

WALDENSTRÖM 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 Waldenström 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

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

Primary Therapy for Waldenström 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,j}	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/LPL¹

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,j}	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

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

Therapy for Previously Treated WM/LPL¹ (continued)

Other Recommended Regimens (continued)

REGIMEN	DOSING
Everolimus¹⁹	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.
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Stem Cell Transplant

Autologous Stem Cell Transplant²¹	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 agent or in combination therapy.
- ^l Should ideally be undertaken in the context of a clinical trial.

References

1. Referenced with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]) for Waldenström's Macroglobulinemia/Lymphoplasmacytic Lymphoma. V1.2018. Available at: http://www.nccn.org/professionals/physician_gls/pdf/waldenstroms.pdf. Accessed May, 24, 2018.
2. Cheson BD, Rummel MJ. Bendamustine: rebirth of an old drug. *J Clin Oncol*. 2009;27(9):1492-1501. Erratum in: *J Clin Oncol*. 2009;27(17):2892.
3. Dimopoulos MA, Gertz MA, Kastritis E, et al. Update on treatment recommendations from the Fourth International Workshop on Waldenström's Macroglobulinemia. *J Clin Oncol*. 2009;27(1):120-126.
4. Treon SP, Ioakimidis L, Soumerai JD, et al. Primary therapy of Waldenström macroglobulinemia with bortezomib, dexamethasone, and rituximab. WMCTG clinical trial 05-180. *J Clin Oncol*. 2009;27(23):3830-3835.
5. Dimopoulos MA, Anagnostopoulos A, Kyrtsonis MC, et al. Primary treatment of Waldenström macroglobulinemia with dexamethasone, rituximab, and cyclophosphamide. *J Clin Oncol*. 2007;25:3344-3349.
6. Treon SP, Hanzis C, Ioakimidis L, Patterson CJ, Manning RJ, Sheehy P. Bendamustine therapy in patients with relapsed or refractory Waldenström's macroglobulinemia. *Clin Lymphoma Myeloma Leuk*. 2011;11(1):133-5.

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References (continued)

7. Ghobrial IM, Hong F, Padmanabhan S, et al. Phase II trial of weekly bortezomib in combination with rituximab in relapsed or relapsed and refractory Waldenstrom macroglobulinemia. *J Clin Oncol*. 2010;28:1422-1428.
8. Jagannath S, Richardson PG, Barlogie B, et al. Bortezomib in combination with dexamethasone for the treatment of patients with relapsed and/or refractory multiple myeloma with less than optimal response to bortezomib alone. *Haematologica*. 2006;91(7):929-934.
9. Dimopoulos MA, Kastritis E, Owen RG, et al. Treatment recommendations for patients with Waldenström macroglobulinemia (WM) and related disorders: IWWM-7 consensus. *Blood*. 2014;124(9):1404-1411.
10. Treon SP, Tripsas CK, Meid K, et al. Carfilzomib, rituximab, and dexamethasone (CaRD) treatment offers a neuropathy-sparing approach for treating Waldenström's macroglobulinemia. *Blood*. 2014;124(4):503-510.
11. Laszlo D, Andreola G, Rigacci L, et al. Rituximab and subcutaneous 2-chloro-2'-deoxyadenosine combination treatment for patients with Waldenström macroglobulinemia: clinical and biologic results of a phase II multicenter study. *J Clin Oncol*. 2010;28(13):2233-2238.
12. Treon SP, Hunter Z, Barnagan AR. CHOP plus rituximab therapy in Waldenström's macroglobulinemia. *Clin Lymphoma*. 2005;5(4):273-277.
13. Buske C, Hoster E, Dreyling M, et al. The addition of rituximab to front-line therapy with CHOP (R-CHOP) results in a higher response rate and longer time to treat failure in patients with lymphoplasmacytic lymphoma: results of a randomized trial of the German Low-Grade Lymphoma Study Group (GLSG). *Leukemia*. 2009;23(1):153-161.
14. Treon SP, Branagan AR, Ioakimidis L, et al. Long-term outcomes to fludarabine and rituximab in Waldenström macroglobulinemia. *Blood*. 2009;113(16):3673-3678.
15. Tedeschi A, Benevolo G, Varettoni M, et al. Fludarabine plus cyclophosphamide and rituximab in Waldenström macroglobulinemia: an effective but myelosuppressive regimen to be offered to patients with advanced disease. *Cancer*. 2012; 118(2):434-443.
16. Treon S, Tripsas C, Yang G, et al. A prospective, multicenter, study of the Bruton's tyrosine kinase inhibitor ibrutinib in patients with relapsed or refractory Waldenström's macroglobulinemia [abstract]. *Hematol Oncol*. 2013;31 (Suppl 1):119:067.
17. Dimopoulos MA, Zervas C, Zomas A, et al. Treatment of Waldenström's macroglobulinemia with rituximab. *J Clin Oncol*. 2002;20(9):2327-2333.
18. Ioakimidis L, Patterson CJ, Hunter ZR, et al. Comparative outcomes following CP-R, CVP-R, and CHOP-R in Waldenström's macroglobulinemia. *Clin Lymphoma Myeloma*. 2009;9(1):62-66.
19. Ghobrial IM, Gertz M, Laplant B, et al. Phase II trial of the oral mammalian target of rapamycin inhibitor everolimus in relapsed or refractory Waldenström macroglobulinemia. *J Clin Oncol*. 2010;28:1408-1414.
20. Furman RR, Eradat H, Switzky JC, et al. A phase II trial of ofatumumab in subjects with Waldenström's macroglobulinemia [abstract]. *Blood*. 2010;116:Abstract 1795.
21. Kyriakou C, Canals C, Sibon D, et al. High-dose therapy and autologous stem-cell transplantation in Waldenström macroglobulinemia: the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. *J Clin Oncol*. 2010;28(13):2227-2232.
22. Kyriakou C, Canals C, Cornelissen JJ, et al. Allogeneic stem-cell transplantation in patients with Waldenström macroglobulinemia: report from the Lymphoma Working Party of the European Group for Blood and Marrow Transplantation. *J Clin Oncol*. 2010;28(33):4926-4934.

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