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Waldenström's macroglobulinemia (WM) is a distinct clinicopathological entity of B-lymphocytes that show maturation to plasma cells constituting a pathognomonic bone marrow lymphoplasmacytic infiltrate, and synthesizing IgM.¹ This condition is considered to correspond to the lymphoplasmacytic lymphoma as defined by the REAL² and WHO classification systems.^{3,4} The disease was first reported by Jan Waldenström (Figure 1), who described two patients with a high level of macroglobulin, i.e. pentameric immunoglobulin M (IgM), marked hyperviscosity with typical fundoscopic picture and lymphocytoid bone marrow infiltration.⁵

EPIDEMIOLOGY

WM is a rare disease, with an incidence that is ten times less frequent than multiple myeloma, and accounts for approximately 2% of all hematologic malignancies. The age-adjusted incidence rate is 3.4 per million among males and 1.7 per million among females in the US, with a geometrical increase with age.⁶ The incidence rate for WM is higher among Caucasians with African descendants representing only 5% of all patients. A previous study had reported an age-standardized annual incidence rate of 6.1 per million in white men and 2.5 per million in white women.⁷

BIOLOGY

Etiology

Genetic factors may contribute to the pathogenesis of WM as suggested by several reports of familial disease, including involvement of monozygotic twins,⁸ as well as frequent familial association with other lymphoproliferative and immunological disorders like hypogammaglobulinemia, autoantibodies (especially rheumatoid factors), increased serum immunoglobulin levels in healthy relatives, and hypereactive B cells.^{9,10} Increased expression of the *bcl-2* gene with enhanced B cell survival may be at the basis of the observed increased immunoglobulin synthesis in familial WM.¹¹ The role of environmental factors in WM is undetermined. There is no clear association with chronic antigenic stimulation from infections, autoimmune diseases or allergy or with specific occupational exposure.¹² The relevance of viral infection to the pathogenesis of this condition remains to be established. Data regarding a possible link between HCV and WM are inconclusive and limited to small patient populations.¹³⁻¹⁶ The role of human herpesvirus-8 remains undetermined in the pathogenesis of WM.¹⁷⁻¹⁹

Biology of the clone

Several studies, usually performed on limited series of patients, have been published on the cytogenetic analysis of WM. A great variety of numerical and structural chromosome abnormalities

have been reported (recently reviewed by GM²⁰) but none is specific. Complex karyotypes are usually associated with more aggressive disease.^{21,22} Notable however is the absence of IgH switch region rearrangements.²³ The WM bone marrow B cell clone shows intraclonal differentiation from small lymphocytes with large, focal deposits of surface immunoglobulins, to lymphoplasmacytic cells to mature plasma cells that contain intracytoplasmic immunoglobulins.²⁴ Clonal B cells are detectable among blood B lymphocytes, and their size increases in patients who fail to respond to therapy or who progress.²⁵ These clonal blood cells present the peculiar capacity to differentiate spontaneously, in *in vitro* culture, to plasma cells through an IL-6 dependent process in IgM-MGUS and mostly IL-6 independent in WM patients.²⁶ All these cells express the monoclonal IgM present in the blood, and a variable percentage of them also express surface IgD. The characteristic immunophenotypic profile for lymphoplasmacytic cells in WM include the expression of the pan B-cell markers CD19, CD20, CD22, CD79 and FMC7.^{2,27-30} The majority of cases do not express CD10 or CD23. Expression of CD5 and CD23, the hallmarks of CLL, is detectable in 5-20% of cases; however, coexpression of these two markers is rare, probably occurring in less than 5%.²⁷

This is a post germinal center phenotype and suggests that the disorder may arise from memory B cells.²⁰ This indication is further strengthened by the results of the analysis of the nature (silent or amino acid replacing) and distribution (in framework or CDR regions) of somatic mutations in Ig heavy and light chain variable regions performed in patients with WM.^{31,32} This analysis showed a high rate of replacement mutations, compared to the closest germline genes, clustering in the CDR regions and without intraclonal variation. Subsequent studies confirmed that tumor V_H genes present somatic mutations and a complete lack of intraclonal variation and no evidence for any isotype-switched transcripts.^{33,34} These data indicate that WM originates from a IgM⁺ and/or IgM⁺IgD⁺ memory B cell. Normal IgM⁺ memory B cells localize in bone marrow where they mature to IgM-secreting cells.³⁵

PATHOGENESIS AND DISEASE FEATURES

WM is a disease of the elderly with a median age of 63 years (range 25-92), with a slight predominance of males over females³⁶. Symptoms are vague and nonspecific, the most common being weakness, anorexia and weight loss. Raynaud's phenomenon and symptoms due to peripheral neuropathy may precede more serious manifestations by many years. Physical findings at diagnosis are summarized in Table 1. Hepatosplenomegaly and lymphadenopathy are prominent in a minority of patients. Purpura is frequently associated with cryoglobulins and seldom with AL amyloidosis, while hemorrhagic manifestations and neuropathies are multifactorial (see below). The morbidity associated with WM is caused by the concurrence of two main components: tissue infiltration by neoplastic cells and, more importantly, the physicochemical and immunological properties of the monoclonal IgM (Figure 2).

Manifestations Related to the Biological Effects of the Monoclonal IgM

As reported in Table 2, the monoclonal IgM can produce clinical manifestations through several different mechanisms related to its physicochemical properties, non-specific interactions with other proteins, antibody activity, and tendency to deposit in tissues.³⁷⁻³⁹

Hyperviscosity syndrome.

Blood hyperviscosity is the most common complication of circulating IgM, occurring in 17% patients.³⁶ The mechanisms behind the marked increase in the resistance to blood flow and the resulting impaired transit through the microcirculatory system are rather complex.⁴⁰⁻⁴² The main determinants are: i) a high concentration of monoclonal IgMs, which may form aggregates and may bind water through their carbohydrate component, and ii) their interaction with blood cells. In fact, monoclonal IgM increase red cell aggregation (*rouleaux* formation) and red cell internal viscosity while reducing deformability. The possible presence of cryoglobulins can contribute to increasing blood viscosity as well as to the tendency to induce erythrocyte aggregation. Serum viscosity is proportional to IgM concentration up to 30 g/L, then increases sharply at higher levels.⁴² Plasma viscosity and hematocrit are directly regulated by the organism. Increased plasma viscosity may also contribute to inappropriate erythropoietin production, which is the major reason for anemia in these patients.⁴³ Clinical manifestations are related to circulatory disturbances that can be best appreciated by ophthalmoscopy, which shows distended and tortuous retinal veins, hemorrhages and papilledema (Figure 3). Symptoms usually occur when the monoclonal IgM concentration exceeds 50 g/L³⁸, or when serum viscosity is > 4 centipoises (cp);⁴⁴ but there is a great individual variability, with some patients showing no evidence of hyperviscosity even at 10 cp. The most common symptoms are oronasal bleeding, visual disturbances due to retinal bleeding and dizziness that may rarely lead to coma.⁴⁵ Heart failure can be aggravated, particularly in the elderly, due to increased blood viscosity, expanded plasma volume and anemia. Inappropriate transfusion can exacerbate hyperviscosity and may precipitate cardiac failure.

In 7 to 20% of WM patients, the monoclonal IgM can behave as a cryoglobulin (type I), but it is symptomatic in 5% or less of the cases.^{28,46} Cryoprecipitation is mainly dependent on the concentration of monoclonal IgM, for this reason plasmapheresis or plasma exchange are commonly effective in this condition. Symptoms result from impaired blood flow in small vessels and include Raynaud's phenomenon, acrocyanosis and necrosis of the regions most exposed to cold (tip of the nose, ears, fingers, toes, see Figure 4), malleolar ulcers, purpura and cold urticaria. Renal manifestations are rather infrequent.

Monoclonal IgM can interact with low affinity, with circulating proteins or with proteins associated with cell membrane such as various clotting factors, including fibrinogen, factors V, VII, and VIII, resulting in prolonged clotting times.³⁸ Platelet function (adhesion and aggregation) is also impaired, probably due to platelet coating by macroglobulins, and results in prolonged bleeding time.³⁸ These abnormalities are IgM concentration dependent and are reversible following therapy.

Monoclonal IgM may exert its pathogenic effects through specific recognition of autologous antigens, the most notable being nerve constituents, immunoglobulin determinants and red blood cell antigens (Table 2). In a series of 215 patients with WM, Merlini *et al*³⁶ reported the clinical presence of peripheral neuropathy in 24% of WM patients (Table 1), though prevalence rates ranging from 5% to 38% have been reported in other series.^{47,48} An estimated 6.5% to 10% of idiopathic neuropathies are associated with a monoclonal gammopathy, with a preponderance of IgM (60 %) followed by IgG (30 %) and IgA (10%) (reviewed in⁴⁹ and⁵⁰). In WM patients the nerve damage is mediated by diverse pathogenetic mechanisms: IgM antibody activity toward nerve constituents causing demyelinating polyneuropathies; endoneurial granulo-fibrillar deposits of IgM without antibody activity, associated with axonal polyneuropathy; occasionally by tubular deposits in the endoneurium associated with IgM cryoglobulin; and, rarely, by amyloid deposits or by neoplastic cell infiltration of nerve structures.⁵¹

Half of the patients with IgM neuropathy have a distinctive clinical syndrome that is associated with antibodies against a minor 100-kDa glycoprotein component of nerve: myelin associated glycoprotein (MAG). Anti-MAG antibodies are generally monoclonal IgMk and usually also exhibit reactivity with other glycoproteins or glycolipids that share antigenic determinants with MAG.⁵²⁻⁵⁴ The anti-MAG-related neuropathy is typically distal and symmetrical, affecting both motor and sensory functions; it is slowly progressive with long period of stability.^{48,55} Most patients present with sensory complaints (paresthesias, aching discomfort, dysesthesias, or lancinating pains), imbalance and gait ataxia due to lack proprioception, and leg muscles atrophy in advanced stage.

Patients with predominantly demyelinating sensory neuropathy in association with monoclonal IgM to gangliosides with disialosyl moieties such as GD1b, GD3, GD2, GT1b and GQ1b have also been reported.^{56,57} Anti-GD1b and anti-GQ1b antibodies were significantly associated with predominantly sensory ataxic neuropathy.⁵⁷ These antiganglioside monoclonal IgM present core clinical features of chronic ataxic neuropathy with variably present ophthalmoplegia and/or red blood cell cold agglutinating activity. The disialosyl epitope is also present on red blood cell glycoporphins, thereby accounting for the red cell cold agglutinin activity of anti-Pr₂ specificity.^{58,59}

Monoclonal IgM that bind to gangliosides with terminal trisaccharide moiety, including GM2 and GalNac-GD1A, are associated with chronic demyelinating neuropathy and severe sensory ataxia,

unresponsive to corticosteroids.⁶⁰ Antigangliosides IgM may also cross-react with lipopolysaccharides of *Campylobacter jejuni*, whose infection is known to precipitate the Miller Fisher syndrome, a variant of the Guillain-Barré syndrome.⁶¹ This finding indicates that molecular mimicry may play a role in this condition.

Anti-sulfatide monoclonal IgM, associated with sensory/sensorimotor neuropathy, have been detected in 5% of patients with IgM monoclonal gammopathy and neuropathy.⁶² Motor neuron disease has been reported in patients with WM and monoclonal IgM with anti-GM1 and sulfoglucuronyl paragloboside activity.⁶³ POEMS syndrome is rarely associated with WM.⁶⁴

The antibody activity of the monoclonal IgM to immunoglobulin (rheumatoid factors) is at the basis of type II cryoglobulinemia. This is an immune complex disease characterized by vasculitis affecting small vessels that is associated with HCV infection.⁶⁵ The clinical manifestations are those of immune complex-mediated vasculitis of small vessels and range from benign purpura to life-threatening severe systemic vasculitis. The main clinical features are weakness, purpura (87%), arthralgias (60-70%), Raynaud's phenomenon (20%) and renal (35-50%), hepatic (40-70%) and peripheral nerve involvement (30-40%). Renal involvement represents one of the most serious complications of type II cryoglobulinemia and is characterized by a membranoproliferative glomerulonephritis with a particular monocyte infiltration.⁶⁶ Clinically, this involvement may range from isolated proteinuria to overt nephritic syndrome with periods of remission and exacerbation, and, if not appropriately treated, may eventually end in renal failure.

Monoclonal IgM may present cold agglutinin activity, i.e. it recognizes specific red cell antigens at temperatures below physiological, producing chronic hemolytic anemia. This disorder occurs in approximately 10% of patients⁶⁷ and is associated with cold agglutinin titers > 1:1000 in most cases. The monoclonal component is usually an IgMk and reacts most commonly with I/i antigens, with complement fixation and activation.^{68,69} Specificity for other red blood cell antigens has been described.³⁷ Mild chronic hemolytic anemia can be exacerbated after cold exposure, but rarely does hemoglobin drop below 70 g/L. The hemolysis is usually extravascular (removal of C3b opsonized cells by the reticuloendothelial system, primarily in the liver) and rarely intravascular from complement destruction of RBC membrane. The agglutination of RBC in the cooler peripheral circulation also causes Raynaud's syndrome, acrocyanosis and livedo reticularis. Macroglobulins with the properties of both cryoglobulins and cold agglutinins with anti-Pr specificity have been reported. These properties may have as a common basis the immune binding of the sialic acid-containing carbohydrate present on red blood cell glycoporphins and on Ig molecules.⁷⁰ Several other macroglobulins with various antibody activity toward autologous antigens (i.e. phospholipids, tissue and plasma proteins, etc.) and foreign ligands have also been reported.³⁷⁻³⁹

Tendency to deposit into tissues

The monoclonal protein can deposit in several tissues as amorphous aggregates. Linear deposition of monoclonal IgM along the skin basement membrane is associated with bullous skin disease.⁷¹ Amorphous IgM deposits in the dermis determine the so-called IgM storage papules on the extensor surface of the extremities: macroglobulinemia cutis.⁷² Deposition of monoclonal IgM in the lamina propria and/or submucosa of the intestine may be associated with diarrhea, malabsorption and gastrointestinal bleeding.^{73,74} It is well known that kidney involvement is less common and less severe in WM than in multiple myeloma, probably because the amount of light chain excreted in the urine is generally lower in WM than in myeloma and because of the absence of contributing factors such as hypercalcemia; although cast nephropathy has been described also in WM.⁷⁵ On the other hand, the IgM macromolecule is more susceptible to being trapped in the glomerular loops where ultrafiltration presumably contributes to its precipitation, forming subendothelial deposits of aggregated IgM proteins that occlude the glomerular capillaries.⁷⁶ Mild and reversible proteinuria may result, and most patients are asymptomatic.

The deposition of monoclonal light chain as fibrillar amyloid deposits (AL amyloidosis) is uncommon in patients with WM.⁷⁷ Clinical expression and prognosis are similar to those of other AL patients with involvement of heart (44%), kidneys (32%), liver (14%), lungs (10%), peripheral/autonomic nerves (38%), and soft tissues (18%). However, the incidence of cardiac and pulmonary involvement was higher in patients with monoclonal IgM than with other immunoglobulin isotypes. Association of WM with reactive amyloidosis (AA) has been documented rarely.^{78,79} Simultaneous occurrence of fibrillary glomerulopathy, characterized by glomerular deposits of wide nonconglomerular fibrils, and amyloid deposits has been reported in WM.⁸⁰

Manifestations Related to Tissue Infiltration by Neoplastic Cells

Tissue infiltration by neoplastic cells is rare and can involve various organs and tissues, from the bone marrow (described below) to the liver, spleen, lymph nodes and possibly the lungs, GI tract, kidneys, skin, eyes and central nervous system. Pulmonary involvement in the form of masses, nodules, diffuse infiltrate or pleural effusions is relatively rare, since the overall incidence of pulmonary and pleural findings reported for WM is only 3 to 5%.⁸¹⁻⁸³ Cough is the most common presenting symptom, followed by dyspnea and chest pain. Chest radiographic findings include parenchymal infiltrates, confluent masses and effusions. Malabsorption, diarrhea, bleeding or obstruction indicate involvement of the gastrointestinal tract at the level of the stomach, duodenum or small intestine.⁸⁴⁻⁸⁷ In contrast to multiple myeloma, infiltration of the kidney interstitium with lymphoplasmacytoid cells is not a rare event in WM,^{76,88} while renal or perirenal masses are unusual.⁸⁹ The skin can be the site of dense lymphoplasmacytic infiltrates, similar to that seen in the liver, spleen, and lymph nodes, forming cutaneous plaques and, rarely, nodules.^{72,90} Chronic

urticaria and IgM gammopathy are the two cardinal features of the Schnitzler syndrome, which is not usually associated initially with clinical features of WM;⁹¹ although evolution to WM is not uncommon.⁷² Thus close follow-up of these patients is warranted. Invasion of articular and periarticular structures by WM malignant cells is rarely reported.⁹² The neoplastic cells can infiltrate the periorbital structures (Figure 5), lacrimal gland and retro-orbital lymphoid tissues, resulting in ocular nerve palsies.^{93,94} Direct infiltration of the central nervous system by monoclonal lymphoplasmacytic cells as infiltrates or as tumors constitutes the rarely observed Bing-Neel syndrome, characterized clinically by confusion, memory loss, disorientation and motor dysfunction (reviewed in Civit et al⁹⁵).

LABORATORY PROCEDURES AND FINDINGS

Laboratory findings are reported in Table 3. High resolution electrophoresis combined with immunofixation of serum and urine are recommended for identification and characterization of the IgM monoclonal protein (Figure 6).⁹⁶ The light chain of the monoclonal IgM is κ in 75-80% of the patients.^{36,44} A few MW patients have more than one M-component. The concentration of the serum monoclonal protein is greatly variable, most of the cases fall within the range of 15 to 45 g/L. Densitometry should be adopted to determine IgM levels for serial evaluations since nephelometry remains unreliable and show large intra-laboratory as well as inter-laboratory variation.⁹⁶ The presence of cold agglutinins or cryoglobulins might affect determination of IgM levels, and therefore testing for cold agglutinins and cryoglobulins should be performed at diagnosis. If present, serum samples should be analyzed under warm conditions for determination of serum monoclonal IgM level. Although Bence Jones proteinuria is frequently present, it exceeds 1 g per day in only 3% of the cases.⁹⁷ Blood viscosity should be measured if the patient has signs or symptoms of hyperviscosity syndrome. Measurement of viscosity in whole blood at low shear rates may be the best indicator of hemorheological changes in patients with WM.⁹⁸ In practice, a correlation between level of M-protein and symptoms may be used to anticipate repeat plasma exchanges as the M-protein approaches the level associated with hyperviscosity. Fundoscopy remains an excellent indicator of clinically relevant hyperviscosity. Cryoglobulins should be searched for (following the method indicated in the guidelines of the College of American Pathologists⁹⁹) in the presence of suggestive clinical features. Rheumatoid factor activity and low C4 levels (<8 mg/dL) are common findings in type II cryoglobulinemia. Increased erythrocyte sedimentation rate is almost constantly observed in WM and may be the first clue to the presence of the macroglobulin.⁵ The clotting abnormality detected most frequently is prolongation of thrombin time. AL amyloidosis should be suspected in all patients with nephrotic syndrome, cardiomyopathy, hepatomegaly or peripheral neuropathy. Diagnosis requires the demonstration of green birefringence under polarized light of amyloid deposits stained with Congo red. Anemia is the most common finding in patients with symptomatic WM and is caused by a combination of factors: mild decrease in red cell survival, impaired erythropoiesis, hemolysis, moderate plasma

volume expansion and blood loss from the GI tract. Blood smears are usually normocytic and normochromic, and *rouleaux* formation is often pronounced. Electronically measured mean corpuscular volume may be elevated spuriously due to erythrocyte aggregation. In addition, the hemoglobin estimate can be inaccurate, i.e. falsely high, because of interaction between the monoclonal protein and the diluent used in some automated analyzers.¹⁰⁰

Serum β_2 -microglobulin was above the upper limit of the reference range (3 mg/L) in approximately 60% of WM patients at diagnosis in our study population (Table 3). Leukocyte and platelet counts are usually within the reference range at presentation, although patients may occasionally present with severe thrombocytopenia. As reported above, the population of monoclonal B lymphocytes, which can be detected in blood by flow cytometry, expresses surface IgM and late differentiation B cell markers.

The bone marrow is always involved in WM. Bone marrow biopsy is necessary since aspiration frequently yields a “dry tap”. Three cytological subtypes have been identified in conjunction with patterns of bone marrow infiltration: lymphoplasmacytoid, constituted by small lymphocytes and plasmacytoid cells characterized by a nodular pattern (47% of all patients); lymphoplasmacytic in which small lymphocytes and mature plasma cells predominate and mast cells may be conspicuous, associated mainly with an interstitial/nodular pattern (42%); polymorphous, with a packed marrow and characterized by a wide spectrum of cells including small lymphocytes, plasmacytoid cells, plasma cells, large transformed cells and immunoblasts with mitotic figures (11%).¹⁰¹ “Intranuclear” PAS-positive inclusions (Dutcher-Fahey bodies, see Figure 7)¹⁰² consisting of IgM deposits in the perinuclear space, and sometimes in intranuclear vacuoles, may be seen occasionally in lymphoid cells.

Magnetic resonance imaging (MRI) of the spine in conjunction with computer tomography (CT) of the abdomen and pelvis are useful in evaluating the disease status in WM.¹⁰³ Bone marrow involvement can be documented by MRI studies of the spine in over 90% of patients, while CT of the abdomen and pelvis demonstrated enlarged nodes in 43% of WM patients.¹⁰³ Lymph node biopsy may show preserved architecture or replacement by infiltration of neoplastic cells with lymphoplasmacytoid, lymphoplasmacytic or polymorphous cytological patterns. The residual disease after high-dose chemotherapy with allogeneic or autologous stem-cell rescue can be monitored by PCR-based methods using primers specific for the monoclonal Ig variable regions.

DIFFERENTIAL DIAGNOSIS

A monoclonal IgM may be seen in most forms of B-cell lymphoproliferative disorder as well as in IgM monoclonal gammopathy of unknown significance (MGUS).^{44,104} Recent papers have focused on the necessity to develop diagnostic criteria.^{28,105} Actually, the lack of accepted criteria for the

diagnosis of WM has triggered an international initiative to define them. There is a wide consensus that the diagnosis should rely on three main criteria:

1. central to the diagnosis of WM is the demonstration, by trephine biopsy, of bone marrow infiltration by a lymphoplasmacytic cell population constituted by small lymphocytes with evidence of plasmacytoid/plasma cell differentiation constituting more than 20% of the total bone marrow cells. The pattern of bone marrow infiltration may be diffuse, interstitial or nodular showing usually an intertrabecular pattern of infiltration. A solely paratrabecular pattern of infiltration is unusual and should raise the possibility of follicular lymphoma;
2. the bone marrow infiltration should routinely be confirmed by immunophenotypic studies (flow cytometry and/or immunohistochemistry) showing the following profile: sIg+CD19+CD20+CD22+CD79+. The majority of cases will not express CD10 or CD23, while a proportion of patients (5-20%) appear to express the CD5 antigen. In these cases care should be taken to satisfactorily exclude chronic lymphocytic leukemia and mantle cell lymphoma;
3. a serum monoclonal IgM is present by definition and usually at significant concentration (>20 g/L).^{1,20,106} However, most of the experts agree that a diagnosis of WM could be made irrespective of IgM concentration in presence of bone marrow infiltration by a lymphoplasmacytic cell population with characteristic immunophenotype. Patients with serum IgG and IgA monoclonal protein, or without monoclonal component (non-secretory lymphoplasmacytic lymphoma) have been reported and they present similar clinical problems to those seen in WM patients. However their relationship to WM is unclear at present.

These criteria identify a large group of patients diagnosed as WM who can be asymptomatic, and most probably not in need of treatment, or symptomatic. It is well recognized that a population of patients exist who have clinically overt manifestations due to the biological effects of the monoclonal IgM but without evidence of bone marrow infiltration by lymphoplasmacytic lymphoma, and therefore lacking the central diagnostic criteria for WM. Such patients will usually have peripheral neuropathy, cryoglobulins, cold agglutinin disease, AL amyloidosis, or any of the other rare conditions reported in Table 2. It is appropriate to consider these patients as having a "IgM related disorders".^{96,107}

Patients with asymptomatic monoclonal IgM without bone marrow infiltration, or with a bone marrow infiltrate < 20%, can be classified as having IgM-MGUS. This condition is by far the most common among individuals with a monoclonal IgM.^{44,108} Differentiation of a patient with IgM-MGUS from one with asymptomatic WM may be difficult.¹⁰⁹ For instance, some patients may have a detectable bone marrow clonal B-cells by flow cytometry but without morphological evidence of

bone marrow infiltration at trephine biopsy. These patients should be classified as IgM-MGUS until further outcome data become available.

The clinicopathological correlates of monoclonal IgMs constitute a broad spectrum, including chronic lymphocytic leukemia (CLL), diffuse large B-cell lymphoma, extranodal marginal-zone lymphoma, follicular lymphoma, and mantle-cell lymphoma.¹⁰⁴ Virtually a monoclonal IgM is demonstrable in all subtypes of peripheral B-cell disorders and, although monoclonal protein concentrations are generally higher in WM, there is considerable overlap. Immunophenotypic criteria are therefore essential for the accurate diagnosis of WM.¹⁰⁴ A differential diagnosis between WM, CLL and small lymphocytic lymphoma may be sometimes difficult.¹¹⁰ Patients with chronic lymphocytic leukemia generally have a monoclonal B-cell lymphocytosis of more than $5 \times 10^9/L$ and leukemic B cells with the following markers: coexpression of CD5 and pan-B cell antigens CD19, CD20 and CD23, weak surface immunoglobulin (most often IgM or IgM and IgD with either kappa or lambda light chain), weak/negative CD22 and negative FMC7 and CD79B.¹¹¹ Guidelines for subtyping small B-cell lymphomas in bone marrow biopsies have been established¹¹² and molecular biology techniques are increasingly being used in the differential diagnosis of these lymphomas.¹¹³ In patients with μ heavy chain disease, immunofixation or immunoselection studies are necessary to confirm the presence of Ig heavy chain fragment without the corresponding light chain.^{96,114} A lymphoplasmacytic bone marrow infiltration producing a significant serum monoclonal IgM could occur in association with some small B cell lymphoma such as MALT lymphoma,^{115,116} marginal zone lymphoma, nodal monocytoid B cell lymphoma and a variant of chronic lymphocytic leukemia.^{117,118}

Patients with bone marrow infiltrate consisting entirely of IgM-producing plasma cells (cytoplasmic IgM+, CD20-, CD138+) possibly associated with lytic skeletal lesions and hypercalcemia should be diagnosed as IgM myeloma.¹¹⁹⁻¹²² IgM myeloma and WM can have overlapping clinical features;⁴⁴ and the cells may show a hybrid multiple myeloma-WM phenotype.¹¹⁹ Hypercalcemia may also indicate the development of an aggressive diffuse large cell lymphoma (Richter's syndrome).¹²³

TREATMENT OPTIONS FOR THE FIRST LINE THERAPY OF WALDENSTRÖM'S MACROGLOBULINEMIA

A precise therapeutic algorithm for the upfront treatment of WM remains to be defined given a paucity of randomized clinical trials in this uncommon disorder. In view of this situation, a consensus panel composed of experts who treat WM was recently organized as part of the Second International Workshop on Waldenström's macroglobulinemia which considered alkylator agents

(e.g. chlorambucil), nucleoside analogues (cladribine or fludarabine), and the monoclonal antibody rituximab as reasonable choices for upfront therapy of WM¹²⁴. Importantly, the panel felt that individual patient considerations including the presence of cytopenias, need for more rapid disease control, age, and candidacy for autologous transplant therapy should be taken into account in making the choice of a first line agent. For patients who are candidates for autologous transplant therapy, and in whom such therapy is seriously considered, the panel recommended that exposure to alkylator or nucleoside analogue therapy should be limited.

Alkylator based therapy

Oral alkylating drugs, alone and in combination therapy with steroids have been extensively evaluated in the upfront treatment of WM. The greatest experience with oral alkylator therapy has been with chlorambucil which has been administered both on a continuous (i.e. daily dose schedule) as well as an intermittent schedule. Patients receiving chlorambucil on a continuous schedule typically receive 0.1 mg/kg/day, whilst on the intermittent schedule patients will typically receive 0.3 mg/kg for 7 days, every 6 weeks. In a prospective randomized study, Kyle *et al* reported no significant difference in the overall response rate between these schedules (Table 4), though interestingly the median response duration was greater for patients receiving intermittent versus continuously dosed chlorambucil (46 vs. 26 months)¹²⁵. Despite the favorable median response duration in this study for use of the intermittent schedule, no difference in the median overall survival was observed. Moreover, an increased incidence for development of myelodysplasia and acute myelogenous leukemia with the intermittent (3 of 22 patients) versus the continuous (0 of 24 patients) chlorambucil schedule prompted the authors of this study to express preference for use of continuous chlorambucil dosing.

The use of steroids in combination with alkylator therapy has also been explored. Dimopoulos and Alexanian⁹⁷ evaluated chlorambucil (8 mg/m²) along with prednisone (40 mg/m²) given orally for 10 days, every 6 weeks and reported a major response (i.e. reduction of IgM by greater than 50%) in 72% of patients. Non-chlorambucil based alkylator regimens employing melphalan and cyclophosphamide in combination with steroids have also been examined by Petrucci *et al*¹²⁶ and Case *et al*¹²⁷ producing slightly higher overall response rates and response durations, though the benefit of these more complex regimens over chlorambucil remains to be demonstrated.

Facon *et al*¹²⁸ have evaluated parameters predicting for response to alkylator therapy. Their studies in patients receiving single agent chlorambucil demonstrated that age ≥ 60 , male sex, symptomatic

status, cytopenias but interestingly not high tumor burden and serum IgM levels were associated with poor response to alkylator therapy. Additional factors to be taken into account in considering alkylator therapy for patients with WM include necessity for more rapid disease control given the slow nature of response to alkylator therapy, as well as consideration for preserving stem cells in patients who are candidates for autologous transplant therapy.

Nucleoside analogue therapy

Both cladribine and fludarabine have been extensively evaluated in untreated as well as previously treated WM patients. Cladribine administered as a single agent either by continuous IV infusion, 2 hour daily infusion or subcutaneous bolus injections for 5-7 days has resulted in major responses in 40-90% of patients who received primary therapy¹²⁹⁻¹³³, whilst in the salvage setting responses have ranged from 38-54%^{129,130,132-134} (Table 5,6). Median time to achievement of response in responding patients following cladribine ranged from 1.2-5 months.^{129,132} The overall response rate with daily infusional fludarabine therapy administered mainly on 5 day schedules in previously untreated and treated WM patients has ranged from 38-100%¹³⁵⁻¹³⁸, and 30-40%^{135,138-140}, respectively, which are on par with the response data for cladribine (Table 5, 6). Median time to achievement of response for fludarabine was also on par with cladribine at 3-6 months. In general, response rates and durations of responses have been greater for patients receiving nucleoside analogues as first line agents, though in four studies wherein both untreated and previously treated patients were enrolled, no substantial difference in the overall response rate was reported^{130,132,133,138}. Myelosuppression commonly occurred following prolonged exposure to either of the nucleoside analogues, as did lymphopenia with sustained depletion of both CD4⁺ and CD8⁺ T-lymphocytes observed in WM patients one year following initiation of therapy^{129,131}. Treatment related mortality due to myelosuppression and/or opportunistic infections attributable to immunosuppression occurred in up to 5% of all treated patients in some series with either nucleoside analogue.

Factors predicting for response to nucleoside analogues in WM included age at start of treatment (<70 years), pretreatment hemoglobin > 95 g/L, platelets >75,000/mm³, disease relapsing off therapy, patients with resistant disease within the first year of diagnosis and a long interval between first line therapy and initiation of a nucleoside analogue in relapsing patients.^{129,135,141} There is limited data on the use of an alternate nucleoside analogue to salvage patients whose disease relapsed or demonstrated resistance off of cladribine or fludarabine therapy. Three of four (75%)

patients responded to cladribine to salvage patients who progressed following an unmaintained remission to fludarabine, whereas only 1/10 (10%) with disease resistant to fludarabine responded to cladribine¹⁴². However, Lewandowski *et al*¹⁴³ recently reported response in 2 of 6 patients (33%) and disease stabilization in the remainder patients to fludarabine following in spite of an inadequate response or progressive disease following cladribine therapy.

Monoclonal antibody therapy

Monoclonal antibody therapy has been extensively evaluated as upfront therapy in patients with WM. Rituximab, a chimeric antibody which targets CD20 was reported by Treon *et al*¹⁴⁴ to induce a remission, and reverse anemia in a patient with WM which lasted over 19 months. Byrd *et al*¹⁴⁵ subsequently demonstrated a 57% response rate (all PR) for 7 heavily pre-treated WM patients who received 4 infusions of rituximab (375 mg/m²/week). The median progression-free survival for patients in this series was 6.6+ months. In a preliminary report, Weber *et al*¹⁴⁴ reported a 75% response rate (2 CR, 4 PR) for patients who received 4 weekly infusions of rituximab, with a median time to remission of 2 months and an unmaintained remission duration of 9 months. In addition to these studies, Foran *et al*¹⁴⁶ demonstrated responses (both PR) in 2 of 7 (29%) heavily pretreated WM patients who received 4 weekly infusions of rituximab. Analysis of data pertaining to those WM patients who responded in the Foran *et al*¹⁴⁶ study could not be distinguished since WM patients were grouped together and analyzed with B-CLL patients under the Kiel classification of immunocytomas. In a larger experience of single agent rituximab use in WM, Treon *et al*¹⁴⁷ reported on the outcome of 30 WM patients who had a median of 1 prior therapy and received treatment with rituximab (median 4; range 1-11.3 weekly infusions). Overall, 18 of 30 (60%) WM patients who were treated in this study had a response, with 8 (27%) patients achieving a PR, and 10 (33%) patients achieving a MR. Moreover, 9 (30%) patients in this series had stable disease (SD) following treatment with rituximab. The time to treatment failure (TTF) for responding patients in this study was 8.9 months (3-20+ months), and 6.1 months (3-12+ months) for patients with SD. In addition, 19/30 (63%) and 15/30 (50%) patients had an increase in their hematocrit (HCT) and platelet (PLT) counts, respectively. Pre-rituximab therapy, 7/30 (23.3%) patients were either transfusion or erythropoietin dependent, whereas only 1/30 (3.3%) patients required transfusions (no erythropoietin) after rituximab.

The use of an extended schedule of rituximab (i.e. 4 infusions of weekly rituximab followed by 4 additional weekly infusions at week 12) has also been explored in WM with improvements in response duration suggested by the outcome of two studies (Table 7). In a study involving 27

patients, Dimopoulos *et al*¹⁴⁸ reported a major response rate of 56% (all PRs) with a median duration of response of 16 months using an extended dose schedule in patients with a median of 1 prior therapy. Treon *et al*¹⁴⁹ reported an ORR of 73% with 12/26 (46%) and 7/26 (27%) of patients attaining a PR and MR, respectively, while 3/26 (12%) of patients attained SD in a study using an extended schedule of rituximab in patients with a median of 1 prior therapy. The median duration of response in this study is estimated at 20+ months. Improvements in hematological function were again observed. Prior to therapy anemia (HCT <30%) and thrombocytopenia (PLT <100,000/mm³) were observed in 34.5% and 27.6% of patients, respectively. Post-rituximab therapy anemia and thrombocytopenia were observed in only 4.5% and 9.0% of patients.

The level of circulating IgM may predict those patients who are more likely to benefit from rituximab therapy. Dimopoulos *et al*¹⁴⁸ in their study of extended rituximab therapy in WM patients observed a response rate of 58% for those patients who had a serum IgM level of <4,000 mg/dL versus 13% in those who with a serum IgM level of >4,000 mg/dL. Similarly, Treon *et al*¹⁴⁹ in their study of extended rituximab therapy observed that the overall response rate was 90% for patients who had a serum IgM level of <6,000 mg/dL whilst only 17% of patients with a serum IgM level of >6,000 mg/dL demonstrated a response. Importantly, no correlation between bone marrow involvement and response to rituximab was observed in the study by Treon *et al*¹⁴⁹, suggesting that serum IgM levels per se may modulate response to rituximab. The mechanism for this finding remains to be clarified.

The genetic background of patients may also be important for determining response to rituximab. In particular, a correlation between polymorphisms at position 158 in the Fc gamma RIIIa receptor (CD16), an activating Fc receptor on important effector cells which mediate antibody dependent cell mediated cytotoxicity (ADCC), and rituximab response was observed in WM patients. Individuals may encode either the amino acid valine or phenylalanine at position 158 in the Fc gamma RIIIa receptor. WM patients who carried the valine amino acid (either in a homozygous or heterozygous pattern) had a fourfold higher major response rate (i.e. $\geq 50\%$ decline in serum IgM levels) to rituximab versus those patients who expressed phenylalanine in a homozygous pattern¹⁵⁰.

The combination of rituximab therapy in conjunction with chemotherapy has also been explored. Weber *et al*¹⁵¹ examined the combination of cladribine and cytoxan in combination with rituximab in 17 patients with newly diagnosed WM. Patients received 2 cycles which were administered 6 weeks apart of cladribine (1.5 mg/m² subcutaneous thrice daily x 7 days), cytoxan (40 mg/m² orally twice daily x 7 days) and rituximab (375 mg/m² IV weekly x 4 weeks). A greater than 75%

reduction in serum IgM levels, which defined a partial response, was observed in 94% of patients who received combination therapy with cladribine, cytoxan and rituximab. While the response rate appeared to be on par with the outcomes of historical controls who had received treatment with cladribine alone (93%), and cladribine plus cytoxan (92%), median response durations appeared to have been greatly extended with the addition of cytoxan and rituxan to cladribine therapy. Treon *et al*¹⁵² have also examined the combination of rituximab with fludarabine. Patients received 6 cycles of fludarabine along with 8 infusions of rituximab over 31 weeks. An overall response rate, defined as $\geq 25\%$ reduction in serum IgM levels, was observed in 85.7% of patients. Delays in therapy due to cytopenias were common however, and the impact on response duration remains to be defined.

While therapy with rituximab has been well tolerated in the above series, abrupt increases in serum IgM levels have been observed in certain patients following treatment with rituximab, including in one patient who experienced a CNS bleed after her serum viscosity level tripled following rituximab therapy. The cause for this finding remains to be defined, and close monitoring of serum IgM and serum viscosity levels (if IgM levels climb) appears reasonable while patients are receiving therapy with rituximab.

While the experience with monoclonal antibody therapy in WM has largely been confined to rituximab, the use of radioconjugated serotherapy targeting CD20, as well as the use of monoclonal antibodies directed at other serotherapy target antigens is being explored. Emmanouilides *et al*¹⁵³ reported a response in a WM patient who received the yttrium-90 conjugated CD20 directed monoclonal antibody Zevalin. More recently, Crowley *et al*¹⁵⁴ have recently reported activity of the CD52 monoclonal antibody Campath-1H in several WM patients with advanced disease. Serotherapies directed at other target antigens including CD22 and CD40 are being contemplated in view of the expression of these antigens on WM tumor cells.¹⁵⁵

Treatment Options for Relapsed and Refractory Disease in Waldenström's macroglobulinemia

A consensus panel on therapeutics for WM also considered options for patients with relapsed and refractory disease¹²⁴. For patients in relapse or who have refractory disease, the use of an alternate first line agent as defined above was considered as a reasonable choice, with the caveat that for those patients for whom autologous transplantation was seriously being considered further exposure to stem cell damaging agents (i.e. many alkylator agents and nucleoside analogue drugs) should be avoided, and a non-stem cell toxic agent such as rituximab should be considered if stem cells have not been previously harvested.

Thalidomide as a single agent, and combination with dexamethasone and clarithromycin has also been examined in patients with WM, in view of the success of these regimens in patients with advanced multiple myeloma. Dimopoulos *et al*¹⁵⁶ demonstrated a major response in 5 of 20 previously untreated and treated patients (25%) who received single agent thalidomide. Dose escalation from the thalidomide start dose of 200 mg daily was hindered by development of side effects, including the development of peripheral neuropathy in 5 patients obligating discontinuation or dose reduction. Low doses of thalidomide (50 mg orally daily) in combination with dexamethasone (40 mg orally once a week) and clarithromycin (250 mg orally twice a day) have also been examined with 10 of 12 (83%) previously treated patients demonstrating at least a major response¹⁵⁷. However, in a follow up study by Dimopoulos *et al*¹⁵⁸ using a higher thalidomide dose (200 mg orally daily) along with dexamethasone (40 mg orally once a week) and clarithromycin (500 mg orally twice a day) only 2 of 10 (20%) previously treated patients responded.

The activity of interferon-alpha has been examined in WM patients. Rotoli *et al*¹⁵⁹ used interferon-alpha (3 million IU daily for 1 month, then thrice weekly) to treat 38 WM patients with a high paraprotein (>3,000 mg/dL) and observed a 50% ORR (12 PR, 6 MR). Patients tolerated therapy well, and disappearance of hyperviscosity, along with increases in hemoglobin levels and reduction in bone marrow lymphoplasmacytosis was observed in responding patients. Legouffe *et al*¹⁶⁰ treated 14 WM patients with progressive disease with very low doses of interferon-alpha (1 million IU thrice weekly) for a median duration of 10.3 (range 2-44) months and noted increases in hemoglobin levels in 6/14 (42%) of patients, while 4/14 (28%) demonstrated a decrease of >20% in paraprotein levels following therapy. Treatment was stopped for three patients due to flu-like symptoms, and in one patient due to thrombocytopenia. De Rosa *et al*¹⁶¹ reported the outcome of 3 WM patients who received interferon-alpha (3 million IU daily or thrice weekly) and reported 1 PR, and 2 MR following four months of therapy. Lastly, Bhavnani *et al*¹⁶² described a WM patient with symptomatic cryoglobulinemia who received interferon-alpha (3 million IU thrice weekly) and demonstrated a PR, and resolution of symptoms attributable to cryoglobulinemia following interferon-alpha therapy. Interestingly, this patient's paraprotein, cryoglobulin levels and attributable symptoms increased after cessation of interferon-alpha therapy which subsequently subsided following re-introduction of interferon-alpha.

The use of transplant therapy has also been explored in WM. Desikan *et al*¹⁶³ reported their initial experience of high dose chemotherapy and autologous stem cell transplant, which has more

recently been updated by Munshi et al¹⁶⁴. Their studies involving 8 previously treated WM patients between the ages of 45-69 years, who received either melphalan at 200 mg/m² (n=7) or melphalan at 140 mg/m² along with total body irradiation. Stem cells were successfully collected in all 8 patients, however a second collection procedure was required for 2 patients who had extensive previous nucleoside analogue exposure. There were no transplant related mortalities and toxicities were manageable. All eight patients responded with 7 of 8 patients achieving a major response, and one patient achieving a complete response with durations of response ranging from 5+ to 77+ months. Dreger et al¹⁶⁵ investigated the use of the DEXA-BEAM (dexamethasone, BCNU, etoposide, cytarabine, melphalan) regimen followed by myeloablative therapy with cyclophosphamide and total body irradiation and autologous stem cell transplantation in 7 WM patients, which included 4 untreated patients. Serum IgM levels declined by >50% following DEXA-BEAM and myeloablative therapy for 6 of 7 patients with progression free survival ranging from 4+ to 30+ months. All three evaluable patients, who were previously treated also attained a major response in a study by Anagnostopoulos et al¹⁶⁶ in which WM patients received various preparative regimens and showed event free survivals of 26+, 31, and 108+ months. Tournilhac et al¹⁶⁷ recently reported the outcome of 18 WM patients in France who received high dose chemotherapy followed by autologous stem cell transplantation. All patients were previously treated with a median of 3 prior regimens (range 1-5). Therapy was well tolerated with an improvement in response status observed for 7 patients (6 PR to CR; 1 SD to PR), while only 1 patient demonstrated progressive disease. The median event free survival for all non-progressing patients was 12 months. There have also been a other reports of WM patients achieving durable responses to high dose chemotherapy and autologous transplant.^{168,169} Reports on the use of high dose chemotherapy and allogeneic transplantation in WM are limited. Martino et al¹⁷⁰ reported event free survivals of 3 and 9 years for 2 young patients (ages 34, 39) with progressive disease, including one patient who progressed after high dose chemotherapy and autologous stem cell transplantation. Tournilhac et al¹⁶⁷ reported the outcome of allogeneic transplantation in 10 previously treated WM patients, ages 35-46 who received a median of 3 prior therapies, including 3 patients with progressive disease despite therapy. Two of 3 patients with progressive disease responded, and an improvement in response status was observed in 5 patients. The median event free survival for non-progressing, evaluable patients was 31 months. Concerning in this series were the death of three patients due to transplantation related toxicity. Similarly, Giralt et al¹⁷¹ reported that 2 of 3 patients in their series who underwent allogeneic transplantation experienced an early death or death from complicating graft versus host disease. The third patient in this series did not respond to therapy. In view of the high rate of mortality associated with high dose chemotherapy

and allogeneic transplantation, Maloney *et al*¹⁷² have evaluated the use of non-myeloablative allogeneic transplantation in 5 patients with refractory WM. In this series, 3 of 3 evaluable patients (all of whom had matched sibling donors) responded with 2 CR and 1 in PR, 1-3 years post transplant.

PROGNOSIS

WM presents with a chronic, indolent course and with a highly variable prognosis. The median survival reported in large series ranges from 5 to 6 years^{28,36,44,97,128,139,173-175} although an observed survival of 9 years⁴⁶ and a 10-year projected overall survival of 55%¹⁷⁶ have been reported (Figure 8). Because WM is a rare disease, relatively few studies on prognosis have been conducted on large patient populations.^{36,97,128,139,173-176} Advanced age, anemia and thrombocytopenia were correlated, by univariate analysis with a poorer outcome in virtually all studies. Neutropenia and male sex,¹²⁸ weight loss and cryoglobulinemia,¹⁷⁵ albumin level^{36,174} and blood cell counts,¹⁷⁴ serum β_2 -microglobulin level^{36,139,176} and IgM level less than 40 g/L,¹³⁹ and hyperviscosity and β_2 -microglobulin level¹⁷⁶ were also significantly correlated with survival. A few scoring systems have been proposed based on these analyses:

- age \geq 70 year, hemoglobin $<$ 90 g/L, weight loss, cryoglobulinemia,¹⁷⁵
- age $<$ 65 year, serum albumin $<$ 40 g/L, hemoglobin $<$ 120 g/L, cytopenias (platelets $<$ 150, leucocytes $<$ 4.0, neutrophils $<$ $1.5 \times 10^9/L$),¹⁷⁴
- serum β_2 -microglobulin \geq 3 mg/L, hemoglobin $<$ 120 g/L, serum IgM $<$ 40 g/L.¹³⁹

An update of the study of the Italian group which included 215 patients indicated that serum β_2 -microglobulin, hemoglobin, albumin and age defined prognosis of patients with WM thoroughly.³⁶ In agreement with other studies, serum β_2 -microglobulin and hemoglobin level appeared to be the most consistent prognostic determinants^{36,139,176}. It is possible that with validation from future studies that both prognostic stratification and decision to start treatment may result from serum β_2 -microglobulin level and hemoglobin.

Asymptomatic patients with low serum β_2 -microglobulin levels and preserved hemoglobin can be observed over long periods without therapy.¹⁷³

Since WM is a disease of the elderly, up to 32% of patients die of unrelated causes¹⁷⁴ and the association with malignancy, both before therapy and during follow-up is common (39% of patients in a series¹⁷⁴).^{44,97,174,176} The most common causes of death in these patients are progression of the lymphoproliferative process (in about 50%),¹⁷⁴ infections and cardiac failure.⁴⁴ Few patients die of cerebrovascular accidents, renal failure or gastrointestinal bleeding.⁴⁴ In the pre-terminal stage of the disease the development of aggressive large cell lymphomas, usually of the immunoblastic type (Richter's syndrome),^{123,177} have been reported in 6% of patients treated for WM.^{176,178} This

transformation is characterized by unexplained fever, weight loss, rapidly enlarging lymph nodes, extranodal extension, and reduction of the level of monoclonal IgM. Rarely, WM may be complicated by acute^{179,180} or chronic myeloid leukemia,¹⁸¹ in most cases after treatment with alkylating agents, although patients who had not been previously treated have also been reported.

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Table 1. Presenting Features and Physical Findings at Diagnosis in 215 Patients with Waldenström's Macroglobulinemia (from Merlini³⁶)

Symptoms	Frequency (%)	Feature	Frequency (%)
Weakness	66	Hepatomegaly (> 2 cm from the	20
Anorexia	25	costal margin)	
Weight loss	17	Splenomegaly	19
Raynaud's phenomenon	11	Lymphadenopathy	15
Peripheral neuropathy	24	Purpura	9
Fever	15	Hemorrhagic manifestations	7

Table 2. Clinical Manifestations Caused by Monoclonal IgM.²⁰

Properties of the Monoclonal IgM	Resulting Condition	Clinical Manifestations
Physicochemical Intrinsic viscosity	Hyperviscosity syndrome	Fatigue, headache, blurred vision, easy mucosal bleeding, impaired mentation up to coma
Precipitation on cooling	Cryoglobulinemia type I	Raynaud's phenomenon, acrocyanosis, necrosis, ulcers, purpura, cold urticaria
Protein-protein interaction	Hemostatic abnormalities	Bleeding diathesis: bruising, purpura, mucosal bleeding; rarely, brain hemorrhages
Antibody activity versus: nerve constituents	Polyneuropathies	Anti-MAG-related: symmetric, distal, progressive, sensorimotor neuropathy, ataxic gait, bilateral foot drop. IgM with other specificities: - symmetric, distal, progressive painful sensory neuropathy; - pure motor neuron disease
IgG	Cryoglobulinemia type II	Weakness, purpura, arthralgias, proteinuria, renal failure, progressive, symmetric distal sensorimotor neuropathy combined with mononeuropathies (e.g. foot or wrist drop)
RBC antigens	Cold agglutinin hemolytic anemia	Mild, chronic hemolytic anemia exacerbated after cold exposure; Raynaud's phenomenon, acrocyanosis and livedo reticularis
Tendency to deposit into tissues as amorphous aggregates in skin, GI tract, kidney	Specific organ dysfunction	Skin: bullous skin disease, papules on extremities GI: diarrhea, malabsorption, bleeding Kidney: mild, reversible proteinuria, mostly asymptomatic
as amyloid fibrils (light chains)	AL amyloidosis	Fatigue, weight loss, periorbital purpura, edema, hepatomegaly, macroglossia. Dysfunction of organs involved: kidneys, heart, liver, peripheral sensory and autonomic neuropathies

From: Merlini, G. Waldenström's Macroglobulinemia - Clinical Manifestations and Prognosis. In: Schechter GP., Hoffman R., and Schrier SL. (eds) *Hematology 1999*. Washington DC: American Society of Hematology, 1999: 358-69. Copyright American Society of Hematology, used with permission.

Table 3. Laboratory Findings in 215 Patients with Waldenström's Macroglobulinemia³⁶

Parameter	Value, median (range)	Frequency (%)
Hemoglobin, g/L	109 (40-157)	
< 120 g/L		63
WBC, x10 ⁹ /L	6.9 (1.5-12.3)	
< 3x10 ⁹ /L		4
Platelets, x10 ⁹ /L	192 (18-534)	
< 100 x10 ⁹ /L		16
IgM monoclonal component g/L	23.3 (10.5-98.7)	
κ/λ		80/20
> 30 g/L		35
Bence Jones proteinuria		38
Serum beta-2-microglobulin > 3 mg/L		62
Serum viscosity (relative to water)	1.9 (1.75-5.0)	
Relative serum viscosity > 4		17

Table 4. Alkylator Based Therapy in Waldenström's macroglobulinemia

	(N)	Setting	Regimen	Major RR*	Median Response Duration
Facon ¹²⁸	110	UnRx	Chlorambucil (Continuous)	31%	NA
Kyle ¹²⁵	24	UnRx	Chlorambucil (Continuous)	75%	26 months
	22	UnRx	Chlorambucil (Intermittent)	64%	46 months
Dimopoulos ⁹⁷	77	UnRx	Chlorambucil, Prednisone	72%	NA
Petrucci ¹²⁶	31	UnRx	Melphalan, Cyclophosphamide, Prednisone→Cyclophosphamide, Prednisone (Continuous)	74%	66 months
Case ¹²⁷	33	UnRx & Rx	M-2 (BCNU, Cyclophosphamide, Vincristine, Melphalan, Prednisone)	82%	43 months (CR) 39 months (PR)

* $\geq 50\%$ reduction in serum IgM levels

Table 5. Cladribine in Untreated Waldenström's macroglobulinemia

	(N)	Median # Courses	Major RR*	Median Response Duration
Dimopoulos¹²⁹	26	2	85%	2+ to 39+ months
Delannoy¹³⁰	5	2	40%	NA
Fridrik¹³¹	10	4	90%	NA
Liu¹³²	7	3	57%	NA
Hellman¹³³	9	4	44%	NA

Fludarabine in Untreated Waldenström's macroglobulinemia				
	(N)	Median # Courses	Major RR*	Median Response Duration
Dimopoulos¹³⁶	2	3	100%	NA
Foran¹³⁷	15	5.2**	79%	40 months
Thalhammer- Scherrer¹³⁸	7	6	85%	44+ months
Dhodapkar¹³⁹	118	4-8	38%	59 months

* $\geq 50\%$ reduction in serum IgM levels
**Mean # of infusions

Table 6. Cladribine in Previously Treated Waldenström's macroglobulinemia

	(N)	Median # Courses	Major RR*	Median Response Duration
Dimopoulos¹³⁵	46	2	43%	12 months
Delannoy¹³⁰	13	2	38%	NA
Betticher¹³⁴	25	3	40%	8 months
Liu¹³²	13	3	54%	NA
Hellman¹³³	13	4	38%	NA

Fludarabine in Previously Treated Waldenström's macroglobulinemia				
	(N)	Median # Courses	Major RR*	Median Response Duration
Dimopoulos¹³⁶	26	3	31%	NA
Zinzani¹⁴⁰	12	6	41%	10+ months
Leblond¹⁴¹	71	6	30%	32 months
Dhodapkar¹³⁹	64	4-8	33%	30 months

* $\geq 50\%$ reduction in serum IgM levels

Table 7. Rituximab Therapy in Waldenström's macroglobulinemia

	(N)	Median # Courses	Major RR*	Median Response Duration
Byrd¹⁴⁵	6	4	57%	6.6+ months
Weber¹⁴⁴	7	4	75%	9.0 months
Foran¹⁴⁶	7	4	29%	NA
Treon¹⁴⁷	30	4	27%	8.0 months
Dimopoulos¹⁴⁸	27	8	56%	16 months
Treon¹⁴⁹	26	8	46%	20+ months

* $\geq 50\%$ reduction in serum IgM levels

Legends to Figures

Figure 1. Jan Waldenström at the age of 38, when he described the two prototypic cases of macroglobulinemia on *Acta Medica Scandinavica*.

Figure 2. The morbidity associated with WM is caused by the concurrence of two main components: tissue infiltration by neoplastic cells and, more importantly, the physicochemical and immunological properties of the monoclonal IgM.

Figure 3. The circulatory disturbances caused by blood hyperviscosity are best appreciated by ophthalmoscopy which shows distended and tortuous retinal veins, hemorrhages and papilledema.

Figure 4. Necrosis of the tip of the fingers in a patient with WM and type I cryoglobulinemia.

Figure 5. Involvement of the periorbital structures in a patient with WM.

Figure 6. High resolution agarose gel electrophoresis combined with immunofixation of serum and urine are recommended for identification and characterization of the monoclonal IgMs which are best quantified by densitometry.

Figure 7. Lymphoplasmacytic population with abundant plasma cell component and presence of a Dutcher-Fahey body in a lymph node.

Figure 8. Overall survival of 215 WM patients (Kaplan-Meier analysis)