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

Clinical Trials: The NCCN 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 National Comprehensive Cancer Network 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*†‡]	**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[3,4‡]	**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 followed by 4 maintenance cycles that begin 3 months after induction therapy and then administered every 3 months until overall response occurs.
Bortezomib + dexamethasone + rituximab[3*†‡]	**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 continuous cycles followed by a 12-week pause and then 4 additional cycles spaced 12 weeks apart.
CaRD (Carfilzomib + rituximab + dexamethasone)[5,6*¶]	**Induction:** **Days 1, 2, 8, 9, 15, and 16:** Carfilzomib 20mg/m^2 IV (cycle 1), then 36mg/m^2 (cycles 2 and beyond) **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*‡]	**Day 1:** Cyclophosphamide 750mg/m^2 **Day 1:** Doxorubicin 50mg/m^2 **Day 1:** Vincristine 1.4mg/m^2 (max 2mg) **Day 1:** Rituximab 375mg/m^2 **Days 1–5:** Prednisone 100mg PO. Repeat every 3 weeks for 6 cycles.
Ibrutinib[9]	Ibrutinib 420mg PO once daily. Continue treatment until disease progression or unacceptable toxicity.
Rituximab[10*]	**Day 1:** Rituximab 375mg/m^2 IV. Repeat every 7 days for 4 weeks
Rituximab + cyclophosphamide + prednisone[11*]	**Day 1:** Rituximab 375mg/m^2 **Day 1:** Cyclophosphamide 1000mg/m^2 **Days 1–5:** Prednisone 100mg PO. Repeat every 21 days for 6 cycles.
Rituximab + cyclophosphamide + dexamethasone[12,13*]	**Day 1:** Dexamethasone 20mg IV followed by rituximab 375mg/m^2 IV **Days 1–5:** Cyclophosphamide 100mg/m^2 PO BID. Repeat every 21 days for 6 courses.
Thalidomide ± rituximab[14*‡]	•Thalidomide 200mg PO days 1–14 followed by 400mg PO daily, for 52 weeks, ± •Rituximab 375mg/m^2 weekly during weeks 2–5 and weeks 13–16 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*]	**Days 1–2:** Bendamustine 90mg/m^2 IV, ± **Day 1:** Rituximab 375mg/m^2 IV. Repeat every 4 weeks for 4 cycles.
Cladribine ± rituximab[11*§]	**Days 1–5:** Cladribine 0.1mg/kg SQ, ± **Day 1:** Rituximab 375mg/m^2 IV. Repeat every 4 weeks for 4 cycles.
Chlorambucil[16§]	Chlorambucil 0.1mg/kg PO daily until overall response occurs **OR** **Days 1–7:** Chlorambucil 0.3mg/kg PO. Repeat every 6 weeks.
Fludarabine ± rituximab[17*§]	•Fludarabine 25mg/m^2 daily for 5 days at weeks 5, 9, 13, 19, 23, and 27, ± •Rituximab 375mg/m^2 per week on weeks 1–4, 17, 18, 30, and 31.
Fludarabine + cyclophosphamide + rituximab[18*§]	**Day 1:** Rituximab 375mg/m^2 IV **Days 2–4:** Fludarabine 25mg/m^2 IV **Days 2–4:** Cyclophosphamide 250mg/m^2. Repeat every 28 days for a maximum of 6 cycles.

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

Alemtuzumab[19]	Alemtuzumab test doses: 3 doses using gradual dose escalation over 1 week (3mg, 10mg, 30mg) followed by 36 additional treatment phase infusions at 30mg dose IV 3 times per week over 12 weeks.
Bortezomib ± rituximab[20*†‡]	**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. Repeat every 28 days for 6 cycles.
Bortezomib + dexamethasone[21‡]	**Days 1, 4, 8, and 11:** Bortezomib 1.3mg/m^2 IV Dexamethasone 20mg PO day of and after each dose of bortezomib (total dose of 160mg every 21 days) in patients who exhibited progressive disease after 2 cycles or no change after the first four cycles of bortezomib monotherapy. Repeat every 21 days for up to 8 cycles.
Bortezomib + dexamethasone + rituximab[3*†‡]	**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 continuous cycles followed by a 12-week pause and then 4 additional cycles spaced 12 weeks apart.
Cyclophosphamide + doxorubicin + vincristine + prednisone + rituximab[7,8*‡]	**Day 1:** Cyclophosphamide 750mg/m^2 **Day 1:** Doxorubicin 50mg/m^2 **Day 1:** Vincristine 1.4mg/m^2 (max 2mg) **Day 1:** Rituximab 375mg/m^2 **Days 1–5:** Prednisone 100mg PO. Repeat every 3 weeks for 6 cycles.
Everolimus[22]	Everolimus 10mg PO daily for 4 weeks (1 cycle). Repeat until disease progression.
Ibrutinib[9,23]	Ibrutinib 420mg PO daily for 2 years.
Ofatumumab (for rituximab-intolerant individuals)[24*‖]	Ofatumumab 300mg week 1 and 1000mg weeks 2–4.
Rituximab[10*]	**Day 1:** Rituximab 375mg/m^2 IV. Repeat every 7 days for 4 weeks.
Rituximab + cyclophosphamide + prednisone[11*]	**Day 1:** Rituximab 375mg/m^2 **Day 1:** Cyclophosphamide 1000mg/m^2 **Days 1–5:** Prednisone 100mg PO. Repeat every 21 days for 6 cycles.
Rituximab + cyclophosphamide + dexamethasone[13*]	**Days 1–5:** Cyclophosphamide 100mg/m^2 PO BID **Day 1:** Dexamethasone 20mg IV followed by rituximab 375mg/m^2 IV. Repeat every 21 days for 6 courses.

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*‡]	**Days 1–14:** Thalidomide 200mg PO followed by thalidomide 400mg PO daily, for 52 weeks, ± Rituximab 375mg/m^2 weekly during weeks 2–5 and weeks 13–16 for a total of 8 infusions.

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

Bendamustine ± rituximab[25*]	**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*§]	**Days 1–5:** Cladribine 0.1mg/kg SQ , ± **Day 1:** Rituximab 375mg/m^2 IV. Repeat every 4 weeks for 4 cycles.
Chlorambucil[16§]	Chlorambucil 0.1mg/kg PO daily until overall response occurs **OR** **Days 1–7:** Chlorambucil 0.3mg/kg PO. Repeat every 6 weeks.
Fludarabine ± rituximab[17*§]	•Fludarabine 25mg/m^2 daily for 5 days at weeks 5, 9, 13, 19, 23, and 27, ± •Rituximab 375mg/m^2 per week on weeks 1–4, 17, 18, 30, and 31.
Fludarabine + cyclophosphamide + rituximab[18*§]	**Day 1:** Rituximab 375mg/m^2 IV **Days 2–4:** Fludarabine 25mg/m^2 **Days 2–4:** Cyclophosphamide 250mg/m^2. 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[26]	Treatment varied depending on local protocols.
Allogeneic stem cell transplant (ablative or nonablative)[1]	Undertaken in the context of a clinical trial.

* In patients with symptomatic hyperviscosity, plasmapheresis should first be performed; plasmapheresis should also be considered before treatment with rituximab or ofatumumab for asymptomatic Waldenstrom's Macroglobulinemia patients with an IgM 5,000mg/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.

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

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

‖ Serial IgA and IgG levels should be carefully monitored as these patients can be depleted with carfilzomib therapy

¶ Avoid in patients who are potential autologous stem cell transplant candidates.

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

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