Chapter 4
Waldenstrom's Macroglobulinemia

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Introduction

Waldenstrom's macroglobulinemia is an indolent B-cell malignancy defined by a lymphoplasmacytic infiltration in the bone marrow or in other organs including lymph nodes, liver, and spleen, as well as a monoclonal immunoglobulin M protein (IgM) in the serum [1, 2]. The infiltration of the bone marrow and extramedullary sites by malignant B lymphocytes, as well as elevated IgM levels, typically leads to symptoms associated with this disease. Patients may develop constitutional symptoms, pancytopenia, or organomegaly due to infiltration by malignant cells. They may also develop neuropathy, symptoms associated with immunoglobulin deposition or hyperviscosity due to the presence of increased serum levels of the monoclonal IgM protein [3, 4].

There is, however, significant heterogeneity in the clinical presentation of patients with this disease. Some patients may present with the symptoms listed above, but many patients are

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asymptomatic at the time the diagnosis is made. Some of these asymptomatic patients have very low serum IgM levels, a modest increase in lymphoplasmacytic cells in the bone marrow and no evidence of anemia or organomegaly. Many of the asymptomatic patients have a very indolent disease course, and some do not develop overt disease. Based on the extent of infiltration in the bone marrow and the serum IgM levels, asymptomatic patients can be further categorized as having a monoclonal gammopathy of undetermined significance (MGUS) or smoldering Waldenstrom's macroglobulinemia.

While Waldenstrom's macroglobulinemia typically follows an indolent course, the disease remains incurable with current therapy and the median survival for symptomatic patients is approximately 8 years [5]. Furthermore, many patients are diagnosed with Waldenstrom's macroglobulinemia at an advanced age and approximately half of the patients die from causes unrelated to the disease. Therefore, due to the incurable nature of the disease, the heterogeneous clinical presentation, as well as the presence of multiple comorbidities and competing causes of death, the decision to treat patients as well as the choice of treatment can be complex. A number of consensus meetings involving experts in the field have outlined recommended treatment approaches [6–8]. Despite this, the treating physician may still be faced with a difficult treatment decision in a complex patient with an uncommon disease.

Epidemiology

The incidence of Waldenstrom's macroglobulinemia is approximately 5 cases per million persons per year, and Waldenstrom's macroglobulinemia accounts for approximately 1–2 % of all hematological cancers [9, 10]. The incidence of this disease is highest among Caucasians, but is rare in other population groups [11]. The majority of new patients are male, and the median age at diagnosis varies between 63 and 68 years [3]. Patients with a previously diagnosed MGUS are at increased risk for progression to Waldenstrom's macroglobulinemia [12]. In population-based studies of individuals with MGUS, the rate of progression from

IgM-MGUS to Waldenstrom's macroglobulinemia has been noted to be approximately 1.5–2 % per year [13–15].

While the development of Waldenstrom's macroglobulinemia is generally thought to be sporadic, there are studies suggesting a familial predisposition for the disease [16–18]. Familial clustering of Waldenstrom's macroglobulinemia, as well as a significant increase in the frequency of IgM-MGUS in first-degree relatives of Waldenström patients, is strongly suggestive of familial risk [17]. Based on the assumption that Waldenstrom's macroglobulinemia and IgM-MGUS may share common susceptibility genes, strong linkages have been identified involving chromosomes 1q, 3q, and 4q [13]. Furthermore, several studies have suggested a familial association between MGUS/Waldenstrom's macroglobulinemia and chronic antigenic stimulation [18–21]. It was recently shown that a sizable minority of patients with IgM-MGUS/Waldenstrom's macroglobulinemia reacted with a protein of unknown function called paratarg-7 (P-7) [22]. Relatives of patients with IgM-MGUS/Waldenstrom's macroglobulinemia analyzed using an anti-P-7-paraprotein showed that the hyperphosphorylated state of this protein (pP7) is inherited as a dominant trait. It was also shown that carriers of pP7 have a substantially increased risk of developing IgM-MGUS/Waldenstrom's macroglobulinemia [22]. Hyperphosphorylated P-7 is therefore the first biological entity that provides a potential explanation for the familial clustering of cases of IgM-MGUS/Waldenstrom's macroglobulinemia.

Diagnosis

In recent years, efforts to more clearly define Waldenstrom's macroglobulinemia have been made by the World Health Organization (WHO) Lymphoma Classification [23], the consensus group formed at the Second International Workshop on Waldenstrom's Macroglobulinemia [1], and the Mayo Clinic [24]. However, the diagnostic criteria for Waldenstrom's macroglobulinemia by these respective groups are not identical. All groups recognize Waldenstrom's macroglobulinemia as a lymphoplasmacytic lymphoma associated with an IgM monoclonal protein in the serum. The WHO definition, however, includes lymphomas other

than lymphoplasmacytic lymphoma and does not restrict the monoclonal protein to IgM but also allows IgG or IgA. In contrast, the Second International Workshop on Waldenström's Macroglobulinemia restricts the diagnosis of Waldenstrom's macroglobulinemia exclusively to cases with lymphoplasmacytic lymphoma and an IgM monoclonal protein. The Second International Workshop on Waldenström's Macroglobulinemia also removed the requirement for a minimum degree of bone marrow involvement or a threshold serum level of IgM to fulfill the diagnosis, but instead allowed for any detectable amount of either. In contrast, Mayo Clinic criteria require at least 10 % involvement of the bone marrow by lymphoplasmacytic lymphoma in asymptomatic patients. As regards the analysis of pathologic features, the WHO criteria focus predominantly on nodal involvement, whereas studies at Mayo Clinic suggest that the analysis of most cases of Waldenstrom's macroglobulinemia should be bone marrow based.

Lymphoplasmacytic lymphoma, whether involving the bone marrow or nodal sites, typically exhibits a cytologic spectrum ranging from small lymphocytes with clumped chromatin, inconspicuous nucleoli, and sparse cytoplasm to well-formed plasma cells [1, 25]. Also commonly present are "plasmacytoid lymphocytes," which have cytologic features of both lymphocytes and plasma cells, although the cytology and extent of plasmacytic differentiation may vary from case to case. Involvement of lymph nodes is typically characterized by paracortical and hilar infiltration with frequent sparing of the subscapular and marginal sinuses. The bone marrow involvement usually exhibits a combination of nodular, paratrabecular, and interstitial infiltration. Plasma cells containing Dutcher bodies are commonly present.

The lymphoplasmacytic cells present in Waldenstrom's macroglobulinemia display a broad cytologic spectrum and the immunophenotypic features of the lymphocytic and plasmacytic components can be rather varied. The lymphocytic infiltrate commonly displays high levels of surface CD19, CD20, and immunoglobulin light-chain expression, but the malignant B lymphocytes typically lack CD10 expression [25]. In approximately half of the cases, malignant lymphocytes show some degree of CD5 expression; however, the intensity of expression is not as strong as on malignant B cells from patients with chronic lymphocytic leukemia/small lymphocytic lymphoma or mantle cell

lymphoma. The plasmacytic component expresses the same immunoglobulin light chain as the lymphocytic component, is positive for CD138 and shows diminished expression of B-cell-associated antigens such as CD19, CD20, and PAX5. Overall, the lymphoplasmacytic lymphoma cells are positive for surface IgM, and on the basis of the WHO criteria, they may express any immunoglobulin isotype. In cases that have undergone isotype switching, the phenotype of the plasma cells closely resembles that of myeloma plasma cells with strong CD38 and CD138 co-expression and complete lack of CD19 expression. Waldenstrom's macroglobulinemia tumor cells have also been shown to variably express CD25, CD27, FMC7, and Bcl2, and lack expression of Bcl6 and CD75.

Conventional cytogenetic analyses initially determined deletions of chromosome 6q to be the most common recurrent abnormality in Waldenstrom macroglobulinemia, and this abnormality was identified in approximately half of the patients studied [26]. In a study by Schop et al. [27], 23 % of patients with an abnormal karyotype had a 6q deletion, while FISH analysis found deletions of 6q in 42 % of patients. Further analysis to assess minimal areas of deletion used multiple FISH probes on the 6q arm, and the results suggested a minimal deleted region at 6q23–24.3 [28]. Although the deletion of 6q is present in around 50 % of Waldenstrom macroglobulinemia patients, its presence cannot be used for diagnosis of the disease as the deletion is widely observed in other B-cell malignancies, such as marginal zone lymphoma, multiple myeloma and chronic lymphocytic leukemia [29–32].

Recent data obtained from whole-genome sequencing of Waldenstrom's macroglobulinemia patients reported a mutation in *MYD88* in 90 % of cases (46/51), which leads to a leucine-to-proline substitution in codon 265 (L265P) [33]. This *MYD88* mutation is likely to become a biomarker for differentiating Waldenstrom's macroglobulinemia from other related entities such as marginal zone lymphoma, where *MYD88* L265P was detected in less than 10 % of cases. Furthermore, a low prevalence of *MYD88* mutations in IgM-MGUS suggests that the mutation is associated with disease progression or that there is more than one type of IgM-MGUS, with only certain types of IgM-MGUS progressing to Waldenstrom's macroglobulinemia.

Gene expression profile (GEP) analysis of Waldenstrom's macroglobulinemia has also provided useful information about the transcriptional signature of the disease. Two studies have studied the similarities and differences in GEP between Waldenstrom's macroglobulinemia, chronic lymphocytic lymphoma (CLL), multiple myeloma, normal B cells, and normal plasma cells [34, 35]. These studies have identified similarities between GEP in Waldenstrom's macroglobulinemia and CLL. When analyzed in an unsupervised fashion, gene expression in Waldenstrom's macroglobulinemia cells clustered with CLL rather than with multiple myeloma [34]. This may not be surprising as both Waldenstrom's macroglobulinemia and CLL have a strong B-cell signature, are characterized by expression of similar B-cell markers and are defined by low proliferation rates and a lack of immunoglobulin heavy-chain mutations [35]. The GEP of Waldenstrom's macroglobulinemia and CLL shared similar profiles, particularly with regard to cell surface markers and cytokines such as IL-10 [34, 35].

A significant finding in both studies was the high level of IL-6 transcript expression in Waldenstrom's macroglobulinemia when compared to multiple myeloma, CLL, and normal B cells [34, 35]. IL-6 is an inflammatory cytokine that increases lymphocyte activity, including antibody production [36]. IL-6 plays a key role by activating the MAPK pathway, and while the genetic studies found no specific mutations in *MAPK*, its activity was notably increased, likely due to the upregulation of IL-6 [34]. The increase in IL-6 expression in Waldenstrom's macroglobulinemia cells, more so than in normal B cells, is suggestive of an autocrine loop. IL-6 binds to the tyrosine kinase receptor Janus kinases (JAK) 1 and 2, which activate the downstream transcription factor Stat3, leading to increases in gene transcription and IgM production [37]. Recently, a functional relationship between IL-6, RANTES (CCL5), and IgM secretion was observed and appears to be mediated through the JAK/STAT and PI3K pathways [38]. Although the specific mechanisms of increased immunoglobulin secretion in Waldenstrom's macroglobulinemia are still not entirely understood, the pathogenic role of IL-6 and the JAK/STAT pathway in Waldenstrom's macroglobulinemia merits further study.

Clinical Presentation

Infiltration of the bone marrow by malignant cells and the increased levels of circulating IgM protein in patients with Waldenstrom's macroglobulinemia are responsible for the majority of the signs and symptoms associated with this malignancy. While some patients with Waldenstrom's macroglobulinemia are asymptomatic at diagnosis, others present with anemia, bleeding, or neurological complaints [39]. Additionally, because IgM protein circulates in the serum as a large pentameric molecule, many patients present with symptoms associated with immunoglobulin deposition and hyperviscosity syndrome [40]. Symptoms due to hyperviscosity syndrome have been reported in approximately one-third of Waldenstrom's macroglobulinemia patients and include skin and mucosal bleeding, retinopathy, other visual disturbances, and cold sensitivity [39, 41].

Due to an absence of curative therapies, as well as significant variability in clinical presentation and comorbidities, when and how to treat patients diagnosed with Waldenstrom's macroglobulinemia can be a challenging decision. Before treatment can even be considered, it is important to differentiate between Waldenstrom's macroglobulinemia, IgM-MGUS and smoldering Waldenstrom's macroglobulinemia, as the appropriate treatment strategy varies depending on the diagnosis. To aid in this decision-making process, Mayo Clinic has described diagnostic criteria to differentiate between these IgM gammopathies based on the extent of bone marrow involvement and the presence or absence of symptomatic disease (see Table 4.1) [24].

Prognostic Factors

After the diagnosis of Waldenstrom's macroglobulinemia is made, the next step is to use a risk-adapted approach to determine how best to manage the disease. The International Prognostic Staging System for Waldenstrom Macroglobulinemia (IPSSWM), a multicenter collaborative project, used five adverse prognostic factors to define three different risk groups for patients with Waldenstrom's macroglobulinemia [42]. These factors include age >65 years,

Table 4.1 Diagnostic criteria for Waldenstrom's macroglobulinemia [24]

Waldenstrom's macroglobulinemia	IgM monoclonal gammopathy (regardless of the size of the M protein) with >10 % bone marrow lymphoplasmacytic infiltration (usually intertrabecular) by small lymphocytes that exhibit plasmacytoid or plasma cell differentiation and a typical immunophenotype (surface IgM^+, $CD5^-$, $CD10^-$, $CD19^+$, $CD20^+$, $CD23^-$) that satisfactorily excludes other lymphoproliferative disorders including chronic lymphocytic leukemia and mantle cell lymphoma
IgM-MGUS	Serum IgM monoclonal protein level <3 g/dL, bone marrow lymphoplasmacytic infiltration <10 %, and no evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly
Smoldering Waldenstrom's macroglobulinemia (also referred to as indolent or asymptomatic Waldenstrom's macroglobulinemia)	Serum IgM monoclonal protein level ≥3 g/dL and/or bone marrow lymphoplasmacytic infiltration ≥10 %, and no evidence of end-organ damage, such as anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly that can be attributed to a lymphoplasmacytic disorder

hemoglobin <11.5 g/dL, platelet count <100,000/mcL, β_2-microglobulin >3 mg/L, and monoclonal IgM protein >7 g/dL. Patients with 0–1, 2, or >2 of these factors are considered to be at low risk, intermediate risk, or high risk, with 5-year survival rates of 87, 68, and 37 % respectively. While the IPSSWM is not specifically used to determine the most appropriate treatment regimen, understanding a patient's risk group may be helpful in deciding whether and when treatment is necessary. Conversely, many asymptomatic patients may not require any therapy at all. To illustrate this point, a study by Garcia-Sanz et al. found that 50 % of patients who were

asymptomatic at diagnosis did not require therapy for almost 3 years [39]. Similarly, one in ten patients who were initially observed without therapy did not require therapy for ten years. These data highlight the need to carefully consider a patient's prognostic risk prior to starting treatment so as to limit therapy to only those patients in whom it is necessary.

Indications for Treatment

To better identify the patients with Waldenstrom's macroglobulinemia who should receive therapy, a consensus panel at the Second International Workshop on Waldenstrom Macroglobulinemia agreed that treatment should be initiated in patients with a specific set of clinical findings and/or laboratory parameters [43]. Specifically, it was recommended that treatment be initiated in patients presenting with any of the following: constitutional symptoms including fever, night sweats or weight loss; lymphadenopathy or splenomegaly; hemoglobin <10 g/dL or a platelet count lower than 100×10^9/L due to bone marrow infiltration; as well as complications of Waldenstrom's macroglobulinemia including symptomatic sensorimotor peripheral neuropathy, systemic amyloidosis, renal insufficiency, or symptomatic cryoglobulinemia. It was also recommended that patients with IgM-MGUS and smoldering (asymptomatic) Waldenstrom's macroglobulinemia with preserved hematological function should be observed without treatment. Furthermore, all patients should be evaluated for symptoms of hyperviscosity (rarely observed with IgM levels <4 g/dL) such as visual deterioration, neurological symptoms, or unexplained bleeding. These patients should undergo plasmapheresis if necessary prior to receiving chemotherapy or a monoclonal antibody such as rituximab [44].

Initial Therapy

Initial therapy for previously untreated patients with symptomatic Waldenstrom's macroglobulinemia may involve various chemotherapeutic combinations typically with the addition of the

$CD20^+$-directed antibody, rituximab [45]. However, low-risk patients with symptomatic Waldenstrom's macroglobulinemia may sometimes receive rituximab alone as first-line treatment. Treatment regimens containing nucleoside analogs, such as fludarabine, have demonstrated good efficacy in symptomatic Waldenstrom's macroglobulinemia patients particularly when used in combination, including fludarabine/cyclophosphamide/rituximab (FCR) and fludarabine/rituximab (FR). In a multicenter prospective study of previously untreated patients with symptomatic disease, the FCR regimen was associated with an overall response rate of 79 %, including 12 % who had a complete remission and 21 % who had very good partial remissions [46]. Significant myelosuppression, however, is a limitation of this combination, as grade 3 or 4 neutropenia was reported in 45 % of treatment courses and was the main reason for discontinuing treatment. A separate study similarly examined patients who received six cycles of fludarabine combined with eight infusions of rituximab (FR) [47]. Of the 43 patients enrolled, complete responses were achieved in two patients, with 81 % of patients achieving either a very good partial response or partial response. Similar toxicities to the FCR regimen were seen, and neutropenia, thrombocytopenia, and pneumonia of grade 3 or higher were reported in 63 % of patients treated with FR.

Despite the clinical activity of nucleoside analog-based therapies in the treatment of Waldenstrom's macroglobulinemia, an increased incidence of transformation to large cell lymphoma, as well as the development of myelodysplasia, has been associated with the use of these agents. A recent study followed 439 patients with Waldenstrom's macroglobulinemia, of whom 193 were previously treated with nucleoside analogs, 136 who were treated without a nucleoside analog, and 110 who were observed without treatment. All were followed for a median of five years [48]. Among the nucleoside analog-treated cohort, 5 % of patients transformed and 2 % developed myelodysplasia, whereas only one patient transformed within the other groups. These data suggest that while nucleoside analog-based therapeutic regimens are effective, the additional long-term risks associated with these therapies must be taken into account when deciding upon an initial treatment strategy for patients with Waldenstrom's macroglobulinemia.

Initially considered to be the standard of care, alkylating agents have also been used in patients with Waldenstrom's macroglobulinemia. Over time, combinations of alkylating agents, such as chlorambucil and cyclophosphamide, have been studied with vinca alkaloids, nucleoside analogs, and anthracyclines and have been shown to be effective [49–52]. The addition of rituximab to alkylator-based combinations has further increased patient response rates. In a prospective, randomized trial including patients with Waldenstrom's macroglobulinemia treated with R-CHOP or CHOP without rituximab, a significantly higher overall response rate was achieved in the patient group receiving chemoimmunotherapy as compared to chemotherapy alone (94 % vs. 67 %, $p = 0.008$), with no major differences noted in toxicity [53]. Furthermore, patients in the R-CHOP group experienced a significantly longer time to treatment failure as compared to patients in the CHOP arm (63 months vs. 22 months, $p = 0.003$). Similarly, significant activity with less toxicity has been achieved in Waldenstrom macroglobulinemia patients with other combinations containing alkylating agents and rituximab, suggesting that such regimens may be preferable as initial therapy for this disease [44]. For example, treatment with dexamethasone, rituximab, and cyclophosphamide (DRC) yielded an overall response rate of 83 % in previously untreated patients, 7 % of whom had a complete response to therapy [54]. Toxicity was mild, and only 9 % of patients experienced grade 3 or 4 neutropenia.

Bendamustine, a newer alkylating agent, has also shown significant activity in Waldenstrom macroglobulinemia, particularly when combined with rituximab. In a cohort of relapsed and refractory patients treated with bendamustine in combination with rituximab, an overall response rate of 83 % was seen [55]. While the therapy was well tolerated, there was an increased incidence of myelosuppression in patients who had previously been treated with nucleoside analogs [48]. Bendamustine plus rituximab has now become a standard frontline therapy in Waldenstrom macroglobulinemia based on a randomized comparison with R-CHOP [56]. When compared with R-CHOP, treatment with bendamustine plus rituximab resulted in fewer relapses, was better tolerated and was associated with a longer progression-free survival, despite identical response rates for both regimens.

Rapid and durable patient responses have also been achieved with the proteasome inhibitor bortezomib when used in combination with rituximab in this disease. When bortezomib, dexamethasone, and rituximab (BDR) were administered to previously untreated, but symptomatic Waldenstrom's macroglobulinemia patients, the overall response rate was extremely high (96 %) and responses occurred at a median of 1.4 months [57]. Unfortunately, a high incidence of peripheral neuropathy led to the discontinuation of bortezomib in almost two-thirds of patients. Similar results were seen in a separate study that reported an overall response rate of 88 % in patients with symptomatic Waldenstrom's macroglobulinemia who received only bortezomib and rituximab [58]. In this study, no grade 3 or 4 neuropathies were reported, and the most significant adverse event was neutropenia in 12 % of patients.

When used as a single-agent, rituximab has been associated with response rates ranging from 29 to 65 %, and single-agent rituximab is a reasonable option in the treatment of Waldenstrom's macroglobulinemia. This approach may be most appropriate in low-risk patients with symptomatic disease and minimal hematological compromise, as well as in patients with IgM-related neuropathy requiring treatment [44]. In a study of 69 symptomatic patients, an overall response rate of 52 % was reported following administration of rituximab as a single agent [59]. When using rituximab as a single agent, clinicians need to be aware of the paradoxical increase in IgM protein levels seen in some patients, known as the rituximab "flare" [44, 60]. IgM levels may remain elevated for up to 4 months following treatment with rituximab, and while this does not necessarily indicate treatment failure, additional treatment such as plasmapheresis may be necessary to alleviate symptoms of hyperviscosity.

Based on the variety of different agents that are clinically active in this disease, a risk-adapted approach to the management of Waldenstrom's macroglobulinemia is necessary. Three groups of patients have previously been identified [44]. Firstly, patients with IgM-MGUS or smoldering (asymptomatic) Waldenstrom's macroglobulinemia and normal hematological function constitute a low-risk group. Second, symptomatic Waldenstrom's macroglobulinemia patients with modest hematological compromise, IgM-related neuropathy or hemolytic anemia are at intermediate risk of disease progression and subsequent morbidity or mortality.

Thirdly, Waldenstrom's macroglobulinemia patients who have constitutional symptoms, significant hematological compromise, bulky disease or hyperviscosity have a high risk of disease progression and early mortality. Utilizing these risk groups, we recommend the following: (1) Patients with IgM-MGUS or smoldering (asymptomatic) Waldenstrom macroglobulinemia and preserved hematological function should be observed without initial therapy. (2) Symptomatic Waldenstrom's macroglobulinemia patients with modest hematological compromise, IgM-related neuropathy, or hemolytic anemia unresponsive to corticosteroids should receive four standard doses of rituximab alone without maintenance therapy. (3) Waldenstrom's macroglobulinemia patients who have significant constitutional symptoms, profound hematological compromise, bulky disease, or hyperviscosity should be treated with chemoimmunotherapy using either bendamustine in combination with rituximab or the DRC regimen (dexamethasone, rituximab, and cyclophosphamide). Any patient with symptoms of hyperviscosity should first be treated with plasmapheresis (see mSMART algorithm in Fig. 4.1) [44].

Management of Relapsed Disease

Even though there are high overall response rates associated with the upfront treatment regimens and despite the introduction of new therapeutic agents into initial treatment combinations, studies have not clearly demonstrated a significant improvement in the overall outcome of patients with Waldenstrom's macroglobulinemia treated during the last 25 years [61]. These findings highlight the need for more effective agents to further improve patient survival, especially in patients who have failed previous treatment regimens. Fortunately, new therapies and new treatment combinations are currently being tested in patients with refractory and relapsed disease.

Examples of new agents being used in patients with relapsed disease include immunomodulating drugs (IMiDs), including thalidomide and lenalidomide, which have been studied in Waldenstrom's macroglobulinemia in combination with rituximab as these agents enhance rituximab-mediated antibody-dependent

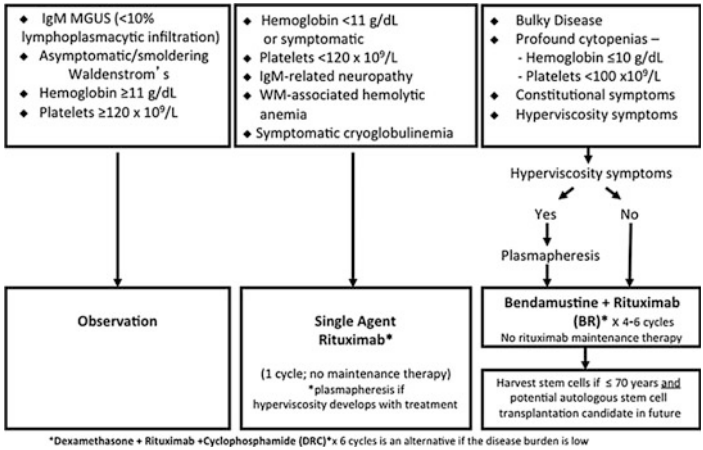

Fig. 4.1 Mayo clinic [mayo stratification of macroglobulinemia and risk-adapted therapy (mSMART)] consensus for management of newly diagnosed Waldenstrom's macroglobulinemia [44]. *MGUS* monoclonal gammopathy of undetermined significance. SI conversion factor: to convert hemoglobin values to g/L, multiply by 10

cellular cytotoxicity (ADCC) [62]. However, despite relatively high overall response rates, treatment with both thalidomide and lenalidomide has been associated with significant toxicity [63]. In the case of lenalidomide and rituximab, the clinical trial was closed early due to reports of significant anemia, which occurred in 13 of 16 treated patients [64]. Therefore, while these agents have demonstrated significant clinical activity, further studies are necessary to identify the optimal dose and schedule of the drug that results in maximal activity with minimal toxicity.

Everolimus, a mammalian target of rapamycin (mTOR) inhibitor, has also been studied in patients with Waldenstrom's macroglobulinemia, due to the previously described role of the PI3K/Akt/mTOR signal transduction pathway as a driver of tumor viability in various hematological diseases, including Waldenstrom's macroglobulinemia [65]. When everolimus was used as a single agent in patients with relapsed or refractory Waldenstrom's macroglobulinemia, an overall response rate of 70 % was reported with a 12-month progression-free survival of 62 % [66]. The drug did have significant toxicity with 56 % of patients developing grade 3 or greater

toxicities that required dose reductions in more than half of the patients. However, despite its toxicity profile, single-agent everolimus appears to be a potential new therapeutic option for the treatment of Waldenstrom's macroglobulinemia.

Due to antitumor activity seen in preclinical studies of the histone deacetylase inhibitor panobinostat in Waldenstrom's macroglobulinemia cell lines, this agent has been studied in a phase II trial of patients with refractory or relapsed disease [67]. Panobinostat was found to be an active in this patient population with an overall response rate of 60 %. Because of frequent hematological toxicities, the dose of panobinostat was decreased from 30 mg three times per week to 25 mg three times per week, and the lower dosing schedule was better tolerated.

In addition to chemotherapeutics, other novel antibodies targeting CD20 are also in development in Waldenstrom's macroglobulinemia to improve upon the response rates seen with single-agent rituximab and to limit the "flare" in IgM often seen with rituximab therapy. One such monoclonal antibody is ofatumumab that targets a different epitope on CD20. Ofatumumab targets an epitope encompassing both the large and small extracellular loops of CD20, whereas rituximab targets only the large loop [68]. Ofatumumab has been studied as a single agent in 37 patients with Waldenstrom's macroglobulinemia, 28 of whom had received a median of three prior therapies [69]. An overall response rate of 59 % was reported, and there was a lower incidence of IgM "flare" as compared to what is typically seen with rituximab. The toxicity profile, which included the development of infection in 15 patients, was deemed to be acceptable, making ofatumumab a further therapeutic option in Waldenstrom's macroglobulinemia, particularly in patients with refractory disease.

Whole-genome sequencing of tumor cells in Waldenstrom's macroglobulinemia has revealed a highly prevalent somatic mutation in *MYD88* [33]. *MYD88* L265P is present in >90 % of patients with Waldenstrom's macroglobulinemia, and supports malignant growth via signaling involving Bruton's tyrosine kinase (BTK). Ibrutinib, an inhibitor of BTK signaling, induces apoptosis of malignant cells bearing *MYD88* L265P. In a clinical trial of ibrutinib in relapsed or refractory patients with Waldenstrom's macroglobulinemia [70], the overall response rate including minor

responses or better was 90.5 %, with a major response rate (partial response or better) of 73 % and a median time to response of 4 weeks. Rapid reductions in serum IgM and improvement in hematocrit occurred in most patients receiving ibrutinib, and the estimated 2-year progression-free survival was 69 %. Furthermore, response rates were higher in patients with mutated *MYD88* compared to wild type. The study confirmed that ibrutinib is highly active and well tolerated in patients with relapsed or refractory Waldenstrom's macroglobulinemia and this agent is now an approved therapy in this disease. It is typically used as the standard second-line agent in relapsed patients.

Finally, stem cell transplantation (SCT) is another potential option in the treatment of patients with advanced Waldenstrom's macroglobulinemia. Autologous SCT is relatively well tolerated, and durable complete responses have been reported [44]. In a retrospective analysis of 158 heavily pretreated patients with Waldenstrom's macroglobulinemia who underwent autologous (SCT), nearly half of the patients remained in remission at 5 years, with a non-relapse mortality rate of only 3.8 %. Five-year progression-free survival and overall survival rates were 40 and 68 %, respectively [71]. While additional prospective studies are needed, these initial results suggest that autologous SCT may have a place in the treatment of Waldenstrom's macroglobulinemia, particularly in younger patients.

A similar retrospective study has also been performed to assess the role of allogeneic SCT in the treatment of Waldenstrom's macroglobulinemia. In a review of 86 patients with Waldenstrom's macroglobulinemia who received an allograft after either myeloablative or reduced-intensity conditioning (RIC) regimens, both the myeloablative and RIC regimens were associated with significantly higher risks of non-relapse mortality at 3 years (33 and 23 %, respectively) [72]. At present, allogeneic SCT is not considered a routine therapeutic option for patients with Waldenstrom's macroglobulinemia outside of a clinical trial.

As there is currently no standard approach to the management of patients with relapsed Waldenstrom's macroglobulinemia, the approach of our group (Fig. 4.2) is to consider all patients for participation in a clinical trial either as definitive therapy for their disease or as preparative therapy prior to considering an autologous SCT [44]. For patients who are ineligible or unwilling to go on a

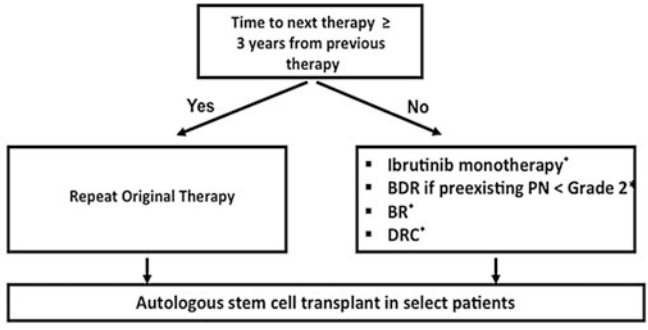

Fig. 4.2 Mayo clinic [mayo stratification of macroglobulinemia and risk-adapted therapy (mSMART)] consensus for management of relapsed Waldenstrom's macroglobulinemia [44]

clinical trial, the choice of therapy is determined by their response to frontline treatment. Because responses to initial therapies are often delayed and can occur a year or more after initiating treatment, we recommend using a 3-year cutoff to determine treatment. For patients with a durable response that lasted >3 years, the original therapy can be repeated. For patients who have an inadequate response to initial therapy or a response lasting <3 years, an alternative approach should be used. Our group will commonly use ibrutinib in these patients if not previously used. An autologous stem cell transplant can also be considered in eligible patients with relapsed disease.

Conclusions

Waldenstrom's macroglobulinemia is a rare disease, and practicing physicians may infrequently treat these patients. Patients may present with a variety of clinical findings, and many patients do not require treatment initially. When patients do require therapy, it is important to select therapies that do not limit future treatment

options. To provide a simple risk-adapted approach to managing patients with Waldenstrom's macroglobulinemia, we have outlined what we feel to be a rational approach to this disease [44]. These recommendations are regularly updated as new data become available and the most current guidelines are available at www.mSMART.org.

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