Waldenström’s Macroglobulinemia

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Note: Consider Clinical Trials as treatment options for eligible patients.

ESSENTIAL:
- History and physical
- CBC with differential, BUN, creatinine, electrolytes, liver function test, hepatitis B and C serology, cryocrit\(^1\), cold agglutinins titer, LDH, beta-2 microglobulin, serum protein electrophoresis and immunofixation, serum free light chain assay (kappa and lambda), immunofixation, and quantitative immunoglobulins (IgG, IgM, IgA)
- 24 hour urine protein electrophoresis and immunofixation
- Unilateral bone marrow aspirate and biopsy
  - CXCR4 and MYD 88 L265P AS-PCR
  - PET/CT or CT neck, chest, abdomen and pelvis with IV contrast
- Lifestyle risk assessment\(^2\)

USEFUL IN CERTAIN PATIENTS:
- Fundoscopic examination\(^3\)
- Coomb’s Test
- Anti-myelin associated glycoprotein (MAG) antibody
- Anti-ganglioside monosialosyl 1 (GM1) antibody
- Electromyogram (EMG)
- Nerve conduction studies (NCS)
- Congo red staining of abdominal fat pad biopsy and/or bone marrow biopsy\(^4\)
- Serum viscosity\(^5\)
- Pseudo-von Willebrand disease testing\(^6\)

INITIAL WORK-UP

Indications for treatment:
- Symptomatic hyperviscosity
  - (eye grounds, neurologic changes)
- Anemia (Hgb less than 10 grams/dL), pancytopenia (due to marrow involvement/hypersplenism, cold agglutinin hemolytic anemia)
- Bulky adenopathy
- Symptomatic organomegaly
- Symptomatic cryoglobulinemia
- Amyloidosis
- Neuropathy
- Pseudo-von Willebrand disease

PRIMARY TREATMENT\(^7\)

- Clinical trial
- Bruton’s Tyrosine Kinase (BTK) inhibitor:
  - Ibrutinib with or without rituximab
- Proteasome inhibitor based regimen:
  - Bortezomib/rituximab with or without dexamethasone
  - Carfilzomib/rituximab with dexamethasone
- Conventional chemotherapy based regimen:
  - Alkylating agent\(^8\)/rituximab
    - Bendamustine/rituximab (preferred)
    - Rituximab/cyclophosphamide/dexamethasone
  - Nucleoside analog\(^9\)/rituximab
    - Cladribine/cyclophosphamide/rituximab
- Single-agent rituximab
- Adjunctive treatment as indicated (see Appendix A)

\(^1\) Cryocrit sample should be maintained at 37°C. If positive, maintain all SPEP samples at 37°C until processed in the lab.
\(^2\) See Physical Activity, Nutrition, and Tobacco Cessation algorithms; ongoing reassessment of lifestyle risks should be a part of routine clinical practice
\(^3\) When hyperviscosity is suspected
\(^4\) When amyloidosis suspected
\(^5\) Most patients with serum viscosity of less than 4 cP will not have symptoms of hyperviscosity
\(^6\) If clinical bruising or bleeding present
\(^7\) The use of single-agent rituximab is discouraged, particularly in patient with M-protein greater than 5 grams/dL
\(^8\) Use alkylating agents and nucleoside analog-based regimen with caution in stem cell transplant candidates

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Department of Clinical Effectiveness V4
Approved by The Executive Committee of the Medical Staff 05/28/2019
Waldenstrom’s Macroglobulinemia

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Note: Consider Clinical Trials as treatment options for eligible patients.

FOLLOW-UP/ SURVEILLANCE

- Order the following prior to each cycle during systemic therapy and at least every 3-4 months during periods of observation:
  - CBC with differential
  - SPEP
  - Quantitative immunoglobulins (cryocrit and/or cold agglutinins if initially positive)
  - Serum viscosity if symptomatic
- If abnormal finding were present during initial work-up scan, order the following every 3-6 months initially, then every 6-12 months:
  - PET/CT or CT neck, chest, abdomen and pelvis with IV contrast

MANAGEMENT OF DISEASE RELAPSE

If response to initial therapy with relapse greater than or equal to 12 months
  - Choose alternate therapy

If response to initial therapy with relapse in less than 12 months
  - Choose alternate therapy

If greater than or equal to partial response achieved (see Appendix B for response), observe until symptomatic or signs of end organ damage develop

APPRAOCH TO CHOICE OF SALVAGE TREATMENT

- If refractory to primary treatment or response to initial therapy with relapse in less than 12 months
  - Choose alternate therapy

RELAPSED/REFRACTORY TREATMENT OPTIONS

- Clinical trial
- BTK inhibitor:
  - Ibrutinib with or without rituximab
- Proteasome inhibitor based regimen
  - Bortezomib/rituximab with or without dexamethasone
  - Carfilzomib/rituximab with dexamethasone
- Conventional chemotherapy based regimen:
  - Alkylation agent\textsuperscript{1}/rituximab
    - Bendamustine/rituximab (preferred)
    - Rituximab/cyclophosphamide/dexamethasone
  - Nucleoside analog\textsuperscript{2}/rituximab
    - Cladribine/cyclophosphamide/rituximab
  - Autologous stem cell transplant (see Appendix C)
  - Allogeneic stem cell transplant (ablative or non-ablative)
- Monoclonal antibody based regimen:
  - Rituximab\textsuperscript{3}
  - Ofatumumab\textsuperscript{4}
- BCL-2 inhibitor:
  - Venetoclax
- Immunomodulator based regimen:
  - Thalidomide\textsuperscript{5}
  - Lenalidomide\textsuperscript{6}
  - Pomalidomide\textsuperscript{7}
  - miTOR inhibitor:
    - Everolimus
- Adjunctive treatment as indicated (see Appendix A)

\textsuperscript{1} Cryocrit sample should be maintained at 37\textdegree{}C. If positive, maintain all SPEP samples at 37\textdegree{}C until processed in the lab.
\textsuperscript{2} Most patients with serum viscosity of less than 4 cP will not have symptoms of hyperviscosity
\textsuperscript{3} Use alkylating agent and nucleoside analog-based regimens with caution in stem cell transplant candidates
\textsuperscript{4} For patients with M-protein greater than 5 grams/dL, use of rituximab alone is discouraged. Reports of transient increase in M-protein have been noted with the use of rituximab alone.
\textsuperscript{5} Ofatumumab can be considered in patients intolerant to rituximab

\textsuperscript{6} Caution: thalidomide is associated with high rates of treatment emergent neuropathy
\textsuperscript{7} Caution: lenalidomide may be associated with worsening anemia
\textsuperscript{8} Caution: maximum tolerated dose for pomalidomide is 1 mg
APPENDIX A: Adjunctive Treatment

Infection:
- Intravenous immunoglobulin therapy should be considered in the setting of recurrent life-threatening infection, hypogammaglobulinemia, and/or if greater than or equal to 3 infections/year.
- Consider pneumococcal vaccinations (PCV13 and PPSV23) per CDC guidelines.
- Consider annual influenza vaccine.
  - Consider high-dose influenza vaccine for patients greater than or equal to 65 years old and patients who have previously undergone a stem cell transplant (SCT)\(^1\)
  - Herpes zoster prophylaxis is indicated for patients treated with proteasome inhibitors, daratumumab, and/or high dose dexamethasone.
  - Consider use in patients receiving elotuzumab.
- Consider avoiding concomitant quinolone therapy for patients on bortezomib-containing regimens.
- Antifungal, antibacterial, and anti-zoster prophylaxis is indicated for patients receiving hyperfractionated cyclophosphamide-based therapy.
- See Appendix D for post-transplant infection prophylaxis and vaccination schedule.

Symptomatic Hyperviscosity:
- Plasmapheresis should be used as adjunctive therapy.

GI Prophylaxis:
- Patients receiving steroids should receive prophylaxis with a proton pump inhibitor or H\(_2\)-receptor antagonist.

\(^1\)While high-dose influenza vaccine appears to be safe and well-tolerated, further data is needed before recommendations can be given advocating administration for other patients.

CDC = Centers for Disease Control and Prevention
PCV13 = pneumococcal conjugate vaccine
PPSV23 = pneumococcal polysaccharide vaccine
### APPENDIX B: Response Criteria for Waldenstrom’s macroglobulinemia

<table>
<thead>
<tr>
<th>Standard IWWM Criteria</th>
<th>Response Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete response</strong></td>
<td>• IgM in normal range, <strong>and</strong> disappearance of monoclonal protein by immunofixation</td>
</tr>
<tr>
<td></td>
<td>• No histologic evidence of bone marrow involvement and resolution of any adenopathy/organomegaly, if present at baseline, along with no signs or symptoms attributable to Waldenstrom’s macroglobulinemia (WM)</td>
</tr>
<tr>
<td></td>
<td>• Reconfirmation of the complete response status is required by repeat immunofixation studies</td>
</tr>
<tr>
<td><strong>Very good partial response</strong></td>
<td>≥90% reduction of serum IgM and decreases in adenopathy/organomegaly, if present at baseline, on physical examination or on CT scan <strong>and</strong> no new symptoms or signs of active disease</td>
</tr>
<tr>
<td><strong>Partial response</strong></td>
<td>≥50% reduction of serum IgM and decrease in adenopathy/organomegaly, if present at baseline, on physical examination or on CT scan <strong>and</strong> no new symptoms or signs of active disease</td>
</tr>
<tr>
<td><strong>Minor response</strong></td>
<td>≥25% but &lt; 50% reduction of serum IgM and no new symptoms or signs of active disease</td>
</tr>
<tr>
<td><strong>Stable disease</strong></td>
<td>&lt;25% reduction <strong>and</strong> &lt;25% increase of serum IgM without progression of adenopathy/organomegaly, cytopenias, or clinically significant symptoms due to disease and/or signs of WM</td>
</tr>
<tr>
<td><strong>Progressive disease</strong>&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Any one or more of the following criteria:</td>
</tr>
<tr>
<td></td>
<td>• ≥25% increase in serum IgM by protein confirmed by a second measurement <strong>or</strong> progression of clinically significant findings due to disease (i.e., anemia, thrombocytopenia, leukopenia, bulky adenopathy/organomegaly)</td>
</tr>
<tr>
<td></td>
<td>• Symptoms (unexplained recurrent fever ≥38.4°C, drenching night sweats, ≥10% body weight loss, hyperviscosity, neuropathy, symptomatic cryoglobulinemia or amyloid) attributable to WM</td>
</tr>
</tbody>
</table>

IWWM = International Workshop on Waldenstrom’s macroglobulinemia

<sup>1</sup> CT scan may include chest, abdomen, and pelvis with contrast

<sup>2</sup> Requires two consecutive assessments made at any time before the institution of any new therapy

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**APPENDIX C: Considerations for Undergoing Autologous SCT**

<table>
<thead>
<tr>
<th>Clinical Eligibility Criteria</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>● No uncontrolled cardio/pulmonary conditions</td>
<td></td>
</tr>
<tr>
<td>● Adequate peripheral venous access or adequate option for central venous access for autologous apheresis donors</td>
<td></td>
</tr>
<tr>
<td>● Negative pregnancy test for women of child-bearing potential</td>
<td></td>
</tr>
<tr>
<td>● No known allergy to cytokines if cytokines are to be used</td>
<td></td>
</tr>
<tr>
<td>● Patients with sickle cell anemia and other hemoglobinopathies are candidates for autologous stem cell transplant as long as their clinical condition permits the collection of sufficient stem cells</td>
<td></td>
</tr>
<tr>
<td>Labs:</td>
<td></td>
</tr>
<tr>
<td>○ WBC - recommend greater than 3 K/microliter (minimum greater than 2 K/microliter)</td>
<td></td>
</tr>
<tr>
<td>○ Platelets - recommend greater than 75 K/microliter (minimum greater than 50 K/microliter)</td>
<td></td>
</tr>
<tr>
<td>● Negative pregnancy test for women of child-bearing potential</td>
<td></td>
</tr>
<tr>
<td>● No known allergy to cytokines if cytokines are to be used</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Suitability Criteria</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>● Adequate cardiac, renal, pulmonary, and hepatic function</td>
<td></td>
</tr>
</tbody>
</table>
APPENDIX D: Post-SCT Infection Prophylaxis and Vaccination Schedule (Adults)

<table>
<thead>
<tr>
<th>Antibacterial Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Levofloxacin 500 mg IV/PO once daily, starting Day -1 or if patient neutropenic at start of chemotherapy/admission (ANC ≤ 1 K/microliter)</td>
</tr>
<tr>
<td>○ Continue until ANC is &gt; 1 K/microliter after engraftment or until patient becomes febrile</td>
</tr>
<tr>
<td>○ Adjust dose for CrCl &lt; 50 mL/minute</td>
</tr>
<tr>
<td>● Alternative options (i.e., allergy or intolerance to fluoroquinolones)</td>
</tr>
<tr>
<td>○ Cefpodoxime 200 mg PO twice daily, starting Day -1 or if patient neutropenic at start of chemotherapy/admission (ANC ≤ 1 K/microliter)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antifungal Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Fluconazole 400 mg PO/IV daily from Day -1 until engraftment</td>
</tr>
<tr>
<td>○ Alternative options (i.e., allergy or intolerance to azoles)</td>
</tr>
<tr>
<td>○ Caspofungin 50 mg IV once daily</td>
</tr>
<tr>
<td>● Prior history of mold infection:</td>
</tr>
<tr>
<td>○ Voriconazole 200 mg PO twice daily</td>
</tr>
<tr>
<td>○ Posaconazole 300 mg PO once daily</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PCP Prophylaxis (continued)</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Second line options (if sulfa intolerant):</td>
</tr>
<tr>
<td>○ Consider sulfamethoxazole/trimethoprim desensitization in patients with mild rash or unknown reaction to sulfa</td>
</tr>
<tr>
<td>○ Inhaled pentamidine 300 mg every 21-28 days via Respirgard II nebulizer</td>
</tr>
<tr>
<td>○ Pentamidine 4 mg/kg IV over 90 minutes every 21 days</td>
</tr>
<tr>
<td>○ Atovaquone 1500 mg PO once daily</td>
</tr>
<tr>
<td>○ Dapsone 100 mg PO once daily</td>
</tr>
<tr>
<td>- Test for G6PD deficiency prior to initiation of therapy</td>
</tr>
<tr>
<td>- Avoid if history of life threatening reaction to sulfamethoxazole/trimethoprim</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Antiviral Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>● Herpes simplex virus (HSV)</td>
</tr>
<tr>
<td>○ Valacyclovir 500 mg PO daily starting Day -1 and continue for 6-12 months after transplant</td>
</tr>
<tr>
<td>○ Alternative option: acyclovir 400 mg PO twice daily</td>
</tr>
<tr>
<td>○ If patient unable to take medications by mouth:</td>
</tr>
<tr>
<td>- Acyclovir 250 mg/m² or 5 mg/kg IV every 12 hours</td>
</tr>
<tr>
<td>- Patients with severe mucositis: acyclovir 250 mg/m² or 5 mg/kg IV every 8 hours</td>
</tr>
<tr>
<td>○ Adjust for renal impairment</td>
</tr>
<tr>
<td>● Varicella zoster virus (VZV)</td>
</tr>
<tr>
<td>Patients with a history of shingles or VZV seropositive</td>
</tr>
<tr>
<td>○ Valacyclovir 500 mg PO twice daily, starting Day -1 for 1 year</td>
</tr>
<tr>
<td>○ Alternative option: acyclovir 800 mg PO twice daily</td>
</tr>
<tr>
<td>○ If patient unable to take medications by mouth: acyclovir 250 mg/m² or 5 mg/kg IV every 8 hours</td>
</tr>
</tbody>
</table>

Continued on next page
## APPENDIX D: Post-SCT Infection Prophylaxis and Vaccination Schedule (Adults) - continued

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Dose/Route</th>
<th>Time Post Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>6 months</td>
</tr>
<tr>
<td>Pneumococcal conjugate (PCV, Prevnar 13&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>0.5 mL IM</td>
<td>X</td>
</tr>
<tr>
<td>Pneumococcal polysaccharide (PPSV23, Pneumovax&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>0.5 mL SC or IM</td>
<td>X</td>
</tr>
<tr>
<td>Haemophilus influenzae (Hib)</td>
<td>0.5 mL IM</td>
<td>X</td>
</tr>
<tr>
<td>Diphtheria, tetanus, acellular pertussis (DTaP)&lt;sup&gt;1,2&lt;/sup&gt;</td>
<td>0.5 mL IM</td>
<td>X</td>
</tr>
<tr>
<td>Inactive polio (IPV)&lt;sup&gt;3&lt;/sup&gt;</td>
<td>0.5 mL SC or IM</td>
<td>X</td>
</tr>
<tr>
<td>Hepatitis B (HepB)</td>
<td>≤ 19 years: 0.5 mL IM, ≥ 20 years: 1 mL IM</td>
<td>X</td>
</tr>
<tr>
<td>Seasonal influenza&lt;sup&gt;4&lt;/sup&gt; (September to January/February)</td>
<td>6-35 months: 0.25 mL IM, ≥ 3 years: 0.5 mL IM</td>
<td>X</td>
</tr>
<tr>
<td>Recombinant varicella zoster vaccine (Shingrix&lt;sup&gt;®&lt;/sup&gt;)&lt;sup&gt;5&lt;/sup&gt;</td>
<td>0.5 mL IM</td>
<td>X&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

1. May substitute Tdap if DTaP unavailable
2. DTaP and IPV may be given via the combination Kinrix<sup>®</sup> at the same intervals per chart above
3. Continue yearly for life
4. Based on current studies, the recombinant varicella zoster vaccine (Shingrix<sup>®</sup>) appears to be a safe and efficacious option for post-autologous SCT patients 18 years and older
5. For post-allogeneic patients, give when recipients are greater than 2 years post SCT, greater than 1 year off immunosuppression, and greater than 8 months since IVIG
6. Second dose is 2 to 6 months after first dose

Continued on next page
# APPENDIX D: Post-SCT Infection Prophylaxis and Vaccination Schedule (Adults) - continued

## Optional Vaccines

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Dose/Route</th>
<th>Time Post Transplant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>6 months</td>
</tr>
<tr>
<td>Measles, mumps, and rubella (MMR – live vaccine)</td>
<td>0.5 mL SC</td>
<td>X</td>
</tr>
<tr>
<td>Varicella virus vaccine (Varivax® – live vaccine)</td>
<td>0.5 mL SC</td>
<td>X</td>
</tr>
<tr>
<td>Human papilloma virus (HPV, Gardasil 9®)</td>
<td>0.5 mL IM</td>
<td></td>
</tr>
<tr>
<td>Meningococcal conjugate vaccine (MCV4, Menactra®)</td>
<td>0.5 mL IM</td>
<td>X</td>
</tr>
<tr>
<td>Meningococcal type B vaccine (Bexsero®)</td>
<td>0.5 mL IM</td>
<td>X³</td>
</tr>
</tbody>
</table>

1 For live attenuated vaccines, patients must be greater than 2 years post SCT, greater than 1 year off immunosuppression, and greater than 8 months since IVIG
2 For male and female patients age 9 to 45 years
3 Two doses 4 weeks apart

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SUGGESTED READINGS

The following is not meant to be a comprehensive list of available effective treatments for Waldenstrom's macroglobulinemia (WM); WM treatments are changing rapidly and new treatments and added information regarding previous treatments are available frequently. As a result updates should be taken into consideration and for similar reasons regimens reported only by abstract have been included on this reference list.

General Overview


Alkylating Agent Based Regimens


Nucleoside Analogue Based Regimens


Continued on next page
Waldenstrom’s Macroglobulinemia

Rituximab Based Regimens


Ofatumumab Based Regimens

SUGGESTED READINGS - continued

Continued on next page
Bortezomib Based Regimens


Carfilzomib Based Regimens

Ibrutinib Based Regimens


BCL-2 Inhibitor


mTOR Inhibitor


Thalidomide/Lenalidomide/Pomalidomide Based Regimen


Stem Cell Transplant


SUGGESTED READINGS - continued
SUGGESTED READINGS - continued

Vaccinations


This practice algorithm is based on majority expert opinion of the Myeloma Center Faculty at the University of Texas MD Anderson Cancer Center. It was developed using a multidisciplinary approach that included input from the following:

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