Novel Treatment Options for Waldenström Macroglobulinemia

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Abstract

Waldenström macroglobulinemia (WM), first described by Jan Waldenström in 1944, is a lymphoplasmacytic lymphoma characterized by the presence of an immunoglobulin M monoclonal gammopathy in the blood and monoclonal small lymphocytes and lymphoplasmacytoid cells in the bone marrow. WM is a rare and indolent disease but remains incurable. In this review we discuss the pathogenesis of WM and focus on novel treatment options that target pathways deregulated in this disease. Recent studies have helped us identify specific genetic mutations that are commonly seen in WM and might prove to be important therapeutic targets in the future. We discuss the role of epigenetics and the changes in the bone marrow microenvironment that are important in the pathogenesis of WM. The commonly used drugs are discussed with a focus on novel agents that are currently being used as single agents or in combination to treat WM. We finally focus on some agents that have shown preclinical efficacy and might be available in the near future.

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Introduction

Waldenström macroglobulinemia (WM) was first described by Jan Waldenström in 1944 when he identified 2 patients with oronasal bleeding, cytopenias, and bone marrow showing predominantly lymphoid cells. WM is classified as a lymphoplasmacytic lymphoma according to the Revised European American Lymphoma and World Health Organization. WM is an incurable low-grade B-cell lymphoproliferative disorder characterized by the presence of an immunoglobulin (Ig) M monoclonal gammopathy in the blood and monoclonal small lymphocytes and lymphoplasmacytoid cells in the bone marrow.[1-3] WM is a rare disease with 1500 new cases diagnosed per year in the United States.[4] The main risk factor for the development of WM is the presence of IgM-monoclonal gammopathy of undetermined significance, which confers a 46-fold higher relative risk to develop WM than the general population. In addition, approximately 20% of patients with WM have at least 1 first-degree relative with a B-cell neoplasm.[5] The clinical manifestations of WM include anemia and other cytopenias, hyperviscosity symptoms, deposition in tissues including amyloidosis, and other related disorders including peripheral neuropathy, hemolytic anemia, and cryoglobulinemia. Other rare manifestations include Schnitzler syndrome, infiltration of organs such as the central nervous system (Bing-Neel syndrome), lung infiltrates, and lytic bone lesions. The median overall survival of patients with WM is 5 to 10 years. Patients with asymptomatic disease should not be treated based on monoclonal protein level alone.[2,6,7]

In this review, we discuss the pathogenesis of WM. We then focus on novel treatment options that target pathways deregulated in this disease.

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Pathogenesis of WM

Waldenström macroglobulinemia is defined as a lymphoplasmacytic lymphoma with bone marrow involvement and an IgM monoclonal gammopathy.[8] In addition to characteristic bone marrow infiltration, some adenopathy and extranodal involvement are common. Approximately 15% to 20% of patients with WM also have splenomegaly, hepatomegaly, and/or adenopathy.[3]

Morphologically, bone marrow in WM is characterized by nodular, diffuse, and/or interstitial infiltrate usually composed predominantly of small lymphocytes admixed with variable number of plasma cells and plasmacytoid lymphocytes.[9] The cells express B-cell associated antigens (CD19, CD20, CD79a) and also surface Ig. The plasmacytic cells express cytoplasmic Ig, usually IgM. An increased number of mast cells are noted close to the lymphoid aggregates. Dutcher bodies (Periodic Acid-Schiff+ intranuclear pseudo-inclusions) are present in the plasma cells. Lymph nodes

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that are involved with WM commonly show retention of the normal architecture with dilated sinuses and a relatively monotonous proliferation of small lymphocytes, plasma cells, and plasmacytoid lymphocytes.

Cell of Origin

Waldenström macroglobulinemia is thought to arise from B-cells that are arrested after somatic hypermutation in the germinal center and before terminal differentiation to plasma cells.[10,11] Analysis of the nature and distribution of somatic mutation in Ig heavy- and light-chain variable regions obtained from patients with WM indicate that WM might originate from an IgM^+ and/or IgM^+IgD^+ memory B-cell with a deficiency in the initiation of the switching process.

Genetics of WM

Waldenström macroglobulinemia usually arises sporadically but approximately 20% to 25% of cases are familial with at least 1 first-degree relative with WM or other B-cell disorders.[12] Genome-wide association studies have identified certain polymorphisms that increase susceptibility to multiple myeloma, Hodgkin lymphoma, and chronic lymphocytic leukemia.[13-15] These polymorphisms might explain some of the familial associations seen in these disorders but similar variants have not been identified in WM. Genetic linkage analysis with WM families has shown evidence of linkage on chromosomes 1q and 4q.[16] Population-based studies have also shown an increased risk of WM and other lymphomas associated with autoimmune and other inflammatory conditions.[17] At this time, the most important risk of developing WM is the presence of monoclonal gammopathy of undetermined significance (MGUS).

In WM, the malignant clone is characterized by specific epigenetic and genetic changes. The most common cytogenetic abnormality identified using fluorescence in situ hybridization analysis is the deletion of 6q which was reported in up to 55% of cases.[18,19] Other cytogenetic abnormalities including trisomy 4, trisomy 5, monosomy 8, and deletion of long arm of chromosome 20 have also been reported but deletion of long arm of chromosome 6 remains the most common chromosomal abnormality.[20-22] Among the candidate genes located on 6q, positive regulatory (PR) domain containing 1, with zinc finger protein domain (*PRDM1*) is particularly interesting. It is a zinc finger-containing protein that is important in the terminal differentiation of mature B-cells into differentiated plasma cells.[23] Gene expression profiling of WM bone marrow samples has shown a homogenous transcription profile irrespective of the 6q deletion status.[24] Using single-nucleotide polymorphism-based array, Poulain et al detected copy number abnormalities in 75% of patients with partial deletion of 6q being the most common abnormality.[25]

Array-based comparative genomic hybridization approaches showed that 83% of WM patients have chromosomal abnormalities with a median of 3 abnormalities per patient.[26] Gain of 6p was seen in 17% of patients and was always concomitant with 6q loss. A minimal deleted region, including miR-15a and miR-16-1, was delineated on 13q14 in 10% of patients. Biallelic deletions and/or inactivating mutations were observed with uniparental disomy in tumor necrosis factor (TNF) receptor-associated factor 3 (*TRAF3*) and TNFα-induced protein 3 (*TNFAIP3*), 2 negative regulators of the nuclear factor (NF)-κB signaling pathway. The study also found an association between TNF receptor-associated factor inactivation and increased transcriptional activation of NF-κB target genes, highlighting a mutation-driven mechanism of NF-κB pathway activation.

Recently another mutation in the NF-κB signaling pathway was identified using whole-genome sequencing (WGS). Treon et al performed WGS of bone marrow lymphoplasmacytic lymphoma (LPL) cells in 30 patients with WM, with paired normal tissue and tumor tissue sequencing in 10 patients.[27] A single nucleotide variant was identified in the myeloid differentiation primary response 88 (*MYD88*) gene that predicted an amino acid change (L265P) in more than 90% of LPL samples tested. MYD88 L265P was absent in paired normal tissue samples from patients with WM or non-IgM LPL and in B cells from healthy donors. MYD88 is an adaptor molecule in toll-like receptor and interleukin (IL)-1 receptor activation of NF-κB signaling. Ngo et al have previously shown that *MYD88* mutations are present in approximately 40% of Activated B-cell type diffuse large B cell lymphoma.[28] This study also showed that MYD88 L265P, is a gain-of-function driver mutation, that promotes cell survival by spontaneously assembling a protein complex containing interleukin 1 receptor-associated kinase (IRAK1) and IRAK4, leading to IRAK4 kinase activity, IRAK1 phosphorylation, NF-κB signaling, JAK kinase activation of STAT3, and secretion of IL-6, IL-10, and interferon-beta. The role of MYD88 L205P in transforming IgM MGUS to WM will need further investigation. In the study by Treon et al, MYD88 L265P was present in only 10% of IgM MGUS patients, and in a small study Landgren et al, the mutation was found in 5 of 9 patients (56%).[29] Larger studies will be needed to ascertain whether MYD88 L265P is a transforming event that facilitates progression from IgM MGUS to WM and the overall role of the mutation in the pathogenesis of WM. Direct targeting of MYD88-IRAK signaling can be a potential novel therapeutic approach for patients with WM.

Epigenetic Modifications in WM Pathogenesis

In addition to the cytogenetic and genetic changes seen in WM, several studies have also examined the effect of epigenetic modifications as key regulators in the pathogenesis of WM. MicroRNA (miRNA) aberrations and modifications in histone acetylation status have been shown to play an important role in WM biology.

MicroRNA expression profiling of WM cells and normal B cells were compared using unsupervised clustering.[30] A WM-specific signature is characterized by increased expression of miRNA-363*/-206/-494/-155/-184/-542-3p, and a decreased expression of miRNA-9*. miRNA-155 is expressed from an exon of the noncoding *B-cell integration cluster* gene and has been shown to be important in the initiation and progression of B-cell malignancies like diffuse large B cell lymphoma, primary mediastinal B-cell lymphomas, and Hodgkin lymphoma.[31,32] In this study, miRNA-155 was found to have an important functional role in WM cell proliferation, adhesion, and migration. miRNA-155 knockdown modulated cell cycle progression in WM cells, as demonstrated by an increased fraction of cells in G1-phase and decreased S-phase fraction. miRNA-155 knockdown was also shown to strongly inhibit ERK and AKT phosphorylation, and phosphorylated glycogen synthase kinase-3α/β and phosphorylated ribosomal protein S6, both AKT downstream target proteins.

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