WALDENSTROM MACROGLOBULINEMIA/LYMPHOPLASMACYTIC LYMPHOMA TREATMENT REGIMENS (Part 1 of 4)

Clinical Trials: The National Comprehensive Cancer Network recommends cancer patient participation in clinical trials as the gold standard for treatment.

Cancer therapy selection, dosing, administration, and the management of related adverse events can be a complex process that should be handled by an experienced healthcare team. Clinicians must choose and verify treatment options based on the individual patient; drug dose modifications and supportive care interventions should be administered accordingly. The cancer treatment regimens below may include both U.S. Food and Drug Administration-approved and unapproved indications/regimens. These regimens are only provided to supplement the latest treatment strategies.

These Guidelines are a work in progress that may be refined as often as new significant data becomes available. The NCCN Guidelines® are a consensus statement of its authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult any NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The NCCN makes no warranties of any kind whatsoever regarding their content, use, or application and disclaims any responsibility for their application or use in any way.

Primary Therapy for Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma (WM/LPL)[1]

Note: All recommendations are Category 2A unless otherwise indicated.

Preferred Regimens

REGIMEN	DOSING
Bendamustine + rituximab[2,a,b]	**Days 1–2:** Bendamustine 90mg/m^2 IV, ± **Day 1:** Rituximab 375mg/m^2 IV. Repeat every 4 weeks for 4 cycles.
Bortezomib + dexamethasone + rituximab[3,4,b,c,d,e]	**Days 1, 4, 8, and 11:** Bortezomib 1.3mg/m^2 IV + dexamethasone 40mg IV. **Day 11:** Rituximab 375mg/m^2 IV. Repeat for 4 consecutive cycles as induction therapy and follow with 4 maintenance cycles, each given 3 months apart.
Rituximab + cyclophosphamide + dexamethasone[5,b]	**Day 1:** Dexamethasone 20mg IV followed by rituximab 375mg/m^2 IV **Days 1–5:** Cyclophosphamide 100mg/m^2 orally twice daily. Repeat every 21 days for 6 months.

Other Recommended Regimens

Bendamustine[6]	**Days 1-2:** Bendamustine 90mg/m^2 IV over 10 minutes **OR** IV over 30 minutes (based on product selection) **OR** **Days 1-2:** Bendamustine 70mg/m^2 over 10 minutes **OR** IV over 30 minutes (based on product selection; if advanced age, previously received nucleoside analogue, renal insufficiency). Repeat every 4 weeks for 6 cycles.
Bortezomib ± rituximab[7,b,c,d,e]	**Days 1, 8, and 15:** Bortezomib 1.6mg/m^2 IV, ± **Days 1, 8, 15, and 22 on cycles 1 and 4:** Rituximab 375mg/m^2 IV. Repeat every 28 days for 6 cycles.
Bortezomib + dexamethasone[8,d,e]	**Days 1, 4, 8, and 11:** Bortezomib 1.3mg/m^2 IV **Days 1, 4, 8, and 11:** Dexamethasone 40mg IV. Repeat for 4 consecutive cycles as induction therapy and follow with 4 maintenance cycles, each given 3 months apart.
CaRD (Carfilzomib + rituximab + dexamethasone)[9,10,b,d,f]	**Induction:** **Days 1, 2, 8, 9, 15, and 16:** Carfilzomib 20mg/m^2 20-minute IV infusion (cycle 1), then 36mg/m^2 30-minute IV infusion (cycles 2–6) **Days 1, 2, 8, and 9:** Dexamethasone 20mg IV **Days 2 and 9:** Rituximab 375mg/m^2 **Maintenance:** **Days 1, 2, 8, 9, 15, and 16:** Carfilzomib 36mg/m^2 IV **Days 1 and 2:** Dexamethasone 20mg IV **Day 2:** Rituximab 375mg/m^2. Repeat every 21 days for 6 induction cycles, then 8 weeks later, begin maintenance every 8 weeks for 8 cycles.
Cladribine ± rituximab[11,b,d,h,i]	**Days 1–5:** Cladribine 0.1mg/kg subcutaneous injection, ± **Day 1:** Rituximab 375mg/m^2 IV. Repeat every 4 weeks for 4 cycles.
Cyclophosphamide + doxorubicin + vincristine + prednisone + rituximab[12,13,b,e,j]	**Day 1:** Cyclophosphamide 750mg/m^2 IV + doxorubicin 50mg/m^2 IV + vincristine 1.4mg/m^2 (max 2mg) IV + rituximab 375mg/m^2 IV **Days 1–5:** Prednisone 100mg orally. Repeat every 3 weeks for 6 cycles.

continued

WALDENSTROM MACROGLOBULINEMIA/LYMPHOPLASMACYTIC LYMPHOMA TREATMENT REGIMENS (Part 2 of 4)

Primary Therapy for Waldenstrom Macroglobulinemia/Lymphoplasmacytic Lymphoma (WM/LPL)[1] (continued)

Other Recommended Regimens (continued)

REGIMEN	DOSING
Fludarabine ± rituximab[14,b,d,h,i]	**Weeks 5, 9, 13, 19, 23, and 27:** Fludarabine 25mg/m^2 IV daily for 5 days, ± **Weeks 1–4, 17, 18, 30, and 31:** Rituximab 375mg/m^2 IV per week.
Fludarabine + cyclophosphamide + rituximab[15,a,b,d,h,i]	**Day 1:** Rituximab 375mg/m^2 IV **Days 2–4:** Fludarabine 25mg/m^2 IV + cyclophosphamide 250mg/m^2 IV. Repeat every 28 days for a maximum of 6 cycles.
Ibrutinib[16,g]	Ibrutinib 420mg orally once daily. Continue treatment until disease progression or unacceptable toxicity.
Rituximab[17,b]	**Day 1:** Rituximab 375mg/m^2 IV. Repeat every 7 days for 4 weeks.
Rituximab + cyclophosphamide + prednisone[18,b]	**Day 1:** Rituximab 375mg/m^2 IV + cyclophosphamide 1,000mg/m^2 IV **Days 1–5:** Prednisone 100mg orally. Repeat every 21 days for 6 cycles.

Therapy for Previously Treated WM/LPL[1]

Preferred Regimens

Bendamustine + rituximab[2,a,b]	**Days 1–2:** Bendamustine 90mg/m^2 IV, ± **Day 1:** Rituximab 375mg/m^2 IV. Repeat every 4 weeks for 4 cycles.
Bortezomib + dexamethasone + rituximab[3,4,b,c,d,e]	**Days 1, 4, 8, and 11:** Bortezomib 1.3mg/m^2 IV **Day 11:** Rituximab 375mg/m^2 IV **Days 1, 4, 8, and 11:** Dexamethasone 40mg IV. Repeat for 4 consecutive cycles as induction therapy and follow with 4 maintenance cycles, each given 3 months apart.
Ibrutinib[16,g]	Ibrutinib 420mg orally daily for 2 years or until disease progression or unacceptable drug toxicity.
Rituximab + cyclophosphamide + dexamethasone[5,b]	**Days 1–5:** Cyclophosphamide 100mg/m^2 orally twice daily **Day 1:** Dexamethasone 20mg IV followed by rituximab 375mg/m^2 IV. Repeat every 21 days for 6 months.

Other Recommended Regimens

Bendamustine[6]	**Days 1-2:** Bendamustine 90mg/m^2 IV over 10 minutes **OR** IV over 30 minutes (based on product selection) **OR** **Days 1-2:** Bendamustine 70mg/m^2 over 10 minutes **OR** IV over 30 minutes (based on product selection; if advanced age, previously received nucleoside analogue, renal insufficiency). Repeat every 4 weeks for 6 cycles.
Bortezomib ± rituximab[7,b,c,d,e]	**Days 1, 8, and 15:** Bortezomib 1.6mg/m^2 IV, ± **Days 1, 8, 15, and 22 on cycles 1 and 4:** Rituximab 375mg/m^2 IV. Repeat every 28 days for 6 cycles.
Bortezomib + dexamethasone[8,d,e]	**Days 1, 4, 8, and 11:** Bortezomib 1.0 or 1.3mg/m^2 If disease progression after 2 cycles of stable disease or after first 4 cycles of bortezomib: Dexamethasone 20mg orally on the day of and the day after each bortezomib dose.
Cladribine ± rituximab[11,b,d,h,i]	**Days 1–5:** Cladribine 0.1mg/kg subcutaneous injection, ± **Day 1:** Rituximab 375mg/m^2 IV. Repeat every 4 weeks for 4 cycles.
Cyclophosphamide + doxorubicin + vincristine + prednisone + rituximab[12,13,b,e,j]	**Day 1:** Cyclophosphamide 750mg/m^2 IV + doxorubicin 50mg/m^2 IV + vincristine 1.4mg/m^2 (max 2mg) IV + rituximab 375mg/m^2 IV **Days 1–5:** Prednisone 100mg orally. Repeat every 3 weeks for 6 cycles.

continued

WALDENSTROM MACROGLOBULINEMIA/LYMPHOPLASMACYTIC LYMPHOMA TREATMENT REGIMENS (Part 3 of 4)

Therapy for Previously Treated WM/LPL[1] (continued)

Other Recommended Regimens (continued)

REGIMEN	DOSING
Everolimus[19]	Everolimus 10mg orally daily for 4 weeks (1 cycle). Repeat until disease progression or unacceptable drug toxicity.
Fludarabine ± rituximab[14,b,d,h,i]	**Weeks 5, 9, 13, 19, 23, and 27:** Fludarabine 25mg/m^2 IV daily for 5 days, ± **Weeks 1–4, 17, 18, 30, and 31:** Rituximab 375mg/m^2 IV per week.
Fludarabine + cyclophosphamide + rituximab[15,a,b,d,h,i]	**Day 1:** Rituximab 375mg/m^2 IV **Days 2–4:** Fludarabine 25mg/m^2 IV + cyclophosphamide 250mg/m^2 IV. Repeat every 28 days for a maximum of 6 cycles.
Rituximab[17,b]	**Day 1:** Rituximab 375mg/m^2 IV. Repeat every 7 days for 4 weeks.
Rituximab + cyclophosphamide + prednisone[18,b]	**Day 1:** Rituximab 375mg/m^2 IV + cyclophosphamide 1,000mg/m^2 IV **Days 1–5:** Prednisone 100mg orally. Repeat every 21 days for 6 cycles.
Useful in Certain Situations	
Ofatumumab (for rituximab-intolerant individuals)[20,b,k]	**Week 1:** Ofatumumab 300mg IV **Weeks 2–4:** Ofatumumab 1,000mg IV. **OR** **Week 1:** Ofatumumab 300mg IV **Weeks 2–5:** Ofatumumab 2,000mg IV.
Stem Cell Transplant	
Autologous Stem Cell Transplant[21]	Treatment varied depending on local protocols.
Allogeneic stem cell transplant (ablative or nonablative)[22,l]	Preferably undertaken in the context of a clinical trial.

[a] Pneumocystis jiroveci pneumonia (PJP) prophylaxis should be considered for patients receiving bendamustine/rituximab or fludarabine/cyclophosphamide/rituximab.

[b] In patients with symptomatic hyperviscosity, plasmapheresis should first be performed; plasmapheresis should also be considered before treatment with rituximab or ofatumumab for asymptomatic Waldenström's macroglobulinemia patients with an IgM ≥4,000 mg/dL to avoid aggravation of serum viscosity on the basis of rituximab-related IgM flare. Rituximab or ofatumumab may also be held in patients with elevated serum IgM levels for initial treatment cycles.

[c] Consider for patients presenting with symptomatic hyperviscosity, or in whom rapid IgM reduction is required.

[d] Herpes zoster prophylaxis should be considered for patients receiving these regimens.

[e] These regimens are associated with treatment-related neuropathy and should be avoided in patients with disease-related neuropathy. See Discussion.

[f] Serial serum IgA and IgG levels should be carefully monitored as these can be depleted with carfilzomib-based therapy.

[g] Lower overall and absence of major responses observed in MYD88 wild-type patients.

[h] May be associated with disease transformation and/or development of MDS/AML in Waldenström's macroglobulinemia patients.

[i] Avoid in patients who are potential autologous stem cell transplant candidates.

[j] Vincristine is associated with a high risk of peripheral neuropathy in patients with WM/LPL. Consider alternative regimens without vincristine (eg, cyclophosphamide, dexamethasone, rituximab) if cyclophosphamide-based therapy is being considered.

[k] Ofatumumab may be used for rituximab-intolerant individuals as a single agnet or in combination therapy.

[l] Should ideally be undertaken in the context of a clinical trial.

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