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.

Systemic Therapy for Waldenstrom Macroglobulinemia

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

Primary Therapy—Non-Stem Cell Toxic[1]

REGIMEN	DOSING
Bortezomib ± rituximab[2,a,b,c,d]	**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[3,c,d]	**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.
Bortezomib + dexamethasone + rituximab[3,4,a,b,c,d]	**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.
CaRD (Carfilzomib + rituximab + dexamethasone)[5,6,a,c,e]	**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.
Cyclophosphamide + doxorubicin + vincristine + prednisone + rituximab[7,8,a,d,f]	**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.
Ibrutinib[9,g]	Ibrutinib 420mg orally once daily. Continue treatment until disease progression or unacceptable toxicity.
Rituximab[10,a]	**Day 1:** Rituximab 375mg/m^2 IV. Repeat every 7 days for 4 weeks.
Rituximab + cyclophosphamide + prednisone[11,a]	**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.
Rituximab + cyclophosphamide + dexamethasone[12,13,a]	**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.
Thalidomide ± rituximab[14a,d]	**Weeks 1 and 2:** Thalidomide 200mg orally daily **Weeks 3–52:** Thalidomide 400mg orally daily **Weeks 2–5 and 13–16:** Rituximab 375mg/m^2 IV once weekly for a total of 8 infusions.

continued

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

Systemic Therapy for Waldenstrom Macroglobulinemia (continued)

Primary Therapy—Possible Stem Cell Toxicity and/or Risk of Transformation (or unknown)[1]

REGIMEN	DOSING
Bendamustine ± rituximab[15,a]	**Days 1–2:** Bendamustine 90mg/m^2 IV, ± **Day 1:** Rituximab 375mg/m^2 IV. Repeat every 4 weeks for 4 cycles.
Cladribine ± rituximab[16,a,c,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.
Chlorambucil[17,g,h]	**Days 1–7:** Chlorambucil 0.1mg/kg orally daily OR 0.3mg/kg orally daily. Repeat every 6 weeks.
Fludarabine ± rituximab[18,a,c,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[19,a,c,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.

Previously Treated WM/LPL—Non-Stem Cell Toxic[1]

Alemtuzumab[20]	Alemtuzumab doses gradually escalated over 1 week (3, 10, and 30 mg), followed by 36 additional treatment-phase infusions at 30-mg IV 3 times weekly for 12 weeks.
Bortezomib ± rituximab[21,a,b,c,d]	**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[22,c,d]	**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.
Bortezomib + dexamethasone + rituximab[3,a,b,c,d]	**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.
Cyclophosphamide + doxorubicin + vincristine + prednisone + rituximab[7,8,a,d,f]	**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.
Everolimus[23]	Everolimus 10mg orally daily for 4 weeks (1 cycle). Repeat until disease progression or unacceptable drug toxicity.
Ibrutinib[9,24]	Ibrutinib 420mg orally daily for 2 years or until disease progression or unacceptable drug toxicity.
Ofatumumab (for rituximab-intolerant individuals)[25,a,j]	**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.
Rituximab[10,a]	**Day 1:** Rituximab 375mg/m^2 IV. Repeat every 7 days for 4 weeks.
Rituximab + cyclophosphamide + prednisone[11,a]	**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.
Rituximab + cyclophosphamide + dexamethasone[13,a]	**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.

continued

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

Systemic Therapy for Waldenstrom Macroglobulinemia (continued)

Previously Treated WM/LPL—Non-Stem Cell Toxic[1] (continued)

REGIMEN	DOSING
Thalidomide ± rituximab[14,a,d]	**Weeks 1 and 2:** Thalidomide 200mg orally daily **Weeks 3–52:** Thalidomide 400mg orally daily, ± **Weeks 2–5 and 13–16:** Rituximab 375mg/m^2 IV once weekly for a total of 8 infusions.

Previously Treated WM/LPL—Possible Stem Cell Toxicity and/or Risk of Transformation (or unknown)[1]

Bendamustine ± rituximab[26,a]	**Days 1–2:** Bendamustine 90mg/m^2 IV, ± **Day 1 or 2:** Rituximab 375mg/m^2 IV. Repeat every 4 weeks for 5 cycles.
Cladribine ± rituximab[11,a,c,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.
Chlorambucil[17,h,i]	**Days 1–7:** Chlorambucil 0.1mg/kg orally daily OR 0.3mg/kg orally daily. Repeat every 6 weeks.
Fludarabine ± rituximab[18,a,c,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[19,a,c,h,i]	**Day 1:** Rituximab 375mg/m^2 IV **Days 2–4:** Fludarabine 25mg/m2 IV + cyclophosphamide 250mg/m^2 IV. Repeat every 28 days for a maximum of 6 cycles.

Previously Treated WM/LPL—Stem Cell Transplant[1]

High-dose therapy with stem cell rescue[27]	Treatment varied depending on local protocols.
Allogeneic stem cell transplant (myeloablative or non-myeloablative)[28,k]	Preferably undertaken in the context of a clinical trial.

[a] In patients with symptomatic hyperviscosity, plasmapheresis should first be performed. Plasmapheresis should also be considered before treatment with rituximab or ofatumumab in patients with asymptomatic Waldenström's macroglobulinemia and an IgM ≥4,000mg/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.

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

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

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

[e] Serial serum IgA and IgG levels should be carefully monitored as these patients can be depleted with carfilzomib therapy

[f] Vincristine is associated with a high risk of peripheral neuropathy in patients with Waldenström's macroglobulinemia/lymphoplasmacytic lymphoma. Consider alternative regimens without vincristine (eg, cyclophosphamide, dexamethasone, rituximab), if cyclophosphamide-based therapy is being considered.

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

[h] May be associated with disease transformation and/or development of myelodysplastic syndrome /acute myeloid leukemia in patients with Waldenström's macroglobulinemia.

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

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

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

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