Waldenstrom's Macroglobulinemia

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

INITIAL WORK-UP

ESSENTIAL:

- History and physical exam
- CBC with differential, CMP, 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), 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]
- Serum viscosity[4]
- Coomb's Test[5]
- Anti-myelin associated glycoprotein (MAG) antibody[6]
- Anti-ganglioside monosialosyl 1 (GM1) antibody[6]
- Electromyogram (EMG)[6]
- Nerve conduction studies (NCS)[6]
- Congo red staining of abdominal fat pad biopsy and/or bone marrow biopsy[6,7]
- Prothrombin time (PT), Activated partial thromboplastin time (aPTT), Factor VIII (FVIII) coagulant activity, Ristocetin cofactor (RCoF) activity and Concentration of vWF antigen (vWF:Ag)[8]
- Brain/Spine MRI[9]
- Lumbar puncture[9]

Indications for treatment:

- Symptomatic hyperviscosity (eye grounds, neurologic changes)
- Anemia (Hgb < 10 grams/dL) or other cytopenias (due to marrow involvement/hypersplenism, cold agglutinin hemolytic anemia)
- Bulky adenopathy
- Symptomatic organomegaly
- Symptomatic cryoglobulinemia
- Amyloidosis
- Neuropathy
- Acquired von Willebrand disease
- CNS Involvement (Bing-Neel Syndrome)
- B symptoms

PRIMARY TREATMENT

- Clinical trial
- Bruton's Tyrosine Kinase (BTK) inhibitor:
  - Zanubrutinib
  - Ibrutinib with or without rituximab[10]
- Proteasome inhibitor based regimen:
  - Bortezomib/rituximab[10] with or without dexamethasone
  - Carfilzomib/rituximab[10] with dexamethasone
- Conventional chemotherapy based regimen:
  - Alkylating agent[11]/rituximab[10]
    - Bendamustine/rituximab
    - Rituximab/cyclophosphamide/dexamethasone
  - Nucleoside analog[11]/rituximab[10]
    - Cladribine/cyclophosphamide/rituximab
- Single-agent rituximab[10, 12]

See Appendix A for supportive care measures

See Page 2 for follow-up and surveillance

[1] Cryocrit sample should be maintained at 37°C. If positive, maintain all Serum Protein Electrophoresis (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] Most patients with serum viscosity of < 4 cP will not have symptoms of hyperviscosity
[5] When hemolytic anemia is suspected
[6] When symptoms or signs or peripheral neuropathy present
[7] When amyloidosis suspected
[8] If clinical bruising or bleeding present (concern for acquired von Willebrand disease)
[9] When central nervous system involvement suspected
[10] For rituximab intolerant patients, ofatumumab may be substituted in all rituximab containing regimens
[11] Use alkylating agents and nucleoside analog-based regimen with caution in stem cell transplant candidates
[12] The use of single-agent rituximab is discouraged, particularly in patients with M-protein > 5 grams/dL

Department of Clinical Effectiveness V5
Approved by The Executive Committee of the Medical Staff on 11/16/2021

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])
  - Free kappa and free lambda light chains
  - 24-hour UPEP
- 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 ≥ 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 < 12 months → Choose alternate therapy

If response to initial therapy with relapse ≥ 12 months →
- May return to prior therapy **or**
- Choose alternate therapy

RELAPSED/REFRACTORY TREATMENT OPTIONS

- Clinical trial
- BTK inhibitor:
  - Zanubrutinib
  - Ibrutinib with or without rituximab
  - Acalabrutinib
- Proteasome inhibitor based regimen
  - Bortezomib/rituximab with or without dexamethasone
  - Carfilzomib/rituximab with dexamethasone
- Conventional chemotherapy based regimen:
  - Alkylating agent[2]/rituximab
    - Bendamustine/rituximab
    - Rituximab/cyclophosphamide/dexamethasone
  - Nucleoside analog[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[3]
  - Ofatumumab[4]
- BCL-2 inhibitor:
  - Venetoclax

See Appendix A for supportive care measures

SPEP = Serum Protein Electrophoresis
UPEP = Urine Protein Electrophoresis

[1] Cryocrit sample should be maintained at 37°C. If positive, maintain all SPEP samples at 37°C until processed in the lab.
[2] Use alkylating agent and nucleoside analog-based regimens with caution in stem cell transplant candidates
[3] For patients with M-protein > 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.
[4] For rituximab intolerant patients, ofatumumab may be substituted in all rituximab containing regimens

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APPENDIX A: Supportive Care Measures

Infection:

- Intravenous immunoglobulin therapy should be considered in the setting of recurrent life-threatening infection, hypogammaglobulinemia, and/or if ≥ 3 infections/year
- Recommend COVID-19 vaccinations per CDC guidelines
- Recommend pneumococcal vaccinations (PCV13 and PPSV23) per CDC guidelines
- Recommend annual influenza vaccine
  - Recommend high-dose influenza vaccine for patients ≥ 65 years old and patients who have previously undergone a stem cell transplant (SCT)
- Herpes zoster prophylaxis is indicated for patients treated with proteasome inhibitors, daratumumab, and/or high dose dexamethasone
- Anti-Hepatitits B viral therapy is indicated in patients with active hepatitis B and those at risk of reactivation, who will be receiving rituximab or ofatumumab
- 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

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 > 3 K/microliter (minimum > 2 K/microliter)
  - Platelets - recommend > 75 K/microliter (minimum > 50 K/microliter)
- No known allergy to cytokines if cytokines are to be used

Clinical Suitability Criteria

- Adequate cardiac, renal, pulmonary, and hepatic function

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

- Fluconazole 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

- Hepatitis B Virus (HBV)
  - Entecavir 0.5 mg PO daily
- 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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Waldenstrom's Macroglobulinemia

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

Vaccine	Dose/Route	Time Post Transplant								
		> 3 months	4 months	5 months	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			
Pneumococcal polysaccharide (PPSV23, Pneumovax®)	0.5 mL SC or IM									
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			
Hepatitis A (Havrix®)	• ≤ 18 years: 0.5 mL IM • ≥ 19 years: 1 mL IM				X		X			
Seasonal influenza[3] (Sept-March) (Fluzone High-Dose Quadrivalent®)	0.7 mL IM				X[3]					
Recombinant varicella zoster vaccine (Shingrix®)[4]	0.5 mL IM				X		X[5]			
COVID-19 [6]	3 Doses: • Pfizer: 0.3 mL IM **or** • Moderna: 0.5 mL IM	X	X	X						

[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. In the setting of community outbreak, may start influenza vaccine as early as 3 months
[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. Continue herpes simplex virus (HSV)/VZV prophylaxis until vaccine series complete. This vaccine will not protect against HSV.
[5] Second dose is 2 to 6 months after first dose
[6] Wait until greater than 3 months from high dose chemotherapy/SCT. Pfizer-BioNTech vaccine is administered two doses 21 days apart with third dose administered ≥28 days after the second dose. Moderna vaccine is administered two doses 28 days apart with third dose administered ≥28 days after the second dose. CDC recommends third dose of the same mRNA vaccine to be used. Information may be subject to change, please refer to most updated CDC, FDA and ASH-ASTCT guidance.

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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[2] (MMR – *live vaccine*)	0.5 mL SC	Contraindicated[3] in patients less than 24 months post-SCT, on immunosuppression (should be off immunosuppression for at least 12 months)					X
Human papilloma virus (HPV, Gardasil 9®) *Patients age 9-45*	0.5 mL IM			X	X	X	
Meningococcal conjugate vaccine (MCV4, Menactra®)	0.5 mL IM	X	X				
Meningococcal type B vaccine (Bexsero®)	0.5 mL IM			X	X[4]		

[1] For live attenuated vaccines, patients must be ≥ 2 years post SCT, ≥ 1 year off immunosuppression, and ≥ 5 months since IVIG
[2] For patients that are candidates for early vaccination need 2 doses. Minimum time interval between vaccines are 4 weeks
[3] Additional contraindications to receive MMR
- Pregnancy
- CD4 count less than 200 for age 6 and older; CD4 count less than 500 for age 1 to 5 years
  - For autologous patients, if CD4 is not available, a normal lymphocyte count is adequate
- On maintenance therapies to prevent relapse (i.e. tyrosine kinase inhibitors, etc)
- Relapse leukemia or lymphoma and undergoing chemotherapy
  - Patients should be at least 3 months post-chemotherapy and in remission
- Hypogammaglobulinemia, agammaglobulinemia or other severe immunodeficiency states
  - IgG should be within normal limits

[4] 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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