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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™)

Waldenström's Macroglobulinemia / Lymphoplasmacytic Lymphoma

Version 2.2011

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NCCN Guidelines™ Version 2.2011 Panel Members Waldenström's Macroglobulinemia/ Lymphoplasmacytic Lymphoma

NCCN Guidelines Index
WM/LPL Table of Contents
Discussion

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Continue

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NCCN Guidelines™ Version 2.2011 Table of Contents Waldenström's Macroglobulinemia/ Lymphoplasmacytic Lymphoma

NCCN Guidelines Index
WM/LPL Table of Contents
Discussion

Panel Members

Updates

Diagnosis, Workup, Indications for Treatment (WMLPL-1)

Primary Treatment, Relapse (WMLPL-2)

WHO Criteria for Lymphoplasmacytic Lymphoma and Waldenströms Macroglobulinemia
Waldenströms Macroglobulinemia International Workshop Criteria (WMLPL-A)

Suggested Treatment Regimens (WMLPL-B)

Suggested References (WMLPL-C)

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 2.2011 Updates Waldenström's Macroglobulinemia/ Lymphoplasmacytic Lymphoma

NCCN Guidelines Index
WM/LPL Table of Contents
Discussion

Updates in version 2.2011 NCCN Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma Guidelines include:

Discussion

- **The Discussion section has been updated to correspond with the revised algorithm.**

Updates in version 1.2011 NCCN Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma Guidelines include:

General:

Waldenströms Macroglobulinemia was originally included in the NCCN Multiple Myeloma Guidelines, it has been completely updated and reformatted as an additional Guideline to the NCCN Library of Clinical Practice Guidelines in Oncology.
The name has been changed to Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma

WMLPL-1

- **Added a new diagnostic section.**
  - **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**
- **The Workup section has been expanded to include essential tests and those that are considered useful in certain circumstances such as:**
  - **Neurology consult**
  - **Anti-MAG antibodies/anti-GM1**
  - **Electromyelogram**
  - **Fat pad biopsy and/or congo red staining of bone marrow for amyloid**
  - **Retinal exam (if IgM $\geq$ 3.0 gm/dL)**

WMLPL-A

- **A new page which includes the WHO Criteria for Lymphoplasmacytic Lymphoma and Waldenström's Macroglobulinemia and Waldenström's Macroglobulinemia International Workshop Criteria.**

WMLPL-B

- **A new page that lists suggested treatment regimens for primary therapy and salvage therapy.**

WMLPL-C

- **A new page of suggested reading.**

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NCCN Guidelines™ Version 2.2011 Waldenström's Macroglobulinemia/ Lymphoplasmacytic Lymphoma

NCCN Guidelines Index
WM/LPL Table of Contents
Discussion

DIAGNOSIS

Essential[a]

- 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[b]
- Unilateral aspirate and biopsy
- Chest/abdominal/pelvic CT

Useful in certain circumstances

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

→

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] Most patients with serum viscosity of less than 4 cP will not have symptoms of hyperviscosity.
[c] Consider in patients with suspected cryoglobulinemia.
[d] If cryocrit positive, then repeat testing of initial serum IgM, and obtain all subsequent serum IgM levels under warm conditions.
[e] In patients presenting with suspected disease related peripheral neuropathy.

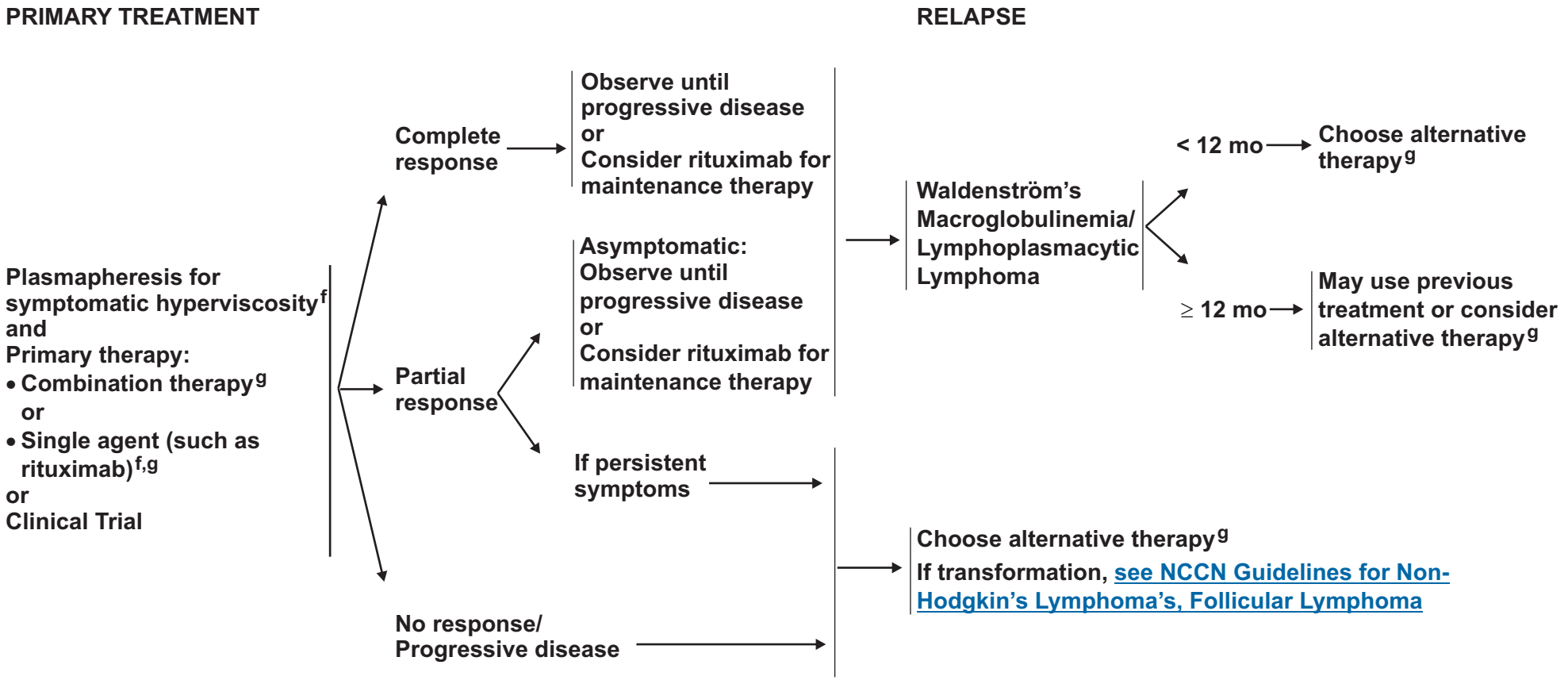
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NCCN Guidelines™ Version 2.2011
Waldenström's Macroglobulinemia/ Lymphoplasmacytic Lymphoma

NCCN Guidelines Index
WM/LPL Table of Contents
Discussion



[f]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.

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

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WHO CRITERIA FOR LYMPHOPLASMACYTIC LYMPHOMA AND WALDENSTRÖM'S MACROGLOBULINEMIA

- **Lymphoplamacytic lymphoma:**
  - **Neoplasm of small B lymohocytes, 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

Primary Therapy:

Non-stem cell toxic
- Bortezomib ± rituximab[1,2,3]
- Bortezomib, dexamethasone, rituximab[1,2,3]
- Rituximab[1]
- Rituximab/cyclophosphamide/prednisone[1]
- Rituximab/cyclophosphamide/dexamethasone[1]
- Thalidomide ± rituximab[1]

Possible stem cell toxicity and/or risk of transformation (or unknown)
- Bendamustine ± rituximab[1]
- Cladribine ± rituximab[1,4,5]
- Chlorambucil[4,5]
- Fludarabine ± rituximab[1,4,5]

Salvage Therapy:

Non-stem cell toxic
- Alemtuzumab
- Bortezomib ± rituximab[1,2,3]
- Bortezomib, dexamethasone, rituximab[1,2,3]
- Everolimus
- Rituximab[1]
- Rituximab/cyclophosphamide/prednisone[1]
- Rituximab/cyclophosphamide/dexamethasone[1]
- Thalidomide ± rituximab[1]

Possible stem cell toxicity and/or risk of transformation (or unknown)
- Bendamustine ± rituximab[1]
- Cladribine ± rituximab[1,4,5]
- Chlorambucil[4,5]
- Fludarabine ± rituximab[1,4,5]

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)[6]

[1]In patients with symptomatic hyperviscosity plasmapheresis should first be performed; plasmapheresis should also be considered before treatment with rituximab 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 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]Consider herpes zoster prophylaxis for patients treated with bortezomib.
[4]May be associated with disease transformation and/or development of MDS/AML in Waldenström's Macroglobulinemia patients.
[5]Avoid in patients who are potential autologous stem cell transplant candidates.
[6]Should ideally be undertaken in the context of a clinical trial.

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Discussion

NCCN Categories of Evidence and Consensus

Category 1: The recommendation is based on high-level evidence (e.g. randomized controlled trials) and there is uniform NCCN consensus.

Category 2A: The recommendation is based on lower-level evidence and there is uniform NCCN consensus.

Category 2B: The recommendation is based on lower-level evidence and there is nonuniform NCCN consensus (but no major disagreement).

Category 3: The recommendation is based on any level of evidence but reflects major disagreement.

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]

B_2M and albumin levels are important prognostic markers in WM.[6, 7] Their use in making treatment-related decisions remains to be clarified.[6]

Since bone marrow is 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

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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. These patients should also be considered for referral for neurologic consultation. 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), or rituximab alone, or rituximab in combination with cyclophosphamide based therapy, bortezomib based therapy, nucleoside analogue based therapy, 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]

Primary Treatment Regimens Not Toxic to Stem Cells

The suggested primary treatment regimens which are stem cell sparing listed in the NCCN guidelines include: rituximab alone, or in combination with cyclophosphamide and steroids such as R-CD (rituximab, cyclophosphamide, dexamethasone) or R-CP (rituximab, cyclophosphamide. prednisone); with bortezomib and dexamethasone

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(BDR); or with bortezomib alone (BR); or with thalidomide (Thal-R).[16-22] Response rates of 70-90% have been reported with rituximab based combination therapies.[12,13]

Single agent rituximab is also active in patients with WM, however the response rates to single agent rituximab utilizing either standard or extended dosing vary between 25% and 45%.[17-19] Transient increases in IgM titers (also called the IgM flare) have been reported in 40-50% of patients after initiation of rituximab therapy, including in circumstances when rituximab has been used in combination therapy.[23,24] 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.[25]

In a phase II study, 27 patients with either untreated or previously treated disease received bortezomib using the standard schedule until they demonstrated progressive disease or were two cycles beyond best response.[26] 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.

Addition of rituximab and corticosteroids to bortezomib has also 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, and 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 bortezomib, rituximab, and prednisone. 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, and dexamethasone induces overall and complete responses in 78% and 7% of WM patients, respectively.[16] The 2-year progression-free survival in responders was found to be 80%. Cyclophosphamide, rituximab, and 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, and prednisone.[20] The addition of vincristine to cyclophosphamide containing regimens is associated with risk of neuropathy in WM patients.[21]

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

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70%, and a median progression-free survival of 3 years.[27] 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.[28]

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 (claridribine or fludarabine) alone or with rituximab; 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 have been studied in previously untreated WM and found to induce good overall response rates with prolonged survivals.[29-33] However, nucleoside analogues can cause immunosuppressive complications.[34] In addition, there are reports indicating that nucleoside analogs increase incidence of disease transformation and development of myelodysplastic syndromes and secondary acute myelogenous leukemia in WM patients treated with nucleoside analog–containing therapy.[17] Exposure to nucleoside analogs should therefore be limited, particularly in younger patients who may be potential stem cell candidates.

The alkylating agent, chlorambucil as a single agent has shown response rates varying between 31% and 92%.[35] Chlorambucil treatment also carries with it long term complications such as myelodysplasia and acute leukemia from therapy-induced chromosomal breakage.[36] 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 recent study by the Study Group Indolent Lymphomas (STIL) group, 40 patients with WM were included in a larger study of indolent non-Hodgkin's lymphoma patients that randomized patients between CHOP-R (cyclophosphamide, doxorubicin, vincristine, prednisone with rituximab) and bendamustine-rituximab. Progression free survival for WM patients receiving bendamustine-rituximab was 80% at 4 years, which compared favorably to those patients who received CHOP-R.[37]

Follow-up after Primary Treatment

Following primary therapy, the response to treatment should be assessed using consensus panel criteria.[38]

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.[39]

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

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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, bortezomib alone or in combination with rituximab and/or steroids, bendamustine alone or in combination with rituximab, everolimus, or alemtuzumab may be considered.[37, 40-46]

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.[40,43,45,46] 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. The use of everolimus has been explored in WM patients with relapsed/refractory disease.[41,42] 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. The use of alemtuzumab was explored by the WMCTG in patients with WM/LPL.[44] The overall response rate reported in this study was 76%, with major responses in 32% of patients. Cytopenias and cytomegalovirus (CMV) re-activation were among major toxicities.

Stem cell transplantation (SCT) is also an option for the salvage therapy of WM in selected patients.[47] SCT options listed in the NCCN Guidelines 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.

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

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