WALDENSTROM'S MACROGLOBLINEMIA/LYMPHOPLASMACYTIC LYMPHOMA

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INTRODUCTION

Waldenström's macroglobulinemia (WM) is a distinct clinicopathological entity resulting from the accumulation, predominantly in the bone marrow, of clonally related lymphocytes, lymphoplasmacytic cells and plasma cells which secrete a monoclonal IgM protein **(Figure 1)**.[1] This condition is considered to correspond to the lymphoplasmacytic lymphoma (LPL) as defined by the Revised European American Lymphoma (REAL) and World Health Organisation classification systems.[2,3] Most cases of LPL are WM, with less than 5% of cases made up of IgA, IgG and non-secreting LPL.

EPIDEMIOLOGY AND ETIOLOGY

WM is an uncommon disease, with a reported age-adjusted incidence rate of 3.4 per million among males and 1.7 per million among females in the USA, and a geometrical increase with age.[4,5] The incidence rate for WM is higher among Caucasians, with African descendants representing only 5% of all patients. Genetic factors appear to be an important factor to the pathogenesis of WM. Approximately 20% of WM patients have an Ashkenazi (Eastern European) Jewish ethnic background, and there have been numerous reports of familiar disease, including multigenerational clustering of WM and other B-cell lymphoproliferative diseases.[6-10] In a recent study, approximately 20% of 257 serial WM patients presenting to a tertiary referral had a first degree relative with either WM or another B-cell disorder.[7] Frequent familiar association with other immunological disorders in healthy relatives, including hypogammaglobulinemia and hypergammaglobulinemia (particularly polyclonal IgM), autoantibody (particularly to thyroid) production, and manifestation of hyperactive B cells have also been reported.[9,10] Increased expression of the *bcl-2* gene with enhanced B-cell survival may underlie the increased immunoglobulin synthesis in familial WM.[9] The role of environmental factors in WM remains to be clarified, but chronic antigenic stimulation from infections, certain drug and agent orange exposures remain suspect. An etiological role for hepatitis C virus (HCV) infection has been suggested though in a recent study examining one-hundred consecutive patients with WM, no association could be established using both serological and molecular diagnostic studies for HCV infection [11-13]

BIOLOGY

Cytogenetic findings

Several studies, usually performed on limited series of patients, have been published on cytogenetic findings in WM demonstrating a great variety of numerical and structural chromosome abnormalities. Numerical losses involving chromosomes 17, 18, 19, 20, 21, 22, X, and Y have been commonly observed, though gains in chromosomes 3, 4, and 12 have also been reported.[7,14-19] Chromosome 6q deletions encompassing 6q21-22 have been observed in up to half of WM patients, and at a comparable frequency amongst patients with and without a familial history.[7,19] The presence of 6q deletions have been suggested in one study to discern patients with WM from those with IgM monoclonal gammopathy of unknown significance (MGUS), and to have potential prognostic significance though others have reported no prognostic significance to the presence of 6q deletions in WM[20,21]. While 6q deletions have been reported in other B-cell malignancies, several candidate tumor suppressor genes in this region are under investigation in WM patients including BLIMP-1[22], a master regulatory gene implicated in lymphoplasmacytic differentiation. Notable, however, is the absence of IgH switch region rearrangements in WM, a finding which may be used to discern cases of IgM myeloma where IgH switch region rearrangements are a predominant feature.[23]

Nature of the clonal cell

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 number 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. This is through an interleukin-6 (IL-6)-dependent process in IgM MGUS and mostly an IL-6-independent process 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 of the lymphoplasmacytic cells in WM includes the expression of the pan B-cell markers CD19, CD20, CD22, CD79, and FMC7.2. [27–29] Expression of CD5, CD10 and CD23 may be found in 10–20% of cases, and does not exclude the diagnosis of WM.[30]

The phenotype of lymphoplasmacytic cells in WM cell suggests that the clone is a post-germinal center B-cell. 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 with the closest germline genes, clustering in the CDR regions and without intraclonal variation. Subsequent studies showed a strong preferential usage of VH3/JH4 gene families, no intraclonal variation, no evidence for any isotype-switched transcripts.[33,34] These data indicate that WM may originate 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]

Bone marrow microenvironment

Increased numbers of mast cells are found in the bone marrow of WM patients, wherein they are usually admixed with tumor aggregates.[29,36] Recent studies have helped clarify the role of mast cells in WM. Co-culture of primary autologous or mast cell lines with WM LPC resulted in dose-dependent WM cell proliferation and/or tumor colony, primarily through CD40 ligand (CD40L) signaling. Furthermore, WM cells through elaboration of soluble CD27 (sCD27), induced the upregulation of CD40L on mast cells derived from WM patients and mast cell lines[37].

CLINICAL FEATURES

The clinical and laboratory findings at time of diagnosis of WM in one large institutional study[7] are presented in **Table 1**. Unlike most indolent lymphomas, splenomegaly and lymphadenopathy are prominent in only a minority of patients ($\leq$15%). Purpura is frequently associated with cryoglobulinemia and more rarely with AL amyloidosis, while hemorrhagic manifestations and neuropathies are multifactorial (see later). 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. As shown 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.[38–40]

MORBIDITY MEDIATED BY THE EFFECTS OF IGM

Hyperviscosity syndrome

Blood hyperviscosity is effected by increased serum IgM levels leading to hyperviscosity related complications[41] The mechanisms behind the marked increase in the resistance to blood flow and the resulting impaired transit through the microcirculatory system are rather complex.[41–43] The main determinants are: (1) a high concentration of monoclonal IgMs, which may form aggregates and may bind water through their carbohydrate component; and (2) their interaction with blood cells. Monoclonal IgMs increase red cell aggregation (*rouleaux* formation) and red cell internal viscosity while also 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. Plasma viscosity and hematocrit are directly regulated by the body. Increased plasma viscosity may also contribute to inappropriately low erythropoietin production, which is the major reason for anemia in these patients.[44] Clinical manifestations are related to

circulatory disturbances that can be best appreciated by ophthalmoscopy, which shows distended and tortuous retinal veins, hemorrhages and papilledema[45] **(Figure 2)**. Symptoms usually occur when the monoclonal IgM concentration exceeds 50 g/L or when serum viscosity is >4.0 centipoises (cp), but there is a great individual variability, with some patients showing no evidence of hyperviscosity even at 10 cp.[41] The most common symptoms are oronasal bleeding, visual disturbances due to retinal bleeding, and dizziness that may rarely lead to coma. Heart failure can be aggravated, particularly in the elderly, owing to increased blood viscosity, expanded plasma volume, and anemia. Inappropriate transfusion can exacerbate hyperviscosity and may precipitate cardiac failure.

Cryoglobulinemia

In up 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.[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 such as the tip of the nose, ears, fingers, and toes **(Figure 3)**, malleolar ulcers, purpura, and cold urticaria. Renal manifestations may occur but are infrequent.

Auto-Antibody Activity

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:

IgM related neuropathy

In a series of 215 patients with WM, Merlini *et al.*[46] reported the clinical presence of peripheral neuropathy in 24% of WM patients, although prevalence rates ranging from 5% to 38% have been reported in other series.[47,48] An estimated 6.5–10% of idiopathic neuropathies are associated with a monoclonal gammopathy, with a preponderance of IgM (60%) followed by IgG (30%) and IgA (10%) (reviewed in Nemni *et al*[49] and Ropper and Gorson[50]). In WM patients, the nerve damage is mediated by diverse pathogenetic mechanisms: IgM antibody activity toward nerve constituents causing demyelinating polyneuropathies; endoneurial granulofibrillar 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 IgMκ, 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 a long period of stability.[48,55] Most patients present with sensory complaints (paresthesias, aching discomfort, dysesthesias, or lancinating pains), imbalance and gait ataxia, owing 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.[61] These antiganglioside monoclonal IgMs 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 glycophorins, thereby accounting for the red cell cold agglutinin activity of anti-Pr2 specificity.[58,59] Monoclonal IgM proteins that bind to gangliosides with a terminal trisaccharide moiety, including GM2 and GalNac-GD1A, are associated with chronic demyelinating neuropathy and severe sensory ataxia, unresponsive to corticosteroids.[60] Antiganglioside IgM proteins may also cross-react with lipopolysaccharides of C*ampylobacter 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. Antisulfatide monoclonal IgM proteins, 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 (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes) syndrome is rarely associated with WM.[64]

Cold agglutinin hemolytic anemia

Monoclonal IgM may present with cold agglutinin activity, i.e. it can recognize specific red cell antigens at temperatures below physiological, producing chronic hemolytic anemia. This disorder occurs in <10% of WM patients[65] and is associated with cold agglutinin titers >1:1000 in most cases. The monoclonal component is usually an IgMκ and reacts most commonly with I/i antigens, with complement fixation and activation.[66,67] 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 reticuloendotelial system, primarily in the liver) and rarely intravascular from complement destruction of red blood cell (RBC) membrane. The agglutination of RBCs 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 glycophorins and on Ig molecules. 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.

Tissue deposition

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.[68] Amorphous IgM deposits in the dermis determine the so-called IgM storage papules on the extensor surface of the extremities – macroglobulinemia cutis.[69] Deposition of monoclonal IgM in the lamina propria and/or submucosa of the intestine may be associated with diarrhea, malabsorption, and gastrointestinal bleeding.[70,71] 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 also been described in WM.[72] 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.[73] 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.[74] 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 is higher in patients with monoclonal IgM than with other immunoglobulin isotypes. The association of WM with reactive amyloidosis (AA) has been documented rarely.[75,76] Simultaneous occurrence of fibrillary glomerulopathy, characterized by glomerular deposits of wide non-congophilic fibrils and amyloid deposits, has been reported in WM.[77]

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 later) to the liver, spleen, lymph nodes, and possibly the lungs, gastrointestinal 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 3–5%.[78-80] 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 may indicate involvement of the gastrointestinal tract at the level of the stomach, duodenum, or small intestine.[81-84] In contrast to multiple myeloma, infiltration of the kidney interstitium with lymphoplasmacytoid cell has been reported in WM,[85] while renal or perirenal masses are not uncommon.[86] 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.[87] 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,[88] although evolution to WM is not uncommon. Thus, close follow-up of these patients is warranted. Invasion of articular and periarticular structures by WM malignant cells is rarely reported.[89] The neoplastic

cells can infiltrate the periorbital structures, lacrimal gland, and retro-orbital lymphoid tissues, resulting in ocular nerve palsies.[90,91] 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 al.*[92]).

LABORATORY INVESTIGATIONS AND FINDINGS

Hematological abnormalities

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 gastrointestinal tract. Blood smears are usually normocytic and normochromic, and rouleaux formation is often pronounced. Electronically measured mean corpuscular volume may be elevated spuriously owing 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.[93] Leukocyte and platelet counts are usually within the reference range at presentation, although patients may occasionally present with severe thrombocytopenia. As reported above, monoclonal B-lymphocytes expressing surface IgM and late-differentiation B-cell markers are uncommonly detected in blood by flow cytometry. A raised erythrocyte sedimentation rate is almost constantly observed in WM and may be the first clue to the presence of the macroglobulin. 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.

Biochemical investigations

High-resolution electrophoresis combined with immuno-fixation of serum and urine are recommended for identification and characterization of the IgM monoclonal protein. The light chain of the monoclonal IgM is κ in 75–80% of patients. A few WM patients have more than one M-component. The concentration of the serum monoclonal protein is very variable but in most cases lies within the range of 15–45 g/L. Densitometry should be adopted to determine IgM levels for serial evaluations because nephelometry is unreliable and shows large intralaboratory as well as interlaboratory variation. The presence of cold agglutinins or cryoglobulins may affect determination of IgM levels and, therefore, testing for cold agglutinins and cryoglobulins should be performed at diagnosis. If present, subsequent 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/24 hours in only 3% of cases. While IgM levels are elevated in WM patients, IgA and IgG levels are most often depressed and do not demonstrate recovery even after successful treatment suggesting that patients with WM harbor a defect which prevents normal plasma cell development and/or Ig heavy chain rearrangements.[94,95]

Serum viscosity

Because of its large size (almost 1,000,000 daltons), most IgM molecules are retained within the intravascular compartment and can exert an undue effect on serum viscosity. Therefore, serum viscosity should be measured if the patient has signs or symptoms of hyperviscosity syndrome. Fundoscopy remains an excellent indicator of clinically relevant hyperviscosity. Among the first clinical signs of hyperviscosity, the appearance of peripheral and mid-peripheral dot and blot-like hemorrhages in the retina, which are best appreciated with indirect ophthalmoscopy and scleral depression.[45] In more severe cases of hyperviscosity, dot, blot and flame shaped hemorrhages can appear in the macular area along with markedly dilated and tortuous veins with focal constrictions resulting in "venous sausaging", as well as papilledema.

Bone marrow findings

The bone marrow is always involved in WM. 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 **(Figure 1)**. 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.[1] The bone marrow infiltration should routinely be confirmed by *immunophenotypic studies* (flow cytometry and/or immunohistochemistry) showing the following profile: $sIgM^{+}CD19^{+}CD20^{+}CD22^{+}CD79^{+}$.[27-29] Up to 20% of cases may express either CD5, CD10 or CD23.[30] In these cases, care should be taken to satisfactorily exclude chronic lymphocytic leukemia and mantle cell lymphoma.[1] 'Intranuclear' periodic acid-Schiff (PAS)-positive inclusions (Dutcher-Fahey bodies; see Fig. 10)[96] consisting of IgM deposits in the perinuclear space, and sometimes in intranuclear vacuoles, may be seen occasionally in lymphoid cells in WM. An increase number of mast cells, usually in association with the lymphoid aggregates is commonly found in WM, and their presence may help in differentiating WM from other B-cell lymphomas.[2,3]

Other investigations

Magnetic resonance imaging (MRI) of the spine in conjunction with computed tomography (CT) of the abdomen and pelvis are useful in evaluating the disease status in WM.[97] 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.[97] 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 polymerase chain reaction (PCR)-based methods using primers specific for the monoclonal Ig variable regions.

PROGNOSIS

Waldenström's macroglobulinemia typically presents as an indolent disease though considerable variability in prognosis can be seen. The median survival reported in several large series has ranged from 5 to 10 years[98-104], though in a recent followup of 436 consecutive patients diagnosed with WM, the median overall survival from time of diagnosis was in excess of 10 years[105]. The presence of 6q deletions have been suggested to have prognostic significance in one study, though others have reported no such association in WM[20,21]. Age is consistently an important prognostic factor (>60-70 years)[98,99,101,104], but this factor is often impacted by unrelated morbidities. Anemia which reflects both marrow involvement and the serum level of the IgM monoclonal protein (due to the impact of IgM on intravascular fluid retention) has emerged as a strong adverse prognostic factor with hemoglobin levels of <9-12 g/dL associated with decreased survival in several series[98-101,104]. Cytopenias have also been regularly identified as a significant predictor of survival[99]. However, the precise level of cytopenias with prognostic significance remains to be determined[101]. Some series have identified a platelet count of <100-150 x 10^9/L and a granulocyte count of <1.5 x 10^9/L as independent prognostic factors[98,99,101,104]. The number of cytopenias in a given patient has been proposed as a strong prognostic factor[99]. Serum albumin levels have also correlated with survival in WM patients in certain but not all studies using multivariate analyses[99,101,102]. High beta-2 microglobulin levels (>3-3.5 g/dL) were shown in several studies[100,101,102,103,104], a high serum IgM M-protein (>7 g/dL)[104] as well as a low serum IgM M-protein (<4 g/dL)[102] and the presence of cryoglobulins[98] as adverse factors. A few scoring systems have been proposed based on these analyses **(Table 3)**.

TREATMENT OF WALDENSTRÖM'S MACROGLOBULINEMIA

As part of the 2nd International Workshops on Waldenström's macroglobulinemia, a consensus panel was organized to recommend criteria for the initiation of therapy in patients with WM.[101] The panel recommended that initiation of therapy should not be based on the IgM level *per se*, since this may not correlate with the clinical manifestations of WM. The consensus panel, however, agreed that initiation of therapy was appropriate for patients with constitutional symptoms, such as recurrent fever, night sweats, fatigue due to anemia, or weight loss. The presence of progressive symptomatic lymphadenopathy or splenomegaly provides additional reasons to begin therapy. The

presence of anemia with a hemoglobin value of $\leq$10 g/dL or a platelet count $\leq$100 x 10^9/L owing to marrow infiltration also justifies treatment. Certain complications, such as hyperviscosity syndrome, symptomatic sensorimotor peripheral neuropathy, systemic amyloidosis, renal insufficiency, or symptomatic cryoglobulinemia, may also be indications for therapy.[101]

FRONTLINE THERAPY

While a precise therapeutic algorithm for therapy of WM remains to be defined given the paucity of randomized clinical trials, consensus panels composed of experts who treat WM were organized as part of the International Workshops on Waldenström's macroglobulinemia and have formulated recommendations for both frontline and salvage therapy of WM based on the best available clinical trials evidence. Among frontline options, the panels considered alkylator agents (e.g. chlorambucil), nucleoside analogues (cladribine or fludarabine), the monoclonal antibody rituximab as well as combinations thereof as reasonable choices for the upfront therapy of WM.[106-108] 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, which typically is reserved for those patients <70 years of age, the panel recommended that exposure to alkylator or nucleoside analogue therapy should be limited. The use of nucleoside analogues should be approached cautiously in patients with WM since there appears to be an increased risk for the development of disease transformation as well as myelodysplasia and acute myelogenous leukemia.

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 on both 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 per 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.*[109] reported no significant difference in the overall response rate between these schedules, although interestingly the median response duration was greater for patients receiving intermittent versus continuously dosed chlorambucil (46 vs. 26 months). 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 Alexanian[110] 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.*[111] and Case *et al.*[112] producing slightly higher overall response rates and response durations, although the benefit of these more complex regimens over chlorambucil remains to be demonstrated. Facon *et al.*[113] 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, and 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 by continuous intravenous infusion, by 2-hour daily infusion, or by subcutaneous bolus injections for 5–7 days has resulted in major responses in 40–90% of patients who received primary therapy, whilst in the salvage setting responses have ranged from 38% to 54%. [113-120] Median time to achievement of response in responding patients following cladribine ranged from 1.2 to 5 months. 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 to 100% and 30–40%, respectively,[121-126] which are on par with the response data for cladribine. 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, although in several of the above studies wherein both untreated and previously treated patients were enrolled, no substantial difference in the overall response rate was reported. 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 1 year following initiation of therapy.[113,115] 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), pre-treatment 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.[113,119,125] There are limited data on the use of an alternate nucleoside analogue to salvage patients whose disease relapsed or demonstrated resistance off cladribine or fludarabine therapy[127,128]. Three of four (75%) patients responded to cladribine to salvage patients who progressed following an unmaintained remission to fludarabine, whereas

only one of ten (10%) with disease resistant to fludarabine responded to cladribine.[127] However, Lewandowski *et al.*[128] reported a response in two of six patients (33%) and disease stabilization in the remaining patients to fludarabine, in spite of an inadequate response or progressive disease following cladribine therapy.

The safety of nucleoside analogues has been the subject of investigation in several recent studies. Thomas et al recently reported their experiences in harvesting stem cells in 21 patients with symptomatic WM in whom autologous peripheral blood stem cell collection was attempted. ASCC succeeded on 1st attempt in 14/15 patients who received non-nucleoside analogue based therapy vs. 2/6 patients who received a nucleoside analogue.[129] The long term safety of nucleoside analogues in WM was recently examined by Leleu *et al*[105] in a large series of WM patients. A 7-fold increase in transformation to an aggressive lymphoma, and a 3-fold increase in the development of acute myelogenous leukemia/myelodysplasia were observed amongst patients who received a nucleoside analogue versus other therapies for their WM. A recent metanalysis by Leleu et al[130] of several trials utilizing nucleoside analogues in WM patients, which included patients who had previously received an alkylator agent showed a crude incidence of 6.6-10% for development of disease transformation, and 1.4-8.9% for development of myelodysplasia or acute myelogenous leukemia. None of the studied risk factors, i.e. gender, age, family history of WM or B-cell malignancies, typical markers of tumor burden and prognosis, type of nucleoside analogue therapy (cladribine versus fludarabine), time from diagnosis to nucleoside analogue use, nucleoside analogue treatment as primary or salvage therapy, as well as treatment with an oral alkylator (i.e. chlorambucil) predicted for the occurrence of transformation or development of myelodysplasia/acute myelogenous leukemia for WM patients treated with a nucleoside analogue[130].

CD20-directed antibody therapy

Rituximab is a chimeric monoclonal antibody which targets CD20, a widely expressed antigen on lymphoplasmacytic cells in WM[131]. Several retrospective and prospective studies have indicated that rituximab, when used at standard dosimetry (i.e. 4 weekly infusions at 375 mg/m^2) induced major responses in approximately 27-35% of previously treated and untreated patients.[132-138] Furthermore, it was shown in some of these studies, that patients who achieved minor responses or even stable disease benefited from rituximab as evidenced by improved hemoglobin and platelet counts, and reduction of lymphadenopathy and/or splenomegaly. The median time to treatment failure in these studies was found to range from 8 to 27+ months. Studies evaluating an extended rituximab schedule consisting of 4 weekly courses at 375 mg/m2/week, repeated 3 months later by another 4 week course have demonstrated major response rates of 44-48%, with time to progression estimates of 16+ to 29+ months.[138,139]

In many WM patients, a transient increase of serum IgM may be noted immediately following initiation of treatment.[138,140-142] Such an increase does not herald treatment failure, and while most patients will return to their baseline serum IgM level by 12 weeks some continue to show prolonged spiking despite demonstrating a reduction in their bone

marrow tumor load. However, patients with baseline serum IgM levels of >50g/dL or serum viscosity of >3.5cp may be particularly at risk for a hyperviscosity related event and in such patients plasmapheresis should be considered in advance of rituximab therapy.[141] Because of the decreased likelihood of response in patients with higher IgM levels, as well as the possibility that serum IgM and viscosity levels may abruptly rise, rituximab monotherapy should not be used as sole therapy for the treatment of patients at risk for hyperviscosity symptoms.

Time to response after rituximab is slow and exceeds 3 months on the average. The time to best response in one study was 18 months.[139] Patients with baseline serum IgM levels of <60g/dL are more likely to respond, irrespective of the underlying bone marrow involvement by tumor cells.[138,139] A recent analysis of 52 patients who were treated with single agent rituximab has indicated that the objective response rate was significantly lower in patients who had either low serum albumin (<35g/L) or elevated serum monoclonal protein (>40g/L M-spike). Furthermore, the presence of both adverse prognostic factors was related with a short time to progression (3.6 months). Moreover patients who had normal serum albumin and relatively low serum monoclonal protein levels derived a substantial benefit from rituximab with a time to progression exceeding 40 months.[143]

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 that 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 FcγRIIIa 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. 50% decline in serum IgM levels) to rituximab versus those patients who expressed phenylalanine in a homozygous pattern.[144]

Combination Therapies

Because rituximab is an active and a non-myelosuppressive agent, its combination with chemotherapy has been explored in WM patients. Weber *et al*[145] administered rituximab along with cladribine and cyclophosphamide to 17 previously untreated patients with WM. At least a partial response was documented in 94% of WM patients including a complete response in 18%. With a median follow-up of 21 months no patient has relapsed. In a study by the Waldenstrom's Macroglobulinemia Clinical Trials Group (WMCTG), the combination of rituximab and fludarabine was evaluated in 43 WM patients, 32 (75%) of whom were previously untreated[146]. The overall response rate was 95.3%, with 83% of patients achieving a major response (i.e. 50% reduction in disease burden). The median time to progression was 51.2 months in this series, and was longer for those patients who were previously untreated and for those achieving a VGPR (i.e. 90% reduction in disease) or better. Hematological toxicity was common with grade 3 neutropenia and thrombocytopenia observed in 27 and 4 patients, respectively. Two

deaths occurred in this study due to non-PCP pneumonia. Secondary malignanices including transformation to aggressive lymphoma and development of myelodysplasia or AML were observed in 6 patients in this series. The addition of rituximab to fludarabine and cyclophosphamide has also been explored in the salvage setting by Tam *et al*, wherein 4 of 5 patients demonstrated a response[147]. In another combination study with rituximab, Hensel *et al*[148] administered rituximab along with pentostatin and cyclophosphamide to 13 patients with untreated and previously treated WM or lymphoplasmacytic lymphoma. A major response was observed in 77% or patients. In a study by Dimopoulos *et al*[149], the combination of rituximab, dexamethasone and cyclophosphamide was used as primary therapy to treat 72 patients with WM. At least a major response was observed in 74% of patients in this study, and the 2 year progression free survival was 67%. Therapy was well tolerated, though one patient died of interstitial pneumonia.

In addition to nucleoside analogue based trials with rituximab, two studies have examined CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) in combination with rituximab (CHOP-R). In a randomized frontline study by the German Low Grade Lymphoma Study Group (GLSG) involving 69 patients, most of whom had WM, the addition of rituximab to CHOP resulted in a higher overall response rate (94% versus 67%) and median time to progression (63 versus 22 months) in comparison to patients treated with CHOP alone.[150]. Treon *et al*[151] have also evaluated CHOP-R in 13 WM patients, 8 and 5 of whom were relapsed or refractory to nucleoside analogues and single agent rituximab, respectively. Among 13 evaluable patients, 10 patients achieved a major response (77%) including 3 CR and 7 PR, and 2 patients achieved a minor response. In a retrospective study, Ioakimidis *et al*[152] examined the outcomes of symptomatic WM patients who received CHOP-R, CVP-R, or CP-R. Baseline characteristics for all 3 cohorts were similar for age, prior therapies, bone marrow involvement, hematocrit, platelet count and serum beta 2 microglobulin, though serum IgM levels were higher in patients treated with CHOP-R. The overall response rates to therapy were comparable among all three treatment groups: CHOP-R (96%); CVP-R (88%) and CP-R (95%), though there was a trned for more CR among patients treated with CVP-R and CHOP-R. Adverse events attributed to therapy showed a higher incidence for neutropenic fever and treatment related neuropathy for CHOP-R and CVP-R versus CPR. The results of this study suggest that in WM, the use of CP-R may provide analogous treatment responses to more intense cyclophosphamide based regimens, while minimizing treatment related complications.

The addition of alkylating agents to nucleoside analogues has also been explored in WM. Weber *et al*[145] administered two cycles of oral cyclophosphamide along with subcutaneous cladribine to 37 patients with previously untreated WM. At least a partial response was observed in 84% of patients and the median duration of response was 36 months. Dimopoulos *et al*[153] examined fludarabine in combination with intravenous cyclophosphamide and observed partial responses in 6 of 11 (55%) WM patients with either primary refractory disease or who had relapsed on treatment. The combination of fludarabine plus cyclosphosphamide was also evaluated in a recent study by Tamburini *et*

al[154] involving 49 patients, 35 of whom were previously treated. Seventy-eight percent of the patients in this study achieved a response and median time to treatment failure was 27 months. Hematological toxicity was commonly observed and three patients died of treatment related toxicities. Two interesting findings in this study was the development of acute leukemia in 2 patients, histologic transformation to diffuse large cell lymphoma in one patient, and 2 cases of solid malignancies (prostate and melanoma), as well as failure to mobilize stem cells in 4 of 6 patients.

In view of the above data, the consensus panel on therapeutics amended its original recommendations for the therapy of WM to include the use of combination therapy with either nucleoside analogues and alkylator agents, or rituximab in combination with nucleoside analogues, nucleoside analogues plus alkylator agents, or cyclophosphamide based therapy as reasonable therapeutics options for the treatment of WM.[107,108]

SALVAGE THERAPY INCLUDING NOVEL AGENTS

For patients in relapse or who have refractory disease, the consensus panels recommended the use of an alternative first-line agent as defined above, with the caveat that for those patients for whom autologous transplantation was being seriously 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 should be considered if stem cells had not previously been harvested.[107,108] Recent studies have also demonstrated activity for several novel agents including bortezomib, thalidomide alone or in combination, alemtuzumab and can be considered in the treatment of relapsed/refractory WM. Lastly, autologous stem cell transplant remains an option for the salvage therapy of WM particularly among younger patients who have had multiple relapses, or have primary refractory disease.

Proteasome inhibitor

Bortezomib, a stem cell sparing agent[155-157], is a proteasome inhibitor which induces apoptosis of primary WM lymphoplasmacytic cells, as well as the WM-WSU WM cell line at pharmacologically achievable levels[158]. Moreover, bortezomib may also impact on bone marrow microenvironmental support for lymphoplasmacytic cells. In a multi-center study of the Waldenstrom's Macroglobulinemia Clinical Trials Group (WMCTG)[159], 27 patients received up to 8 cycles of bortezomib at 1.3 mg/m^2 on days 1, 4, 8, and 11. All but one patient had relapsed/or refractory disease. Following therapy, median serum IgM levels declined from 4,660 mg/dL to 2,092 mg/dL ($p<0.0001$). The overall response rate was 85%, with 10 and 13 patients achieving a minor (<25% decrease in IgM) and major (<50% decrease in IgM) response. Responses were prompt, and occurred at median of 1.4 months. The median time to progression for all responding

patients in this study was 7.9 (range 3-21.4+) months, and the most common grade III/IV toxicities occurring in ≥ 5% of patients were sensory neuropathies (22.2%); leukopenia (18.5%); neutropenia (14.8%); dizziness (11.1%); and thrombocytopenia (7.4%). Importantly, sensory neuropathies resolved or improved in nearly all patients following cessation of therapy. As part of an NCI-Canada study, Chen *et al*[160] treated 27 patients with both untreated (44%) and previously treated (56%) disease. Patients in this study received bortezomib utilizing the standard schedule until they either demonstrated progressive disease, or 2 cycles beyond a complete response or stable disease. The overall response rate in this study was 78%, with major responses observed in 44% of patients. Sensory neuropathy occurred in 20 pts, 5 with grade >3, and occurred following 2-4 cycles of therapy. Among the 20 patients developing a neuropathy, 14 patients resolved and one patient demonstrated a one-grade improvement at 2-13 months. In addition to the above experiences with bortezomib monotherapy in WM, Dimopoulos *et al*[161] observed major responses in 6 of 10 (60%) previously treated WM patients, while Goy *et al*[162] observed a major response in 1 of 2 WM patients who were included in a series of relapsed or refractory patients with non-Hodgkin's lymphoma (NHL). In view of the single agent activity of bortezomib in WM, Treon *et al*[163] have examined the combination of bortezomib, dexamethasone and rituximab (BDR) as primary therapy in patients with WM. An overall response rate of 96%, and a major response rate of 83% were observed with the BDR combination. The incidence of grade 3 neuropathy was about 30% in this study, but was reversible in most patients following discontinuation of therapy. An increased incidence of herpes zoster was also observed prompting the prophylactic use of antiviral therapy with BDR. Alternative schedules for administration of bortezomib (i.e. once weekly at higher doses) in combination with rituximab are also being examined by Ghobrial *et al*[164] and Agathocleous *et al*[165] in patients with WM with overall response rates of 80-90%. The impact of these schedules on the development of bortezomib related peripheral neuropathy remains to be clarified, though in one study appeared diminished.[164]

CD52-directed antibody therapy

Alemtuzumab is a humanized monoclonal antibody which targets CD52, an antigen widely expressed on bone marrow LPC in WM patients, as well as on mast cells which are increased in the BM of patients with WM and provide growth and survival signals to WM LPC through several TNF family ligands (CD40L, APRIL, BLYS).[166] As part of a WMCTG effort[167], 28 subjects with the REAL/WHO clinicopathological diagnosis of LPL, including 27 patients with IgM (WM) and one with IgA monoclonal gammopathy were enrolled in this prospective, multicenter study. Five patients were untreated and 23 were previously treated, all of whom had previously received rituximab. Patients received 3 daily test doses of alemtuzumab (3, 10, and 30 mg IV) followed by 30 mg alemtuzumab IV three times a week for up to 12 weeks. All patients received acyclovir and bactrim or equivalent prophylaxis for the duration of therapy plus 8 week following the last infusion of alemtuzumab. Among 25 patients evaluable for response, the overall response rate was 76%, which included 8 (32%) major responders, and 11 (44%) minor responders. Hematological toxicities were common among previously treated (but not untreated)

patients and included grade 3/4 neutropenia 39%; thrombocytopenia 18%; anemia 7%. Grade 3/4 non-hematological toxicity for all patients included dermatitis 11%; fatigue 7%; and infection 7%. CMV reactivation and infection was commonly seen among previously treated patients and may have been etiological for one death on study. With a median follow-up of 8.5+ months, 11/19 responding patients remain free of progression. High rates of response with the use of alemtuzumab as salvage therapy have also been reported by Owen et al[168] in a small series of heavily pretreated WM patients (with a median prior therapies of 4) who received up to 12 weeks of therapy (at 30 mg IV TIW) following initial dose escalation. Among the 7 patients receiving alemtuzumab, 5 patients achieved a partial response and 1 patient a complete response. Infectious complications were common, with CMV reactivation occurring in 3 patients requiring ganciclovir therapy, and hospitalization for 3 patients for bacterial infections. Opportunistic infection occurred in two patients, and was responsible for their deaths.

Thalidomide and Lenalidomide

Thalidomide as a single agent, and in 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*[169] demonstrated a major response in five of 20 (25%) previously untreated and treated patients 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 five 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 response.[170] However, in a follow-up study by Dimopoulos *et al*[171] using a higher thalidomide dose (200 mg orally daily) along with dexamathasone (40 g orally once a week) and clarithromycin (500 mg orally twice a day), only two of ten (20%) previously treated patients responded. In a previous study, the immunomodulators thalidomide and its analogue lenalidomide significantly augmented rituximab mediated antibody dependent cell mediated cytotoxicity (ADCC) against lymphoplasmacytic cells.[172] Moreover, an expansion of natural killer cells has been observed with thalidomide, which in previous studies have been shown to be associated with rituximab response.[173,174] In view of these data, the WMCTG conducted 2 phase II clinical trials in symptomatic patients with WM combining thalidomide or lenalidomide with rituximab.[175,176] Intended therapy for those patients who treated on the thalidomide plus rituximab study consisted of thalidomide administered at 200 mg daily for 2 weeks, followed by 400 mg daily thereafter for one year. Patients received four weekly infusions of rituximab at 375 mg/m2 beginning one week after initiation of thalidomide, followed by four additional weekly infusions of rituximab at 375 mg/m2 beginning at week 13. The overall and major response rate (i.e. $\geq$50 decrease in IgM) was 72% and 64%, respectively. Median serum IgM levels decreased from 3,670 to 1,590 mg/dL, while the median hematocrit rose from 33.0 to 37.6% at best response. The median time to progression for responders was 38 months in thise series. Dose reduction of thalidomide

occurred in all patients and led to discontinuation in 11 patients. Among 11 patients experiencing grade $\geq$2 neuroparesthesias, 10 demonstrated resolution to grade 1 or less at a median of 6.7 months. Given the high incidence of treatment related neuropathy, the investigators recommended that lower doses of thalidomide (i.e. $\leq$ 200 mg/day) should be considered in this patient population.

In a phase II study of lenalidomide and rituximab in WM[176], patients were initiated on lenalidomide at 25 mg daily on a syncopated schedule wherein therapy was administered for 3 weeks, followed by a one week pause for an intended duration of 48 weeks. Patients received one week of therapy with lenalidomide, after which rituximab (375 mg/m2) was administered weekly on weeks 2-5, then 13-16. The overall and a major response rates in this study were 50% and 25%, respectively, and a median TTP for responders was 18.9 months. In two patients with bulky disease, significant reduction in extramedullary disease was observed. However, an acute decrease in hematocrit were observed during first 2 weeks of lenalidomide therapy in 13/16 (81%) patients with a median absolute decrease inhematocrit of 4.8%, resulting in anemia related complications and hospitalizations in 4 patients. Despite dose reduction, most patients in this study continued to demonstrate aggravated anemia with lenalidomide. There was no evidence of hemolysis or more general myelosuppression with lenalidomide in this study. Therefore, the mechanism for lenalidomide related anemia in WM patients remains to be determined, and the use of this agent among WM patients should be avoided.

HIGH-DOSE THERAPY AND STEM CELL TRANSPLANTATION

The use of stem cell transplantion (SCT) therapy has also been explored in patients WM. Desikan *et al*[177] reported their initial experience of high-dose chemotherapy and autologous stem cell transplant, which has more recently been updated by Munshi *et al.*[178] Their studies involved eight previously treated WM patients between the ages of 45 and 69 years, who received either melphalan at 200mg/m^2 (n = 7) or melphalan at 140mg/m^2 along with total body irradiation. Stem cells were successfully collected in all eight patients, although a second collection procedure was required for two 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 raging from 5+ to 77+ months. Dreger *et al*[179] 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 seven WM patients, which included four 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 al*[180] in which WM patients received various preparative regimens and showed event-free survivals of 26+, 31, and 108+ months. Tournilhac *et al*[181] 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 three (range 1–

5) prior regimens. Therapy was well tolerated with an improvement in response status observed for seven patients (six PR to CR; one SD to PR), while only one patient demonstrated progressive disease. The median event-free survival for all non-progressing patients was 12 months. Tournilhac *et al*[181] have also reported the outcome of allogeneic transplantation in ten previously treated WM patients (ages 35–46) who received a median of three prior therapies, including three patients with progressive disease despite therapy. Two of three 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 was the death of three patients owing to transplantation related toxicity. Anagnostopoulos *et al*[182] have also reported on a retrospective review of WM patients who underwent either autologous or allogeneic transplantation, and whose outcomes were reported to the International Blood and Marrow Transplant Registry. Seventy-eight percent of patients in this cohort had 2 or more previous therapies, and 58% of them were resistant to their previous therapy. The relapse rate at 3 years was 29% in the allogeneic group, and 24% in the autologous group. Non-relapse mortality however was 40% in the allogeneic group, and 11% in the autologous group in this series.

Kyriakou et al[183] recently provided an update of data from the European Bone Marrow Transplant (EBMT) registry on the outcome of WM patients who received either an autologous or allogeneic SCT. Among 202 WM patients receiving an autologous SCT, which included primarily relapsed or refractory patients, the 5 year progression free and overall survival rate was 61% and 33%, respectively. Chemosensitive disease at time of the autologous SCT was the most important prognostic factor for non-relapse mortality, response rate, progression free and overall survival. The EBMT experience with 106 allogeneic transplantation, which included 44 patients who received a conventional myeloablative allogeneic SCT and 62 patients who received a reduced intensity conditioning allogeneic SCT was also presented by Kyriakou et al[183], which included predominately more advanced WM patients and was notable for 3 year non-relapse mortality rate of 33%. The 5 year progression free and overall survival rates in this series were 48% and 63%, respectively. Among the 106 patients who underwent an allogeneic SCT, 48 developed acute, and 16 and 11 patients developed limited and extensive chronic graft versus host disease, respectively. The potential role for reduced intensity conditioning (RIC) allogeneic SCT to induce responses, including complete responses, among patients with very advanced WM was reported by Maloney and Anderson[184] who observed 6 complete, 1 near complete, and 4 partial responses among 12 evaluable patients. In consensus statements adopted at the 5th International Workshop, the use of autologous, as well as RIC allogeneic SCT were deemed appropriate modalities for the treatment of relapsed/refractory WM patients, though the risks and benefits of these modalities should be carefully weighed against other available treatment options.

RESPONSE CRITERIA IN WALDENSTROM'S MACROGLOBULINEMIA

Assessment of response to treatment WM has been widely heterogeneous. As a consequence studies using the same regimen have reported significantly different response rates. As part of the second and third International Workshops on WM, consensus panels developed guidelines for uniform response criteria in WM.[185,186] The category of minor response was adopted at the Third International Workshop of WM, given that clinically meaningful responses were observed with newer biological agents and is based on $\geq$25 to < 50% decrease in serum IgM level, which is used as a surrogate marked of disease in WM. In distinction, the term major response is used to denote a response of $\geq$ 50% in serum IgM levels, and includes partial and complete responses.[186] Response categories and criteria for progressive disease in WM based on consensus recommendations are summarized in **Table 4.** An important concern with the use of IgM as a surrogate marker of disease is that it can fluctuate, independent of tumor cell killing, particularly with newer biologically targeted agents such as rituximab and bortezomib.[134-136,152,178] Rituximab induces a spike or flare in serum IgM levels which can occur when used as monotherapy and in combination with other agents including cyclophosphamide, nucleoside analogues, thalidomide and lenalidomide, and last for several weeks to months[138,141,142,152,159,175,176,187], whereas bortezomib can suppress IgM levels independent of tumor cell killing in certain patients.[159,188] Moreover, Owen et al[189] showed that in patients treated with selective B-cell depleting agents such as rituximab and alemtuzumab, residual IgM producing plasma cells are spared and continue to persist, thus potentially skewing the relative response and assessment to treatment. Therefore, in circumstances where the serum IgM levels appear out of context with the clinical progress of the patient, a bone marrow biopsy should be considered inorder to clarify the patient's underlying disease burden. A recent study by Ho et al[37] suggests that's soluble CD27 may serve as an alternative surrogate marker in WM, and may remain a faithful marker of disease in patients experiencing a rituximab related IgM flare, as well as plasmapheresis.[190]

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	Median	**Range**	**Institutional Normal Reference Range**
Age (yr)	59	34-84	NA
Gender (Male/Female)	85/64		NA
Bone marrow involvement	30%	5-95%	NA
Adenopathy	16%		NA
Splenomegaly	10%		NA
IgM (mg/dL)	2,870	267-12,400	40-230
IgG (mg/dL)	587	47-2,770	700-1,600
IgA (mg/dL)	47	8-509	70-400
Serum Viscosity (cp)	2.0	1.4-6.6	1.4-1.9
Hct (%)	35.0%	17.2-45.4%	34.8-43.6
Plt (x 10^9/L)	253	24-649	155-410
Wbc (x 10^9/L)	6.0	0.3-13	3.8-9.2
B_2M (mg/dL)	3.0	1.3-13.7	0-2.7
LDH	395	122-1,131	313-618

Table 1. Clinical and laboratory findings for 149 consecutive newly diagnosed patients with the consensus panel diagnosis of WM presenting to the Dana Farber Cancer Institute. NA (not applicable).

Properties of IgM Monoclonal Protein	**Diagnostic Condition**	**Clinical Manifestations**
Pentameric Structure	Hyperviscosity	Headaches, blurred vision, epistaxis, retinal hemorrhages, leg cramps, impaired mentation, intracranial hemorrhage.
Precipitation on cooling	Cryoglobulinemia (Type I)	Raynaud's phenomenom, acrocyanosis, ulcers, purpura, cold urticaria.
Auto-antibody activity to Myelin Associated Glycoprotein (MAG), Ganglioside M1 (GM1), Sulfatide moieties on peripheral nerve sheaths	Peripheral neuropathies	Sensorimotor neuropathies, painful neuropathies, ataxic gait, bilateral foot drop.
Auto-antibody activity to IgG	Cryoglobulinemia (Type II)	Purpura, arthralgias, renal failure, sensorimotor neuropathies.
Auto-antibody activity to red blood cell antigens	Cold agglutinins	Hemolytic anemia, Raynaud's phenomenom, acrocyanosis, livedo reticularis.
Tissue deposition as amorphous aggregates	Organ Dysfunction	Skin: bullous skin disease, papules, Schnitzler's syndrome. GI: diarrhea, malabsorption, bleeding. Kidney: proteinuria, renal failure (light chain component).
Tissue deposition as amyloid fibrils (light chain component most commonly)	Organ Dysfunction	Fatigue, weight loss, edema, hepatomegaly, macroglossia, organ dysfunction of involved organs: heart, kidney, liver, peripheral sensory and autonomic nerves.

Table 2. Physicochemical and immunological properties of the monoclonal IgM protein in Waldenstrom's macroglobulinemia.

Study	Adverse prognostic factors	Number of groups	Survival
Gobbi et al[98]	Hb < 9 g/dL Age >70 yr Weight loss Cryoglobulinemia	0-1 prognostic factors 2-4 prognostic factors	Median: 48 mo Median: 80 mo
Morel et al[99]	Age $\geq$ 65 yr Albumin < 4 g/dL Number of cytopenias: Hb <12 g/dL Platelets <150 x 10^9/L Wbc < 4x10^9/L	0-1 prognostic factors 2 prognostic factors 3-4 prognostic factors	5 yr: 87% 5 yr: 62% 5 yr: 25%
Dhodapkar et al[100]	β_2M $\geq$3 g/dL Hb <12 g/dL IgM <4 g/dL	β_2M < 3 mg/dL + Hb $\geq$ 12 g/dL β_2M < 3 mg/dL + Hb < 12 g/dL β_2M $\geq$ 3 mg/dL + IgM $\geq$ 4 g/dL β_2M $\geq$ 3 mg/dL + IgM < 4 g/dL	5 yr: 87% 5 yr: 63% 5 yr: 53% 5 yr: 21%
Application of International Staging System Criteria for Myeloma to WM Dimopoulos et al[102]	Albumin $\leq$3.5 g/dL β_2M $\geq$3.5 mg/L	Albumin $\geq$ 3.5 g/dL + β_2M < 3.5 mg/dL Albumin $\leq$ 3.5 g/dL + β_2M < 3.5 or β_2M 3.5-5.5 mg/dL β_2M > 5.5 mg/dL	Median: NR Median: 116 mo Median: 54 mo
International Prognostic Scoring System for WM Morel et al[104]	Age > 65 yr Hb <11.5 g/dL Platelets <100 x 10^9/L β_2M > 3 mg/L IgM > 7 g/dL	0-1 prognostic factors* 2 prognostic factors** 3-5 prognostic factors *excluding age ** or age >65	5 yr: 87% 5 yr: 68% 5 yr: 36%

Table 3. Prognostic scoring systems in Waldenstrom's macroglobulinemia.

Complete Response	**CR**	Disappearance of monoclonal protein by immunofixation; no histological evidence of bone marrow involvement, and resolution of any adenopathy / organomegaly (confirmed by CT scan), along with no signs or symptoms attributable to WM. Reconfirmation of the CR status is required at least 6 weeks apart with a second immunofixation.
Partial Response	**PR**	A ≥50% reduction of serum monoclonal IgM concentration on protein electrophoresis and ≥ 50% decrease in adenopathy/organomegaly on physical examination or on CT scan. No new symptoms or signs of active disease.
Minor Response	**MR**	A ≥ 25% but < 50% reduction of serum monoclonal IgM by protein electrophoresis. No new symptoms or signs of active disease.
Stable Disease	**SD**	A <25% reduction and <25% increase of serum monoclonal IgM by electrophoresis without progression of adenopathy/organomegaly, cytopenias or clinically significant symptoms due to disease and/or signs of WM.
Progressive Disease	**PD**	A ≥25% increase in serum monoclonal IgM by protein electrophoresis confirmed by a second measurement or progression of clinically significant findings due to disease (i.e. anemia, thrombocytopenia, leukopenia, bulky adenopathy/organomegaly) or symptoms (unexplained recurrent fever ≥ 38.4°C, drenching night sweats, ≥ 10% body weight loss, or hyperviscosity, neuropathy, symptomatic cryoglobulinemia or amyloidosis) attributable to WM.

Table 4. Summary of Updated Response Criteria from the 3rd International Workshop on Waldenstrom's Macroglobulinemia.[186]

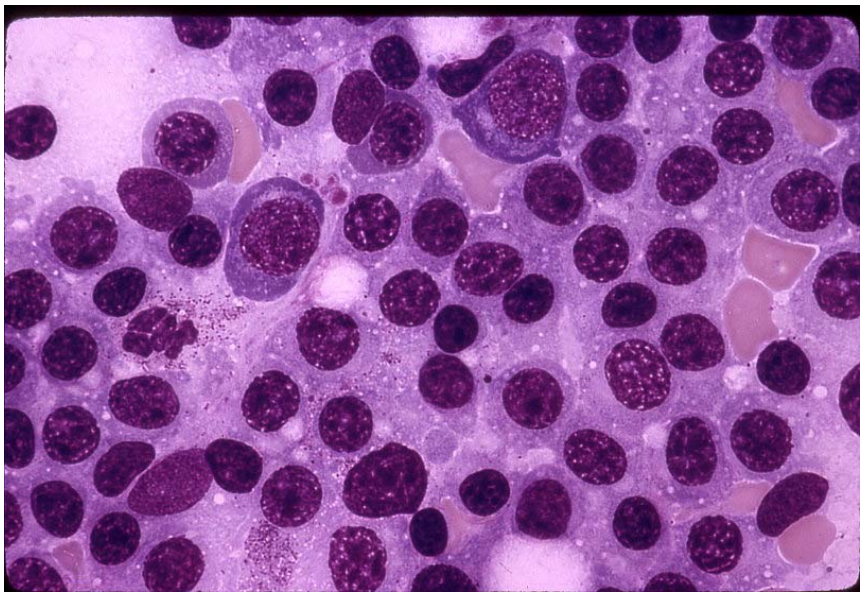

Figure 1. Aspirate from a patient with Waldenstrom's macroglobulinemia demonstrating excess mature lymphocytes, lymphoplasmacytic cells and plasma cells (courtesy of Marvin Stone M.D.).

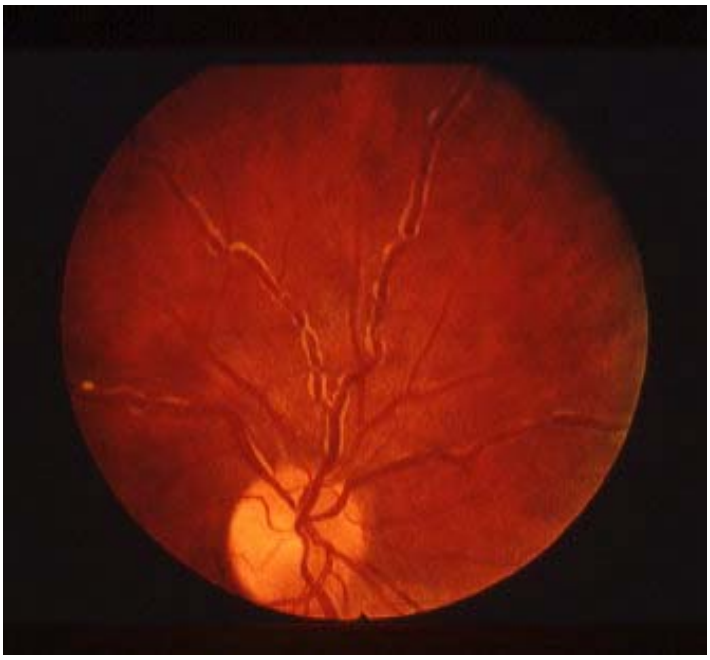

Figure 2. Funduscopic examination of a patient with Waldenstrom's macroglobulinemia demonstrating hyperviscosity related changes including dilated retinal vessels, peripheral hemorrhages, and ""venous sausaging" (courtesy of Marvin Stone M.D.).

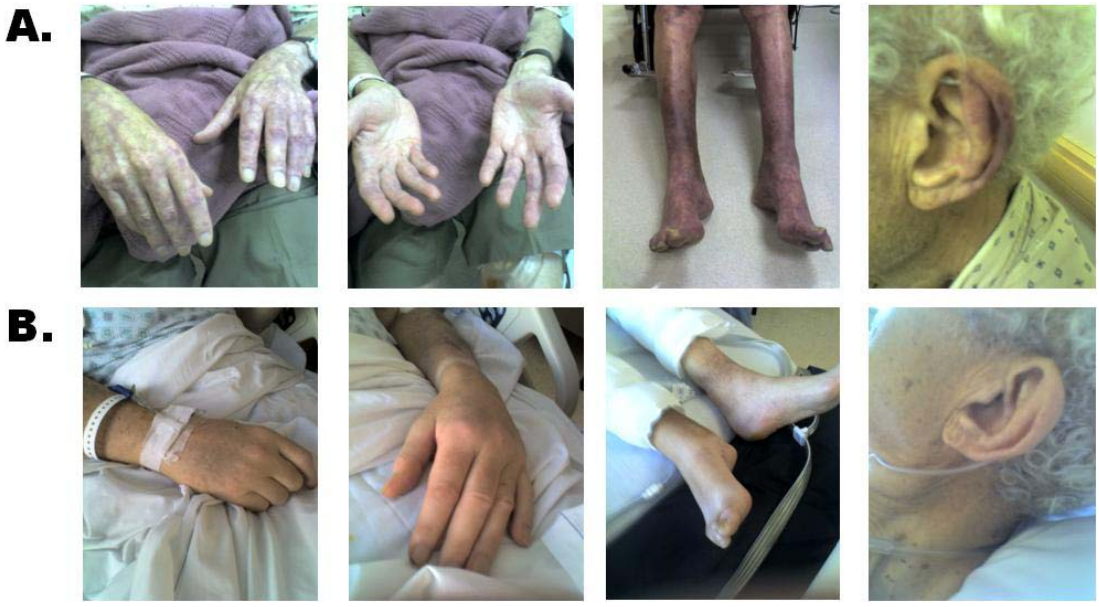

Figure 3. Cryoglobulinemia manifesting with severe acrocyanosis in a patient with Waldenstrom's macroglobulinemia before (A) and following warming and plasmapheresis (B).