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

INITIAL WORK-UP

**ESSENTIAL:**
- History and physical
- CBC, differential and platelets
- BUN, creatinine, electrolytes, liver function tests
- Quantitative immunoglobulins
- Beta-2 microglobulin
- Lactate dehydrogenase (LDH)
- Serum protein electrophoresis (SPEP)
- Serum immunofixation electrophoresis (SIFE)
- Urine protein electrophoresis (UPEP)
- Urine immunofixation electrophoresis (UIFE)
- Serum viscosity¹
- Hepatitis B and C serology
- Cryocrit²
- Cold agglutinins titer
- Unilateral bone marrow aspirate and biopsy
- Chest x-ray
- CT of Chest/abdomen/pelvic

**USEFUL IN CERTAIN PATIENTS:**
- CXCR4 and MYD 88 L265P AS-PCR testing of bone marrow biopsy
- Fundoscopic examination³
- Coomb’s Test
- Anti-Myelin Associated Glycoprotein Antibody/ Anti-GM1 Antibody Electromyogram
- Congo red staining of abdominal fat pad biopsy and/or bone marrow biopsy

**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

**PRIMARY TREATMENT**

- Clinical trial
- BTK inhibitor:
  - Ibrutinib
- Proteosome inhibitor based regimen
  - Bortezomib/rituximab with or without dexamethasone
  - Carfilzomib/rituximab with dexamethasone
- Conventional chemotherapy based regimen:
  - Alkylating agent⁴ – rituximab
  - Nucleoside analog⁴ – rituximab

Note: 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.

¹ Most patients with serum viscosity of less than 4 cP will not have symptoms of hyperviscosity.
² Cryocrit sample should be maintained at 37° C. If positive, maintain all SPEP samples at 37° C until processed in the lab.
³ When hyperviscosity is suspected.
⁴ Use alkylating agents and nucleoside analog-based regimen with caution in stem cell transplant candidates.
### FOLLOW-UP SURVEILLANCE

- At least every 2 cycles:
  - CBC, differential and platelets
  - SPEP
- Quantitative immunoglobulins (cryocrit and/or cold agglutinins if initially positive)
- Every 3-6 months initially then every 6-12 months (if abnormal at presentation)
- CT chest/abdomen/pelvic scans
- Serum viscosity (usually only useful if symptomatic)

### MANAGEMENT OF DISEASE RELAPSE

If primary refractory or had response with relapse less than 12 months

- Choose alternate therapy

If response to initial therapy greater than or equal to 12 months

- May return prior therapy or Choose alternate therapy

### APPROACH TO CHOICE OF SALVAGE TREATMENT

Observe until symptomatic or evidence of hyperviscosity develops

### RELAPSED/REFRACTORY WM TREATMENT OPTIONS

- Clinical trial
- BTK inhibitor:
  - Ibrutinib
- Proteosome inhibitor based regimen
  - Bortezomib-rituximab with or without dexamethasone
  - Carfilzomib-rituximab with dexamethasone
- Conventional chemotherapy based regimen:
  - Alkylating agent-rituximab
  - Nucleoside analog
  - Autologous Stem Cell Transplant
  - Allogeneic Stem Cell Transplant (ablative or non-ablative)
- Immunomodulator based regimen
  - Thalidomide
  - Pomalidomide
  - Lenalidomide
- Monoclonal antibody-based regimen
  - Rituximab
  - Ofatumumab
  - Alemtuzumab
- mTOR inhibitor
  - Everolimus

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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 Caution: thalidomide is associated with high rates of treatment emergent neuropathy.
5 Caution: max tolerated dose for Pomalidomide is 1mg
6 Caution: lenalidomide may be associated with worsening anemia
7 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.
8 Ofatumumab can be considered in patients intolerant to rituximab.
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**


**Nucleoside Analogue-Based**


SUGGESTED READINGS - continued

Rituximab-Based


Alemtuzumab

SUGGESTED READINGS - continued

**Ofatumumab-Based**


**Bortezomib-Based**


**Carfilzomib-Based**


**Ibrutinib-Based**


SUGGESTED READINGS - continued

mTOR


Thalidomide/Lenalidomide/Pomalidomide-Based


Stem Cell Transplant


STRADA NUOVA 134, 27100 PAVIA, ITALY: FERRATA STORTI FOUNDATION.

This practice algorithm has been specifically developed for MD Anderson using a multidisciplinary approach and taking into consideration circumstances particular to MD Anderson, including the following: MD Anderson’s specific patient population; MD Anderson’s services and structure; and MD Anderson’s clinical information. Moreover, this algorithm is not intended to replace the independent medical or professional judgment of physicians or other health care providers. This algorithm should not be used to treat pregnant women.

DEVELOPMENT CREDITS

This practice guideline is based on majority expert opinion of the Myeloma Center Faculty at the University of Texas, MD Anderson Cancer Center.

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