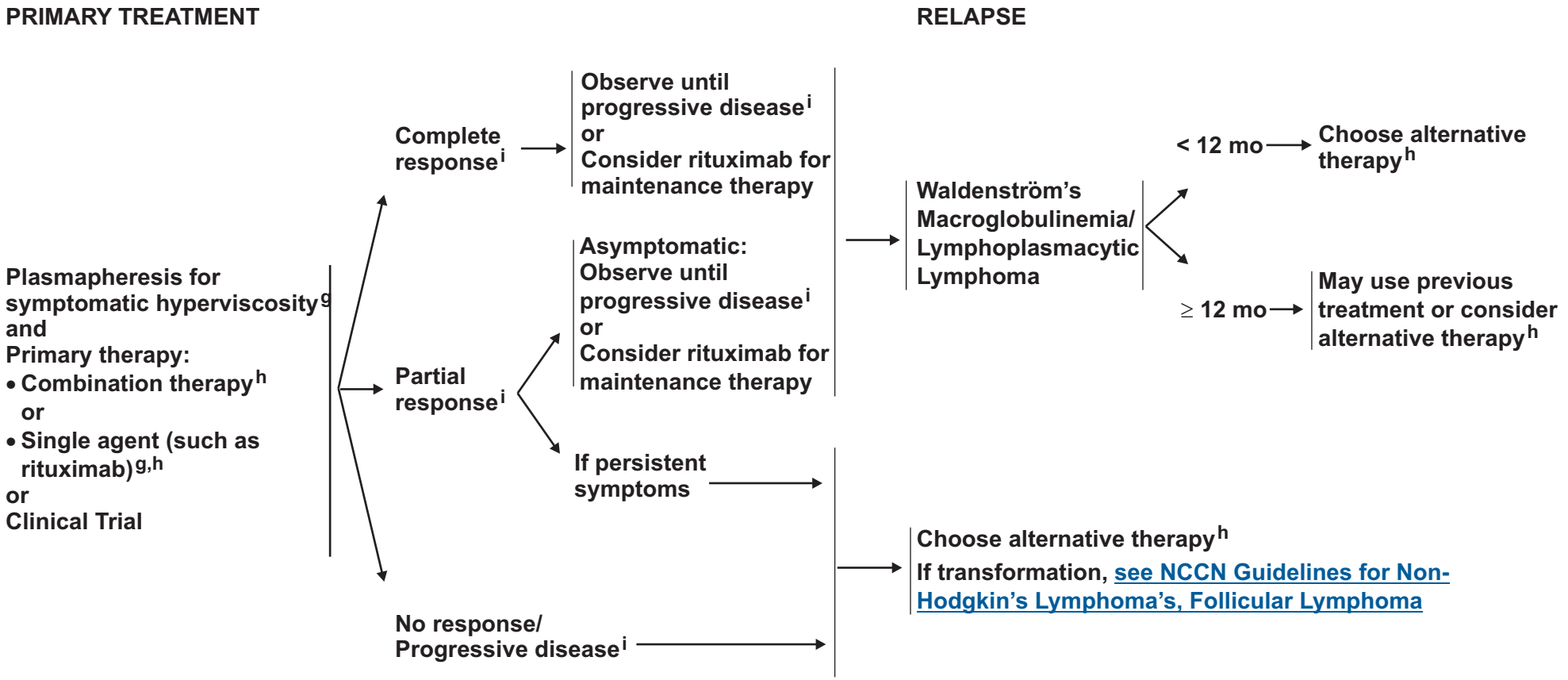

[g]Plasmapheresis should be performed for patients with symptomatic hyperviscosity, and before treatment with rituximab containing regimen in patients with IgM ≥ 5000 mg/dL. IgM should be monitored closely in these patients thereafter and plasmapheresis considered again if symptomatic hyperviscosity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

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

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

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WHO CRITERIA FOR LYMPHOPLASMACYTIC LYMPHOMA AND WALDENSTRÖM'S MACROGLOBULINEMIA

- **Lymphoplamacytic lymphoma:**
  - **Neoplasm of small B lymphocytes, plasmacytoid lymphocytes, and plasma cells**
  - **Usually involving bone marrow and sometimes lymph nodes and spleen**
  - **Does not fulfill criteria of any other small B-cell lymphoid neoplasm that may also have plasmacytic differentiation**

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

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

WALDENSTRÖM'S MACROGLOBULINEMIA INTERNATIONAL WORKSHOP CRITERIA

Proposed Criteria for the Diagnosis of Waldenström's Macroglobulinemia

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

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

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SUGGESTED TREATMENT REGIMENS

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

Primary Therapy:

Non-stem cell toxic

- Bortezomib ± rituximab[1,2,3,4]
- Bortezomib/dexamethasone[3,4]
- Bortezomib/dexamethasone/rituximab[1,2,3,4]
- Cyclophosphamide/doxorubicin/vincristine/prednisone/rituximab[1,4]
- Rituximab[1]
- Rituximab/cyclophosphamide/prednisone[1]
- Rituximab/cyclophosphamide/dexamethasone[1]
- Thalidomide ± rituximab[1,4]

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

- Bendamustine ± rituximab[1]
- Cladribine ± rituximab[1,5,6]
- Chlorambucil[5,6]
- Fludarabine ± rituximab[1,5,6]
- Fludarabine/cyclophosphamide/rituximab[1,5,6]

Salvage Therapy:

Non-stem cell toxic

- Alemtuzumab
- Bortezomib ± rituximab[1,2,3,4]
- Bortezomib/dexamethasone[3,4]
- Bortezomib/dexamethasone/rituximab[1,2,3,4]
- Cyclophosphamide/doxorubicin/vincristine/prednisone/rituximab[1,4]
- Everolimus
- Ofatumumab (for rituximab intolerant individuals)[1]
- Rituximab[1]
- Rituximab/cyclophosphamide/prednisone[1]
- Rituximab/cyclophosphamide/dexamethasone[1]
- Thalidomide ± rituximab[1,4]

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

- Bendamustine ± rituximab[1]
- Cladribine ± rituximab[1,5,6]
- Chlorambucil[5,6]
- Fludarabine ± rituximab[1,5,6]
- Fludarabine/cyclophosphamide/rituximab[1,5,6]

Stem cell transplant

- In selected cases stem cell transplantation may be appropriate with either:
  - High dose therapy with stem cell rescue
  - Allogeneic stem cell transplant (ablative or non-ablative)[7]

[1]In 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.

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

[3]Herpes zoster prophylaxis for patients treated with bortezomib.

[4]Bortezomib may be associated with increased risk of peripheral neuropathy in patients with WM/LPL. Avoid in patients with disease-related peripheral neuropathy. See Discussion.

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

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

[7]Should ideally be undertaken in the context of a clinical trial.

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.

See Suggested References (WMLPL, 2 of 2)

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RESPONSE CRITERIA FOR WM/LPL[1,2]

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

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

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

[1]Treon SP, Merlini G, Morra E, et al. Report from the Sixth International Workshop on Waldenstrom's Macroglobulinemia. Clin Lymph Myeloma Leukemia 2011; 11:69-73.
[2]Varghese AM, Rawstron AC, Ashcroft AJ, et al. Assessment of bone marrow response in Waldenström's macroglobulinemia. Clin Lymph Myeloma 2009; 9:53-5.

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Discussion

NCCN Categories of Evidence and Consensus

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

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

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

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

All recommendations are category 2A unless otherwise noted.

Overview

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

Diagnosis

Key to the diagnosis of WM/LPL is the demonstration of bone marrow infiltration by a lymphoplasmacytic cell population manifested by small lymphocytes with evidence of plasmacytoid/plasma cell differentiation. The bone marrow infiltration should be supported by immunophenotypic studies (flow cytometry and/or immunohistochemistry) showing the following profile: sIgM+, CD19+, CD20+, CD22+.[1] About 10- 20% of cases may express CD5, CD10, or CD23 but this does not exclude diagnosis of WM.[4]

Workup

To establish the diagnosis of WM, it is necessary to demonstrate IgM monoclonal protein in the serum, along with histologic evidence of lymphoplasmacytic cells in the bone marrow.[1] Serum protein electrophoresis (SPEP), quantitative immunoglobulins, and immunofixation is used to identify and quantify the M-protein (which is IgM). The serum IgM should be obtained under warm bath conditions for those patients suspected to have cryoglobulinemia.

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.[5]

Beta-2 microglobulin and the WM IPSS score are useful in prognostication of WM.[6, 7] Their use in making treatment-related decisions remains to be clarified.[6]

Since bone marrow is almost always involved in WM, a unilateral bone marrow aspirate and biopsy to confirm excess lymphoplasmacytoid cells. Computed tomographic scans of the chest, abdomen, and pelvis at time of diagnosis is useful to properly stage the patient and can

assess adenopathy, splenomegaly, and other extramedullary disease sites in patients who are symptomatic.

Patients with WM and peripheral neuropathy may harbor antibodies against myelin-associated glycoprotein (MAG) or other glycoproteins or lipids.[8, 9] 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.

In about less than 10% of WM patients, monoclonal IgM may present with cold agglutinin activity.[10] 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.[9] If present, subsequent serum samples should be analyzed under warm conditions for determination of serum monoclonal IgM level.

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.[11-13] 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, for patients with a diagnosis of WM/LPL, treatment should be initiated 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.[6]

Treatment of WM is discussed in detail in several reviews.[9, 14] For patients requiring immediate disease control, such as those with symptomatic hyperviscosity, initial plasmapheresis is recommended. After plasmapheresis, treatment should be initiated as soon as possible. The primary treatment options include oral alkylators (eg, chlorambucil); nucleoside analogs (cladribine or fludarabine); rituximab as single agent; or rituximab in combination with cyclophosphamide, bortezomib, nucleoside analogues, thalidomide, or bendamustine.

Exposure to continuous oral alkylator therapy or nucleoside analogs should be avoided if a stem cell transplant is being considered. Nucleoside analogs are associated with increased risk of disease transformation, myelodysplasia, and acute myelogenous leukemia.[15]

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.

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%.[16-18] 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.[19, 20] 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.[21] Rituximab may be regarded as a reasonable choice for treating patients with IgM anti-MAG antibody-related neuropathies.[22]

In a phase II study, 27 patients with either untreated or previously treated disease received bortezomib single agent using the standard schedule until they demonstrated progressive disease or were two cycles beyond best response.[23] 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.

Rituximab in combination with corticosteroids and bortezomib has been studied and found to be active in WM patients. In a Waldenström's Macroglobulinemia Clinical Trials Group (WMCTG) study, the time to achieving at least a minimum response in WM patients treated with bortezomib/dexamethasone/rituximab was 1.1 months, whereas the overall response rate was 96%, with 22% of patients achieving a complete response.[21] 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.

Other bortezomib containing regimens active in WM are bortezomib with rituximab and for rituximab intolerant individuals, bortezomib with dexamethasone can be considered.[21, 24]

In all patients receiving bortezomib-containing regimens, herpes zoster prophylaxis is strongly recommended. In addition, patients must be closely watched for the development of bortezomib-related neuropathy.

An alternative to bortezomib-containing therapy is cyclophosphamide-based regimen along with rituximab and a corticosteroid. A study by Dimopoulos et al reported that the combination of rituximab/cyclophosphamide/dexamethasone induces overall and complete responses in 78% and 7% of WM patients, respectively.[25] The 2-year progression-free survival in responders was found to be 80%. Cyclophosphamide/rituximab/dexamethasone 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. Other cyclophosphamide-containing regimen active in WM is cyclophosphamide/rituximab/prednisone (CP-R).[26] The addition of vincristine to cyclophosphamide containing regimens is associated with risk of neuropathy in WM patients.[21]

Cyclophosphamide/doxorubicin/vincristine/prednisone/rituximab (CHOP-R) is another stem cell sparing regimen reported to be active and tolerated by WM patients.[26-29] 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.[29] CHOP-R was evaluated in another small study with 13 WM patients, 8 and 5 of these were relapsed or refractory to nucleoside analogues and single agent rituximab, respectively.[28] Among 13 evaluable patients, 10 patients achieved a major response (77%) including 3 CR and 7 PR, and 2 patients achieved a minor response.[28] A small Eastern Cooperative Oncology Group trial reported the outcome of 16 previously untreated patients who were treated with CHOP-R. This trial (which was closed prematurely because of poor accrual) showed that the CHOP-R combination achieved an overall response rate of 100% with a rapid median time to response of 1.6 months; with a median follow-up time of 18.3 months. Myelosuppression was the main toxicity.[30] A retrospective study, examined the outcomes of symptomatic WM patients who received CHOP-R, CVP-R (cyclophosphamide/vincristine/ prednisone plus rituximab), or CP-R. [26] 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%). Treatment-related adverse effects including neuropathy from vincristine, febrile neutropenia, and hospitalization were higher in patients treated with CHOP-R and CVP-R versus CPR.[26]

The use of thalidomide in combination with rituximab represents an alternative choice non-toxic to stem cells in the management of WM patients. This regimen is associated with an overall response rate of 70%, and a median progression-free survival of 3 years.[31] 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.[32]

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 alone, or rituximab in combination with cyclophosphamide and steroids such as (rituximab/cyclophosphamide/dexamethasone) or (rituximab/cyclophosphamide/prednisone) or CHOP-R; with bortezomib and dexamethasone (bortezomib/dexamethasone/rituximab); with bortezomib (bortezomib/rituximab); with thalidomide (thalidomide/rituximab); [16-18, 21, 24-29] Response rates of 70-90% have been reported with rituximab based combination therapies.[12, 13] For management of rituximab intolerant patients, please see section below (on page MS-7).

Primary Treatment Regimens with Potential or Unknown Toxicity to Stem Cells

Primary treatment regimens potentially toxic to stem cells that are listed in the NCCN guidelines include: Nucleoside analogues (cladribine or fludarabine) alone or with rituximab and/or cyclophosphamide; chlorambucil. The impact of bendamustine alone or with rituximab on stem cells is unknown.

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.[33-38] However, nucleoside

analogues can cause immunosuppressive complications.[39] 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.[16] Exposure to nucleoside analogs should therefore be limited, particularly in younger patients who may be potential stem cell candidates.

The alkylating agent, chlorambucil as a single agent has shown response rates varying between 31% and 92%.[40] Chlorambucil treatment also carries with it long term complications such as myelodysplasia and acute leukemia from therapy-induced chromosomal breakage.[41] In addition, chlorambucil may cause stem cell damage. Although chlorambucil is a treatment that has proven efficacy in WM, with the availability of newer combination therapies, it is reserved for patients with limited therapeutic options.

In a multicenter, prospective clinical trial that included 43 patients with WM who were previously untreated or pretreated with chemotherapy, were treated with fludarabine, cyclophosphamide, and rituximab (FCR) regimen.[38] 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 CR and VGPR in patients with WM. However the potential risk of secondary malignancies and the myelosuppressive with FCR regimen was high.

The Study Group for Lymphomas (Stil) recently examined the activity of bendamustine plus rituximab (BR) versus CHOP-R in a large cohort of previously untreated patients with indolent non-Hodgkin's lymphoma.[42] Included in this study were 42 patients with WM/LPL, 40 of whom were available for response assessment.[43] The overall response rate with BR in this study was similar to CHOP-R (96% versus 94%, respectively). With a median follow-up of 26 months, progressive disease was documented in 2 of 23 patients treated with BR, while 7 of 17 patients treated with CHOP-R progressed. BR was associated with a lower incidence of grade 3 or 4 neutropenia, infectious complications, and alopecia in this study. These results suggest that BR may be a preferable option to CHOP-R in the frontline therapy of WM.

Follow-up after Primary Treatment

Assessment of Response

Consensus-based uniform response criteria for WM have been developed by the International Workshops on WM.[14, 44] Following primary therapy, the response to treatment should be assessed using consensus panel criteria. The updated response categories and criteria from the Sixth International Workshop on Waldenström's Macroglobulinemia[45] are summarized in NCCN treatment algorithms 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 lasts for several weeks to months.[9, 19, 20] On the other hand, bortezomib and everolimus can suppress IgM levels independent of killing tumor cells in certain patients.[46-48] The study by 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.[49] 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.

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.[50]

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

Salvage Therapy

According to the NCCN Guidelines, for relapsed disease, administering the same regimen used for primary treatment is reasonable as second-line or salvage therapy 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 lesser than 12 month 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 keep in mind for patients who are candidates for autologous stem cell transplantation, exposure to stem cell damaging agents, such as alkylators or nucleoside analogs, should be avoided, and 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. In addition, bendamustine alone or in combination with rituximab, everolimus, or alemtuzumab may be considered.[46, 47, 51-58]

In the salvage setting, the use of bortezomib alone is associated with an overall response rate of 60%, and 70-80% in combination with rituximab[23, 46, 47, 51, 54,59] with or without dexamethasone.[60] Grade 3 peripheral neuropathy may occur in up to 30% of WM patients using the twice-a-week dosing schedule, and 10% in those patients receiving once-a-week dosing. Prophylaxis against herpes zoster should be strongly considered with bortezomib and steroid combinations.

The use of everolimus has been explored in WM patients with relapsed/refractory disease.[52] The overall response rate in this study was 70%. Hematological toxicities were the most common toxicities in this study. Pulmonary toxicity may also occur in 10% of patients with everolimus.

Alemtuzumab is a fully humanized human IgG1 monoclonal antibody that targets CD52 and has established efficacy in the treatment of other lymphomas.[61, 62] In patients with WM, CD52 is widely expressed on lymphoplasmacytic cells in the bone marrow. [63] High response rates with alemtuzumab were also reported in another series of heavily pretreated WM patients.[57] In a multicenter phase II study, the activity of alemtuzumab was examined in 28 symptomatic LPL/WM patients.[58] Twenty-three of these patients were previously treated. The overall response rate in this study was 76%, with major responses in 32% of patients, and the median time to progression was 14.5 months. Hematologic and infectious complications, including CMV reactivation, were more common in previously treated patients and were indirectly associated with 3 deaths. Long-term follow-up revealed late-onset autoimmune thrombocytopenia (AITP) in 4 patients in this study which contributed to 1 death.

The FCR regimen was recently reported by Tedeschi et al to be an effective salvage regimen (discussed in the section titled "Primary

Treatment Regimens with Potential or Unknown Toxicity to Stem Cells".[38] Both short and long term toxicities including secondary malignancies need to be carefully with the use of FCR weighed against other available options.

Bendamustine either alone, or in combination with anti-CD20 antibody therapy is associated with an overall repose rate of 80%, with VGPR or better attained in 20% of patients. The median PFS in a mostly refractory population of WM/LPL patients was 13.2 months.[64]

Stem cell transplantation (SCT) is also an option for the salvage therapy of WM in selected patients.[65] 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. For management of rituximab intolerant patients, please see section below.

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 a permanent modality, and consolidation with chemotherapy considered. Post-plasmapheresis, IgM levels will return to baseline in 4-6 weeks. Chemotherapy usually is rituximab based, 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. Treatment directed at symptomatic improvement can also be considered with gabapentin, pre-gabapentin, and duloxetine while patient is undergoing plasmapheresis or is on therapy.[66-68]

Management of Patients intolerant to Rituximab

Two studies recently addressed the role of ofatumumab in patients with WM, including patients who were intolerant to rituximab.[64, 69] These studies demonstrated that ofatumumab could be successfully administered in patients with WM who were intolerant to rituximab, and were associated with responses. Therefore, ofatumumab may be considered in rituximab intolerant patients. There is a risk of IgM flare with ofatumumab as with rituximab and therefore similar precautions as those with rituximab should be considered with ofatumumab in those patients who have evidence of hyperviscosity or who have elevated IgM levels.

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 regimen.[70] 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 (ranging from 2-12) for both cohorts; and median number of rituximab infusions was 8 over a 2-year period for patients receiving M-rituximab. Categorical responses improved in

16 out of 162 (10%) patients being observed, and 36 out of 86 (41·8%) patients receiving M-rituximab respectively, following induction therapy (*P* < .0001). Both progression-free (56·3 vs. 28·6 months; *P* = .0001) and overall survival (Not reached versus 116 months; *P* = .0095) were longer in patients who received M-rituximab. Improved progression-free survival was evident despite previous treatment status, induction with rituximab alone or in combination therapy *(P* ≤ .0001). Best serum IgM response was lower (*P* < .0001), and haematocrit higher (*P* = .001) in patients receiving M-Rituximab.[70] Among patients receiving M-rituximab, an increased number of infectious events were observed, 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.

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