Genomics, Signaling, and Treatment of Waldenström Macroglobulinemia

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A B S T R A C T

Next-generation sequencing has revealed recurring somatic mutations in Waldenström macroglobulinemia (WM). Commonly recurring mutations include MYD88 (95% to 97%), CXCR4 (30% to 40%), ARID1A (17%), and CD79B (8% to 15%). Diagnostic discrimination of WM from overlapping B-cell malignancies is aided by MYD88 mutation status. Transcription is affected by MYD88 and CXCR4 mutations and includes overexpression of genes involved in VDJ recombination, CXCR4 pathway signaling, and BCL2 family members. Among patients with MYD88 mutations, those with CXCR4 mutations show transcriptional silencing of tumor suppressors associated with acquisition of mutated MYD88. Deletions involving chromosome 6q are common and include genes that modulate nuclear factor–κB, BCL2, BTK, apoptosis, differentiation, and ARID1B. Non–chromosome 6q genes are also frequently deleted and include LYN, a regulator of B-cell receptor signaling. MYD88 and CXCR4 mutations affect WM disease presentation and treatment outcome. Patients with wild-type MYD88 show lower bone marrow disease burden and serum immunoglobulin M levels but show an increased risk of death. Patients with CXCR4 mutations have higher bone marrow disease burden, and those with nonsense CXCR4 mutations have higher serum immunoglobulin M levels and incidence of symptomatic hyperviscosity. Mutated MYD88 triggers BTK, IRAK1/IRAK4, and HCK growth and survival signaling, whereas CXCR4 mutations promote AKT and extracellular regulated kinase-1/2 signaling and drug resistance in the presence of its ligand CXCL12. Ibrutinib is active in patients with WM and is affected by MYD88 and CXCR4 mutation status. Patients with mutated MYD88 and wild-type CXCR4 mutation status exhibit best responses to ibrutinib. Lower response rates and delayed responses to ibrutinib are associated with mutated CXCR4 in patients with WM. MYD88 and CXCR4 mutation status may be helpful in treatment selection for symptomatic patients. Novel therapeutic approaches under investigation include therapeutics targeting MYD88, CXCR4, and BCL2 signaling.

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I N T R O D U C T I O N

Waldenström macroglobulinemia (WM) is a distinct clinicopathological entity resulting from the accumulation, predominantly in the bone marrow (BM), of clonally related lymphocytes, lymphoplasmacytic cells, and plasma cells, which secrete a monoclonal immunoglobulin M (IgM) protein. This condition is considered to correspond to the lymphoplasmacytic lymphoma (LPL), as defined by the WHO classification system. Most cases of LPL are WM, with <5% of cases made up of IgA, IgG, and nonsecreting LPL.

P R E D I S P O S I T I O N

WM is an uncommon disease, with a reported age-adjusted incidence rate of 3.4 per million among males and 1.7 per million among females in the United States, and a geometrical increase with age. The incidence rate for WM is higher among white individuals, with African descendants representing only 5% of all patients. The incidence of WM may be higher for individuals of Ashkenazi Jewish decent. Genetic factors seem to be important to the pathogenesis of WM. A common predisposition for WM with other malignancies has been raised, with numerous reports of familiar clustering of individuals with WM alone and with other B-cell lymphoproliferative diseases. In a large single-center experience, 26% of 924 consecutive patients with WM had a first- or second-degree relative with either WM or another B-cell disorder. Several rare germline variants as well as the overexpression of BCL2 have been proposed as predisposition events; however, further confirmation and characterization of these findings is needed. The presence of familial WM...
predisposition was associated with inferior treatment response and progression-free survival, with the notable exception of regimens containing the proteasome inhibitor bortezomib. An increased risk of death associated with familial versus sporadic WM has also been reported in a Swedish registry study. Although further confirmatory studies are needed to establish the importance of familial predisposition in WM, the data support the collection of familial history in patients with WM.

**CYTOGENETICS**

Chromosome 6q deletions encompassing 6q21-25 have been observed in up to half of patients with WM and at a comparable frequency among patients with and without a familial history. The presence of 6q deletions has been suggested to discern patients with WM from those with IgM monoclonal gammopathy of unknown significance (MGUS) and to serve as a prognostic marker, although the latter remains controversial. Gains in 6p are frequently present in 6q-deleted cases. Other abnormalities by cytogenetic or fluorescent in situ hybridization analyses include deletions in 13q14, 17p, and 11q and trisomy 4, 12, and 18. IgH rearrangements are uncommon in WM and may be helpful in discerning cases of WM from IgM myeloma, wherein IgH switch region rearrangements are a prominent feature.

Next-generation sequencing studies have identified highly recurrent somatic mutations in MYD88, CXCR4, ARID1A, and CD79, and other genes, as well as copy number alterations effecting important regulatory genes in chromosome 6q and elsewhere. Transcriptional changes, disease presentation, therapeutic outcome, and overall survival are affected by mutations in MYD88 and/or CXCR4.

### MYD88

A highly recurrent somatic mutation in MYD88 (MYD88 L265P) was first identified in patients with WM by paired tumor/High levels of BCL2
High expression of CXCR4 and CXCL12 compared to healthy donor B cells
Frequent monoallelic loss of chromosome 6q
Few documented translocations
Familial history in up to 20% of patients

Up to 40% of patients with WM
Subclonal and found in context of MYD88 mutations
Therapeutic resistance
Low adenopathy rates
For the nonsense mutational subgroup:
- High serum IgM
- High BM LPC involvement
- More symptomatic

Fig 1. Summary of genome and transcriptome findings in Waldenström macroglobulinemia (WM) and relevance to clinical presentation and treatment outcome. BM, bone marrow; IgM, immunoglobulin M; LPC, lymphoplasmacytic cell; WHIM, autosomal dominant warts, hypogammaglobulinemia, infection, and myelokathexis; WT, wild-type.
normal whole-genome sequencing and subsequently confirmed by multiple groups using Sanger sequencing and allele-specific polymerase chain reaction assays.\textsuperscript{19-24} MYD88 L265P is expressed in up to 90% to 100% of WM cases when allele-specific polymerase chain reaction has been used, using both CD19 sorted and unsorted BM cells.\textsuperscript{21-23} Non-L265P MYD88 mutations have also been identified in patients with WM, including S219C, M232T, and S243N, all of which have been observed in other MYD88 mutated B-cell malignancies.\textsuperscript{25} By comparison, MYD88 mutations are absent or expressed in low frequency in other B-cell malignancies that share similar morphologic and clinicopathological features as WM, including IgM-secreting myeloma (0%), marginal zone lymphoma (6% to 10%), and chronic lymphocytic leukemia (3% to 8%), thereby enabling molecular discrimination.\textsuperscript{20} The presence of mutated MYD88 in cerebrospinal fluid, as well as pleuritic fluid in patients with WM, has also permitted diagnostic and treatment implementation in patients with symptomatic extramedullary disease.\textsuperscript{26,27} Structural events occur on chromosome 3p that increase the allele frequency of the MYD88 mutations in 12% to 13% of untreated patients, and up to 25% of previously treated patients, and seem to segue with CXCR4 mutations in the latter population.\textsuperscript{20,28-30} Deletions of the wild-type (WT) MYD88 allele as well as amplifications of the mutant MYD88 allele have been observed, although the most frequent alterations are acquired uniparental disomy events that transform the genotype of the tumor to homozygous mutated MYD88.\textsuperscript{20,23,28} The clinical significance of these structural changes remains to be determined, although the presence of homozygous MYD88 may confer a favorable treatment outcome in patients undergoing ibrutinib therapy.\textsuperscript{30}

MYD88 mutations encompass the entire WM clone and are detectable in 50% to 80% of IgM but not IgG or IgA MGUS, suggesting an early oncogenic role for WM pathogenesis.\textsuperscript{20,22} Patients with IgM MGUS with mutated MYD88 seem to be at higher risk of progression to WM.\textsuperscript{31} The presence or absence of MYD88 mutations also seems to distinguish two distinct populations of patients with WM. Patients lacking MYD88 mutations show histologically similar disease to patients with MYD88 mutations but present with significantly lower BM disease involvement and serum IgM levels.\textsuperscript{32} Despite the presentation of patients with MYD88 WT with WM with lower BM disease burden and serum IgM levels, overall survival is shorter for these patients, with a 10-fold increased risk of death versus patients with MYD88 mutations with WM.\textsuperscript{32}

MYD88 is an adaptor protein that interacts with the Toll-like receptor and IL1 receptor families and undergoes homodimerization on receptor activation. The homodimerization of MYD88 acts as a scaffold for recruitment of other proteins, resulting in the assembly of a Mydosome that can trigger downstream signaling leading to activation of nuclear factor–κB (NF–κB).\textsuperscript{33} Mutations in MYD88 were first described in activated B-cell (ABC) subtype diffuse large B-cell lymphoma (DLBCL) and were shown to trigger constitutive MYD88 homodimerization NF–κB activation through IRAK1/IRAK4 kinases.\textsuperscript{34} In WM, NF–κB is activated through IRAK1/IRAK4 as well as by BTK, which triggers NF–κB independently of IRAK4/IRAK1 (Fig 2).\textsuperscript{20,23,24,34-37} Recruitment and activation of IRAK1/IRAK4 as well as BTK can be abrogated through either knockdown of MYD88 or use or expression of peptides that block MYD88 homodimerization and induce apoptosis of MYD88-mutated WM cells.\textsuperscript{30,25,35,36} Mutated MYD88 can also transactivate HCK, an SRC family member that is activated by interleukin–6, which is also triggered by mutated MYD88 (Fig 2).\textsuperscript{37} Activated HCK contributes to the growth and survival signaling of mutated WM cells through BTK, phosphatidylinositol 3-kinase/AKT, and mitogen-activated protein kinase/extracellular regulated kinase–1/2 signaling.\textsuperscript{37}

**CXCR4**

Somatic activating mutations in the C-terminal domain of CXCR4 are present in up to 40% of patients with WM and are nearly always observed in conjunction with MYD88 mutations in patients with WM.\textsuperscript{28,32,36} CXCR4 mutations are essentially unique to WM, as they have not been described so far in other diseases, with the exception of a few MZL cases.\textsuperscript{29,39,40} Germline mutations that closely resemble those found as somatic mutations in WM are also present in patients with WHIM syndrome, activation of CXCR4 by its ligand CXCL12 causes extended chemotactic signaling that results in sequestration of neutrophils in the BM (myelokathexis) and impaired lymphocyte development.\textsuperscript{42} In WM, >30 different nonsense and frameshift mutations in the C-terminal domain of CXCR4 have been described.\textsuperscript{32,38-40} Mutations in the C-terminal domain of CXCR4 result in loss of regulatory series, which undergo phosphorylation after CXCR4 receptor activation by CXCL12.\textsuperscript{43} With the rest of this g-protein-coupled receptor left intact, mutated CXCR4 remains fully competent in downstream signaling via g-proteins and β-arrestins, resulting in the constitutive phosphatidylinositol 3-kinase/AKT and mitogen-activated protein kinase/extracellular regulated kinase–1/2 signaling.

Unlike MYD88, CXCR4 mutant clonality is highly variable, and multiple CXCR4 mutations can be present within individual patients that reside in separate clones or are present as compound heterozygous events.\textsuperscript{38,35} The subclonal nature of CXCR4 mutations relative to MYD88 suggests that these mutations are acquired after MYD88, although this could occur early in WM pathogenesis, given their detection in patients with IgM MGUS.\textsuperscript{39,40} Like MYD88, the presence of CXCR4 somatic mutations can affect disease presentation in WM. Patients with CXCR4 mutations present with a significantly lower rate of adenopathy, and those with CXCR4 nonsense mutations have an increased BM disease burden, serum IgM levels, and/or risk of symptomatic hyperviscosity.\textsuperscript{32,38,40} Despite differences in clinical presentation, CXCR4 mutations do not seem to adversely affect overall survival in WM.\textsuperscript{32,38}

Using in vitro models, WM cells transduced with mutated CXCR4 showed increased drug resistance in the presence of CXCL12 to multiple therapeutics, including bendamustine, fludarabine, bortezomib, idelalisib, and ibrutinib.\textsuperscript{44-46} The above studies also showed that CXCL12-mediated drug resistance in mutant CXCR4-transduced WM cells could be reversed by use of CXCR4 blocking agents.

**ARID1A**

Somatic mutations in ARID1A are present in 17% of patients with WM, including single-nucleotide variants leading to premature protein truncation and frameshift changes. Patients with both
ARID1A and MYD88 L265P mutations, compared with patients who did not have ARID1A mutations, had greater BM disease involvement and lower hemoglobin and platelet count. ARID1A and its frequently deleted homolog ARID1B are members of the switch/sucrose nonfermentable (SWI/SNF) family. The SWI/SNF family members regulate chromatin remodeling and can modulate gene regulation. Although still poorly understood in the context of hematologic malignancies, ARID1A can modulate TP53 and is believed to act as an epigenetic tumor suppressor in ovarian cancer, wherein mutations in ARID1A have been more thoroughly evaluated.47,48

CD79A/CD79B

CD79A and CD79B are components of the B-cell receptor (BCR) pathway. CD79A plays diverse roles in B-cell ontogeny and forms a heterodimer with CD79B. The CD79A/B heterodimer associates with the immunoglobulin heavy chain, which is required for cell surface expression of BCR and BCR-induced signaling.49 Activating mutations in the immunotyrosine-based activation motif of CD79A and CD79B have been reported in the ABC subtype of DLBCL and activate BCR growth and survival signaling through a cascade that includes SYK, PLCγ2, and BTK.37 Dual MYD88 and CD79B mutations occur in ABC DLBCL and are associated with ibrutinib response.50 The role of BCR in triggering WM growth and survival signaling remains to be clarified, although aberrantly enhanced BCR signaling was observed in WM cells stimulated with BCR-activating agents.31 Deletions of LYN that are found in 70% of patients with WM could contribute to hyper-responsive BCR signaling as informed by lyn-/- transgenic mice.52 Mutations in both CD79A and CD79B have been observed in WM in 8% to 12% of patients, and although they are mainly found in patients with MYD88 mutations, a CD79B mutation was observed in a patient with MYD88 WT WM.28,38,53 In one study, CD79A and CD79B were nearly exclusive to CXCR4 mutations, suggesting that two distinct MYD88-mutated populations may exist with WM.38 In a small series of patients with WM, the presence of CD79B along with MYD88 mutations was associated with disease transformation.54 The contribution of LYN deletions, as well as CD79A and CD79B mutations, to aberrant BCR-triggered growth and survival signaling, clinical presentation, disease transformation, and treatment outcome remain to be more clearly defined in WM.

Other recurrent somatic mutations have been identified in MYBBP1A, TP53, ML2, HIST1H1E, and HIST1H1B in patients with WM.28,53 ML2 is a histone methyltransferase that methylates Lys-4 of histone H3 (H3K4me). ML2 is a frequent target of somatic mutations in follicular lymphomas (89%) and diffuse large B-cell
lymphomas (32%).25,26 Mutations in MLL2 were identified in two of three patients with WM with WT MYD88 that included a single-nucleotide variant and a deletion resulting in a frameshift mutation. None of the 27 patients with MYD88 mutations with WM who underwent whole-genome sequencing had MLL2 mutations.19

**COPY NUMBER ALTERATIONS**

Copy number alterations are common in patients with WM and affect genes with important regulatory functions in both chromosome 6q and non–chromosome 6q regions (Figs 1 and 3).28 In chromosome 6q, loss of genes that modulate NF-κB activity (TNFAIP3, HIVEP2), BCL2 family of proteins (BCLAF1), apoptosis (FOXO3), BTK (IBTK), plasmacytic differentiation (PRDM1), and ARID1B are observed. Non–chromosome 6q genes that are commonly deleted include ETV6, a transcription repressor; BTG1, which often is deleted in DLBCL and associated with glucocorticoid resistance in acute lymphocytic leukemia; and LYN, a kinase that plays a regulatory role for BCR signaling. PRDM2 and TOP1, which participate in TP53-related signaling, are also frequently deleted in patients with WM.28

Earlier gene expression profiling studies showed overexpression of IL6 as well as a gene profile that closely resembled chronic lymphocytic leukemia.27-29 More recently, next-generation transcriptome studies (RNASeq) have permitted analysis of gene expression in the context of somatic gene mutations (Fig 1). Comparison of B cells derived from the BM of patients with WM with healthy donor B cells showed increased expression of the VDJ recombination genes DNTT, RAG1, and RAG2 as well as the CXCR4 pathway genes CXCL12, VCAM1, and CXCR4 itself.60 These latter findings may indicate a role for CXCR4 signaling regardless of CXCR4 mutation status in WM. Dysregulation of BCL2 family members, including upregulation of BCL2 and BCL2L1, was also observed. Among patients with MYD88 mutations, those with CXCR4 mutations showed transcriptional silencing of tumor suppressors associated with acquisition of mutated MYD88, including WNK2, CDKN1C, PRDM5, and CABLES1. On the basis of both expression and pathway analysis, modulation of MYD88 signaling in the context of CXCR4 mutations was associated with the downregulation of TLR4 and increased transcription of the IRAK4/IRAK3. WM cells derived from patients with MYD88 WT, as well as mutated CXCR4, show impaired B-cell differentiation signaling versus those derived from patients with MYD88-mutated CXCR4 WT. Moreover, BM disease involvement was affected by transcriptional activity of MYD88, CXCR4, and CXCL13.62 Serum CXCL13 levels were found to affect BM disease involvement and hemoglobin levels in an independent cohort of patients with WM, supporting the latter finding.61

**GENOMIC-BASED TREATMENT APPROACH TO WM**

Ibrutinib was recently approved by the US Food and Drug Administration and the European Medicines Agency for the treatment of WM and was adopted into National Comprehensive Cancer Network guidelines62 and WM Consensus Guidelines for the treatment of symptomatic patients with WM.63 Patients with WT MYD88 showed absence of major responses (partial response or better) and inferior progression-free survival to ibrutinib versus those patients with mutated MYD88, including non-L265P mutations.25,64 Moreover, among patients with mutated MYD88, the presence of CXCR4 mutations resulted in lower major response rate versus patients with WT CXCR4 (61.9% v 91.7%). Major response attainment was also delayed among patients with CXCR4 mutations who improved with prolonged (>6 months) therapy.64 Delayed response attainment was also reported among patients with mutated CXCR4 in another multicenter study that administered single-agent ibrutinib to patients with rituximab-refractory WM.65 Major response attainment was also adversely affected by WT MYD88 and mutated CXCR4 mutation status among previously untreated patients who received single-agent everolimus.66 Among patients receiving treatment with carfilzomib, rituximab, and dexamethasone, no major response differences were observed between patients with WT and mutated CXCR4 with WM.66 However, in an ongoing study of ixazomib, dexamethasone, and rituximab, delays in response were observed among patients with CXCR4 mutations.68

Although treatment choice should take into account specific goals of therapy; necessity for rapid disease control; risk of treatment-related neuropathy, immunosuppression, and secondary malignancies; and planning for future autologous stem cell transplantation, MYD88 and CXCR4 mutation status may be
useful in treatment selection for symptomatic patients. A guide recommended by the authors for the use of MYD88 and CXCR4 mutation status in the treatment approach of symptomatic untreated and previously treated patients are presented in Figures 4 and 5.

NOVEL TARGETS

Investigational therapies under development for WM include agents that target MYD88, CXCR4, and BCL2 signaling. IRAK1/IRAK4 kinases mediate mutated MYD88-directed NF-κB signaling, and their inhibition triggers apoptosis in mutated MYD88–expressing malignant cells.28,34,35 Moreover, combined BTK and IRAK1/IRAK4 inhibition induces synergistic killing of malignant cells with MYD88 activation mutations.36 Compounds that inhibit IRAK1/IRAK4 signaling are under intense preclinical investigation for use in MYD88-mutated diseases. HCK is an SRC family member that is transactivated by mutated MYD88 and, along with BTK, is a target of ibrutinib.37 Ibrutinib partially attenuates HCK activity in MYD88-mutated WM and ABC DLBCL cells, and the use of a more potent toolbox HCK inhibitor triggered higher levels of apoptosis in MYD88-mutated WM cell lines and primary cells. In preclinical studies, the CXCR4 antagonists plerixafor and ulocuplumab blocked CXCL12 rescue of apoptosis mediated by ibrutinib, idelalisib, and other therapeutics.44–46 Delayed responses and lower major response rates were also observed among patients with CXCR4 mutations receiving ibrutinib.44,45 A clinical trial examining ibrutinib with ulocuplumab in symptomatic patients with CXCR4 mutations with WM is being planned. The anti-apoptotic factor BCL2 is overexpressed in WM cells, including those derived from patients with WT and mutated MYD88.58,60 The BCL2 inhibitor venetoclax induces apoptosis and shows at least additive antiapoptotic activity against WM cells cotreated with either ibrutinib or idelalisib, regardless of CXCR4 mutation status.71 In a prospective clinical study that included multiple B-cell malignant histologies, three of four previously treated patients with WM responded, including one complete response.72 A dedicated clinical trial examining the activity of venetoclax in previously treated patients with WM is underway (NCT02677324). The presence of ARID1A, HIST1H1B, and HIST1H1E mutations, along with recurrent ARID1B deletions, suggests that epigenetic dysregulation is likely to be present in WM, and further investigation is therefore warranted. EZH2 inhibitors may be particularly effective in the context of ARID1A mutations in WM, and preclinical evaluation of such strategies should also be considered.69

Symptomatic previously treated patient with WM

Consider repeat primary therapy if response > 2 years

MYD88 mutated/no CXCR4 mutation
Same caveats as primary therapy

MYD88 mutated/CXCR4 mutation
If immediate response needed, either BDR or Benda-R

MYD88 WT
Same caveats as primary therapy
✓ non-L265P MYD88 mutations

Fig 5. Author-recommended guide to the use of MYD88 and CXCR4 mutation status in the management of symptomatic, previously treated patients with Waldenström macroglobulinemia (WM). If symptomatic hyperviscosity, severe cryoglobulinemia, cold agglutinemia, or rapidly progressing moderate to severe immunoglobulin M (IgM) demyelinating peripheral neuropathy, plasmapheresis should be considered, then systemic therapy. If not, proceed to systemic therapy. For patients selected to receive rituximab, consider giving chemotherapy alone until IgM < 4,000 mg/dL, or perform empirical plasmapheresis to avoid symptomatic rituximab-induced IgM flare. Maintenance rituximab may be considered if patient responds to rituximab-based induction therapy. Ofatumumab can be considered if the patient is rituximab intolerant. Everolimus can be considered in patients with more than two prior therapies, nucleoside analogs in nonautologous transplantation candidates, and autologous transplantation in patients with multiple relapses and chemoresistant disease.62,71 BDR, bortezomib, dexamethasone, rituximab; Benda-R, bendamustine, rituximab; WT, wild type.

Fig 4. Author-recommended guide to the use of MYD88 and CXCR4 mutation status in the management of symptomatic, previously untreated patients with Waldenström macroglobulinemia (WM). If symptomatic hyperviscosity, severe cryoglobulinemia (severe cryo), cold agglutinin (CAGG), or rapidly progressing moderate to severe immunoglobulin M (IgM) demyelinating peripheral neuropathy (PN), plasmapheresis should be considered, then systemic therapy. If not, proceed to systemic therapy. For patients selected to receive rituximab, consider giving chemotherapy alone until IgM < 4,000 mg/dL, or perform empirical plasmapheresis to avoid symptomatic rituximab-induced IgM flare. Maintenance rituximab may be considered if patient responds to rituximab-based induction therapy. Ofatumumab can be considered if the patient is rituximab intolerant. Everolimus can be considered in patients with more than two prior therapies, nucleoside analogs in nonautologous transplantation candidates, and autologous transplantation in patients with multiple relapses and chemoresistant disease.62,71 BDR, bortezomib, dexamethasone, rituximab; Benda-R, bendamustine, rituximab; WT, wild type.
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