Waldenström's Macroglobulinemia/ Lymphoplasmacytic Lymphoma

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Abstract

Waldenström's macroglobulinemia (WM) is included in the World Health Organization classification as the lymphoplasmacytic lymphoma. It is a rare type of non-Hodgkin lymphoma (NHL) with distinct clinicopathological features resulting from the accumulation of clonally related B lymphocytes, lymphoplasmacytic cells, and plasma cells which secrete a monoclonal IgM protein. Unlike other types of NHL, WM is rarely associated with lymphadenopathy or splenomegaly. WM has a chronic clinical course and treatment options are usually different from other types of indolent B-cell lymphoma. In this chapter, we will review the most recent data on the biology of WM and current treatment strategies.

Keywords

Waldenstrom's macroglobulinemia • Lymphoplasmacytic lymphoma • Myd88 • Igm neuropathy • Cryoglobulinemia • Cold agglutinins • Rituximab • Bortezomib • Bendamustine

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 [1]. This condition is considered to correspond to the lymphoplasmacytic lymphoma (LPL) as defined by the World Health Organization classification system [2]. Most cases of LPL are WM, with less than 5 % of cases made up of IgA, IgG, and nonsecreting LPL.

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Epidemiology

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 United States and a geometrical increase with age [3]. The incidence rate for WM is higher among Caucasians, with African descendants representing only 5 % of all patients. The incidence of WM may be higher among individuals of Ashkenazi Jewish decent [4]. Genetic factors appear to be an important to the pathogenesis of WM. A common predisposition for WM with other malignancies has been raised [4, 5], with numerous reports of familiar clustering of individuals with WM alone and with other B-cell lymphoproliferative diseases [6–10]. In a large single center experience, 26 % of 924 consecutive patients with WM had a first- or second-degree relative with either WM or another B-cell disorder [5]. 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 hyperresponsive B cells have also been reported [10, 11]. Increased expression of the *bcl-2* gene with enhanced B-cell survival may underlie the increased immunoglobulin synthesis in familial WM [10]. The role of environmental factors in WM remains to be clarified, but chronic antigenic stimulation from infections, certain drug, and Agent Orange exposures remains suspect. An etiological role for hepatitis C virus (HCV) infection has been suggested, though in one study no association could be established using both serological and molecular diagnostic studies for HCV infection in a hundred consecutive WM patients [12, 13].

Biology

Cytogenetics

Chromosome 6q deletions encompassing 6q21–25 have been observed in up to half of WM patients and at a comparable frequency among patients with and without a familial history [7, 14–16]. The presence of 6q deletions has been suggested to discern patients with WM from those with IgM monoclonal gammopathy of unknown significance (MGUS) and to have potential prognostic significance including impact on progression-free survival following treatment response though others have reported no prognostic significance to the presence of 6q deletions in WM [14, 16, 17]. Other abnormalities by cytogenetic or FISH analyses include deletions in 13q14, TP53 and ATM, and trisomies 4, 12, and 18 [17, 18]. IgH rearrangements are uncommon in WM and may be helpful in discerning cases of WM from IgM myeloma wherein IgH switch region rearrangements are a prominent feature [19].

Mutation in MYD88

A highly recurrent somatic mutation (MYD88 L265P) has recently been identified in WM patients by paired tumor/normal whole genome sequencing and subsequent confirmation by Sanger sequencing [20]. MYD88 L265P was expressed in tumor cells from 91 % of LPL cases, which included patients with IgM (WM) and IgG secreting LPL. By comparison, MYD88 L265P was absent in myeloma samples, including IgM myeloma, and was expressed in a small subset (6.5 %) of MZL patients, who surprisingly had many WM-related features. Of particular interest in this study was the absence of MYD88 L265P in nearly all cases of IgM MGUS examined. In the sole patient in whom MYD88 L265P was identified, subsequent disease evolution occurred. The expression of MYD88 L265P in familial and sporadic WM patients at the same frequency in this study is also worthy of note. These findings appear to denote that acquisition of MYD88 L265P is a common transforming event for WM, regardless of familial predisposition. Importantly, knockdown of MYD88 decreased survival of MYD88 L265P expressing WM cells, whereas survival was more enhanced by knock-in of MYD88 L265P versus wild-type MYD88. The discovery of a mutation in MYD88 is of

significance given its role as an adaptor molecule in Toll-like receptor (TLR) and interleukin-1 receptor (IL-1R) signaling [21]. All TLRs except for TLR3 use MYD88 to facilitate their signaling. Following TLR or IL-1R stimulation, MYD88 is recruited to the activated receptor complex as a homodimer which then complexes with IRAK4 and activates IRAK1 and IRAK2 [22–24]. Tumor necrosis factor receptor associated factor 6 is then activated by IRAK1 leading to NF-κ[kappa]B activation via Iκ[kappa]Bα phosphorylation [25]. Use of inhibitors of MYD88 pathway led to decreased IRAK1 and Iκ[kappa]Bα phosphorylation as well as survival of MYD88 L265P expressing WM cells. These observations are of particular relevance to WM since NF-κ[kappa]B signaling is important for WM growth and survival [26].

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 [27]. Clonal B cells are detectable among blood B lymphocytes, and their number increases in patients who fail to respond to therapy or who progress [28]. 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 [29]. 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 [30–32]. Expression of CD5, CD10, and CD23 may be found in 10–20 % of cases and does not exclude the diagnosis of WM [33].

The phenotype of lymphoplasmacytic cells in WM cell suggests that the clone is a postgerminal 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 [34, 35]. 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 [36, 37]. These data indicate that WM may originate from an IgM^+ and/or IgM^+ IgD^+ memory B cell. Normal IgM^+ memory B cells localize in bone marrow, where they mature to IgM-secreting cells [38].

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 [2, 32, 39]. The role of mast cells in WM has been investigated in one study wherein coculture of primary autologous or mast cell lines with WM LPC resulted in dose-dependent WM cell proliferation and/or tumor colony formation, 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 suggesting a microenvironmental support system [39, 40]. High levels of CXCR4 and VLA-4 have also been observed in WM cells [41]. In blocking experiments studies, CXCR4 was shown to support migration of WM cells, while VLA-4 contributed to adhesion of WM cells to bone marrow stromal cells.

Clinical Features

The clinical and laboratory findings at the time of diagnosis of WM in one large institutional study are presented in Table 5.1. Unlike most

Table 5.1 Clinical and laboratory findings for 149 consecutive newly diagnosed patients with the consensus panel diagnosis of WM presenting to the Dana-Farber Cancer Institute

	Median	Range	Institutional normal reference range
Age (year)	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 ($\times 10^9$/L)	253	24–649	155–410
Wbc ($\times 10^9$/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

NA not applicable

Table 5.2 Physicochemical and immunological properties of the monoclonal IgM protein in Waldenstrom's macroglobulinemia

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 phenomenon, acrocyanosis, ulcers, purpura, cold urticaria
Autoantibody 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
Autoantibody activity to IgG	Cryoglobulinemia (type II)	Purpura, arthralgias, renal failure, sensorimotor neuropathies
Autoantibody activity to red blood cell antigens	Cold agglutinins	Hemolytic anemia, Raynaud's phenomenon, 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

indolent lymphomas, splenomegaly and lymphadenopathy are prominent in only a minority of patients (<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 5.2, the monoclonal IgM

can produce clinical manifestations through several different mechanisms related to its physicochemical properties, nonspecific interactions with other proteins, antibody activity, and tendency to deposit in tissues [42–44].

Morbidity Mediated by the Effects of IgM

Hyperviscosity Syndrome

Blood hyperviscosity is affected by increased serum IgM levels leading to hyperviscosity-related complications [45]. The mechanisms behind the marked increase in the resistance to blood flow and the resulting impaired transit through the microcirculatory system are rather complex [45–47]. 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 and 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 [48]. Clinical manifestations are related to circulatory disturbances that can be best appreciated by ophthalmoscopy, which shows distended and tortuous retinal veins, hemorrhages, and papilledema [49]. 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 [45]. 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 [50]. Cryoprecipitation is mainly dependent on the concentration of monoclonal IgM; for this reason plasmapheresis or plasma exchange is 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, malleolar ulcers, purpura, and cold urticaria. Renal manifestations may occur but are infrequent.

Autoantibody 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

The presence of peripheral neuropathy has been estimated to range from 5 to 38 % in WM patients [51–55]. The nerve damage is mediated by diverse pathogenetic mechanisms: IgM antibody activity toward nerve constituents causing demyelinating polyneuropathies; endoneurial granulofibrillar deposits of IgM without anti-

body 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 [56]. 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 [57–59]. 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 [52, 60]. 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 [61, 62]. Anti-GD1b and anti-GQ1b antibodies were significantly associated with predominantly sensory ataxic neuropathy. 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 [63, 64]. 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 [65]. 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 [66]. 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 [67]. Motor neuron disease has been reported in patients with WM and monoclonal IgM with anti-GM1 and sulfoglucuronyl paragloboside activity [68]. POEMS (polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes) syndrome is rarely associated with WM [69].

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 [70] and is associated with cold agglutinin titers >1:1,000 in most cases. The monoclonal component is usually an IgMκ[kappa] and reacts most commonly with I/i antigens, with complement fixation and activation [71, 72]. 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 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 activities 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 [73]. Amorphous IgM deposits in the dermis determine the so-called IgM storage papules on the extensor surface of the extremities—macroglobulinemia cutis [74]. Deposition of monoclonal IgM in the lamina propria and/or submucosa of the intestine may be associated with diarrhea, malabsorption, and gastrointestinal bleeding [75, 76]. 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 [77]. 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 [78]. 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 [79]. Clinical expression and prognosis are similar to those of other AL patients with involvement of the 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 [80, 81]. Simultaneous occurrence of fibrillary glomerulopathy, characterized by glomerular deposits of wide non-congophilic fibrils and amyloid deposits, has been reported in WM [82].

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 % [83–85]. 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 [86–89]. In contrast to multiple myeloma, infiltration of the kidney interstitium with lymphoplasmacytoid cell has been reported in WM [90], while renal or perirenal masses are not uncommon [91]. 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 [92]. 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 [93], 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 [94]. The neoplastic cells can infiltrate the periorbital structures, lacrimal gland, and retro-orbital lymphoid tissues, resulting in ocular nerve palsies [95, 96]. 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. [97]).

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 [98]. 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 immunofixation of serum and urine is recommended for identification and characterization of the IgM monoclonal protein. The light chain of the monoclonal IgM is κ[kappa] 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 h 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 [99, 100].

Serum Viscosity

Because of its large size (almost 1,000,000 Da), 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 is the appearance of peripheral and midperipheral dot and blot-like hemorrhages in the retina, which are best appreciated with indirect ophthalmoscopy and scleral depression [49]. 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. 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: $sIgM^+CD19^+CD20^+CD22^+CD79^+$ [30–32]. Up to 20 % of cases may express either CD5, CD10 or CD23 [33]. 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) [101] consisting of IgM deposits in the perinuclear space, and sometimes in intranuclear vacuoles, may be seen occasionally in lymphoid cells in WM. An increased 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 [1, 2].

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 [102]. 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 [102]. 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 [103–109], though in a recent study of 436 consecutive patients with WM, the median overall survival from time of diagnosis was in excess of 10 years [110]. Age is consistently an important prognostic factor (>60–70 years) [103, 104, 106, 109], though it is often impacted by unrelated morbidities. Anemia, which can be multifactorial, is an adverse prognostic factor in WM, with hemoglobin levels of <9–12 g/dL associated with decreased survival in several series [103–105, 109]. Cytopenias have also been regularly identified as a significant predictor of survival. The number of cytopenias in a given patient may predict survival [104]. Serum albumin levels have correlated with survival in WM patients in certain but not all studies using multivariate analyses [104, 107]. High serum beta-2 microglobulin (>3–3.5 g/dL) levels [105, 107, 109], high serum IgM M-protein (>7 g/dL) [109], low serum IgM M-protein (<4 g/dL) [107], the presence of cryoglobulins [103], and the presence of a familial disease background [110] have also been reported to confer adverse outcomes. The presence of 6q deletion as an adverse marker remains controversial [14, 16]. A few prognostic scoring systems have been proposed (Table 5.3). While the use of prognostic markers and/or scoring systems to make therapeutic decisions remains to be clarified [106], patients with familial disease predisposition show better outcomes following bortezomib-based therapy [110].

Table 5.3 Prognostic scoring systems in Waldenstrom's macroglobulinemia

Study	Adverse prognostic factors	Number of groups	Survival
Gobbi et al. [103]	Hb <9 g/dL Age >70 year Weight loss Cryoglobulinemia	Prognostic factors 2–4 prognostic factors	Median: 48 months Median: 80 months
Morel et al. [104]	Age >65 year Albumin <4 g/dL Number of cytopenias: Hb <12 g/dL Platelets <150 × 10^9/L Wbc <4 × 10^9/L	Prognostic factors 2 prognostic factors 3–4 prognostic factors	5 years: 87 % 5 years: 62 % 5 years: 25 %
Dhodapkar et al. [105]	β[beta]$_2$M >3 g/dL Hb <12 g/dL IgM <4 g/dL	β[beta]$_2$M <3 mg/dL + Hb >12 g/dL β[beta]$_2$M <3 mg/dL + Hb <12 g/dL β[beta]$_2$M >3 mg/dL + IgM >4 g/dL β[beta]$_2$M >3 mg/dL + IgM <4 g/dL	5 years: 87 % 5 years: 63 % 5 years: 53 % 5 years: 21 %
Application of International Staging System Criteria for Myeloma to WM Dimopoulos et al. [107]	Albumin <3.5 g/dL β[beta]$_2$M >3.5 mg/L	Albumin >3.5 g/dL + β[beta]$_2$M <3.5 mg/dL Albumin <3.5 g/dL + β[beta]$_2$M <3.5 or β[beta]$_2$M 3.5–5.5 mg/dL β[beta]$_2$M >5.5 mg/dL	Median: NR Median: 116 months Median: 54 months
International Prognostic Scoring System for WM Morel et al. [109]	Age >65 year Hb <11.5 g/dL Platelets <100 × 10^9/L β[beta]$_2$M >3 mg/L IgM >7 g/dL	Prognostic factors[a] 2 prognostic factors[b] 3–5 prognostic factors	5 years: 87 % 5 years: 68 % 5 years: 36 %

[a]excluding age
[b]or age >65

Treatment of Waldenström's Macroglobulinemia

Treatment Indications

Consensus guidelines on indications for treatment initiation were formulated as part of the Second International Workshop on Waldenström's Macroglobulinemia [106]. Initiation of therapy should not be based on the IgM levels since this may not correlate with either disease burden nor symptomatic status [111, 112]. Initiation of therapy is 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 <10 g/dL or a platelet count <100 × 10^9/L on this basis of disease is also a reasonable indication for treatment initiation. Certain complications of WM, such as hyperviscosity syndrome, symptomatic sensorimotor peripheral neuropathy, systemic amyloidosis, renal insufficiency, or symptomatic cryoglobulinemia, are also indications for therapy.

Treatment Options

A precise therapeutic algorithm for therapy of WM remains to be defined given the paucity of randomized clinical trials. Active agents include alkylators (chlorambucil, cyclophosphamide), nucleoside analogues (cladribine, fludarabine), monoclonal antibodies (rituximab, ofatumumab,

alemtuzumab), bortezomib, thalidomide, everolimus, and bendamustine [111, 112]. Combination therapy particularly with rituximab has been associated with improved clinical outcomes. 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, exposure to continuous chlorambucil or nucleoside analogue therapy should be limited given potential for stem cell damage. The use of nucleoside analogues may also increase risk for histological transformation to diffuse large B-cell lymphoma as well as myelodysplasia and acute myelogenous leukemia [113].

Chlorambucil

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/day, while 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. [114] 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 [115] evaluated chlorambucil (8 mg/m^2) along with prednisone (40 mg/m^2) 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. [116] and Case et al. [117] 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. [118] 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 Analogues

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-h 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, while in the salvage setting, responses have ranged from 38 to 54 % [111–125]. Median time for achievement of response following cladribine ranged from 1.2 to 5 months in these studies. 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 [105, 126–132], 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. 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. 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 [125, 126]. 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 [125]. However, Lewandowski et al. [132] 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 combination of nucleoside analogues with cyclophosphamide and/or rituximab has been investigated and discussed below.

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. Autologous stem cell collection succeeded on the first attempt in 14/15 patients who received non-nucleoside analogue-based therapy versus 2/6 patients who received a nucleoside analogue [133]. The long-term safety of nucleoside analogues in WM was recently examined by Leleu et al. [113] in a large series of WM patients. A sevenfold increase in transformation to an aggressive lymphoma and a threefold increase in the development of acute myelogenous leukemia/myelodysplasia were observed among patients who received a nucleoside analogue versus other therapies for their WM. A recent metanalysis by Leleu et al. [134] 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 vs. 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.

Monoclonal Antibodies

Rituximab is a chimeric monoclonal antibody which targets CD20, a widely expressed antigen on lymphoplasmacytic cells in WM [135]. The use of rituximab at standard dosimetry (i.e., 4 weekly infusions at 375 mg/m^2) induces major responses in approximately 27–35 % of previously treated and untreated patients [136, 137]. However, patients who achieved even minor responses benefited from rituximab as evidenced by improved hemoglobin and platelet counts and reduction of lymphadenopathy and/or splenomegaly [136]. 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/m^2/week, repeated 3 months later by another

4-week course, have demonstrated higher 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 (IgM flare) may be noted immediately following initiation of rituximab treatment [140–142]. The IgM flare may be related to the release of interleukin-6 by bystander immune in response to the binding of rituximab to Fcγ[gamma]RIIA receptors and also occurs in response to intravenous immunoglobulin administration in WM patients [143]. The IgM flare in response to rituximab does not herald treatment failure, and while most patients will return to their baseline serum IgM level by 12 weeks, some patients may flare for months despite having tumor responses in their bone marrow. Patients with baseline serum IgM levels of >50 g/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 or rituximab omitted for the first few cycles of therapy until IgM levels decline to safer levels [110]. 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 <60 g/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 (<35 g/L) or elevated serum monoclonal protein (>40 g/LM-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 [144].

The genetic background of patients may also be important for determining response to rituximab. A correlation between polymorphisms at amino acid position 158 in the Fcγ[gamma]RIIIa receptor (CD16) and rituximab response has been observed in WM patients. WM patients who carry a valine amino acid (either in a homozygous or heterozygous pattern) at this polymorphic site had a fourfold higher major response rate to rituximab versus patients who expressed phenylalanine in a homozygous pattern [145]. The attainment of better categorical responses, i.e., very good partial response or complete response following rituximab-based therapy, appears also dependent on the presence of at least one valine amino acid at Fcγ[gamma]RIIIa-158 [146].

Ofatumumab is a fully humanized CD20-directed monoclonal antibody that targets the small loop of CD20, a target which is different than that of rituximab. A 59 % overall response rate was observed in a series of 37 symptomatic WM patients following ofatumumab administration, which included untreated and previously treated patients [147]. Responses were higher among rituximab-naïve patients. An IgM flare with symptomatic hyperviscosity was also observed in 2 patients in this series who required plasmapheresis. Ofatumumab has also been successfully administered to WM patients who demonstrated intolerance to rituximab [147, 148].

The activity of alemtuzumab has also been investigated in WM patients given the broad expression of CD52 [135]. The WMCTG recently reported a multicenter study in symptomatic WM patients, whose median prior therapies was 2 (range 0–5), and 43 % had refractory disease [149]. Patients received alemtuzumab intravenously at 30 mg three times weekly for up to 12 weeks, after test dosing, and received hydrocortisone, acyclovir, and bactrim or equivalent prophylaxis. The overall response rate in this series was 75 % and included major responses in 36 % of patients. With a median follow-up of 64 months, the median time to progression was 14.5 months. Hematological and infectious complications, including CMV reactivation were more common in previously treated patients and

indirectly associated with 3 deaths. Long-term follow-up revealed late-onset idiopathic thrombocytopenia in 4 patients at a median of 13.6 months following therapy and contributed to one death. High rates of response with the use of alemtuzumab were also observed by Owen et al. [150] who reported their preliminary experience in a small series of heavily pretreated WM patients. The median number of prior therapies in this series was 4, and similar to this study patients received up to 12 weeks of therapy (at 30 mg IV three times weekly) following initial dose escalation. Among the 7 patients treated with alemtuzumab, 5 achieved a partial response and one a complete response. Disseminated aspergillus and mycobacterial infections contributed to 2 deaths in this series.

Bortezomib

Bortezomib is a proteasome inhibitor which has been extensively investigated in WM. In a multicenter study of the WMCTG, 27 patients received up to 8 cycles of bortezomib at 1.3 mg/m^2 on days 1, 4, 8, and 11 [151]. All but one patient had relapsed/or refractory disease. Following therapy, median serum IgM levels declined from 4,660 to 2,092 mg/dL ($p<0.0001$). The overall response rate was 85 %, with 10 and 13 patients achieving minor (<25 % decrease in IgM) and major (<50 % decrease in IgM) responses. 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. [152] treated 27 patients with both untreated (44 %) and previously treated (56 %) diseases. 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. [153] observed major responses in 6 of 10 (60 %) previously treated WM patients, while Goy et al. [154] 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). The combination of bortezomib with steroids and/or rituximab has also been investigated and is discussed below.

Immunomodulatory Agents

Thalidomide as monotherapy and in combination with dexamethasone and/or clarithromycin has been examined in WM. Dimopoulos et al. [155] 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 the 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 [156]. However, in a follow-up study by Dimopoulos et al. [157] using a higher thalidomide dose (200 mg orally daily) along with dexamethasone (40 g orally once a week) and clarithromycin (500 mg orally twice a day), only two of ten (20 %) previously treated patients responded. Thalidomide, as well as lenalidomide, has also been investigated in combination with rituximab and these studies are discussed below.

Bendamustine

Bendamustine is a recently approved agent for the treatment of relapsed/refractory indolent non-Hodgkin's lymphoma (NHL). Bendamustine has structural similarities to both alkylating agents and purine analogues [158]. Bendamustine in combination with rituximab has been investigated in both previously untreated and relapsed/refractory WM patients and is discussed below.

Everolimus

Everolimus is an oral inhibitor of the mTOR pathway, which is approved for the treatment of renal cell carcinoma. The Akt-mTOR-p70 pathway is active in WM, and inhibition of this pathway leads to apoptosis of primary WM cells and WM cell lines [159, 160]. Fifty patients with a median of 3 prior therapies were treated with everolimus in a joint Dana Farber/Mayo Clinic study [161]. The overall response rate was 70 %, with 42 % of patients attaining a major response. The progression-free survival at 12 months was estimated to be 62 %. Grade 3 or higher related toxicities were observed in 56 % of patients with cytopenias constituting the most common toxicity. Pulmonary toxicity occurred in 10 % of patients. Dose reductions due to toxicity occurred in 52 % of patients.

A clinical trial examining the activity of everolimus in previously untreated patients with WM was completed by the WMCTG [162]. While 67 % of patients achieved at least a minor response by consensus criteria which rely on paraprotein reduction, IgM discordance to underlying disease burden was seen in up to half of patients on this upfront study. Cytopenias, particularly anemia and thrombocytopenia, were common, and pneumonitis occurred in 15 % of patients.

Combination Strategies

Because rituximab is an active and a nonmyelosuppressive agent, its combination with various chemotherapeutic agents has been extensively explored in WM. The combination of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) with rituximab (CHOP-R) was investigated in a randomized frontline study by the German Low Grade Lymphoma Study Group (GLSG) involving 69 patients, most of whom had WM [163]. The addition of rituximab to CHOP resulted in a higher overall response rate (94 % vs. 67 %) and median time to progression (63 vs. 22 months) in comparison to patients treated with CHOP alone. Dimopoulos et al. [164] investigated the combination of rituximab, dexamethasone, and oral cyclophosphamide (RCD) as primary therapy in 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 the salvage setting, the use of CHOP-R has been investigated in relapsed/refractory WM patients [165]. 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. [166] 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 for all three treatments: CHOP-R (96 %), CVP-R (88 %), and CP-R (95 %), though more CRs were observed among patients treated with either CVP-R or CHOP-R. Comparison of adverse events for these regimens showed a higher incidence for neutropenic fever as well as treatment-related neuropathy in patients receiving CHOP-R and CVP-R versus CPR. These results suggest that in WM, the use of doxorubicin and vincristine may be omitted in order to minimize treatment-related complications.

Combination therapy with nucleoside analogues has been investigated as both first-line and salvage therapy in WM. Weber et al. [167] 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. Laszlo et al. [168] recently evaluated the combination of subcutaneous cladribine with rituximab in 29 WM patients with either untreated or previously treated disease. Intended therapy consisted of rituximab on day 1 followed by subcutaneous cladribine 0.1 mg/kg for 5 consecutive days, administered monthly for 4 cycles. With a median follow-up of 43 months, the overall response rate observed was 89.6 %, with seven complete responses (CR), 16 partial responses, and three minor responses. Response activity was similar between untreated and previously treated patients. No major infections were observed despite the lack of antimicrobial prophylaxis. In a study by the WMCTG, the combination of rituximab and fludarabine was administered to 43 WM patients, 32 (75 %) of whom were previously untreated [169]. The overall response rate was 95.3 %, and 83 % of patients achieved a major response. 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 at least a very good partial response. Hematological toxicity was common, particularly neutropenia and thrombocytopenia. Two deaths occurred in this study due to non-pneumocystis carinii pneumonia. Secondary malignancies 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. [170] wherein 4 of 5 patients demonstrated a response. Hensel et al. [171] 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 % of patients. The addition of alkylating agents to nucleoside analogues has also been explored in WM. Weber et al. [167] 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. [172] examined fludarabine in combination with intravenous cyclophosphamide and observed partial responses in 6 of 11 (55 %) patients with either primary refractory disease or who relapsed on treatment. The combination of fludarabine plus cyclosphosphamide (FC) was also evaluated in a recent study by Tamburini et al. [173] 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 were 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. Tedeschi et al. [174] recently completed a multicenter study on fludarabine, cyclophosphamide, and rituximab (FCR) in symptomatic WM patients with untreated or relapsed/refractory disease to one line of chemotherapy. Treatment consisted of rituximab at 375 mg/m^2 on day 1, fludarabine at 25 mg/m^2, and cyclophosphamide at 250 mg/m^2 by intravenous administration on days 2–4 every 4 weeks. Forty-three patients were accrued to this study. The overall response rate was 89 %, with 83 % of patients attaining a major remission and 14 % a complete response. Prolonged neutropenia was observed in up to a third of patients. With a median follow-up of 15 months, the median progression-free survival for this study has not been reached.

The combination of bortezomib, dexamethasone, and rituximab (BDR) has been investigated as primary therapy in patients with WM by the WMCTG. An overall response rate of 96 %, major response rate of 83 %, and complete attainment in 22 % was observed with BDR [175]. The updated median progression-free survival in this study was >56.1 months. The incidence of grade 3 neuropathy was 30 % in this study which utilized a twice a week schedule for bortezomib

administration at 1.3 mg/m^2. Peripheral neuropathy from bortezomib was reversible in most patients in this study following discontinuation of therapy, and patients benefitted with pregabalin. An increased incidence of herpes zoster was also observed with BDR prompting the use of prophylactic antiviral therapy. An alternative schedule for bortezomib administration (i.e., weekly at 1.6 mg/m^2) in combination with rituximab and/or dexamethasone has been investigated in several studies with overall response rates of 80–90 % [176–178]. A lower incidence of peripheral neuropathy was observed in two studies using once a week bortzomib [172, 178]. The impact of once versus twice a week bortezomib administration on progression-free survival remains to be clarified.

The combination of immunomodulator agents (thalidomide, lenalidomide) with rituximab was investigated by the WMCTG. Thalidomide was administered at 200 mg daily for 2 weeks, followed by 400 mg daily and thereafter for 1 year. Patients received four weekly infusions of rituximab at 375 mg/m^2 beginning 1 week after initiation of thalidomide, followed by four additional weekly infusions of rituximab at 375 mg/m^2 beginning at week 13. The overall and major response rate was 72 and 64 %, respectively, and the median time to progression was 38 months in this series [179]. Dose reduction and/or discontinuation of thalidomide was common and mainly attributed to treatment-related neuropathy. The investigators concluded in this study that lower doses of thalidomide (i.e., 50–100 mg/day) should be considered in this patient population. The combination of lenalidomide with rituximab was investigated by the WMCTG using lenalidomide at 25 mg daily on a syncopated schedule wherein therapy was administered for 3 weeks, followed by a 1-week pause for an intended duration of 48 weeks [180]. Patients received 1 week of therapy with lenalidomide, after which rituximab (375 mg/m^2) was administered weekly on weeks 2–5, then 13–16. The overall and 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 was observed during first 2 weeks of lenalidomide therapy in 13/16 (81 %) patients with a median absolute decrease in hematocrit 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.

The use of bendamustine in combination with rituximab was explored by Rummel et al. [181] in the frontline therapy of WM. As part of a randomized study, patients received 6 cycles of bendamustine plus rituximab (Benda-R) or CHOP-R. A total of 546 patients were enrolled in this study for indolent NHL patients and included 40 patients with WM. Patients on the Benda-R arm received bendamustine at 90 mg/m^2 on days 1 and 2 and rituximab at 375 mg/m^2 on day 1 with the frequency of 4 weeks for each cycle. The overall response rate was 96 % for Benda-R and 94 % for CHOP-R-treated patients. With a median observation period of 26 months, 20/23 (87 %) Benda-R versus 9/17 (53 %) CHOP-R-treated WM patients remain free of progression. Importantly, Benda-R was associated with a lower incidence of grade 3 or 4 neutropenia, infectious complications, and alopecia. In the salvage setting, the outcome of 30 WM patients with relapsed/refractory disease who received bendamustine alone or with a CD20-directed antibody was reported by Treon et al. [182]. An overall response rate of 83.3 % and a median progression-free survival of 13.2 months were reported in this study. Overall, therapy was well tolerated though prolonged myelosuppression occurred in patients who received prior nucleoside analogue therapy.

Maintenance Therapy

A role for maintenance rituximab in WM patients following response to a rituximab-containing

regimen was raised in a study examining the outcome of 248 WM rituximab-naïve patients who were either observed or received maintenance rituximab [183]. In this retrospective study, categorical responses improved in 16/162 (10 %) of observed patients and in 36/86 (41.8 %) of patients who received maintenance rituximab following induction therapy. Both progression-free (56.3 vs. 28.6 months) and overall survivals (>120 vs. 116 months) were longer in patients who received maintenance rituximab. Improved progression-free survival was evident despite previous treatment status, induction with rituximab alone or in combination therapy. Best serum IgM response was lower and hematocrit higher in those patients receiving maintenance rituximab. Among patients receiving maintenance rituximab, an increased number of infectious events, predominantly sinusitis and bronchitis, were observed, though were mainly grade 1 or 2.

High-Dose Therapy and Stem Cell Transplantation

The use of stem cell transplantation (SCT) therapy has also been explored in patients with WM. Desikan et al. [184] reported their initial experience of high-dose chemotherapy and autologous stem cell transplant, which has more recently been updated by Munshi et al. [185]. Their studies involved eight previously treated WM patients between the ages of 45 and 69 years who received either melphalan at 200 mg/m^2 or melphalan at 140 mg/m^2 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. [186] 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. [187] wherein WM patients received various preparative regimens and demonstrated event-free survivals of 26+, 31, and 108+ months. Tournilhac et al. [188] 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 nonprogressing patients was 12 months. Tournilhac et al. [188] 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 five patients. The median event-free survival for nonprogressing, evaluable patients was 31 months. Concerning in this series was the death of three patients owing to transplantation related toxicity. Anagnostopoulos et al. [189] 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 two 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. Nonrelapse mortality however was 40 % in the allogeneic group and 11 % in the autologous group in this series.

Kyriakou et al. [190] reported on the outcome of WM patients in the European Bone Marrow Transplant (EBMT) registry who received either an autologous or allogeneic SCT. Among 158 patients receiving an autologous SCT, which included primarily relapsed or refractory patients, the 5-year progression-free and overall survival rate were 39.7 and 68.5 %, respectively. Nonrelapse mortality at 1 year was 3.8 %. Chemorefractory disease and the number of prior lines of therapy at time of the autologous SCT were the most important prognostic factor for progression-free and overall survival. The achievement of a negative immunofixation after autologous SCT had a positive impact on progression-free survival. When used as consolidation at first response, autologous transplantation provided a progression-free survival of 44 % at 5 years. In the allogeneic SCT experience from the EBMT, the long-term outcome of 86 WM patients was reported by Kyriakou [191]. A total of 86 patients received allograft by either myeloablative ($n=37$) or reduced-intensity ($n=49$) conditioning. The median age of patients in this series was 49 years, and 47 patients had three or more previous lines of therapy. Eight patients failed prior autologous SCT. Fifty-nine patients (68.6 %) had chemotherapy-sensitive disease at the time of allogeneic SCT. Nonrelapse mortality at 3 years was 33 % for patients receiving a myeloablative transplant and 23 % for those who received reduced-intensity conditioning. The overall response rate was 75.6 %. The relapse rates at 3 years were 11 % for myeloablative and 25 % for reduced-intensity conditioning recipients. Five-year progression-free and overall survival for WM patients who received a myeloablative allogeneic SCT were 56 and 62 % and for patients who received reduced-intensity conditioning were 49 and 64 %, respectively. The occurrence of chronic graft-versus-host disease was associated with improved progression-free survival and suggested the existence of a clinically relevant graft-versus-WM effect in this study.

Response Criteria in Waldenstrom's Macroglobulinemia

As part of the International Workshops on WM, consensus panels developed guidelines for uniform response criteria in WM [192, 193]. 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 >25 to <50 % decrease in serum IgM level, which is used as a surrogate marker of disease in WM. At the Sixth International Workshop on WM, the categorical response of very good partial response (VGPR), i.e., 90 % reduction in IgM levels, was adopted given reports of improved clinical outcome associated with VGPR or better response achievement [146, 169, 175, 190]. In distinction, the term major response is used to denote a response of >50 % in serum IgM levels and includes partial or better responses [193]. Response categories and criteria for progressive disease in WM based on consensus recommendations are summarized in Table 5.4 [194].

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 biologically targeted agents such as rituximab, bortezomib, and everolimus [140–142, 151, 162, 195]. 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 [140–142, 166, 179, 180, 196], whereas bortezomib and everolimus can suppress IgM levels independent of tumor cell killing in certain patients [151, 162, 196]. Moreover, Varghese et al. [197] 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

Table 5.4 Summary of updated response criteria adopted at the Sixth International Workshop on Waldenstrom's macroglobulinemia [194]

Complete response	CR	IgM in normal range and disappearance of monoclonal protein by immunofixation; no histological evidence of bone marrow involvement, and resolution of any adenopathy/organomegaly (if present at baseline), along with no signs or symptoms attributable to WM. Reconfirmation of the CR status is required by repeat immunofixation studies
Very good partial response	VGPR	A >90 % reduction of serum IgM and decrease in adenopathy/organomegaly (if present at baseline) on physical examination or on CT scan. No new symptoms or signs of active disease
Partial response	PR	A >50 % reduction of serum IgM and decrease in adenopathy/organomegaly (if present at baseline) 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 IgM. No new symptoms or signs of active disease
Stable disease	SD	A <25 % reduction and <25 % increase of serum IgM 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 IgM by protein 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

be considered inorder to clarify the patient's underlying disease burden. Soluble CD27 may serve as an alternative surrogate marker in WM and remains a faithful marker of disease in patients experiencing a rituximab-related IgM flare as well as plasmapheresis [40, 198].

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