

Selecting Initial Therapy for Newly Diagnosed Waldenström Macroglobulinemia

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See accompanying article doi:<https://doi.org/10.1200/JCO.2018.78.6426>

In the article that accompanies this editorial, Treon and colleagues¹ report on 30 newly diagnosed patients with Waldenström macroglobulinemia (WM) treated with ibrutinib. Clinically relevant responses were seen in all patients. Responses occurred rapidly with an 18-month progression-free survival (PFS) of 92%. Their article, along with the recently published article by Dimopoulos et al² (NCT02165397; iNNOVATE Study: A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Ibrutinib or Placebo in Combination With Rituximab in Subjects With Waldenström's Macroglobulinemia), which demonstrated a significantly higher response rate, deeper responses, and superior PFS with the combination of ibrutinib and rituximab compared with rituximab alone, firmly establishes ibrutinib as a reasonable choice for the treatment of newly diagnosed WM.

Ibrutinib is the first-in-class Bruton tyrosine kinase (BTK) inhibitor that is used to treat mantle cell lymphoma, chronic lymphatic leukemia (CLL), and WM. Ibrutinib blocks B-cell receptor signaling, which drives cells into apoptosis and disrupts cell migration and adherence to protective tumor microenvironments. Ibrutinib resistance results from mutations that interfere with its binding to BTK or alterations that result in B-cell receptor signaling independence. It has the advantage of being oral with a single dose per day, but it has unique toxicities that seem to be off-target effects and include pneumonia, upper respiratory tract infection, sinusitis, myelosuppression, headache, joint pain, and edema.

Ibrutinib has several unique toxicities, including bleeding, which has an incidence of 20 episodes per 100 patient-years³ as well as a risk of atrial fibrillation of 10.7%.^{4,5} Atrial fibrillation, with the attendant need for rate control, atrial ablation, long-term anticoagulation, or cardioversion adds a new dimension of toxicities that require attention.

Review of the most recently updated National Comprehensive Cancer Network Guidelines gives 12 options for the initial treatment of WM. The large number of options reflects the fact that, in most instances, they represent phase II trials. Therefore, the level of evidence that would allow one to select a given regimen over another is inherently weak. Given the paucity of phase III trials, how does one select therapy for this patient population? [Table 1](#) provides a review of trials that include patients with newly diagnosed WM. These trials are selected and do not represent all studies. Moreover, they are not comparable because they are not balanced for age and stage. Nonetheless, one can draw several conclusions. All initial combination therapies seem to be highly

effective, with clear superiority over single-agent rituximab, which should no longer be considered appropriate initial therapy for this disorder. In follicular lymphoma, obinutuzumab seems to produce a longer PFS when combined with chemotherapy than rituximab does and may be a superior albeit not widely tested monoclonal antibody choice.¹¹ With these excellent outcomes, how does one decide among available therapies?

There are several important issues to consider when assessing therapeutic options. WM is a disorder that affects a much older patient population (median age, 71 years) than other low-grade lymphomas and CLL. As a consequence, these patients are subject to competing risks of death unrelated to WM.^{12,13} In fact in one study, 40% of patients older than age 75 years did not die of WM. Therefore, one should expect multiple comorbidities and a long natural history, so immediate and late toxicity profiles become as important as the consideration of benefits and response rates in selecting initial therapy.

One of the first combination chemotherapy trials for WM used rituximab, cyclophosphamide, and dexamethasone. The regimen produces a remarkably high response rate using a regimen familiar to all oncologists. More importantly, in this trial, with long follow-up, mortality related to WM and mortality unrelated to WM were identical, suggesting that as many patients succumb to the disease as succumb to unrelated problems.¹⁴ This regimen was a standard of care until the East German Lymphoma Study Group published a comparative trial of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) and rituximab plus bendamustine.¹⁵ Although these regimens demonstrated virtually identical response rates, they showed that rituximab plus bendamustine had a lower toxicity profile and longer PFS. However, both are reasonable options for therapy of fixed duration.

Bortezomib is highly active in the treatment of WM. However, patients with WM are uniquely predisposed to the development of peripheral neuropathy mediated by the immunoglobulin M monoclonal protein.¹⁶ Peripheral neuropathy has been reported in 46% of patients treated with bortezomib, higher than the rate reported for patients with myeloma who were receiving bortezomib, and this should not be unexpected in WM.⁸ Considering that patients are now surviving a median of 8 years, initial therapy with bortezomib and the potential for a subsequent life with neuropathy, which is often painful, becomes an important consideration in selecting initial therapy. Regimens developed for CLL for use in younger patients, such as rituximab, cyclophosphamide,

Table 1. Selected Regimens for Treatment of Waldenström Macroglobulinemia

Regimen	RR (%)	Median PFS (mo)	Progression Free		Surviving		First Author
			%	At Time Point (mo)	%	At Time Point (mo)	
Rituximab	44	23					Santos-Lozano ⁶
Rituximab, cyclophosphamide, dexamethasone	96	NR	61	24	50	166	Paludo ⁷
Rituximab, bortezomib, dexamethasone	85	43			66	84	Gavriatopoulou ⁸
Rituximab, bendamustine	93	NR	88	24	NR		Paludo ⁷
Ibrutinib	100	NR	92	18			Treon ¹
Rituximab, ibrutinib	92	NR	82	30	94	30	Dimopoulos ²
Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone	96	28					Ioakimidis ⁹
Rituximab, cyclophosphamide, fludarabine,	85	NR	67	48	90	36	Souchet ¹⁰

Abbreviations: NR, not reached; PFS, progression-free survival; RR, response rate.

and fludarabine, remain active but are also quite toxic and immunosuppressive to this patient population. With rituximab, cyclophosphamide, and fludarabine, the median PFS was 67% at 48 months. However, long-lasting cytopenias occurred in 19 of 82 patients, reflecting the intensity of myelosuppression associated with this regimen.¹⁰ Everolimus produces a 73% response rate in relapsed refractory WM, with a median time to progression of 21 months.¹⁷ Carfilzomib, an epoxyketone proteasome inhibitor, combined with rituximab and dexamethasone produced an overall response rate of 87%, with a median time to response of only 2.1 months.¹⁸

Another consideration with the use of ibrutinib includes the fact that trials are currently designed for continuous therapy until progression. For many patients, not having a treatment-free interval with planned indefinite therapy is a drawback. There is also increasing evidence that the discontinuation of ibrutinib leads to a rebound phenomenon characterized by rapid progression of the underlying disease.^{19,20}

Cost is a relevant consideration because it limits availability of agents globally and, when patients have a copay, cost becomes a barrier to access. One month of ibrutinib at 420 mg/day costs approximately \$12,000 (GoodRx, June 5, 2018). The cost is \$305 for 1 month of therapy with oral cyclophosphamide at 500 mg once per week on days 1, 8, and 15. The cost is \$8,640 for one cycle of bendamustine therapy (2 days). One would anticipate no more than four to six cycles of cyclophosphamide or bendamustine, for a total cost of approximately \$50,000, which is equivalent to the cost for 4 months of ibrutinib therapy. As a consequence, researchers at Mayo Clinic who study WM have created Mayo Stratification of Macroglobulinemia and Risk-Adapted Therapy (mSMART) guidelines and have selected rituximab plus bendamustine as the treatment of choice because of its moderate expense and relative lack of toxicities outside of myelosuppression.²¹ Rituximab plus bendamustine therapy is time limited, usually 4 to 6 months.

Nonetheless, it is important to have multiple options, and ibrutinib with its high activity is a welcome addition to the current armamentarium. The field is rapidly moving forward, and there are now phase III trials of second-generation BTK inhibitors (BGB-3111) being compared directly to ibrutinib. BGB-3111 seems to have fewer off-target effects (NCT03053440; A Study Comparing BGB-3111 and Ibrutinib in Subjects With Waldenström's Macroglobulinemia [WM]). Finally, patients with WM express BCL2, and venetoclax is actively being investigated in the management of

relapsed WM (NCT02677324; Study of ABT-199 [GDC-199] In Patients With Relapsed or Refractory Waldenström Macroglobulinemia). The future is bright for patients with WM who now have many choices for treatment type, and the likely outcome is that few patients will succumb to this disease in the future.

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the author are available with this article at jco.org.

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DOI: <https://doi.org/10.1200/JCO.2018.79.3273>; published at jco.org on July 27, 2018.



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No relationship to disclose