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 $\geq 10\%$ clonal lymphoplasmacytic cells and/or IgM monoclonal protein of $\geq 3\text{g/dL}$ 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.
mSMART for WM

- 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 10⁹/L

- Hemoglobin <11 g/dL or symptomatic
- Platelets <120 x 10⁹/L
- IgM-related neuropathy
- WM-associated hemolytic anemia
- Symptomatic cryoglobulinemia

- Bulky Disease
- Profound cytopenias –
  - Hemoglobin ≤10 g/dL
  - Platelets <100 x10⁹/L
- Constitutional symptoms
- Hyperviscosity symptoms

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**Observation**

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- Platelets ≥120 x 10⁹/L

**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

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

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