

## Waldenström's Macroglobulinemia: Clinical Features, Complications, and Management

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**Purpose:** To review the clinical features, complications, and treatment of Waldenström's macroglobulinemia, a low-grade lymphoproliferative disorder that produces monoclonal immunoglobulin (Ig) M.

**Methods:** A review of published reports was facilitated by the use of a MEDLINE computer search and by manual search of the *Index Medicus*.

**Results:** The clinical manifestations associated with Waldenström's macroglobulinemia can be classified according to those related to direct tumor infiltration, to the amount and specific properties of circulating IgM, and to the deposition of IgM in various tissues. Asymptomatic patients should be followed without treatment. For symptomatic patients, standard treatment consists primarily of oral chlorambucil; nucleoside analogs, such as fludarabine and cladribine, are effective in one third of previously treated patients and in up to 80% of previously untreated patients. Preliminary evidence

suggests that anti-CD20 monoclonal antibody may be active in about 30% of previously treated patients and that high-dose therapy with autologous stem-cell rescue is effective in most patients, including some with resistance to nucleoside analogs.

**Conclusion:** Waldenström's macroglobulinemia has a wide clinical spectrum that practicing physicians need to recognize early to reach the correct diagnosis. When therapy is indicated, oral chlorambucil is the standard primary treatment, but cladribine or fludarabine can be used when a rapid cytoreduction is desirable. Prospective randomized trials are required to elucidate the impact of nucleoside analogs on patients' survival. A nucleoside analog is the treatment of choice for patients who have been previously treated with an alkylating agent.

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WALDENSTRÖM'S macroglobulinemia (WM) is the result of the malignant proliferation of lymphocytes that produce monoclonal immunoglobulin (Ig) M. This condition was originally described in 1944 by Waldenström, who reported two patients with oronasal bleeding, severe anemia, lymphadenopathy, hypofibrinogenemia, elevated erythrocyte sedimentation rates, and presence of large amounts of a high-molecular-weight gamma globulin in the serum.<sup>1</sup> Examination of bone marrow aspirates of these patients revealed proliferation of cells with lymphocyte and plasma cell characteristics. Subsequently, the serum globulin was identified as an Ig and was designated IgM. According to the Revised European-American Lymphoma classification of lymphoid neoplasms, WM represents the majority of cases that are included under the

diagnosis of lymphoplasmacytoid lymphoma/immunocytoma.<sup>2</sup>

WM is an infrequent disease that affects approximately 1,500 Americans each year; it is approximately 10% to 20% as common as multiple myeloma, and there is a slight male preponderance. The median age of the affected patients is about 65 years, and the disease is significantly more common among whites than blacks.<sup>3,4</sup>

The etiology of WM is unknown, but a genetic predisposition has been suggested by the identification of family clusters and by the detection of the disease in monozygotic twins.<sup>5,6</sup> Occupational exposure may play a role in a few cases, and exposure to leather, rubber dyes, and paints has been incriminated in some but not all studies.<sup>7,8</sup>

### BIOLOGY

The malignant B cells in WM express monoclonal surface and cytoplasmic IgM, and a variable proportion of cells may coexpress IgD. The levels of the surface Ig follow the morphologic pleomorphism of the cells; small lymphocytes express high levels of surface Ig, lymphoplasmacytoid cells express lower levels, and plasma cells are negative. A reciprocal pattern of expression of the CD38 and PCA1 antigens is observed, with plasma cells being strongly positive and small lymphocytes negative. A panel of B-cell antigens (CD19, CD20, CD21, CD22, and CD24) are present on the WM cells, while the CD23 antigen is usually absent (Table 1).<sup>9-11</sup> A spectrum of different CD45 isoforms

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Table 1. Immunophenotype of WM Cells

	PBBC	CLL	WM	MM
slg	++	+	+	0
clg	0	0	+	++
CD5	0	++	±	0
CD10	0	0	±	+
CD19	++	++	++	+
CD20	++	+	++	0
CD21	++	++	+	0
CD22	++	+	++	0
CD23	++	++	0	0
CD38	0	0	+	++
PCA1	0	0	+	++

Abbreviations: c, cytoplasmic; CLL, chronic lymphocytic leukemia; MM, multiple myeloma; PBBC, peripheral-blood B cells; s, surface.

is expressed on WM, consistent with their pleomorphic and differentiation status; some WM cells express the high-molecular-weight CD45 antigen, CD45RA, which is also expressed on resting peripheral-blood B cells. In a proportion of WM cells, however, the low-molecular-weight CD45 antigen, CD45RO, is expressed.<sup>12</sup> In a minority of patients, WM cells express at low intensity the CD5 antigen which is present in a minority of normal B cells and is strongly expressed on chronic lymphocytic leukemia cells.<sup>9-12</sup> A recent report indicated that bone marrow samples from most patients with WM also exhibited positivity for FMC7 and CD138.<sup>13</sup> The authors concluded that the majority of cases classified as WM are characterized by a post-germinal center phenotype (CD19<sup>+</sup>, CD20<sup>+</sup>, CD5<sup>-</sup>, CD10<sup>-</sup>, CD23<sup>-</sup>, IgD<sup>-</sup>) and may therefore arise from marginal zone memory B cells.<sup>13</sup> The immunophenotype of these cells can be used to demonstrate the presence of WM cells in the peripheral blood in patients even if there is no absolute lymphocytosis.

When cultured in vitro, these cells differentiate spontaneously to monoclonal IgM-secreting plasma cells in the absence of cell proliferation. There is evidence that this differentiation is dependent on autologous production of interleukin (IL)-6 by the malignant B cells.<sup>14</sup> Retinoic acid inhibits the spontaneous in vitro differentiation of WM cells due to the inhibition of IL-6 secretion and/or IL-6 receptor downregulation by the malignant cells.<sup>15</sup> Interferons alpha and gamma inhibit the spontaneous differentiation of WM cells to plasma cells, without interference in the IL-6 production or IL-6 receptor expression on WM.<sup>16</sup>

In recent publications, DNA sequences of the Kaposi's sarcoma-associated herpesvirus (KSHV) have been identified in bone marrow biopsy samples from patients with multiple myeloma and WM.<sup>17,18</sup> In other reports, however, no KSHV sequences could be amplified from WM mar-

row.<sup>19</sup> In multiple myeloma there is evidence that KSHV is present on dendritic cells obtained from long-term cultures of bone marrow cells and in myeloma cells.<sup>20</sup> Similarly, the KS 330 fragment of KSHV has been detected on dendritic cells isolated from peripheral blood from four WM patients.<sup>21</sup> A viral IL-6 produced by KSHV may participate in the proliferation and/or inhibition of apoptosis of the malignant cells in myeloma or WM patients. The existence of detectable amounts of the viral IL-6 protein in bone marrow cells of multiple myeloma or WM patients, however, has not been shown yet.

The monoclonal IgM expressed by WM cells often harbors somatic mutations. These are substitutions of nucleotides that affect the coding regions of rearranged *VDJ* genes in both the heavy and light Ig chains. The high rate of somatic mutations indicates that the malignant WM cells are generated under the influence of antigenic stimulation and selection.<sup>22,23</sup> Normally, this antigenic selection is accompanied by antibody class switching to IgG. In WM, the malignant cells express IgM, an antibody isotype associated with primary immune responses. One could speculate that WM cells are B cells in the secondary immune response that carry somatic Ig mutations but have lost the ability to undergo class switching and therefore continue to express IgM.

Various cytogenetic abnormalities involving trisomies or deletions of chromosomes 10, 11, 12, 15, 20, and 21 have been described in up to 30% of bone marrow samples from patients with WM; many patients have complex karyotypes.<sup>24-26</sup> Translocations involving the 14q32 band where the IgH genes map have been found as well; t(14;18)(q32; q21), similar to the translocation involving the *bcl-2* gene observed in follicular lymphomas, and t(8;14)(q24;q32), similar to the translocations in Burkitt-type lymphomas involving the *c-myc* gene have been reported.<sup>27,28</sup> In another translocation, t(9;14)(p13;q32) in WM, the *PAX-5* gene, which encodes a B-cell specific transcription factor, is juxtaposed to the IgH locus in 14q32.<sup>29</sup> Overexpression of genes (*bcl-2*, *myc*, and *PAX-5*) brought to proximity by the strong promoter elements of IgH may contribute to lymphomatogenesis. Mutations in the tumor suppressor gene *p53* have been described and have been associated with a poor response to chemotherapy and with shortened survival in some but not all studies.<sup>30,31</sup>

#### CLINICAL AND LABORATORY FEATURES

The clinical manifestations associated with WM can be classified according to those related to direct tumor infiltration, to the amount and specific properties of circulating IgM, and to the deposition of IgM in various tissues.

### *Manifestations Related to Direct Tumor Infiltration*

WM always involves the bone marrow. The bone marrow aspirate usually shows a diffuse proliferation of small lymphocytes, plasmacytoid lymphocytes (cells with abundant basophilic cytoplasm but lymphocyte-like nuclei), and plasma cells.<sup>2</sup> Mast cells and Dutcher bodies (periodic acid-Schiff–positive intranuclear and intracytoplasmic inclusions consisting of IgM) can also be seen.<sup>32,33</sup> Depending on the degree of marrow infiltration, patients may present with only mild to moderate anemia or with severe pancytopenia.

Magnetic resonance imaging (MRI) is a noninvasive technique that complements bone marrow biopsies by sampling a large volume of bone marrow. Duhem et al<sup>34</sup> found MRI abnormalities in all seven studied patients with WM. We found evidence of marrow involvement on the MRI scans of 91% of 23 patients with WM.<sup>35</sup> Diffuse involvement was noted in 13 patients and a variegated pattern was found in eight. The diffuse and variegated MRI patterns in WM do not differ from those observed in multiple myeloma and reflect a more dispersed spread of the malignant cells in the bone marrow compared with focal MRI patterns. The absence of focal MRI patterns of bone marrow involvement is in keeping with the rarity of lytic bone lesions in WM; focal bone marrow MRI patterns are more frequently associated with destructive changes on skeletal radiographs. Increased grades of contrast uptake on enhanced MRI scans correlated with increased tumor burden.<sup>35</sup> Approximately one third of patients present with lymphadenopathy, splenomegaly or hepatomegaly.<sup>36-40</sup> Occasionally, patients with WM have been reported with lung, renal, gastrointestinal, or leptomeningeal involvement.<sup>41-46</sup>

### *Manifestations Related to Circulating Macroglobulin*

*Hyperviscosity syndrome.* IgM is a large pentameric molecule, two thirds of which is in the intravascular space. An increased concentration of this monoclonal protein may result in an increase of plasma viscosity and an expansion of plasma volume; blood circulation becomes sluggish and the hyperviscosity syndrome occurs. Symptoms usually appear when the relative serum or plasma viscosity is above 5 cp (normal values: 1.4 to 1.8 cp), and in such cases, the corresponding serum IgM is virtually always above 3 g/dL.<sup>47-49</sup> The symptomatic threshold, however, varies from patient to patient. At diagnosis, the hyperviscosity syndrome is clinically evident in 10% to 30% of patients with WM and is characterized by fatigue, bleeding from the gums and nose, and ocular, neurologic, and cardiovascular complications.

*Cryoglobulinemia.* Cryoglobulins are serum proteins or protein complexes that undergo reversible precipitation at low temperatures. Type I cryoglobulins consist of monoclonal IgM and are detected in 10% to 20% of patients with WM, but clinically evident cryoglobulinemia causing Raynaud's phenomenon, palpable purpura, or glomerulonephritis occurs in less than 5% of patients.<sup>39,40,50-52</sup>

*Cold agglutinin disease.* In approximately 10% of patients, the monoclonal IgM may behave as a cold-reactive antibody that seldom interacts with erythrocyte antigens at normal body temperatures but displays progressively greater affinity for RBCs as the temperature approaches 0°C.<sup>53,54</sup> Patients may develop acrocyanosis or Raynaud's phenomenon along with an episodic or chronic hemolytic process, usually of moderate severity.

### *Manifestations Related to IgM Deposition*

*Neurologic manifestations.* Approximately 10% of patients with WM present or develop symptoms and signs suggestive of a polyneuropathy. These neuropathies are clinically and immunochemically heterogeneous owing to various pathogenetic mechanisms, including plasma cell infiltration of the peripheral nerves, antibodies against various glycoproteins or glycolipids of the peripheral nerves, and amyloid deposition. These neuropathies can be best divided into the following subsets: (a) demyelinating polyneuropathy with IgM anti-MAG antibodies, (b) demyelinating polyneuropathies with monoclonal IgM reacting with gangliosides (but not myelin-associated glycoprotein [MAG]), (c) polyneuropathies with monoclonal IgM non-reactive with known peripheral nerve antigens, (d) cryoglobulinemic neuropathy, and (e) amyloid polyneuropathy.

*Demyelinating polyneuropathy with IgM anti-MAG antibodies.* Sera from approximately 50% of these patients react with MAG, a 100-kDa glycoprotein of the central and peripheral-nerve myelin, as well as other glycoproteins or glycolipids that share antigenic determinants with MAG.<sup>55,56</sup> Most patients with anti-MAG antibodies present with sensory complaints of numbness, paresthesias, imbalance, and gait ataxia caused by lack of proprioception. Some patients may have aching discomfort, dysesthesias, or lancinating pains. Weakness of the distal leg muscles with variable atrophy occurs as the illness advances.<sup>57,58</sup>

Nerve conduction studies are consistent with demyelination characterized by slow conduction velocity and by prolonged distal motor and sensory latencies. Conduction block is not common. The amplitude of the muscle action potential can be diminished by a progressive loss of axons as the disease progresses. The needle electromyogram often shows denervation potentials caused by a concomitant axonal degeneration. The CSF protein is elevated, up to 250

mg/dL (normal,  $\leq 50$  mg/dL). The monoclonal IgM may also enter the CSF compartment, despite its high molecular weight, via the dorsal root ganglia that lack a blood-CSF barrier or from a disrupted root-CSF barrier.<sup>59</sup>

The sural nerve biopsy demonstrates a diminished number of myelinated axons. Lymphocytic infiltrates can be seen at times within the endoneural parenchyma or in the perivascular space. By electron microscopy, there is splitting of the outer myelin lamellae, linked to the presence of IgM deposits in the same area of the split myelin sheath.<sup>60-62</sup>

With immunocytochemistry, the patient's IgM is deposited on the myelin sheath. By Western blot analysis, the IgM immunoreacts with MAG. The antigenic determinant for the anti-MAG IgM resides in the carbohydrate component of the MAG molecule, as demonstrated by the loss of reactivity after deglycosylation of purified human MAG.<sup>63</sup> The anti-MAG IgM paraproteins coreact with an acidic glycolipid in the ganglioside fraction of the human peripheral nerve, which is separated from the whole ganglioside fraction by ion-exchange chromatography.<sup>64</sup> This antigenic glycolipid, chromatographed between GM1 and GD1a, has been characterized as a novel sulfoglucuronyl glycosphingolipid.<sup>65</sup> In contrast to MAG, which is mostly present within the CNS, sulfoglucuronyl glycosphingolipid is found only in the peripheral nerve and may be the most specific antigenic target accessible by the circulating IgM. The IgM may be pathogenic because it causes splitting of myelin lamellae, fixes complement, and can cause demyelination when injected in experimental animals.<sup>66</sup>

*Demyelinating polyneuropathies with monoclonal IgM reacting with gangliosides (but not MAG).* The sera of some of these patients may not react with MAG, despite clinical similarities with the anti-MAG-reacting paraproteins, but may react with various gangliosides, such as those containing a disialosyl moiety, or with GalNac-GM1b and GalNac-GD1a, two gangliosides that share epitopes with GM2 or with a combination of GM2 and GM1, or GM1 and GD1b.<sup>66-71</sup>

*Polyneuropathies with monoclonal IgM nonreactive with known peripheral nerve antigens.* In about 30% of the patients, IgM does not recognize a known antigen, even though the clinical picture is the same as in the polyneuropathies described above. A number of these patients may, however, have a prominent axonal rather than demyelinating component.<sup>72</sup>

*Cryoglobulinemic neuropathy.* In WM, cryoglobulinemic neuropathy occurs most often with type I cryoglobulinemia and is characterized by a precipitation in the cold of the monoclonal IgM. Patients present with distal, sensory, symmetric polyneuropathy or with mononeuropathy multiplex. The neuropathy is often axonal. Nerve biopsy shows

perivascular inflammatory cuffing with axonal degeneration, which, if focal, may suggest ischemia.<sup>73</sup>

*Amyloid polyneuropathy.* Approximately half of the patients with primary amyloidosis related to an IgM monoclonal protein present with or develop a polyneuropathy.<sup>74</sup> Amyloid deposition in the nerve or the endoneural vessels is common. Patients present with an asymmetric or symmetric sensorimotor peripheral neuropathy, burning and aching pains with lancinating electrical sensations, and impaired pain or thermal sensation in the distal limbs. Autonomic symptoms are the hallmark of amyloid polyneuropathy and consist of postural hypotension, diarrhea, impotence, and bladder dysfunction.<sup>72</sup>

*Amyloidosis.* The occurrence of amyloidosis in patients with monoclonal IgM was reviewed recently.<sup>74</sup> In a large series of patients from the Mayo Clinic, amyloidosis developed in 2% of patients with monoclonal IgM, and 76% of cases showed a lambda light chain. Cardiac, renal, hepatic, and pulmonary involvement predominated and were the cause of death more often than the underlying WM. The incidence of cardiac and pulmonary involvement seemed to be higher in patients with IgM-related amyloidosis than patients with in the other cases of primary amyloidosis.<sup>74</sup>

*Renal manifestations.* Renal abnormalities occur infrequently in patients with WM, but their spectrum and pathogenesis are different from those in multiple myeloma. Hypercalcemia and significant Bence Jones proteinuria of more than 1.0 g/d occur in less than 5% of patients with WM.<sup>40</sup> The low incidence of these abnormalities explains the rarity of renal tubular cast formation in these patients. However, glomerular abnormalities are more frequently seen in WM than in multiple myeloma. IgM has characteristics of aggregability, polymerization, and cryoprecipitation. The high concentration of IgM brought about in the capillary lumen by the ultrafiltration process may lead to its local deposition. Thus, IgM can precipitate on the endothelial side of the glomerular basement membrane, occlude the capillary lumen, and cause nonselective proteinuria.<sup>75</sup> These lesions do not trigger any glomerular proliferation, may be asymptomatic, and are usually reversible. Few patients have been described in whom IgM behaved as an antibody against the glomerular basement membrane and caused an immune-mediated glomerulonephritis manifested as nephritic or nephrotic syndrome.<sup>76,77</sup> In the presence of significant albuminuria, the possibility of renal amyloidosis should be considered and the presence of rapidly progressive glomerulonephritis should raise the possibility of cryoglobulinemia.

*IgM skin deposits.* Firm, translucent, flesh-colored papules characterized by intraepidermal deposits of IgM have occasionally been reported.<sup>78,79</sup> Monoclonal IgM gam-

mopathy, and sometimes frank WM, has also been associated with urticarial skin lesions (Schnitzler's syndrome).<sup>80</sup>

*IgM deposits in the gut.* Occasionally, patients with WM may present with or develop diarrhea and malabsorption. In some of these patients, hyalin deposits, which stain positive for periodic acid-Schiff but negative for amyloid and consist of monoclonal IgM, have been detected.<sup>81,82</sup>

#### DIFFERENTIAL DIAGNOSIS

The diagnosis of WM is obvious when the patient presents with large amounts of monoclonal IgM, depressed uninvolved Igs, anemia with or without lymphadenopathy or hepatosplenomegaly, and infiltration of the bone marrow by small lymphocytes, plasmacytoid lymphocytes, and plasma cells. Most series require the presence of at least 30% lymphoplasmacytic infiltrate on bone marrow smears. Some series have required the presence of at least 1.0 g/dL or 0.5 g/dL monoclonal IgM in order to confirm the diagnosis of WM.<sup>38,39</sup> However, Kyle and Garton<sup>51</sup> have shown that all patients with bone marrow lymphoplasmacytic infiltration associated with a serum monoclonal IgM should be included under the diagnosis of WM regardless of the amount of IgM.

In some individuals who undergo screening blood tests or who are being evaluated for a medical disorder, a monoclonal IgM of less than 2 g/dL is detected but there are no symptoms or signs suggestive of WM; anemia, hepatosplenomegaly, and lymphadenopathy are absent and results of bone marrow examinations are normal or reveal a mild lymphocytosis. These individuals meet the diagnostic criteria for monoclonal gammopathy of undetermined significance (MGUS) of IgM type.<sup>51,83</sup> The incidence of IgM MGUS is approximately four times higher than that of WM.<sup>37,51</sup> Such individuals should not be treated at diagnosis but must be followed indefinitely because some of them will develop a malignant lymphoproliferative disorder in the future. Furthermore, no findings at the diagnosis of MGUS reliably distinguish patients who will remain stable from those in whom a malignant condition will develop.<sup>51</sup>

Some individuals present with a complication caused by the macroglobulin, such as peripheral neuropathy, cold agglutinin disease, cryoglobulinemia, or amyloidosis, but the concentration of monoclonal IgM is low, there is no evidence of organomegaly or lymphadenopathy, and a lymphoplasmacytic infiltration of the bone marrow is absent. Presumably, in such patients, the specific property of monoclonal IgM caused symptoms several years before overt WM developed.<sup>84</sup> The treatment of these patients focuses on the management of the primary IgM-induced complications, and systemic chemotherapy may be of benefit.

Finally, some patients with monoclonal IgM are diagnosed by chance and are asymptomatic, but further staging procedures reveal that the marrow is infiltrated by lymphoplasmacytoid cells.<sup>51,85</sup> Such patients usually have no or only mild anemia, and significant lymphadenopathy or splenomegaly is absent. Some patients with asymptomatic WM have monoclonal IgM levels ranging from 2 g/dL to 4 g/dL.<sup>83</sup> It may be difficult to distinguish between IgM MGUS and asymptomatic WM.

#### TREATMENT

When WM patients present with significant anemia, B symptoms (weight loss, fever, and night sweats), symptoms or signs of hyperviscosity, significant hepatosplenomegaly and/or lymphadenopathy, or any complication associated with the monoclonal IgM (cryoglobulinemia, cold agglutinin anemia, neuropathy, amyloidosis, and so on), prompt treatment of the disease is required.<sup>38-40,83</sup> Patients with WM who do not have symptoms, anemia, significant hepatosplenomegaly or lymphadenopathy, or complications associated with the monoclonal protein should be followed without any treatment until there is evidence of disease progression. Although no prospective randomized studies have been performed in order to compare initial versus deferred treatment in patients with asymptomatic WM, there is evidence from other low-grade lymphoproliferative disorders that early treatment of asymptomatic patients does not prolong survival.<sup>86</sup> In several clinical trials, it is unclear whether some asymptomatic patients with WM may have been included. Clearly defined clinical and laboratory parameters that allow a decision to start systemic treatment will enhance the comparability of the results among different phase II studies.

#### *Treatment of IgM-Induced Complications*

In several patients with WM, the predominant symptoms are caused by the elevated serum viscosity. Because 80% of IgM is intravascular, plasmapheresis, conducted with an automatic blood separator that uses albumin and saline replacement, is an effective means of rapidly reducing the amount of circulating IgM.<sup>87</sup> Concomitant administration of systemic therapy is usually necessary in order to reduce the monoclonal protein synthesis. Nevertheless, plasma exchange has been used as the sole treatment in the occasional elderly patient with resistant WM and predominant symptoms of hyperviscosity.<sup>88</sup>

In some patients with WM and peripheral neuropathy or cryoglobulinemia, the tumor load at presentation is low, anemia and organomegaly are absent, and the main discomfort is caused by the neurologic impairment or the cryoglobulin. In such cases, an intensive series of plasma exchange

**Table 2. Primary Treatment of WM With Alkylating Agents**

Regimen (ref)	No. of Patients	Response (%)	Median Survival (years)
ChlP <sup>(40)</sup>	77	57	5.0
M2 protocol <sup>(97)</sup>	33	82	4.2
MChlP <sup>(98)</sup>	34	68	5.5

Abbreviations: ChlP, chlorambucil and prednisone; M2 protocol, melphalan, cyclophosphamide, carmustine, vincristine and prednisone; MChlP, melphalan, chlorambucil, and prednisone.

may rapidly reduce the monoclonal protein, may provide an opportunity for symptomatic improvement and may justify the subsequent administration of systemic treatment to achieve long-term control. In several patients with IgM-demyelinating polyneuropathies, treatment with chemotherapy, plasmapheresis, or high dose intravenous (IV) Ig has been associated with symptomatic improvement.<sup>89-93</sup> Interferon alfa was beneficial in one trial.<sup>94</sup> Fludarabine was effective in four patients with IgM paraproteinemic neuropathy.<sup>95</sup>

#### *Treatment of the Lymphoma*

**Response criteria.** Response criteria are a combination of those used in evaluating patients with multiple myeloma and low-grade lymphoma. In most studies, a partial response is defined as a decrease by at least 50% of monoclonal IgM for at least 2 months with more than a 50% reduction of tumor infiltrate at all involved sites. A complete response is defined as the disappearance of the monoclonal protein by immunofixation, resolution of lymphadenopathy and splenomegaly, and less than 20% lymphocytes in the bone marrow.

**Primary treatment.** Chemotherapy with alkylating agents with or without corticosteroids has been the standard primary therapy for patients with symptomatic macroglobulinemia. The agent most commonly used is oral chlorambucil; 50% of patients respond and several months are required to determine the chemosensitivity of the disease.<sup>36,85</sup> A recent randomized study indicated that daily oral and intermittent chlorambucil were equally active, with both resulting in a median survival of 5.4 years.<sup>96</sup> The combination of chlorambucil and prednisone was associated with response and survival rates similar to those obtained by single-agent chlorambucil (Table 2).<sup>40</sup> Corticosteroids may, however, be of value in patients with immune hemolytic anemia, cold agglutinin disease, or cryoglobulinemia. Other series have used combinations of alkylating agents with or without a vinca alkaloid, or a nitrosurea. Although no prospective randomized trials have compared those regimens to standard chlorambucil, there is no evidence of benefit from these combinations.<sup>40,97,98</sup> Treatment with

**Table 3. Activity of Cladribine in WM**

Series (ref)	No. of Patients	Response	
		No. of Patients	%
<b>Primary treatment</b>			
Dimopoulos <sup>102</sup>	26	22	85
Delannoy <sup>103</sup>	11	8	73
Fridrik <sup>104</sup>	10	9	90
Liu <sup>105</sup>	7	4	57
Hellman <sup>106</sup>	9	4	44
Total	63	47	75
<b>Salvage treatment</b>			
Dimopoulos <sup>127</sup>	46	20	45
Delannoy <sup>103</sup>	16	8	50
Liu <sup>105</sup>	13	7	54
Betticher <sup>128</sup>	24	9	38
Hellman <sup>106</sup>	13	5	38
Total	112	49	44

alkylating agents is usually continued for several months and may expose patients to the risks of myelodysplasia or secondary leukemia.<sup>99,100</sup>

The combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) has been administered to a limited number of patients with WM. Among 132 symptomatic patients who received primary treatment at the M.D. Anderson Cancer Center, 20 patients were treated with CHOP. Their response rate was similar to that achieved with the chlorambucil and prednisone combination (65% v 57%). The median survival associated with CHOP (7.3 years) was not statistically longer than that achieved with the chlorambucil and prednisone combination (5.0 years).<sup>101</sup> The number of patients treated with CHOP was not large enough to assess whether this regimen may be more effective in certain subsets of patients, such as those presenting with high tumor mass or with pancytopenia.

Over the last decade, the newer nucleoside analogs fludarabine and 2-chlorodeoxyadenosine (cladribine) have shown activity in patients with a variety of chronic lymphoproliferative disorders. These agents have also been administered to previously untreated patients with WM. Cladribine has been administered as an IV continuous infusion or as a 2-hour intermittent IV infusion for 5 to 7 days every 4 weeks. As listed in Table 3, most studies have confirmed objective responses in at least 75% of patients.<sup>102-106</sup> To avoid significant myelosuppression and immunosuppression, we administered only two courses of cladribine to outpatients at a dose of 0.1 mg/kg/d for a 7-day continuous infusion, using a portable pump through a central venous catheter. Responding patients were followed without further therapy and were scheduled to receive two additional courses of cladribine if they relapsed. We have observed responses in at least 80% of patients. The median time to a

50% reduction of IgM systems was 1.2 months, and even after cladribine therapy was stopped, a gradual reduction of abnormal protein continued in all responding patients. Most relapsing patients responded again to re-treatment with cladribine.<sup>102</sup> Preliminary data suggest that a limited treatment with subcutaneous cladribine and oral cyclophosphamide is an active regimen for previously untreated patients with WM.<sup>107</sup> In the same series, it was found that cladribine-containing regimens, administered in 58 previously untreated patients, induced a significantly higher response rate (75%) than that observed previously in 115 patients treated with alkylating agent-based therapy (55%;  $P = .01$ ).

Fludarabine has also been studied as front-line treatment of WM. An intergroup trial of the Southwest Oncology Group and the Eastern Cooperative Oncology Group administered fludarabine 30 mg/m<sup>2</sup> IV daily for 5 consecutive days every 4 weeks to patients with untreated WM. At least a 50% reduction of tumor mass was noted in 33% of patients, and the median progression-free survival was 42 months.<sup>108</sup> This response rate seems inferior to that obtained with either cladribine or chlorambucil, but the final analysis and publication of this trial is needed in order to draw firm conclusions. Furthermore, in almost all other chronic lymphoproliferative disorders, with the exception of hairy cell leukemia, cladribine and fludarabine seem equally effective. A recently published European multicenter phase II study included 20 previously untreated patients with WM who received fludarabine 25 mg/m<sup>2</sup> IV daily for 5 consecutive days every 4 weeks. An objective response was noted in 79% of patients and the median time to progression was 40 months.<sup>109</sup>

Although primary treatment of WM with cladribine or with fludarabine has not been prospectively compared with treatment with chlorambucil, because of their rapid cytoreduction, nucleoside analogs may be the treatment of choice in patients with serious complications of the disease, such as hyperviscosity, pancytopenia, or severe peripheral neuropathy. The major adverse effects of cladribine and fludarabine are myelosuppression and immunosuppression. Although the myelosuppression is usually moderate, repetitive courses of these agents can be associated with cumulative and protracted myelotoxicity. After treatment with nucleoside analogs, there is a profound and sustained reduction of monocytes and of CD4<sup>+</sup> and CD8<sup>+</sup> lymphocytes.<sup>102</sup> This results in a substantial risk for opportunistic infections.<sup>110-112</sup> Administration of a limited number of courses of a nucleoside analog and/or reduction of the dose may be associated with less myelosuppression and immunosuppression without impairment of response rate. Moreover, myelodysplasia has been reported after treatment with nucleoside analogs.

**Table 4. Activity of Fludarabine in Previously Treated Patients With WM**

Series	No. of Patients	Response	
		No. of Patients	%
Dimopoulos <sup>122</sup>	26	8	31
Zinzani <sup>123</sup>	12	5	41
LeBlond <sup>124</sup>	71	21	30
Total	109	34	31

In a recent report of a long-term follow-up of 27 patients with WM treated with cladribine, three patients developed myelodysplastic syndromes, including one patient with previous minimal exposure to alkylating agents and another previously untreated patient. Prolonged follow-up of WM patients treated with nucleoside analogs is needed to define the risk of myelodysplasia associated with these agents.<sup>103</sup>

*Salvage treatment.* Several patients with WM do not respond to the initial alkylating agent-based treatment, and virtually all responding patients will eventually experience progression of their disease. There have been limited trials of second-line treatments including doxorubicin, high-dose corticosteroids, gamma-interferon, and splenectomy, with occasional benefits reported.<sup>113-117</sup>

Interferon alfa has been administered to several previously treated patients with WM. With the use of different doses and response criteria, some evidence of antitumor effect was demonstrated in 20% to 50% of patients.<sup>118-120</sup> These data indicate that interferon alfa may have a role in the treatment of WM. Future studies may assess its effect as a remission maintenance treatment or in previously untreated patients.

Fludarabine was the first nucleoside analog to induce responses in about one third of patients who had been resistant to previous treatments.<sup>121</sup> These results were subsequently confirmed by other studies (Table 4).<sup>122-124</sup> The recommended dose of fludarabine is 25 mg/m<sup>2</sup> IV daily for 5 days every 4 weeks. Recently, results were reported of a multicenter randomized trial comparing the efficacy of cyclophosphamide, doxorubicin, and prednisone (CAP) with that of fludarabine in patients with WM in first relapse or with primary refractory disease to alkylating agents.<sup>125</sup> Responses were observed in 11% of patients treated with CAP and in 28% of patients treated with fludarabine ( $P = .019$ ). The median time to progression of the responders and the time to treatment failure were statistically longer in patients treated with fludarabine. The median survival times of the two arms were similar probably because patients resistant to CAP were allowed to receive further treatment with fludarabine.<sup>125</sup> Cladribine has also shown activity in previously treated patients with WM.<sup>105,106,126-128</sup> As listed in Table 3 approximately one half of patients are expected

**Table 5. Nucleoside Analogs in Previously Treated Patients With WM**<sup>122,127</sup>

Disease Status	No. of Patients	Response (%)	Median Survival (months)
Relapse off treatment	9	78	28
Primary resistant	34	44	40
Refractory relapse	29	21	13

to achieve an objective response. Thus, both fludarabine and cladribine provide an opportunity for response in pretreated patients with WM. We have shown that the status of the disease at the time of salvage treatment with a nucleoside analog is an important factor that predicts the likelihood and durability of the response.<sup>122,127</sup> Patients more likely to benefit are those who relapse after an unmaintained remission (relapse off treatment) and those who had never responded to previous treatments (primary resistant). Patients who were treated while their disease was relapsing despite salvage therapy (refractory relapse) had a significantly lower response rate (Table 5). The median progression-free survival of all responding patients is approximately 12 months. Treatment with a nucleoside analog is the treatment of choice for patients who do not respond to primary treatment with alkylating agents, especially when treated early. The much lower response rate among patients with a longer duration of primary resistance or during refractory relapse may be due to the evolution, over time, of subclones that developed resistance to multiple therapies. Prior resistance to fludarabine is also associated with cross-resistance to cladribine, as observed by investigators who used this sequence of agents for chronic lymphocytic leukemia.<sup>129,130</sup> Thus, patient groups unlikely to respond to a nucleoside analog are candidates for new agents or for more intensive chemotherapy.

Three patients with WM (two previously treated and one untreated) received a combination of cladribine, cyclophosphamide, and prednisone; a partial response was obtained in all three patients.<sup>131</sup> Paclitaxel was administered to six previously untreated patients but none responded.<sup>132</sup> Mohammad et al<sup>133</sup> used severe combined immunodeficient mice to test the activity of bryostatin against the WM tumor line WSU-WM. They noted that administration of bryostatin 24 hours before vincristine or melphalan resulted in the highest tumor growth inhibition and tumor-cell kill. This model can be used for the study of new agents and new drug combinations.

*Monoclonal antibody therapy.* Rituximab, a chimeric anti-CD 20 monoclonal antibody which produces a 50% response rate in patients with previously treated low-grade lymphoma, has been administered to a small number of

patients with WM; three of the seven patients achieved a partial reduction of measurable disease and paraprotein.<sup>134</sup> A partial response was noted in six (23%) of 26 pretreated patients with lymphoplasmacytoid lymphoma or WM in a multicenter trial.<sup>135</sup> These data indicate that rituximab merits further study in WM, especially in patients with strong positivity for CD20. This monoclonal antibody could be combined with cytotoxic chemotherapy or could be administered after a response has been obtained with the use of a nucleoside analog.

*High-dose therapy.* Two young patients with aggressive and chemoresistant WM received a total-body irradiation-containing conditioning regimen supported by an allogeneic bone marrow transplantation from an HLA-identical sibling donor. Both patients remain alive and free from progression 3 and 9 years after the transplantation.<sup>136</sup> High-dose therapy with autologous stem-cell rescue is effective in many patients with multiple myeloma and this treatment has also been administered in a small number of patients with WM. Ten of 11 patients treated with high-dose melphalan supported by autologous marrow or blood stem cells achieved a response, including patients with resistance to prior fludarabine treatment.<sup>137,138</sup> Encouraging results have also been reported in a handful of patients treated with cyclophosphamide and total-body irradiation.<sup>139</sup> These preliminary data suggest that high-dose therapy merits further investigation, particularly in patients with poor prognostic features at diagnosis.

## PROGNOSIS

The median survival of patients with WM averages 5 years, but at least 20% of patients survive for more than 10 years and up to one fifth of patients die of unrelated causes.<sup>38-40,51</sup> Because WM is an uncommon disorder, relatively few studies have defined prognostic factors for this disease. Furthermore, in several series, patients with asymptomatic WM or even IgM MGUS were included and thus may have led to misleading conclusions about the prognostic significance of certain variables.<sup>38</sup> In three large contemporary series of patients with WM, advanced age was associated with inferior prognosis.<sup>38-40</sup> Anemia, which reflects both marrow infiltration and the level of serum monoclonal protein, was found to be an independent adverse prognostic factor.<sup>38,39</sup> Neutropenia and male sex were also significant in the Facon et al series, and weight loss and cryoglobulinemia were poor prognostic factors in an Italian series.<sup>38,39</sup> An update of the Facon et al series indicated that the combination of age, albumin level, and blood cell counts provided a simple prognostic model for survival in WM. With these readily available parameters, patients were stratified into three groups with low, intermediate, and high

risk with a probability of 5-year survival at 86%, 61%, and 26%, respectively.<sup>140</sup>

An effect of response to treatment on patients' survival has also been demonstrated. Mackenzie and Fudenberg<sup>36</sup> reported a mean survival of 49 months for patients responding to chemotherapy and 24 months for nonresponders. Facon et al<sup>38</sup> reported that among their 110 patients treated for at least 12 months with oral chlorambucil, those who achieved a more than 50% reduction of serum IgM lived longer than those who achieved a less than 50% reduction (96 v 42 months,  $P = .01$ ). In the M.D. Anderson series, patients who achieved an objective response lived for a median of 7.7 years, compared with a median of 2.5 years for unresponsive patients. Ten percent of patients achieved a complete response and survived for a median of 11 years.<sup>40</sup>

Most patients with WM die of progressive disease that has become refractory to treatment. In advance phases of the disease, many patients suffer from the complications of pancytopenia, which is usually caused by the heavily infiltrated bone marrow. However, in some patients, the cytopenias may be caused by myelodysplastic syndromes associated with the prolonged administration of alkylating agents.<sup>38,99,100</sup> In some patients, the disease may transform into a diffuse large-cell lymphoma (Richter's syndrome). Clinical and laboratory signs of such transformation include unexplained fever, weight loss, rapidly enlarging lymph nodes, extranodal involvement, and reduction of monoclonal protein consistent with tumor dedifferentiation. Despite treatment with combinations of agents with activity in high grade lymphomas, the outcome of these patients is poor.<sup>141,142</sup>

In conclusion, WM is a lymphoplasmacytoid lymphoma that usually presents with anemia, splenomegaly, or lymphadenopathy. However, this disease has unique clinical and laboratory features that rarely occur in other lymphoproliferative disorders. Hyperviscosity, peripheral neuropathy, cryoglobulinemia, and cold agglutinin disease may be the presenting features or may develop during the course of the disease in a significant number of patients with WM. Less

common complications include amyloidosis and renal disease. There is no evidence that treatment of asymptomatic patients is of benefit. Therapy consists of treatment of IgM-induced complications and treatment of the lymphoma. Assessment of response should be based on the reduction of monoclonal IgM along with the reduction of tumor infiltration at all involved sites. The recently published response criteria for lymphoma may improve the comparability among clinical trials for WM.<sup>143</sup> Standard primary chemotherapy consists of oral chlorambucil. Combinations of multiple alkylating agents do not offer any further benefit. Chlorambucil, combined with plasmapheresis when symptomatic hyperviscosity is present, is usually adequate primary treatment for elderly patients without other life-threatening complications. Nucleoside analogs such as cladribine or fludarabine are highly active agents that can induce responses more rapidly than chlorambucil. Although it is not known whether primary therapy with nucleoside analogs may prolong patients' survival, these agents may be the primary treatment of choice when a rapid control of the disease is required. Further studies are needed to elucidate the optimal dose and duration of cladribine or fludarabine treatment and the activity of these agents when combined with other active drugs. For disease resistant to alkylating agents, both fludarabine and cladribine can induce responses in approximately one third of patients. These agents are more effective when administered before several relapses have occurred. Patients in resistant relapse are candidates for treatment with investigational agents. There is preliminary evidence that high-dose therapy with peripheral-blood stem-cell support and treatment with interferon alfa or with monoclonal anti-CD20 antibody may have a role in the treatment of WM, but more data are required to assess the impact of these treatment strategies in the management of this disease.

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