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mSMART

Mayo Stratification of Macroglobulinemia And Risk-adapted Therapy

Version 6. Last reviewed Feb 2023

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- Waldenström 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 malignancy with currently available therapies.
- Treatment continues to evolve as more effective agents become available.
- mSMART is a consensus opinion that considers specific indications for treatment and integrates the effective treatment strategies that are currently available.
- The general off-study approach is presented here (mSMART). However, clinical trials must be considered and are preferred in every setting.
- We recommend that all patients with newly diagnosed WM be evaluated at least once at a referral center with expertise in the management of this rare malignancy.

Ansell S. et al. Mayo Clin Proc. 2010; 85(9):824-833.; Kapoor P et al. JAMA Oncol. 2017;3(9):1257-1265 mSMART v6 //last reviewed Feb 2023

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- Perform MYD88^{L265P} mutational analysis on bone marrow sample in all cases of WM by allele-specific polymerase-chain-reaction (AS-PCR) assay.
- Perform CXCR4 mutational analysis, if available.
- Perform bone marrow (± lymph node/involved tissue) biopsy, monoclonal protein studies and imaging studies (computerized tomography (CT) of chest, abdomen and pelvis or a combined 18F-FDG positron emission tomography (PET)/CT scan to assess lymphadenopathy, extramedullary disease and organomegaly) at diagnosis.
- Check CBC with differential count, liver function tests, serum creatinine, serum beta 2 microglobulin and serum lactate dehydrogenase.
- Check cryocrit, serum viscosity, serum iron studies, electromyogram, coagulation profile, VWF antigen, VWF activity and Factor VIII:C, direct antiglobulin test, cold agglutinin titers and hepatitis C profile depending on the presenting signs/symptoms.
- If coexisting AHL-Amyloidosis is suspected, check NT-pro BNP, troponin T, 2D echocardiogram with strain, coagulation parameters and a fat aspirate.
- Perform fundoscopic examination in all patients with visual disturbance, hyperviscosity symptoms and/or IgM ≥3000 mg/dL.
- Be aware of rituximab-induced IgM flare, the delay in achieving maximal response post-therapy, the discordance between the monoclonal protein and bone-marrow response states with certain therapies (e.g., ibrutinib, everolimus) and BTK inhibitor-discontinuation associated withdrawal symptoms/IgM rebound.

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Newly Diagnosed Waldenström Macroglobulinemia

◆ IgM MGUS (<10%clonal infiltrate) ◆ Smoldering (asymptomatic) WM	◆IgM-related neuropathy ◆ WM-associated hemolytic anemia ◆ Symptomatic cryoglobulinemia	◆ Bulky (≥5 cm max. diameter) or symptomatic lymphadenopathy ◆ Clinically significant cytopenias: -Hemoglobin ≤10g/dL -Platelet count <100 x10^9/L ◆ Hyperviscosity symptoms[3] ◆ Constitutional symptoms ◆ Concurrent ALH amyloidosis[4]
↓	↓	↓
Observation (irrespective of IgM level)	Rituximab x 1 cycle[1,2] (no maintenance therapy)	i) Bendamustine-Rituximab (BR) x 6 cycles[4] (no rituximab maintenance) or ii) Zanubrutinib[5]

[1]Initiate plasmapheresis if symptomatic hyperviscosity develops in the setting of IgM flare. Avoid rituximab monotherapy if baseline IgM level ≥ 4000 mg/dL and consider preemptive plasmapheresis prior to initiating rituximab to avert IgM flare associated hyperviscosity symptoms.

[2]May use Bendamustine-rituximab (BR) X 4 cycles in young, fit patients with symptomatic cold agglutinin anemia. Sutimlimab may be used in patients with symptomatic cold agglutinin anemia, unresponsive to B cell directed therapies.

[3]Measure baseline serum viscosity and initiate plasmapheresis followed by cytoreductive therapy; alternatively, may directly proceed to cytoreductive therapy but omit rituximab for 1-2 cycles to avoid IgM flare induced worsening of symptoms.

[4]May consider auto SCT in select young patients in first remission if concurrent ALH amyloidosis with adequate cardiorenal function.

[5]Continuous zanubrutinib until progression or unacceptable toxicity is an alternative to BR for patients without concurrent AHL, irrespective of the MYD88 gene mutation status.

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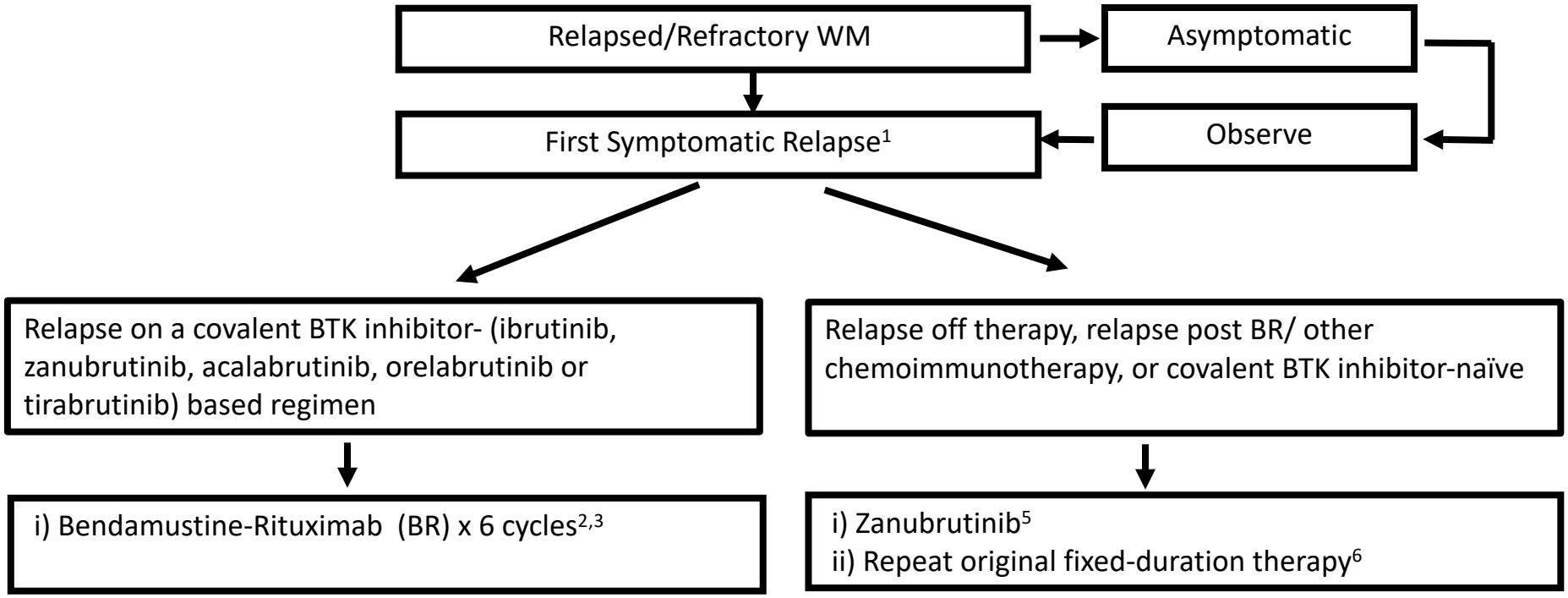
Waldenström Macroglobulinemia: First Relapse



[1]Bulky (≥5 cm max. diameter) or symptomatic lymphadenopathy, clinically significant cytopenias (hemoglobin ≤10 g/dL; platelet count <100 x10^9/L), hyperviscosity-related symptoms or constitutional symptoms.

[2]If symptomatic hyperviscosity suspected, measure baseline serum viscosity, perform fundoscopic examination and initiate plasmapheresis followed by cytoreductive therapy; alternatively, may directly proceed to cytoreductive therapy, but omit rituximab for 1-2 cycles to avoid IgM flare induced worsening of symptoms.

[3]If chemoimmunotherapy not used previously. In the frail patient population, DRC (Dexamethasone, Rituximab, Cyclophosphamide) regimen may be used as an alternative to BR.

[5] If a BTK inhibitor not used previously; ibrutinib alone (only if the patient has $MYD88^{mut}$), ibrutinib-rituximab or acalabrutinib may be used if zanubrutinib unavailable.

[6]May consider repeating original fixed-duration chemoimmunotherapy if durable response obtained previously (time-to- previous therapy ≥4 years) and patient not a candidate for a BTK inhibitor.

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Waldenström Macroglobulinemia: Second or Later Symptomatic Relapse[1,2]

Previously received both chemoimmunotherapy and covalent BTKi-based therapies

Yes

- Venetoclax[3]
- Pirtobrutinib[3]
- BDR[4]
- ASCT in select patients[5]
- Repeat previously used fixed duration therapy[6]

No

- Refer to the algorithm for first relapse

[1]Bulky (≥5 cm max. diameter) or symptomatic lymphadenopathy, clinically significant cytopenias (hemoglobin ≤10 g/dL; platelet count <100 x10^9/L), hyperviscosity-related symptoms or constitutional symptoms.

[2]If symptomatic hyperviscosity suspected, measure baseline serum viscosity, perform fundoscopic examination and initiate plasmapheresis followed by therapy; alternatively, may directly proceed to therapy, but omit rituximab for 1-2 cycles to avoid IgM flare induced worsening of symptoms.

[3] Until progression or unacceptable toxicity

[4]BDR consists of a single 21-day cycle of bortezomib alone (1.3 mg/m2 subcutaneously on days 1, 8, and 15), followed by weekly subcutaneous bortezomib (1.6 mg/m2 on days 1, 8, 15, and 22) for 4 additional 35-day cycles, with IV dexamethasone (40 mg) and IV rituximab (375 mg/m2) on cycles 2 and 5, for a total treatment duration of 23 weeks.). Use only in the absence of peripheral neuropathy or if preexisting peripheral neuropathy < Grade 2 .

[5]May consider autologous stem cell transplantation (ASCT) as an option if not exercised previously for a fit patient with chemosensitive disease or concurrent AHL amyloidosis.

[6]May consider repeating original fixed-duration chemoimmunotherapy if durable response obtained previously (time-to-previous therapy ≥4 years) and patient not a candidate for a BTK inhibitor. Purine analog-based regimens and everolimus are effective, but owing to their side effects, are best reserved for patients without alternatives.

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