Waldenström Macroglobulinemia

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Abstract

In the past 36 months, new developments have occurred both in the understanding of the biology of Waldenström macroglobulinemia (WM) and in therapeutic options for WM. Here, we review the classification, clinical features, and diagnostic criteria of the disease. WM is a B-cell neoplasm characterized by lymphoplasmacytic infiltration of the bone marrow and a monoclonal immunoglobulin M (IgM) protein. The symptoms of WM are attributable to the extent of tumor infiltration and to elevated IgM levels. The most common symptom is fatigue attributable to anemia. The prognostic factors predictive of survival include the patient’s age, $\beta_2$-microglobulin, monoclonal protein, hemoglobin, and platelet count. Therapy is postponed for asymptomatic patients, and progressive anemia is the most common indication for initiation of treatment. The main therapeutic options include alkylating agents, nucleoside analogues, and rituximab. Studies involving combination chemotherapy are ongoing, and preliminary results are encouraging. No specific agent or regimen has been shown to be superior to another for treatment of WM. Novel agents such as bortezomib, perifosine, atacicept, oblimersen sodium, and tositumomab show promise as rational targeted therapy for WM.
**Abbreviations**

- APRIL, a proliferation-inducing ligand
- BLyS, B-lymphocyte stimulator
- CLL, chronic lymphocytic leukemia
- DLBCL, diffuse large B-cell lymphoma
- FISH, fluorescence in situ hybridization
- HAS, hyaluronan synthase
- Ig, immunoglobulin
- IL-6, interleukin-6
- LPL, lymphoplasmacytic lymphoma
- MAG, myelin-associated glycoprotein
- MEK, mitogen-activated protein kinase kinase
- MGUS, monoclonal gammopathy of undetermined significance
- MM, multiple myeloma
- SMZL, splenic marginal zone lymphoma
- TACI, transmembrane activator and calcium-modulator and cyclophilin ligand interactor
- WHO, World Health Organization
- WM, Waldenström macroglobulinemia
Introduction

Nearly 63 years have passed since Jan Gosta Waldenström first described two patients with oronasal bleeding, lymphadenopathy, anemia and thrombocytopenia, elevated erythrocyte sedimentation rate, high serum viscosity, normal bone radiographs, and bone marrow showing predominantly lymphoid cells (1). At a time when paper electrophoresis was unheard of, he attributed hyperviscosity symptoms to an abnormal high-molecular-weight serum protein. These preliminary observations proved to be the cornerstones of the widely recognized but relatively uncommon diagnosis of Waldenström macroglobulinemia (WM). The abnormal high-molecular-weight serum protein subsequently was shown to be monoclonal immunoglobulin M (IgM).

Definition and Pathology

WM is a malignant lymphoplasmo-proliferative disorder with monoclonal pentameric IgM production. The most consistent feature of the bone marrow or lymph nodes of patients with WM is the presence of pleomorphic B-lineage cells at different stages of maturation, such as small lymphocytes, lymphoplasmacytoid cells (abundant basophilic cytoplasm but lymphocyte-like nuclei), and plasma cells (2). Bone marrow is infiltrated in a predominantly intertrabecular pattern. A significant increase in the number of mast cells has been noted in bone marrow biopsies of WM patients (3). Bone marrow mast cells of WM patients overexpress the CD40 ligand (CD154), which is a potent inducer of B-cell expansion.

Classification

WM was initially defined in broad terms with the Kiel classification (4) as a lymphoma of Ig-secreting cells, often associated with a
paraproteinemia. Subsequently, WM was combined with lymphoplasmacytic lymphoma (LPL) and designated LPL/WM in the Revised European-American Lymphoma (5) and World Health Organization (WHO) (6) classifications. The consensus group at the Second International Workshop on WM in 2002 (7) redefined WM as a distinct clinicopathologic entity characterized by bone marrow infiltration by LPL and IgM monoclonal gammopathy.

**Incidence**

WM has an overall incidence of approximately 3 per million persons per year, accounting for approximately 1% to 2% of hematologic cancers (8,9). The incidence of WM is higher among whites, with blacks representing only 5% of all patients (10). In large series of patients, the median age varies between 63 and 68 years, with 55% to 70% men (11). WM remains incurable, and most patients die of disease progression, with a median survival of 5 years (12). Because of the late age of presentation of WM, half of the patients succumb to causes unrelated to WM.

**Etiology and Predisposing Factors**

WM is believed to be predominantly a sporadic disease. Its cause is unknown, but various reports of multigenerational clustering and familial patterns indicate the possible role of a single genetic defect (13). Treon et al (14) analyzed 257 consecutive and unrelated patients with WM: 48 (18.7%) had at least 1 first-degree relative with either WM or another B-cell disorder. Moreover, patients with a familial history of WM or a plasma cell disorder received the diagnosis at a younger age and with greater bone marrow involvement. Deletions in 6q21-22.1 were confirmed in most WM patients
regardless of family history. In short, a high degree of clustering of B-cell disorders was seen among first-degree relatives of patients with WM.

The main risk factor for the development of WM is preexisting IgM—monoclonal gammopathy of undetermined significance (MGUS) (46 times higher relative risk than for the general population) (15). Morra et al (16) showed a progressive increase in the risk of transformation from asymptomatic IgM-MGUS to symptomatic WM, with increasing IgM levels.

A possible association between hepatitis C virus and WM had been suggested (17), but this has been negated recently by Leleu et al (18). Reports of links between human herpes virus-8 and WM are unconfirmed.

**Origin**

The origin of the B-cell clone has been long debated. Distinct B-cell subsets have been demonstrated in the bone marrow, marginal zone of the spleen and lymph nodes, and circulating in the peripheral blood (19). Analysis of 14q32 by fluorescence in situ hybridization (FISH) and Southern blot indicates the absence of Ig heavy chain (IgH) rearrangements in WM (20). Postswitch clonotypic Ig (IgG or IgA) is undetectable in WM B cells, confirming the absence of isotype switch events by deletional recombination (21-23). With the use of variable region (V) gene analysis, evidence shows that VH genes are somatically mutated in WM. Most WM VDJ sequences from the \( VH3/JH4 \) gene families are hypermutated and lack intraclonal heterogeneity (21,23). In contrast, one case has been reported in which WM cells have shown functional class switch recombination (24). This favors the hypothesis that WM cells have normal class switch recombination machinery but defective initiation of the switching process.
Cytogenetic Abnormalities

The only recurrent abnormality identified by Schop and colleagues (20,25) was deletion of the long arm of chromosome 6 in 55% of cases. In contrast, FISH analysis by Terre et al (26) on 39 WM cases found 6q deletions in only 21%, and trisomy 4 was the most recurrent chromosomal abnormality (18%). In a study involving 37 patients with LPL/WM, Mansoor et al (27) reported that the most common chromosomal numeric abnormalities were trisomy 5 and monosomy 8 in 3 cases each; the most common structural abnormality was deletion of 6q in 6 cases.

Liu et al (28) reported a single case of WM with deletion of 20q as the sole initial cytogenetic abnormality. Ten cases with plasma cell dyscrasias and del(20q) were reviewed. None of the cases without genotoxic chemotherapy exposure had development of myelodysplastic syndrome/acute myelogenous leukemia during follow-up. This suggests that the significance of del(20q) differs depending on whether it appears at diagnosis or after chemotherapy.

Of the various genes that have been localized to 6q21, BLIMP-1 is postulated to be of importance in WM. BLIMP-1, a tumor suppressor gene, is the master gene regulator for B-lymphocytic cell proliferation and differentiation (29-31). It facilitates the transition from the mature B-cell stage to the plasma cell stage. Partial or whole losses in this gene could result in the predisposition for B-cell malignancies such as WM.

Another area of interest in WM is the B-lymphocyte stimulator (BLyS), also known as B-cell–activating factor of the tumor necrosis factor family (32). BLyS is expressed on monocytes and is critical for maintenance of normal B-cell development and homeostasis (33,34). It is overexpressed
in various B-cell malignancies and has been shown to inhibit apoptosis in 
malignant B cells. Moreover, in a study by Elsawa et al (35), 
lymphoplasmacytic cell infiltrates in the bone marrow of patients with WM 
stained positive for BLyS expression, and serum BLyS levels in patients 
with WM were significantly higher than in healthy controls. Because of the 
role of BLyS in WM, strategies to inhibit BLyS potentially may have 
therapeutic efficacy.

TACI (transmembrane activator and calcium-modulator and 
cyclophilin ligand interactor), a TNF-receptor family member expressed on 
B lymphocytes, has been shown to have a high affinity for APRIL (a 
proliferation-inducing ligand) and BLyS (36). Mutations in TACI signaling 
are commonly seen in common variable immune deficiency. In WM, IgG 
and IgA hypogammaglobulinemia are more prevalent among cases with 
mutations in the TACI signaling process (37).

Abnormal expression of hyaluronan synthases (HASs) has been 
reported as a possible pathogenetic factor in WM (38). Hyaluronan has a 
role in malignant cell migration and metastasis. Of the 3 HAS isoenzymes 
detected in humans, Adamia et al (38) postulated that overexpressed HAS1 
and HAS3 form a hyaluronan matrix around WM cells, thereby preventing 
their elimination by the immune system and promoting spread of the disease. 
A later report stated that a single nucleotide polymorphism in the \textit{HAS1} gene 
resulted in an enhanced risk of WM development (39). These findings are 
important considering that serum hyaluronan levels have been shown to 
have prognostic value in multiple myeloma.

Serum interleukin-6 (IL-6) levels have been reported to reflect 
disease severity and high tumor burden in patients with WM. It has also
been shown that clonal blood B cells from patients with WM spontaneously differentiate in vitro to plasma cells through an IL-6 pathway. These findings suggest that IL-6 may be a marker reflecting tumor burden and response to treatment in WM (40).

**Immunophenotype**

The typical immunophenotype of WM consists of expression of pan–B-cell surface markers (CD19, CD20, CD22), cytoplasmic Igs, FMC7, BCL2, PAX5, CD38, and CD79a; CD10 and CD23 are mostly absent, and CD5 is expressed in 5% to 20% of cases (41). Variations in the immunophenotypic profile exist, but most patients meet the newly proposed criteria: monoclonal surface Ig positive (5:1 κ:λ ratio), CD19+, CD20+, CD5−, CD10−, and CD23− (7,42). CD5 positivity does not rule out the diagnosis of WM.

According to the WHO classification, WM cells lack CD23 (6), and the 2002 WM consensus group stated that CD23 expression is found in a minority of patients (7). However, in a retrospective study of the immunophenotypic profile of 75 patients by Konoplev et al (43), 61% of LPL/WM cases were CD23+. As part of the 2004 consensus conference on WM, Hunter et al (44) reported the detection of CD23 in 35% of cases.

The immunophenotypic profile in combination with the presence of somatic mutations of V genes (IgM) without intraclonal diversity strongly suggests that the malignant cells in WM originate from cells at a late stage of differentiation (22). The clonal population in WM appears to be derived from a B cell arrested after somatic hypermutation in the germinal center and before terminal differentiation to a plasma cell (45).
Signs and Symptoms

Most patients with the diagnosis of WM have symptoms attributable to tumor infiltration or monoclonal serum protein (or both).

Symptoms Attributable to Tumor Infiltration

Extensive bone marrow infiltration leads to cytopenias, and progressive anemia is the most common indication for initiation of treatment. Lytic bone disease is very uncommon in WM. Although the neoplastic clone predominantly infiltrates the bone marrow, it can also infiltrate other organs, including lymph nodes, liver, and spleen, presenting as organomegalies (46). In rare cases, diffuse lymphoplasmacytic infiltration of the pulmonary parenchyma can occur, and patients present with diffuse pulmonary infiltrates, nodules, or pleural effusion (47). Malignant infiltration of the stomach and bowel as well as the skull base and orbit has also been reported (48). Bing-Neel syndrome (long-standing hyperviscosity altering the vascular permeability and leading to perivascular malignant infiltration) consists of headache, vertigo, impaired hearing, ataxia, nystagmus, diplopia, and eventually coma (49). Malignant vitreitis and conjunctival infiltration are rare ocular manifestations of the disease (50).

Symptoms Attributable to Circulating IgM

The larger size and increased concentration of the monoclonal protein leads to an increase in vascular resistance and viscosity. Serum hyperviscosity is the most distinguishing feature of WM, but it is only observed in less than 15% of patients at diagnosis (51). Symptoms of hyperviscosity usually appear when the normal serum viscosity of 1.4 to 1.8 cP reaches 4 to 5 cP (corresponding to a serum IgM level of at least 3 g/dL) and include constitutional symptoms, bleeding, and ocular, neurologic, and
cardiovascular manifestations (52). High-output cardiac failure may develop because of the expanded plasma volume arising from increased osmotic pressure. Abnormalities in bleeding and clotting times occur from the interaction of IgM with coagulation factors. IgM may also coat platelets, thereby impairing their function. The circulating IgM also may undergo precipitation at cooler temperatures and present as type I or type II cryoglobulinemia. Cryogobulins may be detected in 20% of patients, but fewer than 5% present with symptoms like Raynaud syndrome, arthralgia, purpura, and skin ulcers (53). Priapism has also been described as an unusual complication.

**Symptoms Attributable to Tissue Deposition of IgM**

IgM deposition can occur in glomerular loops, intestine, and skin, presenting as proteinuria, diarrhea, and macroglobulinemia cutis (papules and nodules), respectively. Primary amyloidosis due to deposition of monoclonal light chains occurs mainly in the heart, peripheral nerves, kidneys, soft tissues, liver, and lungs (in descending order of frequency) (54). Secondary amyloidosis is seen rarely in WM, with nephrotic syndrome and gastrointestinal symptoms as the initial presentation (55). Acute renal failure is rare in WM; in most cases, there is slowly progressive loss of function (56). Although most patients have detectable light chains in the urine, renal insufficiency and cast nephropathy are rare (11).

**Symptoms Attributable to Autoantibody Activity of IgM**

The IgM protein has been proved to induce various autoimmune symptoms in WM. In fewer than 10% of patients, the IgM κ reacts with specific red blood cell antigens at temperatures below 37°C to produce a chronic immune hemolytic anemia, which is associated with elevated cold
agglutinin titers (57). Schnitzler syndrome is the term for IgM monoclonal gammopathy associated with urticarial skin lesions, fever, and arthralgia (58,59). Peripheral neuropathies have been reported in 15% to 30% of patients with IgM-MGUS or WM (60). The most commonly encountered symptomatic neuropathy in WM is symmetric polyneuropathy; other forms include cranial nerve palsies and mononeuropathies or multineuropathies (61). In a study of 119 WM patients and 58 controls by Levine et al (62), polyneuropathy symptoms were observed more frequently in patients with WM (47%) than in controls (9%) \((P < .001)\). Other less common neuropathies associated with WM include those related to amyloidosis and cryoglobulinemia. Anti–myelin-associated glycoprotein (MAG) antibody has been implicated in the demyelinating neuropathy found in WM (63). Analyses of nerve tissue from patients with anti-MAG antibodies in nerve or skin biopsy specimens have demonstrated IgM deposits at the site of MAG localization. The antibody properties of IgM toward glomerular basement membrane may present as glomerulonephritis. Angioedema and acquired von Willebrand disease have also been reported.

**Differential Diagnosis**

The presence of clonal B cells with lymphoplasmacytic differentiation in the bone marrow or a serum monoclonal IgM protein are not pathognomonic for WM and may be seen in other B-cell lymphoproliferative disorders including splenic marginal zone lymphoma (SMZL). With increasing frequency, patients who fulfill the diagnostic criteria of WM are being diagnosed without having any symptoms or signs and are classified as having asymptomatic or smoldering WM (64).
Asymptomatic patients with monoclonal IgM and without morphologic evidence of bone marrow infiltration (<10% clonal marrow cells) are classified as having IgM-MGUS, which is the most common differential diagnosis for patients with an IgM monoclonal protein. Some patients may have detectable bone marrow clonal B cells by flow cytometry but no morphologic evidence of bone marrow infiltration at trephine biopsy. These patients should be classified as having IgM-MGUS and monitored without therapeutic intervention (65). Results from FISH studies indicate that deletion of the long arm of chromosome 6 (6q–) is not seen in IgM-MGUS, and 6q– has been suggested as a clinical marker to distinguish WM from IgM-MGUS (25).

SMZL can be distinguished from WM on the basis of immunophenotypic and molecular cytogenetic studies. Ocio et al (66) demonstrated that CD22 and CD11c were overexpressed in patients with SMZL, whereas CD25 was more common in WM (88% vs 44%). The CD103 antigen (which was always negative in WM) was positive in 40% of SMZL cases. The chromosomal abnormality most commonly seen in WM was 6q deletion, whereas in SMZL, it was the loss of 7q along with +3q and +5q.

The clinical differentiation of multiple myeloma (MM) from WM is straightforward. When a patient presents with features typical of MM and an IgM component, a diagnosis of IgM-MM is made. The distinction between IgM-MM and WM is based on the pure plasma cell morphology in myeloma and presence of lytic bone lesions in myeloma. Renal insufficiency is more common in IgM-MM than in WM. Typical WM expresses all the B-cell antigens (CD19, CD20, and CD22), whereas IgM-MM typically
expresses plasma cell antigens CD38 and CD138, which are absent in WM. IgH gene translocations are more common in IgM-MM (67), particularly t(11;14)(q13;q32).

B-cell chronic lymphocytic leukemia (CLL) may mimic WM clinically. The most common physical finding in CLL is lymphadenopathy. Morphology and immunophenotyping are adequate to diagnose CLL. Lymphocytes are typically small and mature, without visible nucleoli, and smudge cells are characteristic (68). The lymphocytes in CLL are positive for CD5 and CD23, whereas both are usually negative in WM. The presence of strong cytoplasmic immunoglobulin in WM also helps in making the distinction (6). Patients with CLL frequently have IgM-MGUS (69).

The evolution of WM to diffuse large B-cell lymphoma (DLBCL) as a result of histologic transformation has been described (70). Onset of DLBCL is usually characterized by an aggressive clinical course and usually manifests as worsening constitutional symptoms, profound cytopenias, extramedullary disease, and organomegaly. It is also associated with a poor outcome. The clinicopathologic features at diagnosis of WM do not predict the risk of DLBCL (70). Ig light chain expression is usually identical in WM and DLBCL.

**Diagnosis**

In practice, a surface IgM positive CD5⁻CD10⁻CD19⁺CD20⁺CD23⁻ immunophenotype in association with a nonparatrabecular pattern of infiltration is diagnostic of WM (41,71). The diagnostic criteria as stated by Owen (71) are summarized in Table 1. The various diagnostic studies required in daily practice for suspected cases of WM are summarized in Table 2.
Prognosis

The median survival of patients with WM ranges between 5 and 10 years in different series. Several studies have evaluated the effects of different clinical and laboratory variables on patient outcome (72). Age, hemoglobin concentration, serum albumin level, and $\beta_2$-microglobulin were identified as the predominant outcome predictors in these studies (73). Most of these studies concluded that IgM levels had no prognostic value (74).

An International Prognostic Scoring System was presented at the 2006 American Society of Hematology panel as a staging system for survival for symptomatic patients in need of therapy (75). The parameters used to stratify risk were age older than 65 years, $\beta_2$-microglobulin level greater than 3 mg/L, monoclonal protein greater than 7.0 g/dL, hemoglobin less than 11.5 g/dL, and platelet count less than $100\times10^9$/L. Low risk was defined as the presence of fewer than 1 adverse characteristic except age; high risk, as the presence of more than 2 adverse characteristics; the remaining patients with 2 adverse characteristics or older than 65 years had intermediate risk.

Treatment

The aim of treatment is to improve the quality and duration of life with minimal adverse effects in the most cost-effective manner. Whether achievement of complete remission confers clinical benefit is still debatable.

Whom to Treat

The Third International Workshop on WM (76) affirmed the previous consensus panel’s recommendations (77) that treatment must be reserved for symptomatic patients and should not be initiated on the basis of serum monoclonal protein levels alone. Some of the considerations for
initiation of treatment include hemoglobin less than 100 g/L, platelet count less than \(100 \times 10^9/L\), significant adenopathy or organomegaly, symptomatic hyperviscosity, severe neuropathy, amyloidosis, cryoglobulinemia, cold-agglutinin disease, or evidence of disease transformation. Nevertheless, a serum monoclonal protein level greater than 50 g/L places patients at considerable risk of hyperviscosity. This finding requires a thorough history and physical and funduscopic examinations to diagnose early symptoms and signs of hyperviscosity, and treatment should not be postponed. Therapeutic outcomes should be evaluated using updated consensus panel criteria (76).

**Treatment Options**

The main choices for primary treatment of WM are alkylating agents (chlorambucil, cyclophosphamide, melphalan), purine analogues (cladribine, fludarabine), and monoclonal antibody (rituximab [anti-CD20]). Plasma exchange (1-1.5 volume) is indicated for the acute management of patients with symptoms of hyperviscosity because 80% of the IgM protein is intravascular. Patients may be candidates for initial combination therapy with purine nucleoside analogues or antibody therapy (76). Table 3 summarizes the largest therapeutic trials, including their overall response rates and median response duration.

Chlorambucil (0.1 mg/kg) was the first agent used, with response rates varying between 31% and 92% (78,94). The most common complication of therapy with alkylating agents is development of myelodysplasia and acute nonlymphocytic leukemia from therapy-induced chromosomal breakage (95). Cladribine (0.1 mg/kg) has shown response rates in the range of 44% to 90% (79,96-98). Response rates to fludarabine (30 mg/m\(^2\)) as initial therapy range from 38% to 100% (80,99-102).
Fludarabine and cladribine are cross-resistant (96). The principal dose-limiting toxicity of both these agents is bone marrow suppression and immunosuppression, predisposing patients to infections. Response rates to rituximab (375 mg/m²) vary between 20% and 50% (81,103-107). Rituximab may be regarded as a reasonable choice for treating patients with IgM autoantibody-related neuropathies (108). Patients with polyneuropathy associated with anti-MAG antibodies treated with high-dose rituximab have shown clinical improvement as well as improvement of nerve conduction velocities and decreased anti-MAG antibody titers (109). Polymorphisms in the FcγRIIIA (CD16) receptor gene may affect response to rituximab (110). Transient increases in IgM titers have been reported in 54% of patients after initiation of rituximab therapy. These levels may persist for up to 4 months and do not indicate treatment failure, but they may necessitate plasmapheresis to reduce hyperviscosity, which may result in the loss of the therapeutic antibody (111,112). Patients who had initial IgM flares had poorer response rates than those who did not (28% vs 80%) (111).

Because several cell cycle regulators and modulators of apoptosis are degraded through the ubiquitin-proteasome pathway, proteasome inhibitors such as bortezomib have become the focus of clinical research in WM. Chen et al (113) described 27 patients in whom bortezomib was found to be active in WM; 21 patients had more than a 25% decrease in IgM.

Experience with the use of thalidomide in WM, as a single agent or in combination with dexamethasone or clarithromycin, is limited. Thalidomide is nonmyelosuppressive, immunomodulatory, and antiangiogenic and may be a reasonable choice for 1) patients for whom first-line therapies have failed, 2) those who have had disease relapse and are
not candidates for alkylating or nucleoside analogue therapy, or 3) patients with pancytopenia (114). Lenalidomide has been studied in MM and myelodysplastic syndrome and found to be more potent and also to lack the neurotoxic and prothrombotic adverse effects of thalidomide (115). High-dose chemoradiotherapy with autologous stem cell transplantation is occasionally used, but the number of patients treated to date is inadequate to assess its overall role in management. Pentostatin is useful for patients who may benefit from high-dose chemotherapy with autologous stem cell transplantation (93,116). Nonmyeloablative allogeneic peripheral blood stem cell transplantation may be a promising alternative in patients with refractory disease (117). Splenectomy is rarely indicated, but limited case reports suggest that it may be helpful for managing symptomatic painful splenomegaly and hypersplenism (108).

The Third International Workshop on WM (76) consensus panel concluded that it was not possible to delineate a particular first-line therapeutic agent and that the choice must be made based on individual patient considerations. Alkylating agents deplete stem cells and hence should not be used among patients who may be eligible for autologous transplantation. The results of ongoing studies will help determine the role of allogeneic or nonmyeloablative allogeneic transplantation in the treatment of WM.

**Novel Advances**

Other therapeutic options currently being evaluated for WM include oblimersen sodium (BCL-2 antisense oligonucleotide) (118), \(^{131}\text{I-}
\text{toositumomab} (119), \text{imatinib mesylate} (targets signaling through the stem
cell factor and platelet-derived growth factor receptors on WM and mast cells), and dolastatin (microtubule inhibitor).

Dimopoulos et al (120) showed that a combination of dexamethasone, rituximab, and cyclophosphamide is an active and well-tolerated treatment for symptomatic patients requiring therapy. Disease control was achieved in the majority of patients without the risks of myelosuppression and immunosuppression, which may occur when nucleoside analogues are used. The interim results of a study by Treon et al (121) suggest that a combination regimen of bortezomib, dexamethasone, and rituximab is highly active and well tolerated in the primary treatment of WM.

One pathway that conveys survival signals in mammalian cells is based on phosphoinositide 3-kinase/Akt. Akt is a principal signaling protein in the cellular pathways that lead to muscle hypertrophy and tissue growth. This pathway also has an important role in the migration, adhesion, and homing of WM in vitro and in vivo (122). Akt inhibitors such as perifosine lower the resistance of tumor cells to various therapeutic modalities and induce apoptosis in WM. Perifosine also activates mitogen-activated protein kinase pathways and protein kinase C (PKC) proteins, thereby promoting cell proliferation. Specific Akt inhibitors such as triciribine induce cytotoxicity without enhancing MEK/ERK (mitogen-activated protein kinase kinase/extracellular signal-regulated kinase) activity. Combining perifosine with MEK inhibitors or protein kinase C inhibitors such as AZD6244 and enzastaurin may provide therapeutic advantages in WM. Perifosine in combination with bortezomib, rituximab, and other agents has been shown to have enhanced cytotoxicity on WM cell lines (123).
Additional clinical trials are required to establish the efficacy and safety of such combinations.

Rossi et al (124) reported a phase I/II study of atacicept (TACI-Ig) in refractory WM. Atacicept is a protein that binds to APRIL and BLyS receptors, thereby enhancing cytotoxicity. Mast cells may have a role in tumor cell expansion through constitutive CD154-CD40 signaling; therefore, CD154 blocking agents may prove to be a therapeutic option in WM (3). Ho et al (125) described the role of sCD27 in the pathogenesis of WM and demonstrated the feasibility of targeting CD70 and sCD27-CD70 interactions with the SGN-70 monoclonal antibody.

WM cells in the bone marrow and mast cells express CD52. In a phase II study by Hunter et al (126), alemtuzumab/campath-1H (humanized monoclonal antibody against CD52) has been reported to be highly active in WM. Sildenafil citrate has been shown to induce apoptosis in WM cell lines (127). In a prospective study (128), 30 patients with slowly progressing WM who did not meet consensus eligibility for active therapy were treated with sildenafil citrate; disease progression was suppressed in more than half the patients. After 3 months of therapy, 63% showed a significant decrease in IgM levels and 17% showed a minor response. These results encourage additional clinical trials.

**Conclusion**

WM is a B-cell neoplasm characterized by lymphoplasmacytic infiltration of the bone marrow and elevated serum monoclonal IgM levels. The symptoms of WM are attributable to the extent of tumor infiltration and/or elevated IgM levels. The prognostic factors of significance include the patient’s age, β2-microglobulin, monoclonal protein, hemoglobin, and
platelet count. Therapy is reserved exclusively for symptomatic patients; the main therapeutic options include alkylating agents, nucleoside analogues, and rituximab. Preliminary results of ongoing studies involving combination chemotherapy are encouraging. At present, no specific agent or regimen is superior to another in the treatment of WM. Other novel agents are being investigated; their unique mechanisms of action and toxicity profiles hold promise in the development of rational targeted therapy in WM.

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Table 1. Diagnostic Criteria for Waldenström Macroglobulinemia

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<th>Criteria</th>
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<td>IgM monoclonal gammopathy of any concentration</td>
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<td>Bone marrow infiltration by small lymphocytes showing plasmacytoid or plasma cell differentiation</td>
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<tr>
<td>Intertrabecular pattern of bone marrow infiltration</td>
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<td>Surface IgM+ CD5±CD10−CD19+CD20+CD22+CD23− CD25+CD27+FMC7+CD103−CD138− immunophenotype*</td>
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Ig, immunoglobulin.

*Variations from this phenotypic profile can occur, and care must be taken to satisfactorily exclude other lymphoproliferative disorders. This is particularly relevant in those that express CD5.

From Owen et al (7). Used with permission.
Table 2. Diagnostic Approach to Confirm a Suspected Case of Waldenström Macroglobulinemia

1. Serum protein electrophoresis.
2. Immunofixation—to characterize the type of light and heavy chains.
3. 24-Hour urine collection for protein electrophoresis—40%-80% have detectable Bence Jones proteinuria.
4. Serum $\beta_2$-microglobulin—for prognostic evaluation.
5. Bone marrow biopsy—intratrabecular monoclonal lymphoplasmacytic infiltrate, ranging from predominantly lymphocytic to lymphoplasmacytic to overt plasma cells.
7. Computed tomography of the abdomen and pelvis—to detect organomegaly and lymphadenopathy. (Skeletal surveys and bone scans are not necessary in absence of symptoms, since lytic bone lesions are unusual.)
8. Blood or serum viscosity—if signs and symptoms of hyperviscosity syndrome are present or IgM >5,000.

Ig, immunoglobulin.
Table 3. Therapeutic Studies in Waldenström Macroglobulinemia

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>No. of patients</th>
<th>ORR, %</th>
<th>Median survival (MS), median response duration (MRD), mo</th>
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<tr>
<td>Facon et al (78)</td>
<td>Chlorambucil</td>
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<td>68</td>
<td>EFS, 66</td>
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<tr>
<td>Case et al (83)</td>
<td>Carmustine, cyclophosphamide, vincristine, melphalan, prednisolone</td>
<td>33</td>
<td>82</td>
<td>MRD, 43 for CR and 39 for PR</td>
</tr>
<tr>
<td>Dimopoulos and Alexanian (84)</td>
<td>Cyclophosphamide, vincristine, prednisolone</td>
<td>16</td>
<td>44</td>
<td>MRD, 36</td>
</tr>
<tr>
<td></td>
<td>CHOP</td>
<td>20</td>
<td>65</td>
<td>MRD, 88</td>
</tr>
<tr>
<td>Leblond et al (85)</td>
<td>CAP (pretreated with an alkylating agent)</td>
<td>45</td>
<td>11</td>
<td>MRD, 3 and OS, 45</td>
</tr>
<tr>
<td>Hunter et al (86)</td>
<td>CHOP/rituximab</td>
<td>13</td>
<td>77</td>
<td>90% remain in remission at 9 mo</td>
</tr>
</tbody>
</table>
Table 3 (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>No. of patients</th>
<th>ORR, %</th>
<th>Median survival (MS), median response duration (MRD), mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimopoulos et al (87)</td>
<td>Dexamethasone, cyclophosphamide, rituximab</td>
<td>34</td>
<td>78</td>
<td>90% progression free at 18 mo</td>
</tr>
<tr>
<td>Annibali et al (88)</td>
<td>Melphalan, cyclophosphamide, prednisone</td>
<td>72</td>
<td>87</td>
<td>EFS, 47</td>
</tr>
<tr>
<td>Weber et al (89)</td>
<td>Cladribine, cyclophosphamide, rituximab</td>
<td>27</td>
<td>94</td>
<td>MRD, 60</td>
</tr>
<tr>
<td></td>
<td>Cladribine, cyclophosphamide</td>
<td>37</td>
<td>84</td>
<td>MRD, 36</td>
</tr>
<tr>
<td>Tam et al (90)</td>
<td>Fludarabine, cyclophosphamide, rituximab</td>
<td>5</td>
<td>80</td>
<td>MRD, 39</td>
</tr>
<tr>
<td>Tamburini et al (91)</td>
<td>Fludarabine, cyclophosphamide</td>
<td>49</td>
<td>78</td>
<td>MRD, 27</td>
</tr>
<tr>
<td>Branagan et al (92)</td>
<td>Thalidomide, rituximab</td>
<td>23</td>
<td>68</td>
<td>No relapses at 10 mo median</td>
</tr>
<tr>
<td>Hensel et al (93)</td>
<td>Pentostatin, cyclophosphamide, rituximab</td>
<td>17</td>
<td>90</td>
<td>No patient had relapse at publication time</td>
</tr>
</tbody>
</table>

CAP, cyclophosphamide, doxorubicin, prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CR, complete response; EFS, event-free survival; ORR, overall response rate; OS, overall survival; PR, partial response.

Data from Treon et al (76).
Waldenstrom Macroglobulinemia

Arun Vijay and Morie A Gertz

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