Biomarkers of Progression and Risk Stratification in Asymptomatic Waldenström Macroglobulinemia

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KEYWORDS

- Waldenström macroglobulinemia
- Monoclonal gammopathy of undetermined significance (MGUS) • Smoldering WM
- Asymptomatic WM • Risk stratification

KEY POINTS

- Waldenström macroglobulinemia is preceded by a heterogeneous asymptomatic stage that could be divided into risk-groups with different progression rates.
- Risk models were developed based on specific biomarkers, such as serum IgM, monoclonal protein, albumin, beta2-microglobulin, and bone marrow infiltration.
- Risk stratification models with discrete cutoffs or continuous variables provide reliable risk assessment for asymptomatic patients.
- Genomic alterations in *MYD88* or *CXCR4* genes and other molecular biomarkers are emerging as promising biomarkers to be included in future risk models.
- To date, the standard of care for asymptomatic patients is observation.

INTRODUCTION

Waldenström macroglobulinemia (WM) is an indolent B-cell lymphoplasmacytic lymphoma characterized by bone marrow infiltration of monoclonal IgM-secreting lymphoplasmacytic cells.[1] Morbidity is often related to the large size and infiltrative properties of involved clonal B cells and their secreted IgM antibodies, which can lead to splenomegaly, lymphadenopathy, hyperviscosity syndrome, extramedullary disease, and bone marrow occupancy with resulting cytopenias. Symptoms can also develop as a result of IgM-associated amyloidosis as well as from immune-related processes, including cryoglobulinemia, demyelinating polyneuropathy, and cold

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agglutinin disease (CAD).[2,3] As an indolent lymphoma, WM is incurable with a median survival of 10 to 12 years, and treatment strategies are thus aimed at mitigating symptoms and preserving the quality of life.[4] Interestingly, the development of WM is highly associated with familial prevalence; in fact, WM and CLL are the 2 non-Hodgkin lymphomas (NHL) most commonly associated with a family history of the disease.[5]

Treatment for WM is typically initiated in the setting of systemic symptoms, cytopenias with defined thresholds for hemoglobin and platelet counts, or any potential end-organ damaging manifestations of the disease.[6] Roughly 20% to 30% of patients with WM are asymptomatic at the time of diagnosis and can be carefully monitored, often for up to 5 to 10 years before treatment is indicated.[7,8] The natural history of the disease, both during pre-treatment and treatment periods, is highly variable.[3] Disease development is partly influenced by several known pathogenic mutations and cytogenetic abnormalities, though many of these prognostic factors remain unknown, making it difficult to predict disease course in individual patients.[3,9] Identifying high-risk patients before overt WM development has recently become an important area of interest to mitigate morbidity and mortality in high-risk patients and initiate therapy sooner in those who would benefit most.

Defining Precursor Stages of Waldenström Macroglobulinemia

Asymptomatic precursor stages precede overt WM, and the thresholds for delineating differences between these stages differ across various institutions. For example, the diagnostic criteria set forth by the Second International Workshop on Waldenstrom Macroglobulinemia define asymptomatic WM (AWM) along a continuum as a state with any percentage of bone marrow infiltrating lymphoplasmacytic cells in the absence of WM symptoms.[10] These criteria define IgM MGUS as an IgM monoclonal gammopathy without IgM-related symptoms or immunophenotypic evidence of WM (**Table 1**).[11] This classification considers that the natural course of IgM MGUS includes the potential for progression to CLL, marginal zone lymphoma (MZL), primary amyloidosis, or IgM myeloma, in addition to WM.[12] In contrast, criteria proposed by the Mayo Clinic define the pre-WM stages of the disease as consisting of smoldering WM (SWM), as a state in which the serum IgM monoclonal protein is greater than or equal to 3 g/dL, or there is a greater than or equal to 10% lymphoplasmacytic cell bone marrow population, and IgM monoclonal gammopathy of undetermined significance (MGUS), defined as an asymptomatic IgM monoclonal gammopathy not meeting criteria for SWM.[7,13,14] The definition of the early stages of WM has remained different regarding how these early disease states can be further subdivided versus viewed along a spectrum of pathologic changes.

When subclassified into IgM MGUS and SWM, these 2 precursor states' progression patterns share many overlapping features while maintaining distinct natural histories. For example, in a retrospective review of 177 patients with an IgM monoclonal gammopathy who underwent bone marrow biopsy, 64% were classified as having IgM-MGUS, 36% as having SWM, and 15% as having symptomatic WM.[16] Among patients with IgM MGUS, 5 and 10 year progression-free survival (PFS) rates were 90% and 81%, respectively, compared with 61% and 46% in patients with SWM.[16] Of note, IgM MGUS most often progresses to WM, rather than to myeloma. Other sequelae of the diagnosis include progression to CLL or other NHL.[17] If the disease progresses, anemia associated with increasing IgM levels and constitutional symptoms is the most common symptom (67%). In addition, peripheral neuropathy occurs in 20% of the patients, whereas 15% develop hyperviscosity symptoms, and 10% present with organomegaly (lymphadenopathy or splenomegaly).[13]

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Table 1
Classification systems for IgM monoclonal gammopathy of undetermined significance and Waldenström macroglobulinemia

	Typical Disease Features					
	Bone Marrow Findings	**Peripheral Blood Findings**	**Clinical Features**	**Other Information Helpful for Diagnosis and/or Prognostication**	**Required for Diagnosis**	**Citation**
Waldenström macroglobulinemia (WM)	IgM-secreting lymphoplasmacytic cells (LPCs); typically CD19+, CD20+, sIgM+; del6q (30%–50% of patients), MYD88 L265P present (90% of patients)	IgM M-protein on SPEP/SIFE	Cytopenias, cold agglutinin disease, cryoglobulinemia, hyperviscosity, neuropathy, organomegaly, adenopathy, amyloidosis, B symptoms	24 h UPEP/UIFE, B2-microglobulin, lactate dehydrogenase (LDH), serum viscosity, CT chest, abdomen and pelvis, Coombs test, tissue staining for amyloid deposition, MYD88 L265P and CXCR4 mutational analysis	1. Evidence of marrow infiltration by a clonal lymphoplasmacytic cell population 2. Clinical signs or symptoms attributable to IgM gammopathy	Gertz et al,[15] 2021.
Asymptomatic Waldenström Macroglobulinemia (AWM)	IgM-secreting LPCs; typically CD19+, CD20+, sIgM+; del6q (30%–50% of patients), MYD88 L265P present (90% of patients)	IgM M-protein on SPEP/SIFE	None	24 h UPEP/UIFE, B2-microglobulin, serum viscosity, CT chest, abdomen, and pelvis	1. Any percentage of bone marrow infiltrating lymphoplasmacytic cells 2. Absence of clinical signs or symptoms	Owen et al,[10] 2003
IgM MGUS	IgM-secreting LPCs; typically CD19+, CD20+, sIgM+; del6q variably present, MYD88 L265P present (in 50%–80% of patients)	IgM M-protein on SPEP/SIFE (must be < 3 g/dL)	None	24 h UPEP/UIFE, B2-microglobulin, serum viscosity, serum calcium, and creatinine	1. Clonal IgM M-protein on SPEP/SIFE <3 g/dL 2. Absence of clinical signs or symptoms 3. Absence of immunophenotypic evidence of WM	Kyle et al,[11] 2003

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Table 1
(*continued*)

	Typical Disease Features					
	Bone Marrow Findings	**Peripheral Blood Findings**	**Clinical Features**	**Other Information Helpful for Diagnosis and/or Prognostication**	**Required for Diagnosis**	**Citation**
Smoldering Waldenström macroglobulinemia (SWM)	IgM-secreting LPCs; typically CD19+, CD20+, sIgM+; del6q (in 30%–50% of patients), MYD88 L265P present (in 90% of patients)	IgM M-protein on SPEP/SIFE	None	24 h UPEP/UIFE, B2-microglobulin, serum viscosity, CT chest, abdomen, and pelvis	1. Serum IgM monoclonal protein ≥3 g/dL and/or a ≥10% lymphoplasmacytic cell bone marrow population 2. Absence of clinical signs or symptoms	Kapoor et al,[14] 2016

Abbreviations: SIFE, serum immunofixation; SPEP, serum protein eletrophoresis; UIFE, urine immunofixation; UPEP, urine protein eletrophoresis.

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Prognostic Scores for Asymptomatic Waldenström Macroglobulinemia

Many models of disease progression to symptomatic WM, NHL, or amyloidosis have relied upon variables with distinct cutoff values to risk-stratify patients. Alexanian and colleagues[18] described a small cohort of 31 patients with AWM in 2003, identifying hemoglobin less than 11.5 g/dL, B2-microglobulin greater than or equal to 3.0 mg/L, and IgM M-protein greater than 3.0 g/dL as risk factors for progression. Kyle and colleagues[7] described 46 patients with SWM in 2012, noting that 71% of patients progressed to WM after 15 years of median follow-up with bone marrow lymphoplasmacytic cell percentage, serum M-protein, hemoglobin, and reduced IgA levels as predictors of progression. In 2011, a multicenter study was published by Greco and colleagues[19] following a cohort of 287 patients divided into those with IgM MGUS and SWM. Using progression to symptomatic WM, amyloidosis, or NHL as a primary endpoint, high IgM M-protein levels, low hemoglobin, and male sex were identified as variables adversely related to the evolution of the disease. Other variables associated with the risk of progression in this study included serum ESR, IgA size, and degree of bone marrow infiltration by lymphoplasmacytic cells. Based on these observations, a scoring system was devised to risk-stratify patients into 3 categories based on predicted risk of progression. SWM was an independent risk factor for progression with a cumulative progression percentage of 8% and 20% at 5 and 10 years, respectively.[19]

Similarly, in 2004, Morra and colleagues[20] identified prognostic features of 384 asymptomatic patients with IgM-monoclonal gammopathies and 74 patients with IgM-related disorders, reporting an increasing rate of progression in patients with IgM-related disorders, which include those with SWM (referred to in this study as indolent WM, or IWM). Based on univariate analysis, hemoglobin, IgM size, lymphocytosis, erythrocyte sedimentation rate (ESR), and bone marrow (BM) lymphoplasmacytic infiltration were associated with progression risk. On multivariate analysis, neutropenia, Bence Jones proteinuria, and high ESR were additionally associated with progression risk. The authors thus argue that IWM and IgM monoclonal gammopathies are distinct clinical entities that necessitate differing monitoring strategies over time.

Conversely, other groups have shifted more toward viewing precursor states of WM as an evolving spectrum of disease rather than as definable subcategories. For example, a European study by Baldini and colleagues[22] in 2005 identified 201 patients with IWM, defined similarly to patients with SWM and 217 patients with IgM MGUS. Over a median follow-up period of 56 months, 7% of patients with IgM MGUS required treatment for symptomatic WM, amyloidosis, or NHL. Approximately 22% of patients with IWM needed treatment for similar indications over a median follow-up period of 60 months. Rising M-spike, decreasing hemoglobin, and male sex were identified as independent risk factors for progression in patients with IgM MGUS and IWM. Given that these variables for the evolution of disease were similar between both groups of patients and that the patients with IWM were more likely to progress to WM, the authors suggested that IgM MGUS, IWM, and WM exist on a spectrum of evolutionary pathology, rather than in discrete, isolated categories. They thus propose approaching prognostication from an evolution-focused approach rather than from a diagnostic system which may create artificial groups of patients with somewhat arbitrary cutoff values between groups.

A recent study by Bustoros and colleagues[13] identified the largest cohort of patients with AWM at the Dana-Farber Cancer Institute. Patients with pathologic evidence of WM in bone marrow biopsies were included in the cohort without further subdividing these patients. Of the 439 patients with AWM, 72% progressed over a

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median follow-up period of 7.8 years. The authors identified discrete and continuous variables predisposing patients to progression to symptomatic disease. Independent risk factors for progression included BM infiltration of 70% or greater, serum IgM 4500 mg/dL or greater, B2-microglobulin 4 mg/dL or greater, and albumin less than 3.5 g/dL. These factors were associated with a 60% to 65% risk of progression at 2 years from diagnosis. Notably, in this study, hemoglobin was purposefully avoided as a predictor of progression, given that its value is also used as a threshold to initiate treatment. The authors took another approach to modeling progression by using biomarker inputs as continuous variables rather than cutoffs. This new model divides patients clearly into 3 risk groups depending on predicted risk of progression a high-risk group with a median time to progression (TTP) of 1.8 years, an intermediate-risk group with a median TTP of 4.8 years, and a low-risk group with a median TTP of 9.3 years. This model was also validated on 2 external cohorts from the Mayo Clinic and Greece, showing similar differences in TTP between the 3 risk groups. The model was made available as an online calculator to help physicians assess the progression risk of patients with AWM. A separate study tested this model and tool on a cohort of AWM from Italy and validated the prediction precision of this model.[23] More recently, 2 studies, one from Spain and another from Mayo Clinic have been published. In the first, the investigators identified bone marrow infiltration of greater than or equal to 20% and the presence of immunoparesis as risk factors for progression to overt WM. The other study by Zanwar and colleagues focused on 143 patients with bone marrow infiltration with greater than or equal to 10% and identified hemoglobin less than 12.3 g/dL and β_2M greater than or equal to 2.7 mg/L as independent progression risk factors. A summary of all the current studies and risk factors is provided in **Table 2**.

GENOMIC ABNORMALITIES CONTRIBUTING TO ASYMPTOMATIC WALDENSTRÖM MACROGLOBULINEMIA PROGRESSION

With the advent of next-generation sequencing technologies, multiple groups identified recurring somatic mutations in *MYD88*, *CXCR4*, *ARID1A*, and *CD79* in WM. In addition, copy number alterations, including those in chromosome 6q that affect regulatory genes for NFKB, Bruton tyrosine kinase (BTK), BCL2, and apoptotic signaling, were also identified.[24–26] MYD88 is an adaptor protein that interacts with the Toll-like and interleukin (IL)-1 receptors and dimerizes upon activation. Dimerization of MYD88 provides a scaffold for the recruitment of other proteins to a Myddosome complex that triggers downstream signaling, leading to increased B-cell survival and growth through constitutive downstream signaling through the JAK/STAT and nuclear factor-kB (NFkB) pathways. Mutated MYD88 also transcriptionally upregulates and transactivates the SRC family member HCK, leading to activation of AKT, ERK, and BTK itself. Activation of BCR signaling through activated SYK also occur, which in turn activates PI3K, STAT3, and AKT prosurvival signaling (**Fig. 1**).[26,27]

Considering the spectrum of asymptomatic disease preceding WM, it becomes necessary to consider the development of known pathogenic mutations and cytogenetic abnormalities often accompanying phenotypic changes. Roughly 80% to 95% of patients with WM harbor the activating *MYD88*^{L265P} mutation, which is associated with more favorable response to therapy in overt WM.[26,28] However, the effect of *MYD88*^{L265P} mutation in precursor states of WM still needs further study. In one study in patients with IgM MGUS, those harboring the MYD88^{L265P} mutation in their peripheral blood were found at increased risk of progression to WM, and a higher mutated allele burden is associated further with increased risk.[29] Conversely, in a cohort of

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Table 2
Selected studies evaluating prognostic factors for disease progression in patients with asymptomatic Waldenström macroglobulinemia

Study	Patient Population	Sample Size	Follow-up (Median)	Risk Factors	TTP/Progression Risk
Alexanian et al,[18] 2003	IgM MGUS SWM	19 31	NR	Hemoglobin <11.5 g/dL β2M ≥ 3 mg/L IgM peak >3 g/dL	Median TTP: 6.9 y
Cesana et al,[21] 2003	SWM	27	6.6	IgM level >3 g/dL Hemoglobin ≤12.5 g/dL	Median TTP: 7.8 y 35% at 5 y 47% at 10 y
Morra et al,[20] 2004	IgM MGUS SWM	138 34	3.8	IgM size Lymphocytosis	8% at 5 y 29% at 10 y
Baldini et al,[22] 2005	IgM MGUS SWM	217 201	4.6 5	Hemoglobin Serum M component Sex	Median TTP: MGUS: NR SWM: 11.8 15% at 10 y (MGUS) 34% at 10 y (SWM)
Kyle et al,[11] 2003	SWM	48	15.4	BM infiltration Hemoglobin Serum M protein IgA reduction	39% at 3 y 59% at 5 y 68% at 10 y
Kastritis et al	IgM MGUS SWM	41 62	5	BM infiltration ≥50% Hemoglobin <120 g/	Median TTP: NR 3% at 5 y (IgM MGUS) 39% at 5 y (SWM)
Bustoros et al,[13] 2019	Asymptomatic WM (Evidence of lymphoplasmacytic involvement, regardless of the extent of BM infiltration)	439	7.8	BM infiltration ≥70% IgM level ≥4.5 g/dL $β_2$M ≥ 4 mg/L Albumin ≤3.5 g/dL	TTP: 3.9 y 39% at 3 y 53% at 5 y
Moreno et al,[32] 2023	IgM MGUS SWM	64 107	4.3	Immunoparesis BM infiltration ≥20%	5.2% at 5 y
Zanwar et al,[31] 2020	SWM	143	9.5	Hemoglobin <12.3 $β_2$M ≥ 2.7 mg/L	TTP: 4.1 y 38% at 3 y 55% at 5 y

Abbreviations: NA, not available; NR, not reached; TTP, time to progression.

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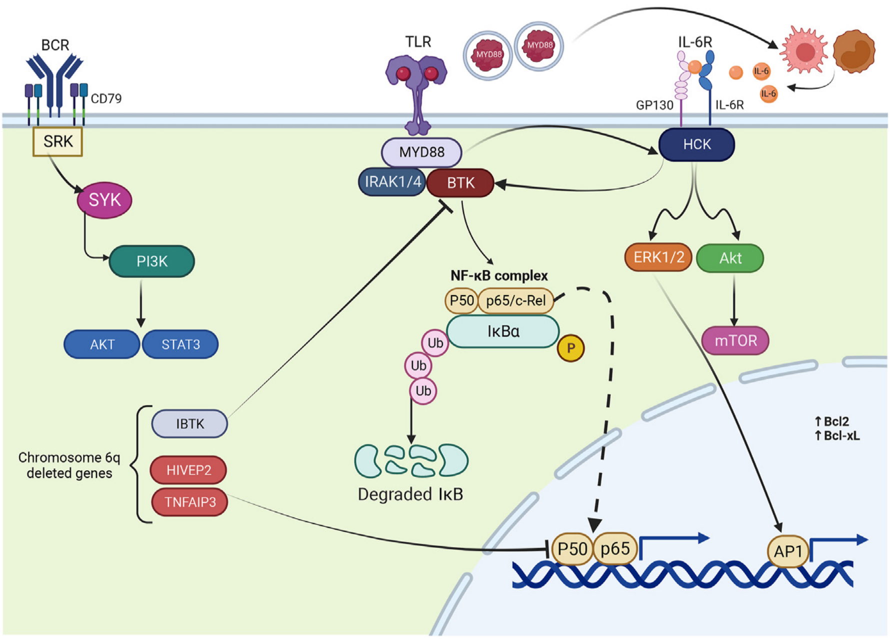

Fig. 1. Signaling pathways and genomic alterations in Waldenström macroglobulinemia. Mutated *MYD88* triggers the activation of NFKB through BTK and IRAK4/IRAK1 Myddosome complex. It also transcriptionally upregulates and transactivates through interleukin (IL)-6 the SRC family member HCK, leading to activation of AKT, ERK, and BTK itself. Mutated *MYD88* activates BCR signaling through activated SYK, which in turn activates PI3K, STAT3, and AKT prosurvival signaling. Deletions in chromosome 6q result in the loss of important regulators of MYD88 signaling, including inhibitor of BTK (IBTK) and the NFKB regulators HIVEP2 and TNFAIP3. Lymphoplasmacytic cells also export mutated MYD88 via extracellular vesicles to induce signaling cascades in the macrophages and other cells, providing a supportive proinflammatory microenvironment. BCR, B-cell receptor; BTK, Broton tyrosine kinase; ERK 1/2, extracellular signal-regulated kinase 1/2; HCK, hematopoietic cell kinase; IBTK, inhibitor of Broton tyrosine kinase; IL-6, interleukin-6; IRAK 1/4, interleukin-1 associated kinases 1/4; LYN, Lck/Yes novel tyrosine kinas; mTOR, mammalian target of rapamycin; MYD88, myeloid differentiation primary response 88; NF-kB, nuclear factor kappa B; STAT3, signal transducer and activator of transcription 3; SYK, spleen tyrosine kinase protein; TLRs, toll-like receptors.

106 patients with AWM, where allele-specific PCR was performed on the bone marrow lymphoplasmacytic cells, *MYD88* WT significantly predicted a higher risk of progression to symptomatic WM.[13] A similar finding was reported in a recent study where MYD88^{WT} was associated with shorter TTP in a cohort of 53 patients with SWM; however, this observation did not reach statistical significance, likely due to a smaller sample size. Interestingly, the median TTP for MYD88^{WT} patients was very similar in both studies (1.8 and 1.7 years). The exact mechanism for rapid progression to active disease in patients with MYD88^{WT} is unclear, but similar lines of evidence showed worse outcomes and higher risk of histologic transformation in MYD88^{WT} WM patient cohorts, implying an underlying genomic instability.[30,31] On the other hand, a recent study on 101 IgM MGUS and 69 patients with SWM, where only 14% progressed to symptomatic WM, used digital droplet polymerase chain reaction (ddPCR) to detect MYD88 mutation status and found no significant difference in progression risk.[32]

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Activating somatic mutations involving the C-terminal domain of CXCR4, which lead to consistent signaling through this chemokine receptor binding CXL12, are present in up to 40% of patients with WM.[25,33,34] Although these mutations almost always occur in those with *MYD88* mutations, some patients with wild-type MYD88 can also express *CXCR4* mutations. One study detected a mutation rate of 43% and 34% in patients with untreated and previously treated WM, respectively, and 17% in patients with IgM MGUS. *CXCR4* mutations are primarily subclonal, and it is thought that their acquisition likely occurs after the *MYD88* mutation develops in the pathogenesis of WM.[35] Importantly, CXCR4 mutated WM displays an increased propensity for drug resistance to several agents, including BTK inhibitors. However, early preclinical evidence suggests that this resistance may be mitigated with CXCR4 inhibitors.[33] Given the importance of accurately detecting CXCR4 mutations for prognostication and therapy initiation, there is an increased focus on improving the sensitivity of available assays for detection. For example, ddPCR was recently shown to be a more sensitive assay, as compared to allele-specific PCR, for detecting CXCR4 and MYD88 mutations in both unsorted bone marrow and cell-free DNA samples taken from patients with IgM MGUS and SWM.[32] With this method of detection, CXCR4 and MYD88 mutational allele burdens were found to be prognostic markers of progression to symptomatic WM.

Clonal chromosome 6q deletions lead to the loss of genes that modulate NFKB activity, such as TNFAIP3 and HIVEP2, the BCL2 transcription repressor BCLAF1, inhibitor of BTK (IBTK), plasma cell differentiation (PRDM1), and ARID1B occur.[24,25] This deletion is found in patients with WM and IgM MGUS and is associated with an increased risk of progression of IgM MGUS to WM.[24] The mechanisms by which this progression occurs remain incompletely understood. However, it has been observed that fully clonal 6q deletions and CXCR4 mutations are mutually exclusive and likely overlap in their pathogenesis, synergistically contributing to the clonal evolution of this disease.[24] Some of these observed effects may be attributable to the impact of mutated CXCR4 on the downregulation of tumor suppressors transcribed by mutated MYD88.[36]

Recently, findings by Tahri and colleagues[37] have highlighted an association between clonal hematopoiesis (CH), occurring in myeloid cells, and increased risk of progression of IgM MGUS and SWM to WM. Using mutations in *DNMT3A*, *TET2*, and *ASXL1* to identify patients with CH that are clonally unrelated to each patient's IgM-producing lymphoplasmacytic cells, the investigators found that a large proportion of patients with active WM, IgM MGUS, and SWM harbored CH mutations. Furthermore, though CH status among patients with WM was not found to be associated with overall survival or PFS, CH status was associated with shorter TTP among patients with IgM MGUS or SWM using the development of WM as a primary endpoint. These findings highlight the need to factor in CH as a potential risk factor for progression to WM and also draw attention to the possible interactions between clonal hematopoietic cells and lymphoplasmacytic cells within the bone marrow microenvironment through growth signaling pathways that can hasten clonal evolution of the lymphoplasmacytic cells.

Therapeutic Intervention in Asymptomatic Waldenström Macroglobulinemia

Early intervention in precursor or asymptomatic stages of various cancers has become big interest in cancer medicine. Its rationale is to target cancer cells as early as possible to prevent end-organ damage and metastasis. The benefit of this approach could depend on each cancer's clinical and biological features. Moreover, implementing early intervention in real world should be based on clear evidence of improved survival outcomes and quality of life in randomized clinical trials for asymptomatic patient groups. To date, randomized control trials in patients with AWM do not yet exist to

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conclusively support a beneficial role. However, future trials investigating the effect of early intervention in the clearly defined high-risk group could address this important topic. Until then, the current consensus is observation of asymptomatic patients until any progression criterion occurs.

SUMMARY

WM is a heterogeneous disease with a broad range of clinical courses dependent on patient- and disease-related factors. Identifying patients at high risk for progression to WM before symptoms begin is attractive in terms of initiating careful monitoring sooner and potentially implementing preventative treatments to minimize progression to severe disease. IgM MGUS and SWM have been defined to clearly capture subsets of patients and adequately monitor them through time. Diagnosing a pre-WM disease state makes it possible to predict certain progression features by association with prior studies. However, differentiating between IgM MGUS and SWM is nuanced, given that diagnostic cutoffs are based on serum IgM levels and bone marrow lymphoplasmacytic cell percentage rather than on distinct biologic processes or transitions, which may, in fact, overlap and lie on a continuum rather than exist in isolation from one another. Importantly, it is critical to maintaining prognostic inputs separated from outputs, including any variables that indicate treatment based on value, such as hemoglobin or platelet count.

Additionally, given the complexity of risk-stratifying patients before progression and the fluid biology that underlies the spectrum of progressive WM, scoring systems that consider continuous variables rather than distinct cutoffs have emerged to more accurately predict the risk of progression. These scoring systems may continue to benefit from incorporating a growing body of knowledge regarding the contribution of multiple known mutations and cytogenetic changes on disease progression. Perhaps most importantly, it will be necessary to increasingly incorporate markers of mechanistic disease progression, such as mutational burden, and rely upon phenotypic changes accompanying advancing disease. Using digital droplet PCR for mutation assessment may be instrumental in following patients with WM precursor disease states over time and ensuring that patients with overt WM can be most accurately evaluated for their mutational status.

By understanding the pathophysiology of WM and its development, which begins before symptoms develop, it will become increasingly possible to predict individual disease courses and initiate preventative therapies with appropriate follow-up and monitoring to prevent the onset of severe disease in high-risk patients.

CLINICS CARE POINTS

- Patients with AWM and proven immunophenotypic findings progress to overt disease at different rates.
- Risk models using disease-specific biomarkers such as serum IgM, monoclonal protein, and bone marrow infiltration are predictive of different progression rates.
- MYD88 mutation status and its association with time to progression still need to be tested on larger studies with good follow-up.
- The standard of care for patients with AWM is observation and close follow-up depending on the progression risk.
- No evidence from clinical trials is available to early therapeutic intervention of AWM.

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