

COUNTERPOINT What should be the goal of therapy for Waldenström macroglobulinemia patients? Complete response should be the goal of therapy

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Despite life-prolonging therapies, Waldenström macroglobulinemia (WM) remains incurable. Treatment options have traditionally relied on rituximab alone, or with alkylators, nucleoside analogs, immunomodulatory agents, or proteasome inhibitors.¹⁻³ Although many lessons were learned from trials examining rituximab monotherapy and combinations, the most important ones have centered on depth and durability of response and toxicity.

Two schedules for rituximab monotherapy were examined in WM⁴⁻⁶: a standard one, with 4 weekly rituximab infusions; and an extended one, in which 4 additional weekly infusions follow standard administration at weeks 12 to 16. With standard rituximab administration, the overall response rate (ORR) that includes minor response is 40%, and the major response (greater than or equal to partial response [PR]) rates are 20% to 30%. With extended rituximab, the ORR is higher (50% to 60%), with major response rates of 40%. Very good partial response (VGPR) and complete response (CR) are rare, and median progression-free survival (PFS) with rituximab monotherapy is 13 to 29 months. Responses to rituximab are slow, with time to best response upwards of 18 months.⁵ Because the malignant WM clone is composed of CD20⁺ mature B cells and lymphoplasmacytic cells, and CD20⁻ plasma cells, sparing of the latter usually follows rituximab monotherapy.⁷ The persistence of paraprotein producing CD20⁻ plasma cells can promulgate immunoglobulin M (IgM) and light chain-mediated morbidities. A flare in serum IgM commonly occurs with rituximab and can induce symptomatic hyperviscosity and/or aggravate IgM-related morbidities.^{5,8,9} With prolonged rituximab use, intolerance can occur in 7% of WM patients.¹⁰ Moreover, prolonged rituximab can potentiate IgA and IgG hypogammaglobulinemia.¹¹ Recurring sinobronchial infections can follow treatment-related IgA and IgG hypogammaglobulinemia, with more severe cases requiring intravenous gamma globulin.²

To extend rituximab activity, rational combinations have been sought. In vitro combination studies showing at least additive cytotoxicity have informed some, but not all, rituximab combinations. Many agents used with rituximab target plasma cells and provide an important overlap to eradicating the entire WM clone. With most combination rituximab therapies, improvements in ORR and deeper responses have occurred.¹²⁻²¹ The ORR with rituximab and alkylators, nucleoside analogs, and proteasome inhibitors are 80% to 90%, with VGPR/CR response rates of 30% to 40% (Table 1). The use of maintenance rituximab has also contributed to deeper responses in WM.²² With deeper responses, improvements in PFS have been recognized. VGPR or better has been observed to predict for longer PFS with many rituximab combinations.^{17-19,21} These findings were also recognized in a retrospective study that examined the outcome of 159 WM patients receiving rituximab-based therapy.²³ CR or VGPR attainment was associated with a median PFS that exceeded 90 and 75 months, respectively. For those that attained PR or minor response, the median PFS was 43 and 31 months, respectively, and 11 months in those without response or stable disease.

Although depth and durability of response have increased with combination rituximab regimens, so has toxicity. Treatment-related adverse events following rituximab combinations have included myelodysplasia, secondary malignancies, prolonged myelosuppression, immunosuppression, and neuropathy.^{15-19,24,25} Avoidance of nucleoside analogs, limitations on alkylator exposure, adoption of weekly bortezomib regimens and use of neuropathy-sparing proteasome inhibitors have impacted short- and long-term toxicity with rituximab combinations.^{1,2} Efforts to maintain and induce deeper responses with rituximab monotherapy or combination therapy have shown promise and continue to be evaluated.^{18,21,22,26} Conversely, consolidation with autologous or allogeneic transplant is avoided because of high risk of nonrelapse mortality.^{1,2,27,28}

Table 1. Impact of combination rituximab regimens on depth of response and PFS

	ORR (%)	VGPR/CR (%)	PFS (mo)
Standard rituximab	40	0-5	13
Extended rituximab	60	5-10	16-29
Thalidomide rituximab	70	10	30%
Cyclophosphamide rituximab	70-80	20-25	30-36
Nucleoside analogs rituximab	70-90	20-30	36-62
Proteasome inhibitors rituximab	80-90	30-40	42-66
Bendamustine rituximab	90	30	69

The discovery of highly recurrent MYD88 (95% to 97%) and CXCR4 (30% to 40%) mutations in WM patients has provided important new insights into WM pathogenesis and development of targeted therapeutics.²⁹⁻³³ Mutated MYD88 promotes constitutive NF- κ B activation through IRAK1/IRAK4 and Bruton tyrosine kinase (BTK), and the BTK-inhibitor ibrutinib abrogates MYD88-driven NF- κ B survival signaling and triggers WM cell apoptosis.³⁴ These findings enabled a pivotal phase 2 clinical trial that supported the first ever drug approval (ibrutinib) for WM by the US Food and Drug Administration and the European Medicines Agency.³⁵ Treatment with ibrutinib results in rapid responses, with a time to response of 4 weeks. In 10% of patients, atrial fibrillation can occur and does not limit ibrutinib continuance in most patients.³⁶ Risk of bleeding with procedures and concurrent use of anticoagulants remain a concern, as do cytopenias in heavily pretreated patients. Unlike rituximab-based therapies, serum IgA and IgG levels remain unchanged with ibrutinib, and infection-related complications are uncommon.³⁵ Persistent low-grade musculoskeletal, skin, and gastrointestinal toxicities can occur with ibrutinib and result in dose reduction and treatment cessation in some WM patients.^{35,37,38}

WM patients with wild-type MYD88 (MYD88^{WT}) show little benefit with ibrutinib, whereas those with mutated CXCR4 (CXCR4^{MUT}) have delayed responses or decreased overall and major responses.^{35,37,38} CXCR4^{MUT} promotes *in vitro* ibrutinib resistance via upregulation of AKT and extracellular signal-regulated kinase 1/2 (ERK1/2) survival signaling.³⁹ Like rituximab-based therapy, deep responses are associated with prolonged PFS. In the pivotal study, the median PFS was not reached among WM patients with MYD88^{MUT}/CXCR4^{WT} in whom VGPR occurred in 44% of patients.⁴⁰ In contrast, the median PFS was 45 months for MYD88^{MUT}/CXCR4^{MUT} patients in whom 90% achieved a VGPR. The median PFS was 21 months for MYD88^{WT} patients, in whom no VGPR occurred.⁴⁰ Although depth of response is associated with longer PFS, withholding ibrutinib for procedures or adverse events can lead to rapid increases in serum IgM, constitutional complaints, and decreased hemoglobin, signifying that residual tumor cells have the potential to rapidly propagate disease.^{35,41} These findings contrast what is typically observed with rituximab-based therapy, wherein the typical posttreatment course is disease latency, followed by slow disease recurrence over time.

The lack of CR observed in WM patients on ibrutinib, regardless of MYD88 or CXCR4 mutation status, also indicates intrinsic resistance.^{35,37,38,40} Signaling studies of surviving WM cells in patients on prolonged ibrutinib (>6 months) therapy show that

although BTK activity is suppressed, IRAK1/IRAK4 remains active and contributes to ongoing NF- κ B survival signaling in WM cells.⁴² Acquired ibrutinib resistance is also an emerging problem in WM patients. BTK^{Cys481} mutations that abrogate ibrutinib-BTK binding were identified in half of WM patients who progressed on ibrutinib.⁴³ Nearly all these patients were CXCR4^{MUT}. Multiple BTK^{Cys481} mutations were also detected within individual patients with acquired ibrutinib resistance, highlighting the importance of BTK in MYD88-driven WM growth and survival. MYD88-mutated WM cells engineered to express BTK^{Cys481} mutations show activation of ERK1/2 survival signaling, inflammatory cytokine production, and ibrutinib resistance.⁴⁴ PLC γ 2 and CARD11 mutations associated with ibrutinib resistance in other B-cell malignancies were also identified in WM patients progressing on ibrutinib.⁴³

Although in many WM patients, deep responses and long-term PFS can be attained with prolonged ibrutinib therapy, those without MYD88 mutations and those with MYD88^{MUT}/CXCR4^{MUT} disease may be at higher risk of either nonresponsive disease, suboptimal responses, or acquired resistance in the latter.⁴³ Intrinsic resistance in MYD88^{MUT}/CXCR4^{WT} patients can also lead to rapid disease progression if ibrutinib is stopped. For these reasons, a strategy dependent on disease control with ibrutinib alone should not be viewed as optimal for WM. Many insights into WM cancer biology, as well as mutated MYD88 and CXCR4 signaling, have provided important clues for rational drug development aimed at eradicating the malignant clone in WM.

As previously mentioned, one of the important limitations of rituximab is sparing of IgM-producing CD20⁻ plasma cells that make up 10% to 15% of the WM clone. Daratumumab targets CD38, a highly expressed antigen on WM plasma cells.^{45,46} Strategies using daratumumab and rituximab, as either dual therapy or with chemotherapeutics, are of interest and offer a means to target the entire WM malignant clone. A phase 2 study of daratumumab in previously treated WM has been initiated (registered at www.clinicaltrials.gov as #NCT03187262) and will offer critical insights into targeting the plasma cell compartment and potential for combination with rituximab and other agents aimed at expunging the entire WM clone. A phase 3 study, iNOVATE, is also examining the combination of ibrutinib with rituximab (#NCT02165397). This fully enrolled study will provide important insights into combining CXCR4 agnostic therapy like rituximab with ibrutinib. Because activating CXCR4 mutations promotes AKT and ERK1/2 pro-survival signaling in WM cells,³⁹ a clinical trial combining the CXCR4-blocking antibody ulocupluma with ibrutinib was initiated in CXCR4^{MUT} WM patients (#NCT03225716). Compounds that inhibit IRAK1 are also under intense preclinical investigation and are aimed at overcoming intrinsic ibrutinib resistance in MYD88 mutated diseases.^{34,47} BCL-2 is overexpressed in WM cells and blocks the proapoptotic activity of ibrutinib.⁴⁸ The BCL-2 antagonist venetoclax produced major responses in all 4 WM patients in a phase 1 study.⁴⁹ A clinical trial examining venetoclax in previously treated WM patients is underway (#NCT02677324) and will inform a planned successor study of venetoclax with ibrutinib. Finally, other BTK inhibitors are currently under investigation, and the spectrum of their kinase activity and adverse event profiling will also impact our understanding of the safety and efficacy of this class of agents in WM.

In summary, although ibrutinib has become an important mainstay of WM therapy, not all patients benefit with this agent, and treatment cessation because of adverse events or acquired resistance can limit long-term effectiveness in many patients. Longer PFS is associated with attainment of VGPR/CR. VGPR/CR should be the goal of therapy for most WM patients, although disease control is appropriate for those patients with low-risk disease, serious comorbidities, and advanced age. Recent insights into WM genomics and biology have provided exciting new opportunities for targeted drug development, enabling efforts aimed at disease eradication.

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Authorship

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