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REVIEW ARTICLE

Genomics, Signaling, and Treatment of Waldenström Macroglobulinemia

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ABSTRACT

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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INTRODUCTION

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.[1] This condition is considered to correspond to the lymphoplasmacytic lymphoma (LPL), as defined by the WHO classification system.[2] Most cases of LPL are WM, with < 5% of cases made up of IgA, IgG, and nonsecreting LPL.

PREDISPOSITION

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.[3] 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 Askenazi Jewish decent.[4] Genetic factors seem to be important to the pathogenesis of WM. A common predisposition for WM with other malignancies has been raised,[4,5] with numerous reports of familiar clustering of individuals with WM alone and with other B-cell lymphoproliferative diseases.[6-9] 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.[4] 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.[9,10] The presence of familial WM

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predisposition was associated with inferior treatment response and progression-free survival, with the notable exception of regimens containing the proteasome inhibitor bortezomib.[11] An increased risk of death associated with familial versus sporadic WM has also been reported in a Swedish registry study.[12] 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.[6,13-15] 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.[13-15] Gains in 6p are frequently present in 6q-deleted cases.[13,14] Other abnormalities by cytogenetic or fluorescent in situ hybridization analyses include deletions in 13q14, 17p, and 11q and trisomy 4, 12, and 18.[16,17] 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.[18]

SOMATIC MUTATIONS

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 (Fig 1). 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/

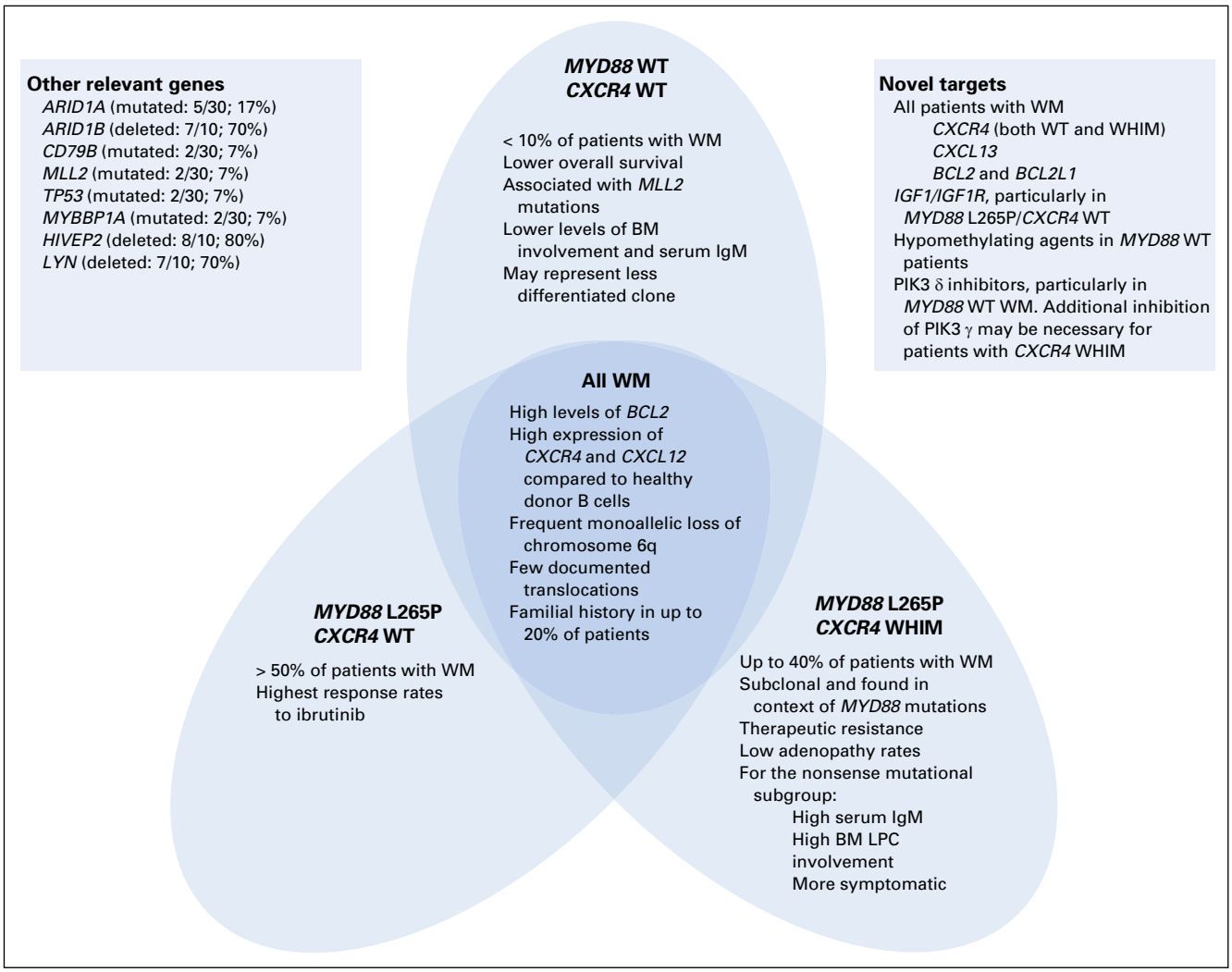

Fig 1. Summary of genome and transcriptome findings in Waldenström macroglobulinemia (WM) and relevance to clinical presentation and treatment outcome. BM, bone marrow; IgM, immunoglobulin M; LPC, lymphoplasmacytic cell; WHIM, autosomal dominant warts, hypogammaglobulinemia, infection, and myelokathexis; WT, wild-type.

normal whole-genome sequencing and subsequently confirmed by multiple groups using Sanger sequencing and allele-specific polymerase chain reaction assays.[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.[21-24] 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.[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.[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.[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.[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*.[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.[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.[20-22] Patients with IgM MGUS with mutated *MYD88* seem to be at higher risk of progression to WM.[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.[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.[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 Myddosome that can trigger downstream signaling leading to activation of nuclear factor–κB (NF-κB).[33] Mutations in MYD88 were first described in activated B-cell (ABC) subtyped diffuse large B-cell lymphoma (DLBCL) and were shown to trigger constitutive MYD88 homodimerization NF-κB activation through IRAK1/IRAK4 kinases.[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).[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.[20,23,35,36] 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).[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.[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.[28,32,38] *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.[29,39,40] Germline mutations that closely resemble those found as somatic mutations in WM are also present in patients with WHIM (autosomal dominant warts, hypogammaglobulinemia, infection, and myelokathexis) syndrome.[41,42] 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.[42] In WM, > 30 different nonsense and frameshift mutations in the C-terminal domain of *CXCR4* have been described.[32,38-40] Mutations in the C-terminal domain of *CXCR4* result in loss of regulatory serines, which undergo phosphorylation after CXCR4 receptor activation by CXCL12.[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.[38,39] 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.[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.[32,38,40] Despite differences in clinical presentation, *CXCR4* mutations do not seem to adversely affect overall survival in WM.[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.[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

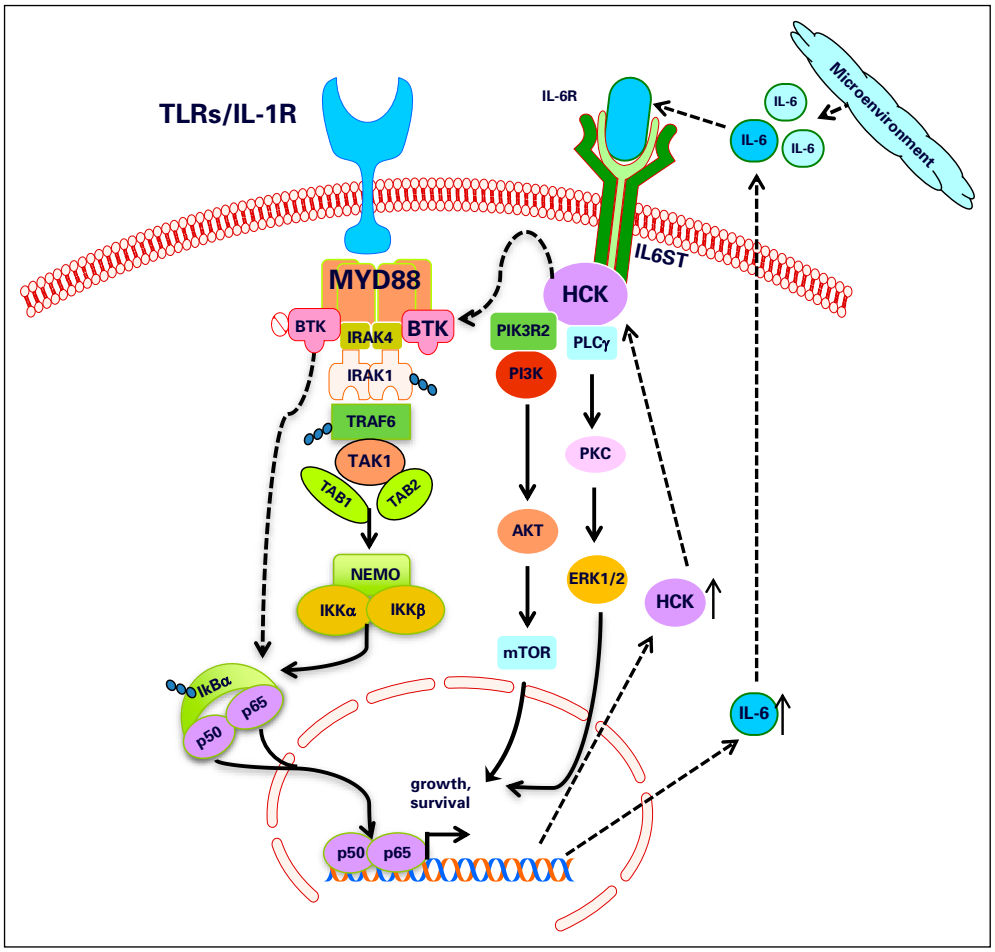

Fig 2. Mutated *MYD88*-related signaling in Waldenström macroglobulinemia (WM). Mutated MYD88 transactivates nuclear factor–κB (NF-kB) through divergent pathways that include IRAK1/IRAK4 and BTK.[35] Mutated MYD88 also triggers transcription and activation of the SRC family member HCK. Activated HCK can then trigger BTK, AKT, and extracellular regulated kinase (ERK)1/2-mediated progrowth and survival signaling in WM cells.[37] IL6, interleukin 6; mTOR, mechanistic target of rapamycin; NEMO, NF-kappa-B essential modulator; PI3K, phosphatidylinositol 3-kinase; TLR, Toll-like receptor.

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.[34] 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.[51] 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 MUTATIONS

Other recurrent somatic mutations have been identified in *MYBBP1A*, *TP53*, *MLL2*, *HIST1H1E*, and *HIST1H1B* in patients with WM.[28,53] *MLL2* is a histone methyltransferase that methylates Lys-4 of histone H3 (H3K4me). *MLL2* is a frequent target of somatic mutations in follicular lymphomas (89%) and diffuse large B-cell

lymphomas (32%).[55,56] 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]

GENE EXPRESSION PROFILING

Earlier gene expression profiling studies showed overexpression of *IL6* as well as a gene profile that closely resembled chronic lymphocytic leukemia.[57-59] 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/IRAK1 inhibitor *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*.[60] 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]

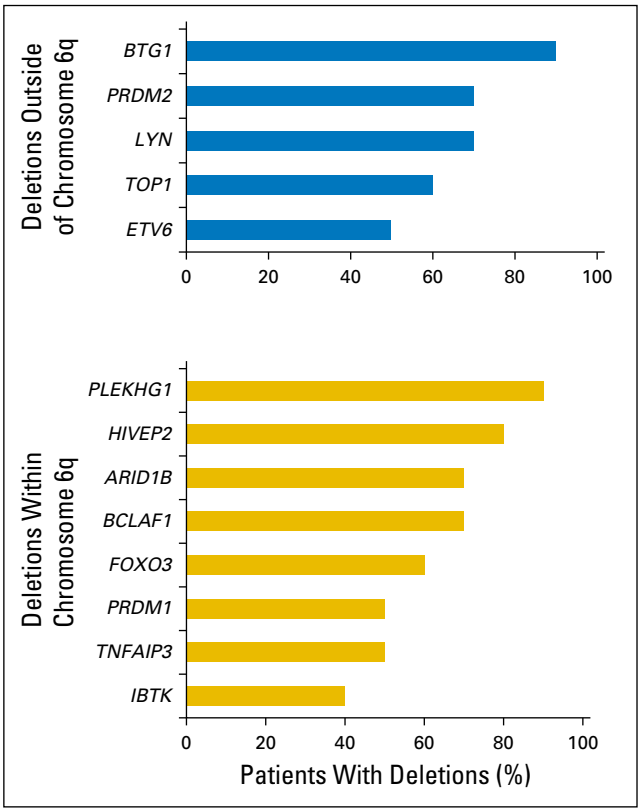

Fig 3. Summary of findings for gene losses in Waldenström macroglobulinemia by chromosome location.

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 guidelines[62] 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.[67] 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.[35] 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.[64,65] A clinical trial examining ibrutinib with ulocuplumab in symptomatic patients with *CXCR4* mutations with WM is being planned. The antiapoptotic 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]

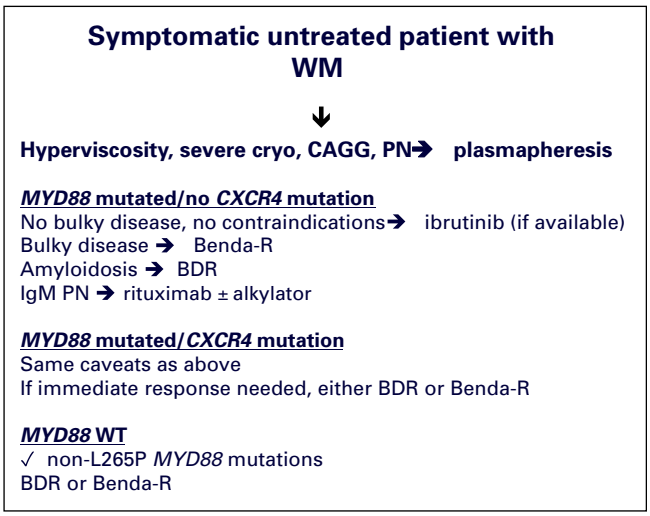

Fig 4. Author-recommended guide to the use of *MYD88* and *CXCR4* mutation status in the management of symptomatic, previously untreated patients with Waldenström macroglobulinemia (WM). If symptomatic hyperviscosity, severe cryoglobulinemia (severe cryo), cold agglutinemia (CAGG), or rapidly progressing 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.[61,70] BDR, bortezomib, dexamethasone, rituximab; Benda-R, bendamustine, rituximab; WT, wild type.

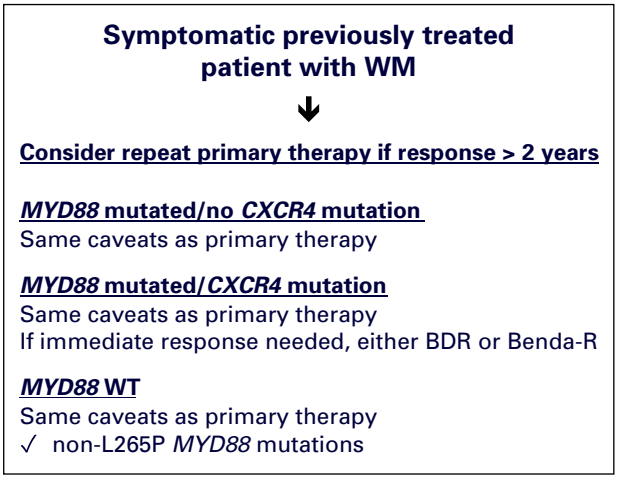

Fig 5. Author-recommended guide to the use of *MYD88* and *CXCR4* mutation status in the management of symptomatic, previously treated patients with Waldenström macroglobulinemia (WM). If symptomatic hyperviscosity, severe cryoglobulinemia, cold agglutinemia, or rapidly progressing moderate to severe 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 chemosenstitive disease.[62,71] BDR, bortezomib, dexamethasone, rituximab; Benda-R, bendamustine, rituximab; WT, wild type.

SUMMARY

Next-generation sequencing has revealed recurring somatic mutations in WM that include *MYD88*, *CXCR4*, *ARID1A*, and *CD79B* and loss of genes with important regulatory functions. Diagnostic discrimination of WM from overlapping B-cell malignancies is aided by *MYD88* mutation status, whereas disease presentation and treatment outcome is affected by both *MYD88* and *CXCR4* mutation status. *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.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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Final approval of manuscript: All authors
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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Genomics, Signaling, and Treatment of Waldenström Macroglobulinemia

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