**Waldenstrom’s Macroglobulinemia**

Disclaimer: This algorithm has been developed for MD Anderson using a multidisciplinary approach considering circumstances particular to MD Anderson’s specific patient population, services and structure, and clinical information. This is not intended to replace the independent medical or professional judgment of physicians or other health care providers in the context of individual clinical circumstances to determine a patient’s care. This algorithm should not be used to treat pregnant women.

**INITIAL WORK-UP**

**ESSENTIAL:**
- History and physical exam
- CBC with differential, comprehensive metabolic panel, hepatitis B and hepatitis C serology, cryocrit, cold agglutinins titer, LDH, beta-2 microglobulin, serum protein electrophoresis and immunofixation, serum free light chain assay (kappa and lambda), and quantitative immunofixation (IgG, IgM, IgA)
- 24 hour urine protein electrophoresis and immunofixation
- Unilateral bone marrow aspirate and biopsy
- PET/CT or CT neck, chest, abdomen and pelvis with IV contrast
- Lifestyle risk assessment

**USEFUL IN CERTAIN PATIENTS:**
- Funduscopic examination
- Serum viscosity
- Coomb’s Test
- Anti-myelin associated glycoprotein (MAG) antibody
- Anti-ganglioside monosialyl 1 (GM1) antibody
- Electromyogram (EMG)
- Nerve conduction studies (NCS)
- Congo red staining of abdominal fat pad biopsy and/or bone marrow biopsy
- Echocardiogram
- Prothrombin time (PT), Activated partial thromboplastin time (aPTT), Factor VIII (FVIII) coagulant activity, Ristocetin cofactor (RCOF) activity and Concentration of vWF antigen (vWF:Ag)
- Brain/Spine MRI
- Lumbar puncture

**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 (unexplained fever > 38°C during the previous month; Recurrent drenching night sweats during the previous month; Weight loss > 10% of body weight ≤ 6 months of diagnosis)

**PRIMARY TREATMENT**
- Clinical trial
- Bruton’s Tyrosine Kinase (BTK) inhibitor:
  - Zanubrutinib
  - 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/rituximab
    - Bendamustine/rituximab
    - Rituximab/cyclophosphamide/dexamethasone
  - Nucleoside analog/rituximab
    - Cladribine/cyclophosphamide/rituximab
- Single-agent rituximab
- See Appendix A for supportive care measures

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

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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 Treatment algorithms; ongoing reassessment of lifestyle risks should be a part of routine clinical practice.

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

### MANAGEMENT OF DISEASE RELAPSE

#### 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
  - Nucleoside analog
  - Autologous stem cell transplant
  - Allogeneic stem cell transplant (ablative or non-ablative)
- Monoclonal antibody based regimen:
  - Rituximab
  - Ofatumumab
- B-cell lymphoma 2 (Bel-2) inhibitor:
  - Venetoclax
- See Appendix A for supportive care measures

### APPROACH TO CHOICE OF SALVAGE TREATMENT

1. If partial response achieved
2. If ≥ partial response achieved
   - Refractory to primary treatment or response to initial therapy with relapse < 12 months
   - Choose alternate therapy
   - Discuss Goal Concordant Care (GCC) with patient or if clinically indicated, with Patient Representative
3. May return to prior therapy or
   - Refractory to primary treatment or response to initial therapy with relapse ≥ 12 months
   - Choose alternate therapy

### 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)
  - Free kappa and free lambda light chains
  - 24-hour UPEP
- If abnormal finding 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

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 GCC should be initiated by the Primary Oncologist. If Primary Oncologist is unavailable, Primary Team/Attending Physician to initiate GCC discussion and notify Primary Oncologist. Patients, or if clinically indicated, the Patient Representative should be informed of therapeutic and/or palliative options. GCC discussion should be consistent, timely, and re-evaluated as clinically indicated. The Advance Care Planning (ACP) note should be used to document GCC discussion. Refer to GCC home page (for internal use only).

3 Use alkylating agent and nucleoside analog-based regimens with caution in stem cell transplant candidates
4 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.
5 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 Centers for Disease Control and Prevention (CDC) guidelines
- Recommend pneumococcal vaccinations 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-Hepatitis 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
- Consider adding pneumocystis jiroveci pneumonia (PJP) prophylaxis for patients receiving bendamustine/rituximab or cladribine/cyclophosphamide/rituximab

Symptomatic Hyperviscosity:
- Plasmapheresis should be used as adjunctive therapy

GI Prophylaxis:
- Patients receiving steroids should receive prophylaxis with a proton pump inhibitor or H₂-receptor antagonist

1 Refer to CDC vaccine schedules
## APPENDIX B: Response Criteria for Waldenstrom’s Macroglobulinemia

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<tr>
<th>Standard IWWM Criteria</th>
<th>Response Criteria</th>
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| 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 CT¹ 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 CT¹ 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 disease²             | 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
Waldenstrom’s Macroglobulinemia

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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


MD Anderson Institutional Policy #CLN1202. Advance Care Planning Policy. Advance Care Planning (ACP) Conversation Workflow (ATT1925)


Alkylating Agent Based Regimens


Nucleoside Analog Based Regimens


Continued on next page
continued

SUGGESTED READINGS - continued

Bortezomib Based Regimens

Carfilzomib Based Regimens

Acalabrutinib Based Regimen

Ibrutinib Based Regimens

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Rituximab Based Regimens


Ofatumumab Based Regimens


BCL-2 Inhibitor


Zanubrutinib


SUGGESTED READINGS - continued

Continued on next page
SUGGESTED READINGS - continued

Stem Cell Transplant


Vaccinations


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DEVELOPMENT CREDITS

This practice algorithm is based on majority expert opinion of the Myeloma Center providers 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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