Waldenström's Macroglobulinemia

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M. Dreyling, M.E. Williams (eds.), *Rare Lymphomas*, Hematologic Malignancies,
DOI 10.1007/978-3-642-39590-1_16,

16.1 Introduction

The diagnostic concept of Waldenström's macroglobulinemia (WM) has changed dramatically since Jan Waldenström originally reported two patients with a syndrome of oronasal bleeding, lymphadenopathy, an elevated sedimentation rate, hyperviscosity, normal bone films, cytopenias, and a predominant bone marrow infiltrate (Waldenström 1944). The second international workshop on WM attempted to refine the working definition of the disease within the context of a LPL (Owen et al. 2003a). 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. This condition is considered to correspond to the lymphoplasmacytic lymphoma (LPL) as defined by the World Health Organization classification system (Swerdlow et al. 2008). Most cases of LPL are WM, with less than 5 % of cases made up of IgA, IgG, and nonsecreting LPL.

16.2 Epidemiology

WM is an uncommon disease, accounting for 1–2 % of hematological neoplasm, 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 (Groves et al. 1998). The median age is 63–68 years with a male predominance. The incidence rate for WM is higher among Caucasians, with African descendants representing only 5 % of all patients. The etiology of WM remains unknown. However, genetic factors appear to be important to the pathogenesis of WM, with numerous reports of familiar clustering of individuals with WM alone and with other B-cell lymphoproliferative diseases (Renier et al. 1989; Treon et al. 2006; Kristinsson et al. 2008; McMaster et al. 2007; Ogmundsdottir et al. 1999). Familial predisposition is common in WM as up to 20 % of WM patients have a first-degree relative with either a WM or a closely related B–cell disorders (Treon et al. 2006). 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 (Ogmundsdottir et al. 1999, 2011). An increased risk of solid tumors has been reported in WM patients analogous to observations in forms of indolent lymphoproliferative disorders (Morel et al. 2000; García-Sanz et al. 2001; Hanzis et al. 2011). The Italian group recently reported an increased incidence of second cancers in a retrospective study of WM patients either untreated or treated with alkylating agents with a cumulative incidence of solid cancers of 12 % at 10 years and 17 % at 15 years (Varettoni et al. 2011). The Surveillance, Epidemiology and End Results program (SEER multiple primary data base) yielded 1,618 WM patients for analysis with population and age-matched controls. The data were consistent with Italian data regarding the increase risk of acute leukemia and non-Hodgkin lymphoma but did not support an increased risk of brain cancer. However, the larger SEER sample yielded evidence that there was an increased risk of myeloma, melanoma, and cancers of colon, uterus, lung, and kidney (Ojha and Thertulien 2012). The greatest risk factor for the development of WM is having an MGUS. These patients have 46 times greater risk of developing WM than the general population (Kyle et al. 2002).

The role of environmental factors in WM remains to be clarified, an etiological role for hepatitis C virus (HCV) infection has been suggested, though in one study no association could

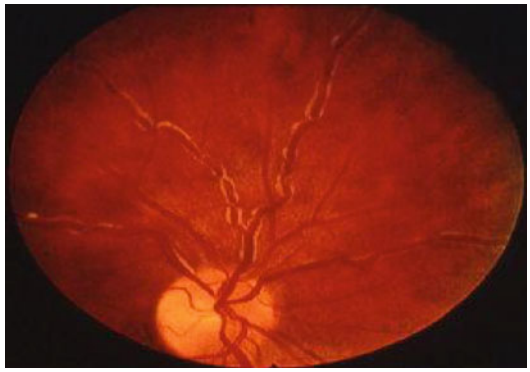

Fig. 16.1 Fundoscopic examination of a patient with Waldenström's macroglobulinemia demonstrating hyperviscosity-related changes including dilated retinal vessels, peripheral hemorrhages, and "venous sausaging" (Courtesy of Marvin Stone M.D.)

be established using both serological and molecular diagnostic studies for HCV infection in a hundred consecutive WM patients (Silvestri et al. 1996; Leleu et al. 2007a).

16.3 Biology

16.3.1 Morphology

The neoplastic lymphoid cells of LPL show a spectrum of appearances including small, mature lymphoid cells with scant cytoplasm, cells with more abundant cytoplasm and eccentrically placed nuclei (lymphoplasmacytoid cells), and fully differentiated, mature plasma cells (Fig. 16.1). Tumor cells of LPL colonize the bone marrow, where they form nodular aggregates that may be paratrabecular, and lymph nodes, where they colonize interfollicular spaces, frequently with preserved, dilated sinuses. Tumor cells can show PAS+ intranuclear inclusions (Dutcher bodies) or cytoplasmic inclusions (Mott cells). Mast cells are frequently intermixed with the neoplastic cells, and morphological evidence of immunoglobulin secretion, such as amyloid deposition, can occasionally be seen. Involvement of the liver, spleen, and peripheral blood can occur (Owen et al. 2003a). Involvement of the central nervous system is a rare but well-recognized phenomenon (Bing–Neel syndrome) (Fintelmann et al. 2009).

16.3.2 Immunophenotype

The lymphoid component of the tumor is positive for mature B-cell antigens, such as CD19, CD20, and CD79a, and expresses monotypic surface immunoglobulin light chain. These cells are most often negative for CD5 and CD10. The plasmacytic component of the tumor is positive for plasma cell antigens such as CD38 and CD138 and expresses monotypic cytoplasmic immunoglobulin light chain. In contrast to most cases of multiple myeloma, the neoplastic plasma cells of LPL are negative for CD56 (Leo et al. 1992; San Miguel et al. 2003).

16.3.3 Genetics

There are no chromosomal translocations associated with LPL, but a subset of cases show loss of chromosome 6q (Chang et al. 2007). Recently mutations in MYD88 have been discovered in the majority of LPLs – a finding that might prove useful for distinguishing LPL from marginal zone lymphoma (Treon et al. 2012).

16.3.4 Differential Diagnosis

Distinguishing LPL from marginal zone lymphoma (MZL) with plasmacytic differentiation can be difficult based on morphology and immunophenotype alone (Owen et al. 2003a). However, the systemic nature of the disease and the marked serum IgM paraprotein can usually rule out the latter diagnosis. Cases of LPL with a predominantly lymphocytic component often raise the diagnostic possibility of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). However, LPL lacks the characteristic proliferation centers and expression of CD5 typical for CLL/SLL. Finally, LPL with extensive plasma cell differentiation can raise the possibility of a plasma cell neoplasm. The demonstration of monotypic surface immunoglobulin expression on the B-cell population and the predilection of LPL for lymphoid tissues facilitate this distinction.

Table 16.1 Physicochemical and immunological properties of the monoclonal IgM protein in Waldenström'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

16.4 Clinical Features

It should be noted that most patients with WM will have limited and nonspecific symptoms at diagnosis, such as fatigue and malaise. Unlike most 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 16.1, 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 (Merlini et al. 1986; Farhangi and Merlini 1986; Marmont and Merlini 1991).

16.4.1 Morbidity Mediated by the Physicochemical Properties of IgM

16.4.1.1 Hyperviscosity Syndrome

Blood hyperviscosity is the most distinguished feature of WM but is only observed in less than 15 % of patients at diagnosis, effected by increased serum IgM levels leading to hyperviscosity-related complications (Gertz and Kyle 1995). The mechanisms behind the marked increase in the resistance to blood flow and the resulting impaired transit through the microcirculatory system are rather complex (Gertz and Kyle 1995; Mackenzie and Babcock 1975; Kwaan and Bongu 1999). 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

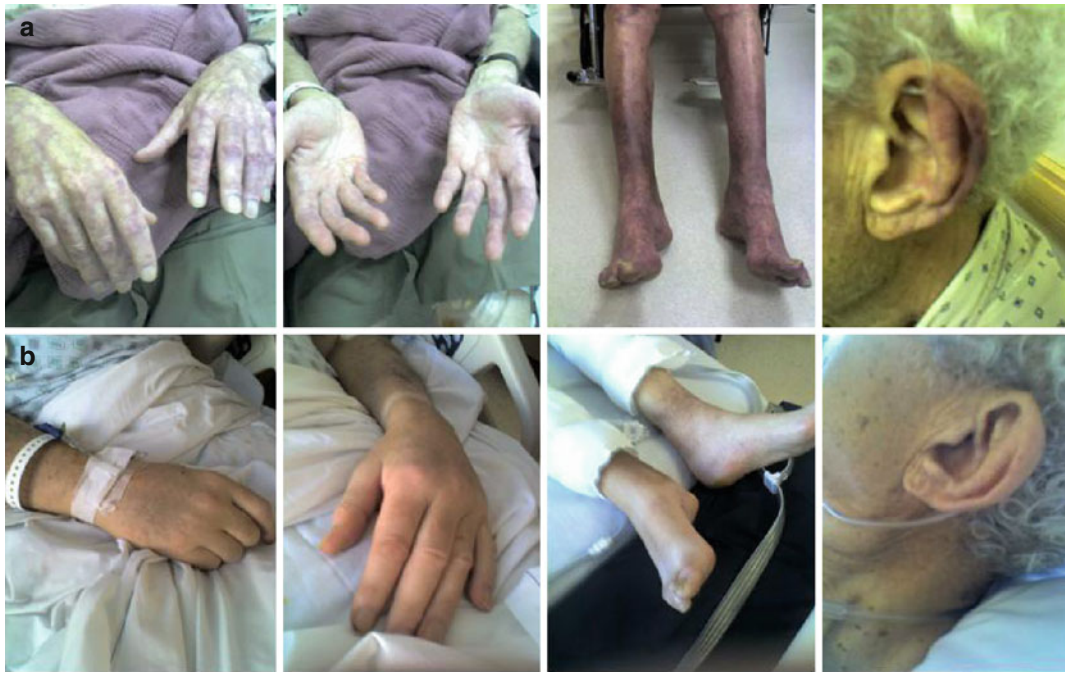

Fig. 16.2 Cryoglobulinemia manifesting with severe acrocyanosis in a patient with Waldenström's macroglobulinemia before (**a**) and following warming and plasmapheresis (**b**)

induce erythrocyte aggregation. 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 (Singh et al. 1993). Clinical manifestations are related to circulatory disturbances that can be best appreciated by ophthalmoscopy, which shows distended and tortuous retinal veins, exudates such as cotton-wool spots, hemorrhages, and papilledema (Menke et al. 2006) (Fig. 16.1). Symptoms usually occur when the monoclonal IgM concentration exceeds 50 g/L or when serum viscosity is >4.0 centipoises (cp) (corresponding to a serum IgM level of at least 30 g/L), but there is a great individual variability, with some patients showing no evidence of hyperviscosity even at 10 cp (Mackenzie and Babcock 1975). 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. Red cell transfusions should therefore be used with caution and sometimes in conjunction with pretransfusion plasmapheresis.

16.4.1.2 Type I Cryoglobulinemia

In up to 20 % of patients, monoclonal IgM may have tendency to precipitate upon cooling and, can thus behave as a type I cryoglobulin, but it is symptomatic in 5 % or less of the cases (Merlini et al. 2003). 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 (Fig. 16.2), malleolar ulcers, purpura, and cold urticaria. Renal manifestations may occur but are infrequent.

16.4.1.3 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 (Whittaker et al. 1996). Amorphous IgM deposits in the dermis determine the so-called IgM storage papules on the extensor surface of the extremities – macroglobulinemia cutis (Daoud et al. 1999). Deposition of monoclonal IgM in the lamina propria and/or submucosa of the intestine may be associated with diarrhea, malabsorption, and gastrointestinal bleeding (Gad et al. 1995; Case records of the Massachusetts General Hospital 1990). 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 (Isaac and Herrera 2002). 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 (Morel-Maroger et al. 1970). 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 (Gertz et al. 1993). In a large series of patients from the Mayo Clinic, amyloidosis develops in 2 % of patients with monoclonal IgM, among those 21 % had WM. 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 %). In a French series of 72 patients, a peculiar pattern of relatively frequent lymph node (31 %) and lung (17 %) involvement was noted in patients with systemic AL amyloidosis (Terrier et al. 2008).

16.4.1.4 Interaction with Circulating Proteins

Monoclonal protein can interact with circulating proteins, including several coagulation factors, mainly factor VIII Willebrand and fibrinogen, and may cause prolonged clotting times. The macroglobulin can coat platelets, may impair their adhesion and aggregation, and may result in prolonged bleeding time (Farhangi and Merlini 1986).

16.4.2 Morbidity Mediated by the Immunological Effects of IgM

16.4.2.1 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 (reviewed in Stone and Pascual 2010).

16.4.2.2 Type II Cryoglobulinemia

In type II or mixed cryoglobulins, monoclonal IgM is an autoantibody to the Fc portion of polyclonal IgG. They are rheumatoid factor positive and often present at a high titer. The cryoprecipitating phenomenon is caused by the immune complex, as separation of the reactants yields clear solution. The manifestations are the same as previously described in type I. Renal manifestation particularly proliferative glomerulonephritis can be observed. Hepatitis C infection must be researched (Stone et al. 2005).

16.4.2.3 IgM-Related Neuropathy

The presence of peripheral neuropathy has been estimated to range from 5 to 38 % in WM patients (Dellagi et al. 1983; Nobile-Orazio et al. 1987; Nemni et al. 1994; Ropper and Gorson 1998; Treon et al. 2010). 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; and occasionally by tubular deposits in the endoneurium associated with IgM cryoglobulin and, rarely, by amyloid deposits or by neoplastic cell infiltration of nerve structures (Vital 2001). 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 (Latov et al. 1981; Chassande et al. 1998; Weiss et al. 1999). 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 (Nobile-Orazio et al. 1987; Latov et al. 1988). 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 (Dalakas and Quarles 1996; Eurelings et al. 2001). 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 (CANOMAD). The disialosyl epitope is also present on red blood cell glycophorins, thereby accounting for the red cell cold agglutinin activity of anti-Pr2 specificity (Ilyas et al. 1985; Willison et al. 2001). 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 (Lopate et al. 2002). 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 (Jacobs et al. 1997). 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 (Nobile-Orazio et al. 1994). Motor neuron disease has been reported in patients with WM and monoclonal IgM with anti-GM1 and sulfoglucuronyl paragloboside activity (Gordon et al. 1997).

However, neuropathy in Waldenström's macroglobulinemia (WM) is very heterogeneous. Neuropathy can be related to specific properties of the circulating IgM, leading to cryoglobulinemic or amyloid neuropathy or to neuropathy with endoneurial IgM deposits (Dellagi et al. 1983; Dimopoulos et al. 2000; Baehring et al. 2008). Neuropathy associated with tumoral infiltration, though rare, has also been described (Vital et al. 1982). For the neurologist and hematologist, diagnosing WM neuropathies is challenging because of their heterogeneous presentation. Yet it is crucially important to identify the mechanism involved in order to adapt the therapeutic strategy (Viala et al. 2012).

16.4.2.4 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 (Crisp and Pruzanski 1982) 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 (Pruzanski and Shumak 1977a, b). The VH4-21 gene segment is necessary to encode anti-I specificity (Pascual et al. 1992). Many cold agglutinins have a high thermal amplitude so agglutination occurs in the 30–35 °C range. 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) and foreign ligands have also been reported.

16.4.3 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 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 % (Rausch and Herion 1980; Fadil and Taylor 1998; Kyrtsonis et al. 2001). Malabsorption, diarrhea, bleeding, or obstruction may indicate involvement of the gastrointestinal tract at the level of the stomach, duodenum, or small intestine (Kaila et al. 1996; Yasui et al. 1997; Rosenthal et al. 1998; Recine et al. 2001). 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 (Mascaro et al. 1982). 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 (Schnitzler et al. 1974), 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 (Roux et al. 1996). The neoplastic cells can infiltrate the periorbital structures, lacrimal gland, and retro-orbital lymphoid tissues, resulting in ocular nerve palsies (Orellana and Friedman 1981; Ettl et al. 1992). 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 Malkani et al. 2010).

16.5 Laboratory Investigations and Findings

16.5.1 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 (McMullin et al. 1995). Leukocyte and platelet counts are usually within the reference range at presentation, although patients may occasionally present with severe thrombocytopenia. 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.

16.5.2 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 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 (Hunter et al. 2010; Treon et al. 2008a).

16.5.3 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, 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 (Menke et al. 2006). 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.

16.6 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 (Morel et al. 2000, 2009; Gobbi et al. 1994; Dhodapkar et al. 2001; Kyle et al. 2003; Dimopoulos et al. 2004; Anagnostopoulos et al. 2006a). Most studies have focused on overall survival from diagnosis to last follow-up, but others have analyzed survival after initiation of treatment in patients with symptomatic WM (Gobbi et al. 1994; Dhodapkar et al. 2001). Indeed, a high proportion of patients die from unrelated causes, because of their advanced age at diagnosis (Morel et al. 2000; García-Sanz et al. 2001; Gobbi et al. 1994). As previously underlines in epidemiology section, some series have shown a high incidence of cancer. The vital prognostic value of events during follow-up is unknown. Preliminary results pointed to the high incidence of long-lasting monoclonal component during the course of WM and the low frequency (6 %) of patients who experienced a rapid rise of the monoclonal component (Stalnikiewicz et al. 2003). These results suggested a heterogeneous disease course.

Age is consistently an important prognostic factor (>60–70 years) (Morel et al. 2000; Gobbi et al. 1994; Kyle et al. 2003; Morel et al. 2009), though 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 (Morel et al. 2000, 2009; Gobbi et al. 1994; Dhodapkar et al. 2001). Cytopenias have also been regularly identified as a significant predictor of survival. The number of cytopenias in a given patient may predict survival (Morel et al. 2000). Serum albumin levels have correlated with survival in WM patients in certain but not all studies using multivariate analyses (Morel et al. 2000; Dimopoulos et al. 2004). High serum beta-2 microglobulin (>3–3.5 g/dL) levels (Dhodapkar et al. 2001; Dimopoulos et al. 2004; Morel et al. 2009), high serum IgM M-protein (>7 g/dL) (Morel et al. 2009), low serum IgM M-protein (<4 g/dL) (Dimopoulos et al. 2004), the presence of cryoglobulins (Gobbi et al. 1994), and the presence of a familial disease background (Treon 2011) have also been reported to confer adverse outcomes. The presence of 6q deletion as an adverse marker remains controversial (Ocio et al. 2007;

Table 16.2 Prognostic scoring systems in Waldenström's macroglobulinemia

Study	Adverse prognostic factors	Number of groups	Survival
Gobbi et al. (1994)	Hb < 9 g/dL Age >70 year Weight loss Cryoglobulinemia	0–1 prognostic factors 2–4 prognostic factors	Median: 48 month Median: 80 month
Morel et al. (2000)	Age ≥ 65 year Albumin < 4 g/dL Number of cytopenias: Hb < 12 g/dL Platelets < 150×10^9/L Wbc < 4×10^9/L	0–1 prognostic factors 2 prognostic factors 3–4 prognostic factors	5 year: 87 % 5 year: 62 % 5 year: 25 %
Dhodapkar et al. (2001)	β_2M ≥ 3 g/dL Hb < 12 g/dL IgM < 4 g/dL	β_2M < 3 mg/dL + Hb ≥ 12 g/dL β_2M < 3 mg/dL + Hb < 12 g/dL β_2M ≥ 3 mg/dL + IgM ≥ 4 g/dL β_2M ≥ 3 mg/dL + IgM < 4 g/dL	5 year: 87 % 5 year: 63 % 5 year: 53 % 5 year: 21 %
Application of International Staging System Criteria for Myeloma to WM Dimopoulos et al. (2004)	Albumin ≤3.5 g/dL β_2M ≥ 3.5 mg/L	Albumin ≥ 3.5 g/dL + β_2M < 3.5 mg/dL Albumin ≤ 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 month Median: 54 month
International Prognostic Scoring System for WM Morel et al. (2009)	Age > 65 year Hb < 11.5 g/dL Platelets < 100×10^9/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 year: 87 % 5 year: 68 % 5 year: 36 %

Nguyen-Khac et al. 2013; Chang et al. 2009). A few prognostic scoring systems have been proposed, and the International Prognostic Scoring System is the most validated (Table 16.2).

16.7 Treatment of Waldenström's Macroglobulinemia

16.7.1 Treatment Indications

Consensus guidelines on indications for treatment initiation were formulated as part of the 2nd International Workshop on Waldenström's macroglobulinemia (Kyle et al. 2003). Initiation of therapy should not be based on the IgM levels since this may not correlate with either disease burden or symptomatic status (Treon and How 2009; Dimopoulos et al. 2009). 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.

16.7.2 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 (Treon and How 2009; Dimopoulos et al. 2009). 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.

16.7.2.1 Plasmapheresis

Because 80 % of IgM is intravascular, plasmapheresis, conducted with a continuous blood flow separator with albumin and saline replacement, is very effective in reducing rapidly the amount of circulating IgM. Plasmapheresis is indicated for the treatment of patients who present with or develop symptomatic hyperviscosity. Even small reductions of serum IgM concentration with plasmapheresis can reduce significantly serum viscosity and can lead to resolution of hyperviscosity-related symptoms. Reductions of IgM by an average of 35 % resulted in a decrease of plasma viscosity from 5 to 2.1 (Kaplan 2001). In most patients with symptomatic hyperviscosity, concomitant administration of systemic treatment is required in order to suppress the underlying malignant process. However, some patients with predominant symptoms of hyperviscosity have been effectively managed for several years with plasmapheresis alone. This strategy may be also considered in patients who fail systemic treatment and who suffer primarily of hyperviscosity. Intensive plasmapheresis has also been used successfully in some patients with an IgM-related disorder such as peripheral neuropathy, cryoglobulinemia, and cold agglutinin disease. In such patients, a series of plasmapheresis may reduce the monoclonal protein, provide an opportunity for symptomatic improvement, and justify the subsequent administration of systemic therapy to achieve long-term control.

16.7.2.2 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) and an intermittent schedule. Kyle et al. (2000) 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). Approximately 50 % will achieve a response, but complete responses are uncommon. The use of steroids in combination with alkylator therapy has also been explored and has not been shown to affect response rate or overall survival but may be of benefit when WM is associated with autoimmune phenomena (Dimopoulos and Alexanian 1994).

Non-chlorambucil-based alkylator regimens employing melphalan and cyclophosphamide in combination with steroids have also been examined by Petrucci et al. (1989) and Case et al. (1991) producing slightly higher overall response rates and response durations, although the benefit of these more complex regimens over chlorambucil remains to be demonstrated. 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.

In a randomized study comparing the efficacy of fludarabine to that of chlorambucil, the response rate of 171 patients treated with chlorambucil was 36 % and the relapse-free survival time was 21.3 months with a response duration of 34.6 months. A higher cumulative incidence of second malignancies with a 6-year cumulative incidence of 3.7 % in the fludarabine arm and 20.6 % in the chlorambucil arm ($p=0.001$) was observed in patients treated with chlorambucil (Leblond et al. 2013).

16.7.2.3 Nucleoside Analogues

Both cladribine and fludarabine have been extensively evaluated in untreated as well as previously treated WM patients (Dimopoulos et al. 1993, 1994a, b, 1995; Delannoy et al. 1994; Fridrik et al. 1997; Liu et al. 1998; Hellmann et al. 1999; Betticher et al. 1997; Foran et al. 1999; Thalhammer-Scherrer et al. 2000; Zinzani et al. 1995; Leblond et al. 1998, 2001; Lewandowski et al. 2002). 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 % (Dimopoulos et al. 1994a, 1995; Delannoy et al. 1994; Fridrik et al. 1997; Liu et al. 1998; Hellmann et al. 1999; Betticher et al. 1997). 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 to 40 %, respectively (Dhodapkar et al. 2001; Dimopoulos et al. 1993; Foran et al. 1999; Thalhammer-Scherrer et al. 2000; Zinzani et al. 1995; Leblond et al. 1998, 2001), which are on par with the response data for cladribine. In a large randomized study in 168 untreated patients, the fludarabine response rate was 46 %, the relapse-free survival time 38.5 months, and the response duration was 50.1 months (Leblond et al. 2013).

Median time to achievement of response for fludarabine was also on par with cladribine at 3–6 months but took more than 6 months and more than 1 year in respectively 17 % and 5 % of responders in a large phase II study (Dhodapkar et al. 2001). In general, response rates and durations of responses have been greater for patients receiving nucleoside analogues as first-line agents.

Purine analogues (both fludarabine and 2 CDA) are effective in patients who are primary resistant or relapse after alkylating agents. Several phase II studies of purine analogues have involved patients who had received prior therapy (usually alkylating agents). The response rates varied from 14 to 78 %. Fludarabine induces responses in about one-third of patients who were resistant to a previous treatment and is highest in patients who are still sensitive to their primary therapy (Dimopoulos et al. 1993; Leblond et al. 2001).

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. 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. The principal toxicity of purine analogues is myelosuppression. For patients in whom high-dose chemotherapy and autologous stem cell transplantation are being considered, nucleoside analogues must be used with precaution, as several published data have shown that stem cell collection can be unsuccessful after fludarabine-containing regimens. The use of stem cell-damaging agents thus has to be reconsidered when the therapeutic strategy includes high-dose therapy and autologous stem cell transplantation (Thomas et al. 2008). The long-term safety of nucleoside analogues in WM was examined by Leleu et al. (2009a) 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 meta-analysis by Leleu et al. (2009b) 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. These results were not confirmed in a large randomized study comparing the efficacy of fludarabine alone to that of chlorambucil with a 6-year cumulative incidence of disease transformation

of 7.7 % in the fludarabine arm versus 11.1 % in the chlorambucil arm. Three MDS/AMLs were observed during the follow-up, all cases in the chlorambucil arm (Leblond et al. 2013). However, there is some evidence to suggest that this complication may be more frequent in patients treated fludarabine-alkylator combinations than with fludarabine monotherapy (Carney et al. 2010; Smith et al. 2011).

16.7.2.4 Monoclonal Antibodies

Rituximab is a chimeric monoclonal antibody which targets CD20, a widely expressed antigen on lymphoplasmacytic cells in WM (Treon et al. 2003). 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 (Treon et al. 2001; Gertz et al. 2004). 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 (Gertz et al. 2004). 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 (Dimopoulos et al. 2002; Treon et al. 2005a).

In many WM patients, a transient increase of serum IgM (IgM flare) may be noted immediately following initiation of rituximab treatment (Donnelly et al. 2001; Treon et al. 2004; Ghobrial et al. 2004). The IgM flare may be related to release of interleukin-6 by bystander immune in response to binding of rituximab to FcγRIIA receptors and also occurs in response to intravenous immunoglobulin administration in WM patients (Yang et al. 2010). 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 >3.5 cp 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. 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 (Treon et al. 2005a). 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 (Dimopoulos et al. 2002; Treon et al. 2005a). An 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/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 (Dimopoulos et al. 2005a).

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 Fc 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 (Treon et al. 2005b). 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 FcγRIIIa-158 (Treon et al. 2011a).

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 (Furman et al. 2011). Responses were higher among rituximab-naïve patients. An IgM flare with symptomatic hyperviscosity was also observed in two patients in this series who required plasmapheresis.

The activity of alemtuzumab has also been investigated in WM patients given the broad expression of CD52 (Treon et al. 2003). 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 (Treon et al. 2011b). 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 three deaths. Long-term follow-up revealed late-onset idiopathic thrombocytopenia in four 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. (2003b) who reported their preliminary experience in a small series of heavily pretreated WM patients.

16.7.2.5 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 (Treon et al. 2007). All but one patient had relapsed/or refractory disease. 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. (2007) 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 two 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 patients, 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. (2005b) observed major responses in 6 of 10 (60 %) previously treated WM patients. The combination of bortezomib with steroids and/or rituximab has also been investigated and is discussed below.

16.7.2.6 Immunomodulatory Agents

Thalidomide as monotherapy and in combination with dexamethasone and/or clarithromycin has been examined in WM. Dimopoulos et al. (2001) 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 (Coleman et al. 2003). However, in a follow-up study by Dimopoulos et al. (2003) using a higher thalidomide dose (200 mg orally daily) along with dexamethasone (40 mg orally once a week) and clarithromycin (500 mg orally twice a day), only 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.

16.7.2.7 Bendamustine

Bendamustine is a recently approved agent for the treatment of relapsed/refractory indolent non-Hodgkin lymphoma (NHL). Bendamustine has structural similarities to both alkylating agents and purine analogues (Cheson and Rummel 2009). Bendamustine in combination with rituximab has been investigated in both previously untreated and relapsed/refractory WM patients and is discussed below.

16.7.2.8 Combination Strategies

Because rituximab is an active and a non-myelosuppressive 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 (Buske et al. 2009). 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. (2007) 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.

Combination therapy with nucleoside analogues has been investigated as both first-line and salvage therapy in WM. Laszlo et al. (2010) 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 (Treon et al. 2009a). 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 six patients in this series.

The addition of alkylating agents to nucleoside analogues has also been explored in WM. Weber et al. (2003a) 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. The combination of fludarabine plus cyclophosphamide (FC) was also evaluated by Tamburini et al. (2005) 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 two 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.

Weber et al. (2003a) 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.

Tedeschi et al. (2012) recently completed a multicenter study on with 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. Similar results were observed in 62 patients treated by rituximab at 375 mg/m^2 on day 1, fludarabine at 40 mg/m^2 orally on D1-D3, and cyclophosphamide at 250 mg/m^2 orally on D1–D3. In this retrospective study, the overall response rate was 85.5 %, with 30 % of patients attaining a major remission and a complete response. Prolonged cytopenia was observed in a third of patients. With a median follow-up of 45 months, the median progression-free survival for this study has not been reached, and the PFS rate was 65 % at 60 months (Compain et al. 2010).

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 (Treon et al. 2009b). 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 % (Ghobrial et al. 2010a; Agathocleous et al. 2010; Dimopoulos et al. 2010). A lower incidence of peripheral neuropathy was observed in two studies using once-a-week bortezomib. 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 (Treon et al. 2008b). 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 (Treon et al. 2008c). 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 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 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. (2013) in the frontline therapy of WM. As part of a randomized study, patients received six 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. (2011c). 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.

16.7.2.9 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 (Treon et al. 2011d). 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 survival (>120 vs. 116 months) were longer in patients who received maintenance rituximab.

These results must be confirmed in randomized trials.

16.8 Novel Agents

Novel therapeutic agents that have demonstrated efficacy in WM include perifosine, enzastaurin, everolimus, and histone deacetylases inhibitors (reviewed in Issa et al. 2011).

16.8.1 Perifosine

Perifosine is a novel AkT inhibitor that belongs to a class of lipid-related compounds called alkyphospholipids (Hideshima et al. 2006). A phase II clinical trial was conducted in 37 patients. Of the patients, 11 % achieved a PR and MR was observed in 24 % of the patients. Stable disease occurred in 54 % of the patients; PFS was 12.6 months (Ghobrial et al. 2010b).

16.8.2 Enzastaurin

Enzastaurin is an oral serine/threonine kinase inhibitor that targets the protein kinase C and PI3K/AKT pathways and had demonstrated activity in preclinical models of WM (Moreau et al. 2007). A multicenter trial was conducted in 42 patients (Ghobrial et al. 2012). Patients were treated with 1–5 prior regimens and received oral enzastaurin 250 mg twice daily (500 mg total) after a loading dose (day 1, cycle 1) of 375 mg 3 times daily (1,125 mg total) for 8 cycles of 28 days each or until progressive disease. The objective response rate (RR) was 38.1 % (2 partial and 14 minor responses). One patient had grade 3

leukopenia, and one patient died during the study from septic shock; both events were considered drug related. A statistically significant association between RR and interleukin 15 (IL-15) was observed, suggesting that higher concentration levels of IL-15 may be associated with better response. Enzastaurin was active and well tolerated in previously treated patients with WM, and these results warrant further investigation of enzastaurin for the treatment of WM.

16.8.3 Everolimus (RAD 001)

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 (Hatjiharissi et al. 2007; Leleu et al. 2007b).

Fifty patients with a median of 3 prior therapies were treated with everolimus in a joint Dana Farber/Mayo Clinic study (Ghobrial et al. 2010c). 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 (Treon et al. 2011e). 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.

16.8.4 Panobinostat

Preclinical studies have demonstrated that primary WM cells exhibit a higher level of histone deacetylases (HDACs), thus providing the rational for testing HDAC inhibitors. The activity of panobinostat was demonstrated in vitro in tumor cells and cell lines (Roccaro et al. 2010). In a phase II study enrolling 27 previously treated patients, the ORR was 60 % (PR: 24 %, MR: 36 %). Main toxicity was hematological with grades 3–4 anemia, neutropenia, and thrombocytopenia in 15 %, 26 %, and 52 %, respectively (Ghobrial et al. 2010d).

16.9 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. (1999) reported their initial experience of high-dose chemotherapy and autologous stem cell transplant, which has more recently been updated by Munshi and Barlogie (2003). 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. All eight patients responded, with 7 of 8 patients achieving a major response and one patient achieving a complete response with durations of response ranging from 5+ to 77+ months. Dreger et al. (1999) 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. (2001) wherein WM patients received various preparative regimens and demonstrated event-free survivals of 26+, 31, and 108+ months. Tournilhac et al. (2003) 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. Anagnostopoulos et al. (2006b) 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.

Garnier et al. (2010) reported on the outcome of 24 high-risk WM patients who underwent allogeneic transplantation in the French registry (myeloablative 12, reduced-intensity: 13). The overall response rate was 92 %. With a median of follow-up of 64 months, 5-year overall survival and progression-free survival were respectively 67 % and 58 %. Only one of the six relapses occurred more than 3 years post-transplant.

Kyriakou et al. (2010a, b) 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. Non-relapse 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 et al. (2010b). 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. Non-relapse 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.

16.10 Response Criteria in Waldenström's Macroglobulinemia

As part of the International Workshops on WM, consensus panels developed guidelines for uniform response criteria in WM (Weber et al. 2003b; Kimby et al. 2006; Owen et al. 2013). 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 6th 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 (Treon et al. 2009a, b, 2011a, f; Kyriakou et al. 2010a). In distinction, the term major response is used to denote a response of ≥50 % in serum IgM levels and includes partial

Table 16.3 Summary of updated response criteria adopted at the 6th international workshop on Waldenström's macroglobulinemia (Owen et al. 2013)

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

or better responses (Kimby et al. 2006; Owen et al. 2013). Response categories and criteria for progressive disease in WM based on consensus recommendations are summarized in Table 16.3.

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 (Donnelly et al. 2001; Treon et al. 2004, 2007, 2011e; Ghobrial et al. 2004, 2010c). 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 (Donnelly et al. 2001; Treon et al. 2004, 2008b, c; Ghobrial et al. 2004), whereas bortezomib and everolimus can suppress IgM levels independent of tumor cell killing in certain patients (Treon et al. 2007, 2011e; Ghobrial et al. 2010c). Moreover, Varghese et al. (2009) 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 in order to clarify the patient's underlying disease burden.

16.11 Treatment Strategies

The four main agents for systemic primary treatment of patients with WM include alkylating agents (chlorambucil, cyclophosphamide), nucleoside analogues (fludarabine, cladribine), bortezomib, and the monoclonal anti-CD20 antibody rituximab. Data from prospective randomized trial support the use of fludarabine over chlorambucil as single agent (Leblond et al. 2013). These agents have advantages and disadvantages which are shown in Table 16.4

Combination of these drugs with rituximab seems to increase the ORR and the duration of the response, but randomized studies are needed to choose the best combination. Outside a clinical

Table 16.4 Primary treatment of WM: advantages and disadvantages of four main agents

	Response (%)	Time to response (months)	Duration of treatment (months)	Cost	Myelosuppression	Opportunistic infections	Stem cell toxic	Miscella neous
Chlorambucil	50	>6	12–24	Low	Moderate	No	Yes	Secondary malignancies
Nucleoside analogues	40–80	1.5–5	2–6	Average	Significant	Yes	Yes	MDS/AML
Rituximab	40	3–5	1	High	None	No	No	IgM flare less active when high peaks
Bortezomib	60–80	1–2	4	High	Moderate	No	No	Neuropathy

trial, several factors should be taken into account in choosing the most appropriate primary treatment. These include the age of the patient and possible comorbid diseases, the presence of cytopenias and especially thrombocytopenia, the presence of symptoms and signs indicative of hyperviscosity, the need for rapid disease control due to severe symptoms, significant splenomegaly or lymphadenopathy, symptomatic peripheral neuropathy, and the candidacy for autologous stem cell transplantation. Based on those data, some suggestions could be made:

1. For patients who present with symptoms and signs of hyperviscosity, plasma exchange should precede any systemic treatment.
2. Patients who are not (and will not be candidates) for high-dose therapy, all four main primary treatments could be used.
3. For patients who are candidates for high-dose therapy (or may be candidates at some point of their disease), every effort should be made to avoid exposure to nucleoside analogues. If these agents seem necessary, a limited exposure is indicated before stem cells are collected.

For patients with refractory or relapsing disease, the use of alternate first-line agent is reasonable. For patients who are resistant to alkylating agents, a nucleoside analog and/or rituximab will be effective in 30–40 % of cases. If those patients are considered for high-dose therapy, rituximab would be preferable unless stem cells have been previously collected. For patients relapsing from unmaintained remission, the readministration of the same agent has a high likelihood of activity. For patients who develop resistance to all four classes of agents, few valid options are available. They can benefit of other monoclonal antibodies (new anti CD20, alemtuzumab) or bendamustine. Such patients are best served when treated within a context of a phase II trial. Every effort should be made to collect blood stem cells and to proceed to high-dose therapy, but this is usually not possible. In the future targeting MYD88 signaling might be a novel approach to impair WM growth.

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