Waldenström macroglobulinemia

Arun Vijay1 and Morie A. Gertz2

1Austin Medical Center–Mayo Health System, Austin, MN; 2Division of Hematology, Mayo Clinic, Rochester, MN

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, β2-microglobulin level, monoclonal protein level, hemoglobin concentration, 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, perfusione, atacicept, oblimersen sodium, and tositumomab show promise as rational targeted therapy for WM. (Blood. 2007;109:5096-5103)

© 2007 by The American Society of Hematology

Introduction

Nearly 63 years have passed since Jan Gosta Waldenström first described 2 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 classification4 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 Lymphoma5 and World Health Organization (WHO)6 classifications. The consensus group at the Second International Workshop on WM in 20027 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 al14 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 pre-existing IgM-monoclonal gammopathy of undetermined significance (MGUS) (46 times higher relative risk than for the general population). Morra et al. 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, but this has been negated recently by Leleu et al. Reports of links between human herpesvirus-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. Analysis of 14q32 by fluorescence in situ hybridization (FISH) and Southern blot indicates the absence of Ig heavy chain (IgH) rearrangements in WM. Postswitch clonotypic Ig (IgG or IgA) is undetectable in WM B cells, confirming the absence of isotype switch events by deletional recombination. 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 families are hypermutated and lack intrachromatid heterogeneity. In contrast, one case has been reported in which WM cells have shown functional class switch recombination. 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 et al. was deletion of the long arm of chromosome 6 in 55% of cases. In contrast, FISH analysis by Terre et al. 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. 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. 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. 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. BlyS is expressed on monocytes and is critical for maintenance of normal B-cell development and homeostasis. 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., 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. 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.

Abnormal expression of hyaluronan synthases (HASs) has been reported as a possible pathogenetic factor in WM. Hyaluronan has a role in malignant cell migration and metastasis. Of the 3 HAS isoenzymes detected in humans, Adamiya et al. 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 HAS1 gene resulted in an enhanced risk of WM development. 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.
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. In rare cases, diffuse lymphoplasmacytic infiltration of the pulmonary parenchyma can occur, and patients present with diffuse pulmonary infiltrates, nodules, or pleural effusion. Malignant infiltration of the stomach and bowel as well as the skull base and orbit has also been reported. Bing-Neel syndrome (long-standing hyperviscosity and bowel as well as the skull base and orbit has also been reported). In fewer than 10% of patients, the IgM symptoms attributable to tissue deposition of IgM occur, and patients present with diffuse pulmonary infiltrates, nodules, or pleural effusion. Malignant infiltration of the stomach and bowel as well as the skull base and orbit has also been reported. In rare cases, diffuse lymphoplasmacytic infiltration of the pulmonary parenchyma can occur, and patients present with diffuse pulmonary infiltrates, nodules, or pleural effusion. Malignant infiltration of the stomach and bowel as well as the skull base and orbit has also been reported.

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. 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 30 g/L [3 g/dL]) and include constitutional symptoms, bleeding, and ocular, neurologic, and cardiovascular manifestations. 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 may also undergo precipitation at cooler temperatures and present as type I or type II cryoglobulinemia. Cryoglobulins may be detected in 20% of patients, but fewer than 5% present with symptoms such as Raynaud syndrome, arthralgia, purpura, and skin ulcers. 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). Secondary amyloidosis is seen rarely in WM, with nephrotic syndrome and gastrointestinal symptoms as the initial presentation. Acute renal failure is rare in WM; in most cases, there is slowly progressive loss of function. Although most patients have detectable light chains in the urine, renal insufficiency and cast nephropathy are rare.

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. Schnitzler syndrome is the term for IgM monoclonal gammapathy associated with urticarial skin lesions, fever, and arthralgia. Peripheral neuropathies have been reported in 15% to 30% of patients with IgM-MGUS or WM. The most commonly encountered symptomatic neuropathy in WM is symmetric polyneuropathy; other forms include cranial nerve palsies and mononeuropathies or multineuropathies. In a study of 119 WM patients and 58 controls by Levine et al, 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. Studies 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.

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. 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.

SMZL can be distinguished from WM on the basis of immunophenotypic and molecular cytogenetic studies. Ocio et al 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, particularly t(11;14)(q13;32).

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. The lymphocytes in CLL are positive for CD5 and CD23, whereas both are usually negative in WM. The presence of strong cytoplasmic Ig in WM also helps in making the distinction. Patients with CLL are usually negative in WM. The presence of strong cytoplasmic Ig in CLL are positive for CD5 and CD23, whereas both frequently have IgM-MGUS.

The evolution of WM to diffuse large B-cell lymphoma (DLBCL) as a result of histologic transformation has been described. 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. 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. The diagnostic criteria as stated by Owen 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. Age, hemoglobin concentration, serum albumin level, and β2-microglobulin level were identified as the predominant outcome predictors in these studies. Most of these studies concluded that IgM levels had no prognostic value.

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. The parameters used to stratify risk were age older than 65 years, β2-microglobulin level higher than 3 mg/L, monoclonal protein level higher than 70 g/L (7.0 g/dL), hemoglobin concentration less than 115 g/L (11.5 g/dL), and platelet count less than 100 × 10^9/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 affirmed the previous consensus panel’s recommendations 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 concentration less than 100 g/L, platelet count less than 100 × 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 higher 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.

#### 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. 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%. The most

---

**Table 1. Diagnostic criteria for Waldenström macroglobulinemia**

<table>
<thead>
<tr>
<th>IgM monoclonal gammapathy of any concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow infiltration by small lymphocytes showing plasmacytoid or plasma cell differentiation</td>
</tr>
<tr>
<td>Interparatrabecular pattern of bone marrow infiltration</td>
</tr>
<tr>
<td>Surface IgM+ CD5+ CD10− CD19+ CD20+ CD22− CD23− CD25− CD138− FMC7+ CD103− CD138− immunophenotype*</td>
</tr>
</tbody>
</table>

*From Owen et al. Used with permission.

Ig indicates 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.

---

**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 β2-microglobulin—for prognostic evaluation.
5. Bone marrow biopsy—intrarabecular 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 > 5000.
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/m\(^2\)) 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 had disease relapse and are not candidates for alkylating or 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),\(^{118}\) I-tositumomab,\(^{119}\) imatinib mesylate (targets signaling through the stem cell factor and platelet-derived growth factor receptors on WM and mast cells), and dolastatin (microtubule inhibitor).\(^{120}\) 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

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>No. of patients</th>
<th>ORR, %</th>
<th>MS or MRD, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facon et al(^{78})</td>
<td>Chlorambucil</td>
<td>128</td>
<td>31</td>
<td>MS, 60</td>
</tr>
<tr>
<td>Dimopoulos et al(^{79})</td>
<td>Cladribine</td>
<td>26</td>
<td>85</td>
<td>MRD, 13</td>
</tr>
<tr>
<td>Dhedapak et al(^{80})</td>
<td>Fludarabine</td>
<td>118</td>
<td>38</td>
<td>OS 5 y, 62%</td>
</tr>
<tr>
<td>Gertz et al(^{81})</td>
<td>Rituximab</td>
<td>34</td>
<td>35</td>
<td>MRD, 27</td>
</tr>
<tr>
<td>Petrucci et al(^{82})</td>
<td>Melphalan, cyclophosphamide, chlorambucil, prednisolone</td>
<td>31</td>
<td>68</td>
<td>EFS, 66</td>
</tr>
<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>
<tr>
<td>Dimopoulos et al(^{87})</td>
<td>Dexamethasone, cyclophosphamide, rituximab</td>
<td>34</td>
<td>76</td>
<td>90% progression free at 18 mo</td>
</tr>
<tr>
<td>Arrasbi 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>Tam et al(^{90})</td>
<td>Fludarabine, cyclophosphamide, rituximab</td>
<td>37</td>
<td>84</td>
<td>MRD, 36</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>

Data from Treon et al\(^{76}\).

ORR indicates overall response rate; MS, median survival; MRD, median response duration; OS, overall survival; EFS, event-free survival; CR, complete response; PR, partial response; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; and CAP, cyclophosphamide, doxorubicin, prednisone.
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 phosphoinositol 3-kinase/Akt. Akt is a principal signaling protein in the cellular pathways that leads 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. 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 proteins, thereby promoting cell proliferation. Specific Akt inhibitors such as triciribine induce cytotoxicity without enhancing MEK/ERK (mitogen-activated protein 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. Additional clinical trials are required to establish the efficacy and safety of such combinations.

Rossi et al. reported a phase 1/2 study of atacicept (TACI-Ig) in refractory WM. Atacicept acts as a decoy receptor by binding to and neutralizing soluble BlyS and APRIL, and preventing these TNF family members from binding to their cognate receptors (TACI, BCMA, and BAFF-R) on B-cell tumors, 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. Ho et al. 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 2 study by Hunter et al., alemtuzumab (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. In a prospective study, 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 level, monoclonal protein level, hemoglobin concentration, 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.

Acknowledgments

Editing, proofreading, and reference verification were provided by the Section of Scientific Publications, Mayo Clinic.

Authorship

Conflict-of-interest disclosure: The authors declare no competing financial interests.

Correspondence: Morie A. Gertz, Division of Hematology, Mayo Clinic, 200 First St SW, Rochester, MN 55905; e-mail: gertz.morie@mayo.edu.

References

immunoglobulin heavy chain locus translocations but have frequent 6q deletions. Blood. 2002;100: 2986-3001.


Waldenström macroglobulinemia

Arun Vijay and Morie A. Gertz