Treatment of Waldenström’s Macroglobulinemia
Mayo Consensus

Scottsdale, Arizona  Rochester, Minnesota  Jacksonville, Florida
Mayo Clinic Consensus for Newly Diagnosed Waldenström’s Macroglobulinemia

- Waldenstrom Macroglobulinemia (WM) is a B-cell lymphoproliferative disorder (LPD) characterized by lymphoplasmacytic infiltration of marrow and/or lymphatic tissue and monoclonal immunoglobulin M protein in the serum.

- For the diagnosis of smoldering WM, the Mayo Clinic criteria require marrow infiltration by ≥ 10% clonal lymphoplasmacytic cells and/or IgM monoclonal protein of ≥ 3g/dL and absence of end-organ damage/symptoms attributable to LPD.

- WM remains an incurable disease with the currently available therapies.

- Treatment is evolving rapidly as more effective agents and combinations become available.

- mSMART is a consensus opinion that takes into account the specific indications for treatment and the currently available therapeutic options.

- The general approach is presented here (mSMART – off-study). However, clinical trials must be considered and are preferred at every level.

- We recommend that all patients with newly diagnosed WM be seen at least once at a referral center with expertise in the management of this rare disease.
In cases of suspected lymphoplasmacytic lymphoma that are histopathologically difficult to interpret, we recommend checking MYD88 L265P mutation status by allele-specific polymerase-chain-reaction (AS-PCR) assay.

In addition to performing a bone marrow (± lymph node/involved tissue) biopsy and monoclonal protein studies at diagnosis, we check CBC, liver function tests, creatinine, serum beta 2 microglobulin, lactate dehydrogenase, computerized tomography (CT) of chest, abdomen and pelvis or a combined 18F-FDG positron emission tomography (PET)/CT scan for assessment of lymphadenopathy, extramedullary disease/organomegaly.

Cryocrit, serum viscosity, Coombs test /cold autoantibody, electromyogram and hepatitis C profile may be checked depending on the presenting signs/symptoms.

If coexisting AL-Amyloidosis is suspected, NT-pro BNP, troponin T, echocardiogram with strain imaging, coagulation parameters and a fat aspirate to detect amyloid material should be performed.

Fundoscopic examination is recommended in all patients with visual disturbance, hyperviscosity symptoms and/or IgM ≥3000 mg/dL.

Clinicians should be aware of rituximab-induced IgM flare, the delay in achieving maximal response post-therapy as well as the discordance between the monoclonal protein and bone-marrow response states with certain therapies (e.g. ibrutinib, everolimus).
Consensus for Newly Diagnosed Waldenström Macroglobulinemia

- IgM MGUS (<10% lymphoplasmacytic infiltration)
- Asymptomatic/smoldering Waldenstrom’s
- Hemoglobin ≥11 g/dL
- Platelets ≥120 x 10^9/L

- Hemoglobin <11 g/dL or symptomatic
- Platelets <120 x 10^9/L
- IgM-related neuropathy
- WM-associated hemolytic anemia
- Symptomatic cryoglobulinemia

- Bulky Disease
- Profound cytopenias –
  - Hemoglobin ≤10 g/dL
  - Platelets <100 x10^9/L
- Constitutional symptoms
- Hyperviscosity symptoms

Observation

- Hyperviscosity symptoms
  - Yes
  - No

Plasmapheresis

Single Agent Rituximab†
(1 cycle; no maintenance therapy)
†plasmapheresis if hyperviscosity develops with treatment

Bendamustine + Rituximab (BR)* x 4-6 cycles
No rituximab maintenance therapy
Harvest stem cells if ≤ 70 years and potential autologous stem cell transplantation candidate in future

* Dexamethasone + Rituximab + Cyclophosphamide (DRC) x 6 cycles is an alternative if the disease burden is low

v4 Revised April 2015
**Waldenström Macroglobulinemia Consensus for Salvage Therapy**

**Time to next therapy**

- ≥ 3 years from previous therapy

### Yes

- Repeat Original Therapy

### No

- Ibrutinib monotherapy*
- BDR if preexisting PN < Grade 2*
- BR*
- DRC*

**Autologous stem cell transplant in select patients**

*If not previously used.

For multiply relapsed or refractory disease, in addition to the regimens listed above, consider nucleoside analog (cladribine or fludarabine)-based regimens or everolimus as alternatives.

DRC = Dexamethasone + Rituximab + Cyclophosphamide; BR = Bendamustine + Rituximab; BDR = Bortezomib (weekly), Dexamethasone + Rituximab; PN = peripheral neuropathy

v4 Revised April 2015