Waldenstrom's Macroglobulinemia

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

INITIAL WORK-UP

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]

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[8]/rituximab
    - Cladribine/cyclophosphamide/rituximab
- Single-agent rituximab
- Adjunctive treatment as indicated (see Appendix A)

See Page 2 for follow-up and surveillance

[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 paient 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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Waldenstrom's Macroglobulinemia

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

MANAGEMENT OF DISEASE RELAPSE

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[1])
  - Serum viscosity[2] 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

APPROACH TO CHOICE OF SALVAGE TREATMENT

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

- If refractory to primary treatment or response to initial therapy with relapse in less than 12 months → Choose alternate therapy
- If response to initial therapy with relapse greater than or equal to 12 months →
  - May return prior therapy **or**
  - 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:
  - Alkylating agent[3]/rituximab
    - Bendamustine/rituximab (preferred)
    - Rituximab/cyclophosphamide/dexamethasone
  - Nucleoside analog[3]/rituximab
    - Cladribine/cyclophosphamide/rituximab
  - Autologous stem cell transplant (see Appendix C)
  - Allogeneic stem cell transplant (ablative or non-ablative)
- Monoclonal antibody based regimen:
  - Rituximab[4]
  - Ofatumumab[5]
- BCL-2 inhibitor:
  - Venetoclax
- Immunomodulator based regimen:
  - Thalidomide[6]
  - Lenalidomide[7]
  - Pomalidomide[8]
- mTOR inhibitor:
  - Everolimus
- 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] Most patients with serum viscosity of less than 4 cP will not have symptoms of hyperviscosity
[3] Use alkylating agent and nucleoside analog-based regimens with caution in stem cell transplant candidates
[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.
[5] Ofatumumab can be considered in patients intolerant to rituximab
[6] Caution: thalidomide is associated with high rates of treatment emergent neuropathy
[7] Caution: lenalidomide may be associated with worsening anemia
[8] Caution: maximum tolerated dose for pomalidomide is 1 mg

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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

CDC = Centers for Disease Control and Prevention
PCV13 = pneumococcal conjugate vaccine
PPSV23 = pneumococcal polysaccharide vaccine

[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

APPENDIX B: Response Criteria for Waldenstrom's macroglobulinemia

Standard IWWM Criteria	Response Criteria
Complete response	• IgM in normal range, **and** disappearance of monoclonal protein by immunofixation • No histologic evidence of bone marrow involvement and resolution of any adenopathy/organomegaly, if present at baseline, along with no signs or symptoms attributable to Waldenstrom's macroglobulinemia (WM) • Reconfirmation of the complete response status is required by repeat immunofixation studies
Very good partial response	≥ 90% reduction of serum IgM and decreases in adenopathy/organomegaly, if present at baseline, on physical examination or on CT[1] scan **and** no new symptoms or signs of active disease
Partial response	≥ 50% reduction of serum IgM and decrease in adenopathy/organomegaly, if present at baseline, on physical examination or on CT[1] scan **and** no new symptoms or signs of active disease
Minor response	≥ 25% but < 50% reduction of serum IgM and no new symptoms or signs of active disease
Stable disease	< 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[2]	Any one or more of the following criteria: • ≥ 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) • Symptoms (unexplained recurrent fever ≥ 38.4°C, drenching night sweats, ≥ 10% body weight loss, hyperviscosity, neuropathy, symptomatic cryoglobulinemia or amyloid) attributable to WM

IWWM = International Workshop on Waldenstrom's macroglobulinemia
[1] CT scan may include chest, abdomen, and pelvis with contrast
[2] Requires two consecutive assessments made at any time before the institution of any new therapy

APPENDIX C: Considerations for Undergoing Autologous SCT

Clinical Eligibility Criteria

- No uncontrolled cardio/pulmonary conditions
- Adequate peripheral venous access or adequate option for central venous access for autologous apheresis donors
- Negative pregnancy test for women of child-bearing potential
- No known allergy to cytokines if cytokines are to be used
- 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
- Labs:
  - WBC - recommend greater than 3 K/microliter (minimum greater than 2 K/microliter)
  - Platelets - recommend greater than 75 K/microliter (minimum greater than 50 K/microliter)
- Negative pregnancy test for women of child-bearing potential
- No known allergy to cytokines if cytokines are to be used

Clinical Suitability Criteria

- Adequate cardiac, renal, pulmonary, and hepatic function

Waldenstrom's Macroglobulinemia

APPENDIX D: Post-SCT Infection Prophylaxis and Vaccination Schedule (Adults)

Antibacterial Prophylaxis

- Levofloxacin 500 mg IV/PO once daily, starting Day -1 **or** if patient neutropenic at start of chemotherapy/admission (ANC ≤ 1 K/microliter)
  - Continue until ANC is > 1 K/microliter after engraftment **or** until patient becomes febrile
  - Adjust dose for CrCl < 50 mL/minute
- Alternative options (*i.e.*, allergy or intolerance to fluoroquinolones)
  - Cefpodoxime 200 mg PO twice daily, starting Day -1 **or** if patient neutropenic at start of chemotherapy/admission (ANC ≤ 1 K/microliter)

Antifungal Prophylaxis

- Fluconzaole 400 mg PO/IV daily from Day -1 until engraftment
- Alternative options (*i.e.*, allergy or intolerance to azoles)
  - Caspofungin 50 mg IV once daily
- Prior history of mold infection:
  - Voriconazole 200 mg PO twice daily
  - Posaconazole 300 mg PO once daily

PCP Prophylaxis

Start by engraftment (Day +30 and ANC > 1.5 K/microliter) and continue for at least 6 months after transplant

- First line option: sulfamethoxazole/trimethoprim (Bactrim)
  Consider initiation of folic acid 1 mg PO once daily when patients started on Bactrim prophylaxis
  - Bactrim DS (800/160 mg) 1 tablet PO daily on Monday, Wednesday, and Friday **or**
  - Bactrim SS (400/80 mg) 1 tablet PO daily **or**
  - Bactrim DS (800/160 mg) 1 tablet PO daily (reserve for patients with history of toxoplasmosis, history of toxoplasmosis IgG positive, or PCP)

PCP Prophylaxis (continued)

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

Antiviral Prophylaxis

- Herpes simplex virus (HSV)
  - Valacyclovir 500 mg PO daily starting Day -1 and continue for 6-12 months after transplant
  - Alternative option: acyclovir 400 mg PO twice daily
  - If patient unable to take medications by mouth:
    - Acyclovir 250 mg/m^2 or 5 mg/kg IV every 12 hours
    - Patients with severe mucositis: acyclovir 250 mg/m^2 or 5 mg/kg IV every 8 hours
  - Adjust for renal impairment
- Varicella zoster virus (VZV)
  Patients with a history of shingles or VZV seropositive
  - Valacyclovir 500 mg PO twice daily, starting Day -1 for 1 year
  - Alternative option: acyclovir 800 mg PO twice daily
  - If patient unable to take medications by mouth: acyclovir 250 mg/m^2 or 5 mg/kg IV every 8 hours

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APPENDIX D: Post-SCT Infection Prophylaxis and Vaccination Schedule (Adults) - continued

Vaccine	Dose/Route	Time Post Transplant					
		6 months	8 to 9 months	12 months	14 months	18 months	≥ 24 months
Pneumococcal conjugate (PCV, Prevnar 13®)	0.5 mL IM	X	X	X		X (if GVHD)	
Pneumococcal polysaccharide (PPSV23, Pneumovax®)	0.5 mL SC or IM					X (if no GVHD)	
Haemophilus influenzae (Hib)	0.5 mL IM	X	X	X			
Diphtheria, tetanus, acellular pertussis (DTaP)[1,2]	0.5 mL IM	X	X	X			
Inactive polio (IPV)[2]	0.5 mL SC or IM	X	X	X			
Hepatitis B (HepB)	• ≤ 19 years: 0.5 mL IM • > 20 years: 1 mL IM	X	X	X			
Seasonal influenza[3] (September to January/February)	• 6-35 months: 0.25 mL IM • ≥ 3 years: 0.5 mL IM	X					
Recombinant varicella zoster vaccine (Shingrix®)[4]	0.5 mL IM	X[5]		X[6]			

[1] May substitute Tdap if DTaP unavailable
[2] DTaP and IPV may be given via the combination Kinrix® at the same intervals per chart above
[3] Continue yearly for life
[4] Based on current studies, the recombinant varicella zoster vaccine (Shingrix®) 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

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APPENDIX D: Post-SCT Infection Prophylaxis and Vaccination Schedule (Adults) - continued

Optional Vaccines[1]

Vaccine	Dose/Route	Time Post Transplant					
		6 months	8 to 9 months	12 months	14 months	18 months	≥ 24 months
Measles, mumps, and rubella (MMR – *live vaccine*)	0.5 mL SC	Contraindicated in patients < 24 months post-SCT, on immunosuppression, **and/or** active GVHD					X
Varicella virus vaccine (Varivax® – *live vaccine*)	0.5 mL SC						X
Human papilloma virus[2] (HPV, Gardasil 9®)	0.5 mL IM			X	X		X
Meningococcal conjugate vaccine (MCV4, Menactra®)	0.5 mL IM			X			
Meningococcal type B vaccine (Bexsero®)	0.5 mL IM			X[3]			

[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

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.

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Nucleoside Analogue Based Regimens

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Rituximab Based Regimens

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SUGGESTED READINGS - continued

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DEVELOPMENT CREDITS

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