Biology, Prognosis, and Therapy of Waldenström Macroglobulinemia

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Abstract

Waldenström Macroglobulinemia (WM) is a rare B-cell lymphoma characterized by the uncontrolled accumulation of malignant lymphoplasmacytic cells, mainly in the bone marrow, and monoclonal IgM production. Despite its rarity, our understanding of the biology of this disease has improved significantly in recent years with the identification of recurrent mutations in the MYD88 and CXCR4 genes. Based on the diversity of clinical features observed in WM patients, therapy should be highly personalized having into account several factors such as age, co-morbidities, IgM levels, and presence of hyperviscosity, coagulopathy, cryoglobulinemia, or cold agglutinin disease. In this chapter, we review the recent advances in the biology of WM and the current therapeutic options for untreated and relapsed WM patients. Finally, we discuss the role of prognostic factors and current evidence supporting an improvement in the survival of WM patients in the last decade.

Keywords

Waldenström Macroglobulinemia · MYD88 · CXCR4 · Biology · Therapy · Survival

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Contents

1 Introduction

Waldenström Macroglobulinemia (WM) is a rare B-cell lymphoproliferative disorder characterized by the uncontrolled accumulation of malignant immunoglobulin M (IgM)-secreting lymphoplasmacytic cells. WM belongs to the lymphoplasmacytic lymphoma (LPL) category as defined by the 2008 World Health Organization classification [1]. However, over 95 % of the cases of LPL are WM with the remainder comprised by IgA, IgG, and non-secreting LPL. WM occurs in adults with a median age in the 60s with a slight male predominance. A familial predisposition has been described in approximately 25 % of the patients with WM, with familial patterns varying from presence of various B-cell malignancies, and families in which multiple cases of WM or IgM MGUS have been observed [2].

2 Clinical Features of WM

WM presents predominantly with bone marrow involvement and only a minority of patients (15–30 %) present with extramedullary disease such as lymphadenopathy or hepatosplenomegaly. The most common clinical features associate with anemia (i.e., fatigue, tiredness, and/or shortness of breath) due to overcrowding of the bone marrow space by LPL or iron deficiency [3]. However, given the physicochemical

Table 1 Diagnostic criteria for Waldenström macroglobulinemia

IgM monoclonal gammopathy of any concentration
Bone marrow infiltration by small lymphocytes showing plasmacytic differentiation
Intertrabecular pattern of bone marrow infiltration
Surface IgM+, CD19+, CD20+, CD22+, CD25+. CD27+, FMC7+, CD5±, CD10−, CD23−, CD103−

characteristics of IgM, patients can experience signs and symptoms associated with other mechanisms such as hyperviscosity, cryoglobulinemia, peripheral neuropathy, coagulopathy, cold agglutinins, and tissue deposition in the skin (Schnitzler syndrome), gastrointestinal tract, central nervous system (Bing-Neel syndrome), or kidneys. Patients can rarely present with amyloid deposition, which can cause edema, hepatomegaly, macroglossia, cardiac, liver and kidney dysfunction, and axonal peripheral neuropathy.

3 Diagnosis of WM

The diagnostic criteria for WM are shown in Table 1. A bone marrow aspiration and biopsy is a key component of the diagnostic work-up. The immunophenotypical profile of WM cells shows expression of surface IgM, CD19, CD20, CD22, CD38, and CD79. Up to 20 % of cases may express CD5, CD10, or CD23. An increased number of mast cells in the bone marrow may help differentiate WM from other indolent B-cell lymphomas. A great variety of cytogenetic abnormalities have been described in WM; however, chromosome 6q deletions have been observed in half of the patients [4]. More recently, a recurrent mutation in the MYD88 gene (MYD88 L265P) has been identified in over 90 % of cases with WM [5]. The occurrence of this mutation in WM has since been validated in several independent cohorts [6–9]. In contrast, the MYD88 L265P gene mutation was not detected in patients with IgM myeloma and was detected in less than 10 % of patients with marginal zone lymphoma. The high specificity and sensitivity of the MYD88 L265P gene mutation has obvious diagnostic implications in patients in whom a diagnosis of WM is suspected but uncertain.

4 Biology of WM

The MYD88 L265P gene mutation has shown to support growth and survival of WM cells in several studies. A knockdown model of MYD88 showed decreased survival of MYD88 L265P expressing WM cells, whereas survival was more enhanced by knock-in of mutant *versus* wild-type MYD88 [10]. MYD88 acts as an adaptor molecule in toll-like receptor (TLR) and interleukin-1 receptor (IL-1R) signaling [11]. Following stimulation of TLR or IL-1R, MYD88 is recruited to the activated receptor complex as a homodimer which complexes with IL-1R-associated

kinase 4 (IRAK4) and subsequently activates IRAK1 and IRAK2 [12]. IRAK1 activation then leads to NF-κB activation via IκBα phosphorylation [13]. Recently, a study has shown that MYD88 L265P also activates the Bruton's Tyrosine Kinase (BTK) pathway [10]. In this preclinical study, the activation of BTK by MYD88 could be abrogated by the use of BTK kinase inhibitors. A diagram of the activation of BTK and NF-κB via MYD88 is shown in Fig. 1.

A recent study from our group first ever reported the occurrence of recurrent somatic CXCR4 gene mutations in approximately 30 % of WM patients [14]. The somatic mutations occur in the C-terminal domain and are similar to those observed in patients with WHIM (Warts, Hypogammaglobulinemia, Infections, and Myelokathexis) syndrome. These mutations regulate signaling of CXCR4 by its ligand SDF-1a [15]. In WM patients, two classes of CXCR4 mutations occur: non-sense ($CXCR4^{WHIM/NS}$) and frameshift ($CXCR4^{WHIM/FS}$) mutations [14, 16]. Non-sense and frameshift mutations are almost equally divided among WM patients, and over 30 different types of CXCR4 mutations have been identified. Preclinical studies with the most common CXCR4 S338X mutation in WM have shown sustained signaling of AKT, ERK, and BTK following SDF-1a binding in comparison with wild-type CXCR4, as well increased cell growth and survival of WM cells [17]. Figure 2 shows (a) the protein sequence for the full-length transcript, (b) the crystal structure of CXCR4, and (c) the location of the WHIM-like mutations.

5 Criteria for Initiation of Therapy

Given the indolent and incurable nature of WM, a large proportion of patients would not need immediate therapy upon diagnosis and will be placed on watchful waiting. Current guidelines do not recommend initiation of therapy based on IgM levels alone since they might not correlate with clinical manifestations of the disease [18]. Initiation of therapy is, however, reasonable in patients demonstrating rising IgM levels along with signs or symptoms associated with disease progression. Criteria for initiation of therapy are shown in Table 2. In patients in whom an immediate control of the disease is warranted, such as symptomatic hyperviscosity, coagulopathy, cryoglobulinemia, or cold agglutinin disease, a rapid reduction of the IgM paraprotein should be achieved with plasmapheresis. Treatment directed at WM should follow as soon as possible since plasmapheresis does not constitute definitive therapy and IgM levels will rise and return to baseline levels within 4 weeks.

6 Frontline Therapy for WM

There are several options for the frontline therapy of patients with WM. These options include alkylating agents (i.e., chlorambucil, cyclophosphamide, and bendamustine), nucleoside analogs (i.e., fludarabine and cladribine), the immunomodulator

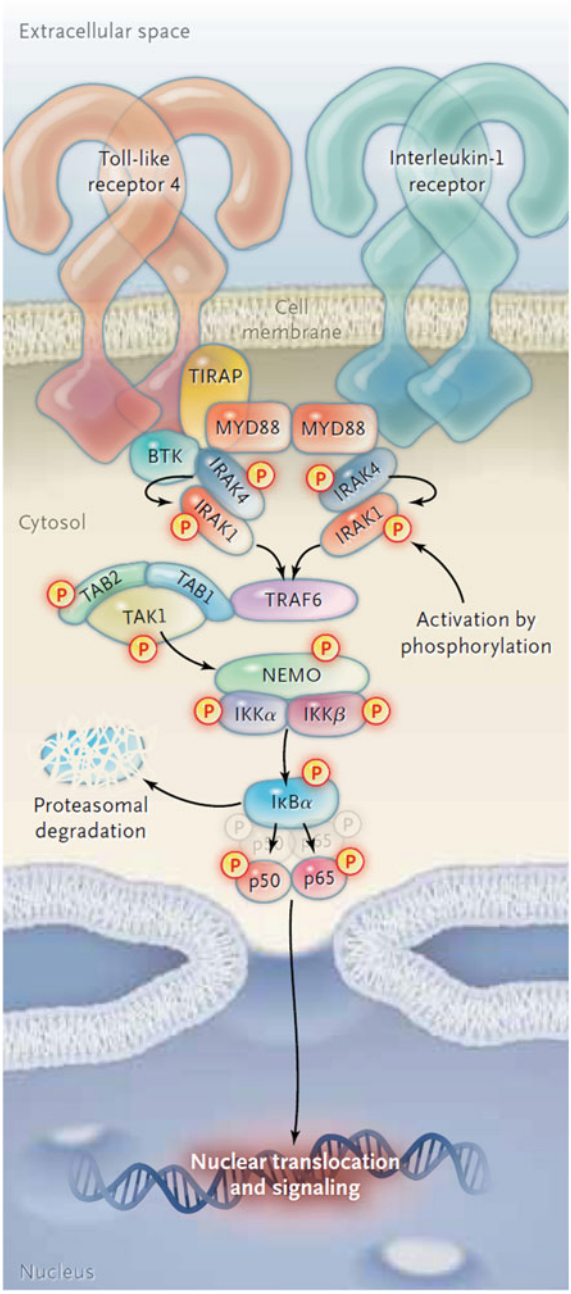

Fig. 1 MYD88-directed BTK and NF-κB signaling. Reproduced with permission from [5]

thalidomide, and the proteasome inhibitor bortezomib, with or without the anti-CD20 monoclonal antibody rituximab [19]. Individual patient considerations should be taken into account when making the choice of frontline treatment including the

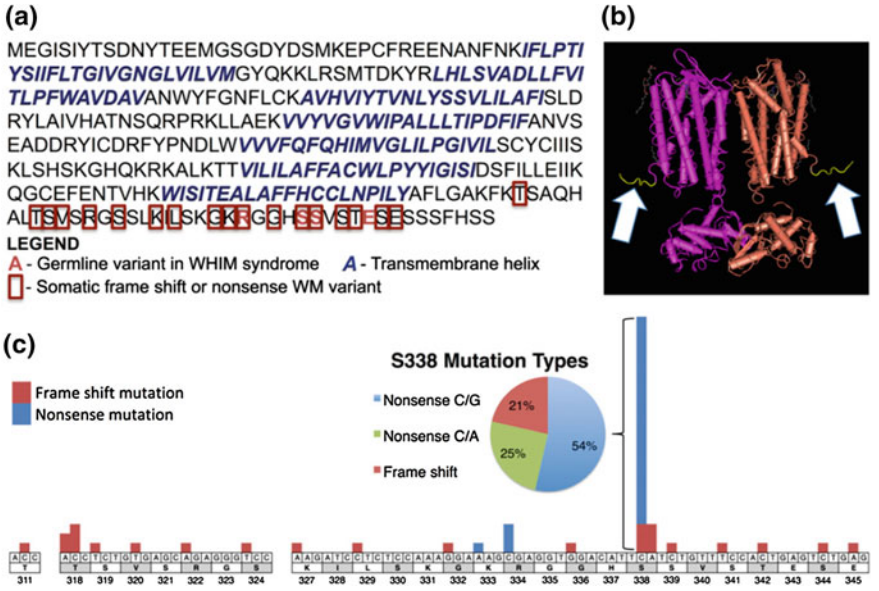

Fig. 2 CXCR4 full-length transcript and structure, and the location of WHIM-like mutations. Reproduced with permission from [14]

Table 2 Criteria for initiation of therapy in Waldenström macroglobulinemia

Constitutional symptoms (i.e., fever, night sweats, fatigue due to anemia or weight loss)
Progressive, symptomatic lymphadenopathy or splenomegaly
Anemia with a hemoglobin ≤10 g/dl
Platelet count <100 × 10^9/L
Hyperviscosity syndrome
Symptomatic sensorimotor peripheral neuropathy
Systemic amyloidosis
Symptomatic cryoglobulinemia

presence of cytopenias, need for rapid disease control, age, pre-therapy IgM levels, pre-existing neuropathy, and candidacy for autologous transplantation therapy. For candidates for autologous transplantation, exposure to alkylator therapy or nucleoside analogs should be limited because of the difficulties with stem cell collection. The use of nucleoside analogs should be approached cautiously given that increased risk of disease transformation, myelodysplasia, and acute myeloid leukemia have been reported.

6.1 Proteasome Inhibitor-Based Therapy

The WM Clinical Trial Group presented data on a study that included 23 patients using bortezomib, dexamethasone, and rituximab (BDR) for the primary therapy of symptomatic WM [20]. Bortezomib was administered at a dose of 1.3 mg/m^2 IV along with dexamethasone 40 mg on days 1, 4, 8, and 11 and rituximab 375 mg/m^2 IV on day 11 every 21 days for four induction cycles, followed by four maintenance cycles administered every 3 months. The overall response rate (ORR) was 96 % with three complete responses (CR), two near complete responses (nCR), and three very good partial responses (VGPR) for a VGPR or better of 35 %. The median time to response was 1.4 months, which makes BDR an excellent choice if a rapid control of disease is required or in young patients to decrease the risk of secondary myeloid malignancies. With a median follow-up of 23 months, 18 out of 23 patients (78 %) remained free of progression. The most common toxicity was peripheral neuropathy; 39 and 30 % of patients, respectively, experienced grade 2 and grade 3 peripheral neuropathy. Grade 2 and grade 3 neutropenia were also reported in 26 % and 26 % of patients, respectively. It is important to note that appropriate Herpes zoster prophylaxis should be instituted in all patients receiving proteasome inhibitor therapy.

Another study evaluated weekly bortezomib in combination with rituximab in 26 untreated patients with WM [21]. In this study, bortezomib was administered at a dose of 1.6 mg/m^2 IV weekly on days 1, 8, and 15 every 28 days for six cycles with rituximab 375 mg/m^2 weekly times four during cycles 1 and 4 only. The ORR was 88 % with a VGPR or better of 8 %. The median time to best response was 3.7 months. The 1-year PFS rate was 75 %. There was 54 % of peripheral neuropathy grade 2 or lower but no grade 3 or higher neuropathy was observed. Grade 3 or higher neutropenia was seen in 12 % of patients. More recently, a study by the European Myeloma Network evaluated the efficacy of weekly bortezomib, low-dose dexamethasone, and rituximab in 59 untreated WM patients [22]. Bortezomib was administered as a single agent at 1.3 mg/m^2 IV on days 1, 4, 8, and 11 (cycle 1) followed 3 weeks later by weekly bortezomib at 1.6 mg/m^2 IV and dexamethasone 40 mg IV on days 1, 8, 15, and 22 and rituximab 375 mg/m^2 IV every 35 days (cycles 2–5). The ORR was 85 % with VGPR or better of 10 %. After a 32-month follow-up, the median PFS was 42 months. Grade 3 or higher peripheral neuropathy occurred in 7 % of patients. The subcutaneous (SQ) administration of bortezomib has shown to be effective and induces less neuropathy than the IV route in patients with myeloma [23]; however, the safety and efficacy of bortezomib SQ has not been formally studied in patients with WM.

A recent study evaluated the combination of carfilzomib, dexamethasone, and rituximab (CaRD) in 31 patients with WM [24]. Carfilzomib was administered at a dose of 20 mg/m^2 IV during cycle 1 and at 36 mg/m^2 IV during cycles 2–6 with dexamethasone 20 mg IV on days 1, 2, 8, and 9 along with rituximab on days 2 and 9 every three weeks during induction therapy. Maintenance therapy consisted on carfilzomib 36 mg/m^2 IV and dexamethasone 20 mg IV on days 1 and 2 and rituximab 375 mg/m^2 on day 2 every 2 months for eight cycles. The ORR was 87 %

with one CR and ten VGPR for a VGPR or better of 35 %. The 15-month PFS rate was 65 %. No grade 3 neuropathy was observed. Grade 3 hyperglycemia and hyperlipasemia were observed in 23 and 16 % of patients, respectively. Of note, the rate of IgG hypogammaglobulinemia increased from 48 % at baseline to 90 % following therapy.

6.2 Alkylator-based Therapy

Cyclophosphamide-based therapy includes regimens in which cyclophosphamide is combined with rituximab and prednisone (CP-R), rituximab, prednisone and vincristine (CVP-R), and rituximab, prednisone, vincristine and doxorubicin (CHOP-R). These regimens would induce an ORR of 70–80 % with CR rate around 10 % [25]. It is unclear if the addition of vincristine or doxorubicin translates into clinical benefits in patients with WM. A retrospective study compared the activity and toxicity of CP-R, CVP-R, and CHOP-R in patients with WM [26]. In that study, CP-R was associated with similar response rates than CVP-R and CHOP-R. However, the rate of treatment complications such as febrile neutropenia, hospitalizations, and neuropathy was lower. Based on these data, CP-R might be preferred over CVP-R or CHOP-R in patients with WM.

The combination of bendamustine and rituximab (BR) has been compared with CHOP-R in a randomized controlled study by the Study Group for Lymphomas in a cohort that included 42 patients with WM [27]. Bendamustine was administered at a dose of 90 mg/m^2 IV on days 1 and 2 along with rituximab 375 mg/m^2 IV on day 1 at 3-week intervals for 6 cycles. The ORR for BR was 96 % and 94 % for CHOP-R. With a median follow-up of 26 months, the PFS rate for BR was 90 % compared with 59 % for CHOP-R. BR was associated with lower rates of grade 3 or higher neutropenia, infectious complications, and alopecia, but with higher rates of skin rash. BR might provide an excellent therapeutic option for patients with lymphadenopathy or patients with pre-existing neuropathy.

6.3 Nucleoside Analog-Based Therapy

In the large randomized controlled study to date, which enrolled 414 patients (339 WM, 37 MZL, and 38 LPL) from 101 centers in five countries, fludarabine was compared with chlorambucil in untreated WM patients [28]. In this study, the ORR for fludarabine was 48 % versus 39 % for chlorambucil. The median PFS was also longer for fludarabine (36 months) in comparison with chlorambucil (27 months). There was a significant improvement in median OS, which was not reached for fludarabine versus 70 months for chlorambucil. Finally, the rate of second malignancies was higher in the chlorambucil arm than in the fludarabine arm (21 % vs. 4 %).

The long-term outcomes of the combination of fludarabine and rituximab (FR) were evaluated in 43 patients with WM, from which 27 patients were untreated

[29]. Therapy consisted of 8 infusions of rituximab at 375 mg/m^2 IV per week administered at weeks 1–4, 17, 18, 30, and 31, along with 6 cycles of fludarabine 25 mg/m^2 IV daily given for 5 days at weeks 5, 9, 13, 19, 23, and 27. The ORR in untreated patients was 96 %. The median time to response was 3.9 months, and the median time to best response was 19 months. The median time to progression in untreated patients was 78 months. Grade 3 or higher adverse events included myelosuppression and infections. Other observed complications were aggressive transformation and secondary malignancies, although most of these events were seen in the previously treated group of patients.

It is unclear at this time whether the combination of an alkylating agent such as cyclophosphamide, a nucleoside analog such as fludarabine, and rituximab (FCR) provides any additional benefits in patients with WM. A study evaluated FCR in 43 patients with WM of which 28 were previously untreated [30]. The FCR regimen consisted of rituximab 375 mg/m^2 IV on day 1 and fludarabine 25 mg/m^2 and cyclophosphamide 250 mg/m^2 IV on days 2 through 4. Cycles were repeated every four weeks for a maximum of six cycles. The ORR was 79 % with no difference between untreated and previously treated patients. Grade 3 or higher neutropenia was seen in 88 % of the patients. After a median follow-up of 39 months, 11 patients (25 %) have died, including five from progressive disease, three from pneumonia, and one from acute myeloid leukemia.

6.4 Other Options

The combination of thalidomide and rituximab (TR) has been associated with an ORR of 70 % and a median PFS of 3 years [31]. TR could be useful in myelosuppressed patients in whom an immediate disease control is not required. The main adverse event associated with thalidomide is neuropathy, which can be seen in up to 40 % of patients treated with TR.

The use of rituximab as single agent can be considered in selected patients with low IgM levels or concurrent autoimmune processes such as cold agglutinin disease, autoimmune thrombocytopenia, or IgM-related neuropathy. The ORR to 4 weekly infusion of rituximab is 20–30 % [32] and to 4 weekly infusions followed by 4 weekly infusions 12 weeks later of 40–50 % [33]. The use of single-agent rituximab in patients with high IgM levels has been associated with IgM flares with an occurrence rate of 40–50 % [34]. These flares might lead to symptomatic hyperviscosity as well as worsening IgM-related neuropathy or cryoglobulinemia. Hence, rituximab monotherapy should be avoided in patients with IgM levels >4,000 mg/dl.

7 Salvage Therapy for Relapsed/Refractory WM

For those patients with relapsed/refractory disease, any of the frontline therapies mentioned above are appropriate options. Therapies in the relapsed setting should also be personalized to the individual patient considering age, performance status, pre-existing neuropathy, IgM levels, and/or need for immediate control of the disease. One must also have in mind to avoid the use of stem cell toxic therapy in patients in whom high-dose chemotherapy with autologous stem cell rescue is being considered.

7.1 Bortezomib

Bortezomib-based therapy has shown to be effective in relapsed or refractory WM patients in several studies, either alone or in combination with rituximab [35–38]. The ORR ranged between 30 and 80 % depending on the study with the most common adverse events being peripheral neuropathy, neutropenia, and thrombocytopenia. Once-weekly administration of bortezomib has been associated with lower rates of neuropathy when compared with the twice-weekly regimen. In one study, bortezomib seemed to be less effective on inducing lymph node responses [35]. As mentioned previously, patients undergoing therapy with proteasome inhibitors should receive prophylaxis against herpes zoster.

7.2 Nucleoside Analogs and Alkylating Agents

Fludarabine has single-agent activity in relapsed WM with an approximate 40 % ORR [39]. The combination FR showed high activity in relapsed/refractory WM patients with ORR of 93 % [29]. The most common adverse events were neutropenia and infections. There were also concerns about aggressive transformation and the development of secondary myeloid malignancies.

The combination BR showed an ORR of 83 % with a median PFS of 13 months [40]. The most common adverse events were prolonged myelosuppression, specifically in patients who had received prior nucleoside analog therapy.

7.3 Ofatumumab

The fully human anti-CD20 monoclonal antibody ofatumumab is also useful in the relapsed/refractory setting. Ofatumumab has shown to be effective and well tolerated in WM patients who develop rituximab intolerance [40]. A study published in abstract form showed an ORR of 57 % in patients with relapsed/refractory WM [41]. The occurrence rate of IgM flare to ofatumumab in this study was 5 %. The most common adverse events were infections.

7.4 Everolimus

Everolimus is an oral mammalian target of rapamycin inhibitor and has induced an ORR of 50 % in patients with relapsed/refractory WM [42]. The median time to response in patients who achieved a PR was 2 months with a median PFS of 21 months. The most common adverse events were anemia, leukopenia, thrombocytopenia, and stomatitis. Everolimus has also been studied in the frontline setting [43]. In this multicenter prospective study, 33 WM patients who were not previously treated received everolimus at a dose of 10 mg PO once daily. The best ORR was 72 % with a median time to best response of 6 months. Interestingly, the bone marrow burden of disease remained unchanged. This bone marrow–IgM discordance complicated response assessment. The most common adverse events were anemia, oral ulcerations, and pneumonitis.

7.5 Ibrutinib

The oral Bruton tyrosine kinase inhibitor ibrutinib has been evaluated in 63 patients with relapsed/refractory WM [44]. Ibrutinib was administered at a dose of 420 mg PO daily. The ORR was 81 % with a median time to response of 4 weeks. The most common adverse events were thrombocytopenia and neutropenia. Of note, WM patients with CXCR4 gene mutations experienced lower response rates to ibrutinib than patients with wild-type CXCR4.

8 Maintenance Therapy

A retrospective study examined the outcome of 248 WM rituximab-naïve patients who were treated with rituximab-containing regimen and then either observed or received maintenance rituximab [45]. In this study, further improved responses after induction therapy were seen in 10 % (16 out of 162) of observed patients and in 42 % (36 out of 86) of patients who received maintenance rituximab. Both PFS (56 vs. 29 months) and OS (>120 vs. 116 months) were longer in patients who received maintenance rituximab. Improved PFS was evident despite previous treatment status or type of induction therapy. Among patients receiving maintenance rituximab, an increased number of infectious events, predominantly grades 1 and 2 sinusitis and bronchitis, were observed. A prospective study examining the role of maintenance rituximab in patients with WM has been initiated by the German STiL group [46]. After undergoing induction therapy with BR, 100 out 162 patients responded to BR (ORR 86 %). From these patients, 43 were then randomized to observation and 47 to maintenance rituximab. Enrollment for this study is complete, and final results are awaited.

9 High-Dose Therapy and Stem Cell Transplantation

The use of stem cell transplantation (SCT) therapy has been explored in patients with WM. Several small series have been reported for autologous and allogeneic transplantation, with variable outcomes. Kyriakou and colleagues reported the largest experience using European Bone Marrow Transplant (EBMT) data for WM patients receiving autologous SCT [47]. Among 158 relapsed/refractory WM patients receiving an autologous SCT, the 5-year PFS and OS rates were 49 and 69 %, respectively. Non-relapse mortality at 1 year was 4 %. Chemorefractory disease and number of prior lines of therapy at time of autologous SCT were the most important prognostic factors for PFS and OS. When used as consolidation at first response, autologous SCT provided a PFS rate of 44 % at 5 years. Long-term outcomes of WM patients undergoing allogeneic SCT from EBMT have been reported [48]. A total of 86 patients received allograft by either myeloablative or reduced-intensity conditioning (RIC). The median age was 49 years, and 47 patients had 3 or more previous lines of therapy. Eight patients failed prior autologous SCT. Fifty-nine patients (69 %) had chemotherapy-sensitive disease at the time of allogeneic SCT. Non-relapse mortality rate at 3 years was 33 % for patients receiving myeloablative transplant and 23 % for those who received RIC. The ORR was 76 %. The relapse rates at 3 years were 11 % for myeloablative and 25 % for RIC recipients. Five-year PFS and OS rates for WM patients who received a myeloablative allogeneic SCT were 56 and 62 %, respectively, and for patients who received RIC were 49 and 64 %, respectively. The occurrence of chronic graft-versus-host disease was associated with improved PFS and suggested the existence of relevant graft-versus-WM effect in this study.

10 Prognostic Factors for Survival in WM

In 2003, the Consensus Panel Recommendation from the Second International Workshop on WM emitted a statement on prognostic markers for survival in patients with WM [18]. In this paper, prognostic factors such as age, hemoglobin level, white blood cell count, platelet count, weight loss, cryoglobulinemia, serum albumin level, IgM level, and beta-2-microglobulin level were identified based on three separate multivariate analyses. However, these studies reported on the survival of WM patients treated with chemotherapy alone 5–10 years before the actual report and, likely, are no longer representative of current outcomes. Since then, multiple studies have aimed at developing prognostic scores that can guide practitioners and WM patients.

Arguably, the most widely used prognostic score is the International Prognostic Scoring System for WM (IPSSWM) [49]. In this study, data on 597 previously untreated WM patients from seven institutions were analyzed. After univariate and multivariate evaluation, five adverse prognostic factors were identified: age >65 years,

hemoglobin ≤11.5 g/dl, platelet count ≤100 × 10^9/L, beta-2-microglobulin >3 mg/dl, and monoclonal IgM concentration >7 g/dl. The hazard ratio (HR) for OS of most of the factors ranged between 1.5 and 1.9, with the exception of age (HR 2.8). Patients were stratified in three risk groups: low (0 or 1 factor except for age), intermediate (age or 2 factors), and high risk (≥3 factors). The distribution of the groups was as follows: low (27 %), intermediate (38 %), and high risk (35 %). The median OS for the low, intermediate, and high-risk groups were 143, 99, and 44 months, respectively. One of the caveats of this study is that 63 % of patients were treated with alkylating agents and 32 % with fludarabine alone; only 4 % of patients received rituximab.

In several other recent studies, age, hemoglobin, and beta-2-microglobulin have been identified as prognostic factors. Selected studies and their results are shown in Table 3. However, most of the studies included patients diagnosed and/or treated before 2003, which implies that the large majority of the patients included in those analyses were not treated with anti-CD20 monoclonal antibodies or proteasome inhibitors. It is important to note that the VGPR and CR rates in WM patients appear higher with the combination of proteasome inhibitors and rituximab than with alkylating agents or nucleoside analogs. It is likely that deeper responses will be associated with prolonged survival times, which has been seen in chronic lymphocytic leukemia and multiple myeloma (references).

Table 3 Selected studies evaluating prognostic factors for overall survival in patients with Waldenström macroglobulinemia

Reference	Country	Accrual period	*N*	Prognostic factors
Dimopoulos et al. [22]	Greece	1985–2001	122	Age ≥65 years
				Hemoglobin <10 g/dl
Dimopoulos et al. [36]	Greece	1990–2003	83	Beta-2-microglobulin <3.5, 3.5–5.5, > 5.5 mg/dl
				Albumin <3.5 mg/dl
Ghobrial et al [37, 42]	USA	1960–2001	337	Age >65 years
				Organomegaly
[62]	USA	1992–1998	59	Age ≥70 years
				Previous non-protocol therapy
				Beta-2-microglobulin ≥3 mg/dl
				Elevated LDH level
Morel et al. [49]	Multinational	Before 2002	587	Age >65 years
				Hemoglobin ≤11.5 g/dl
				Platelets ≤100 × 10^9/L
				Beta-2-microglobulin >3 mg/dl
				Serum monoclonal protein >7 g/dl
Kastritis et al [51]	Greece	Unknown	232	IPSSWM
				Elevated LDH level

A recent study evaluated differences in PFS in WM patients who obtained a CR or VGPR with rituximab-containing therapy [50]. In this study, 159 rituximab-naïve WM patients were treated with rituximab-containing regimens that included rituximab alone or in combination with cyclophosphamide, fludarabine, immunomodulatory agents, or bortezomib. Patients who achieved a CR or VGPR had a median PFS over 75 months compared with 43 months and 31 months in patients who achieved a PR or a minor response to therapy, respectively. Neither age, IgM level, hematocrit, platelet count, beta-2-microglobulin, IPSSWM, or treatment group were predictors of the attainment of CR/VGPR.

11 Trends in Survival in WM

Previous epidemiologic studies suggested that the survival of WM patients could be prolonged and sometimes measured in decades. It is unclear, however, if the survival of patients with WM has improved with the advent of novel therapies.

A Greek study included 345 patients with WM, of who 130 initiated therapy before the year 2000 and 215 who started after 2000, and showed no evidence of overall survival improvement in the latter group. A survival benefit was expected based on the availability of the chimeric anti-CD20 antibody rituximab in Greece after 2000 [51]. However, the group treated after the year 2000 was older (70 vs. 65 years) and presented with higher-risk disease when compared with those treated before 2000. Also, the median follow-up for both groups was rather short, approximately 9 and 3 years for the groups before and after 2000, respectively. It is possible that given the small sample size and short follow-up, the study might have been underpowered to detect the expected benefit.

A Swedish study included 1,555 patients with WM diagnosed between 1980 and 2005 [52]. In this study, in which 1,187 patients were diagnosed before 2000 and 368 after 2000, a continuous RS benefit was identified with improvements seen in 1990s as well as the 2000s. Older patients and men had worse outcomes. The authors evaluated lead-time bias (i.e., longer survival in patients diagnosed earlier in the course of the disease) as one of the factors associated with the improvement seen in the outcomes of patients with WM and did not find differences in the proportion of asymptomatic patients diagnosed before or after 2000.

More recently, a large study based on data from the Surveillance, Epidemiology, and End Results database included over 6,000 patients and aimed at evaluating survival trends in US patients with WM [53]. In this study, the RS of patients with WM has improved over the last decade when compared with the 1980s and the 1990s. Figure 3 shows 5-year RS in WM patients over the last 3 decades in 5-year period. The survival benefits were observed regardless of age, sex, extramedullary disease, histological subtype (LPL vs. WM), and US region. Survival benefits were seen in whites but not in blacks. Blacks have had consistently worse outcomes than whites in previous epidemiological studies in various lymphoproliferative disorders [54–58]. This disparity in outcomes seen in blacks has been ascribed to differences

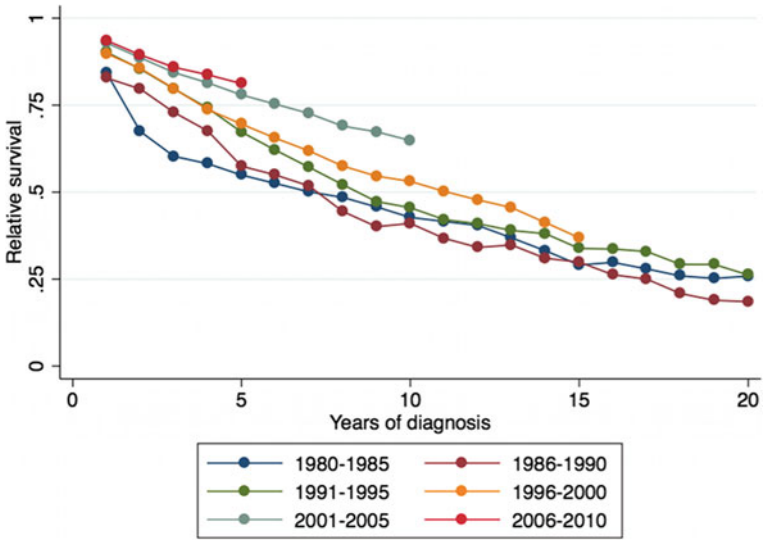

Fig. 3 5-year relative survival estimates in patients with Waldenström Macroglobulinemia from the SEER database (1980–2010), according to 5-year period of diagnosis. Reproduced with permission from [51]

in socioeconomical status, health insurance coverage, and patients' or providers' attitudes toward therapy. Purely biological factors may also play a role, considering that blacks have an increased incidence of IgG and IgA MGUS but a lower incidence of IgM MGUS. It is unclear, however, if this difference is responsible for the worse outcomes seen in black patients with WM.

12 Conclusion

There are multiple options for the treatment of patients with WM in the frontline as well as the relapsed setting. However, the treatment regimens would have to be thoughtfully selected depending on the patient's characteristics such as age, comorbidities, IgM levels, and genetic mutations. Age, beta-2-microglobulin level, and hematological parameters seemed to be the best prognostic factors associated with OS in patients with WM. However, studies evaluating these factors in large cohorts of patients treated with novel agents are lacking. Finally, the survival of patients with WM appears to be improving in the last decade, probably associated with the advent of novel agents and better supportive therapy. Novel agents such as the phosphatidylinositol 3-kinase inhibitor idelalisib (CAL-101, GS-1101), the bcl-2 inhibitor GDC-199 (ABT-199), the oral proteasome inhibitor ixazomib (MLN9708), and the glycoengineered anti-CD20 monoclonal antibody obinutuzumab (GA-101), to cite a few, will shortly enter clinical trials for WM. A recent phase II study studied idelalisib in 125 patients with relapsed/refractory indolent

lymphoma, of which 10 patients had LPL/WM [59]. From these, 2 patients achieved a PR and 6 a minor response for an ORR of 80 %. In a smaller phase I study on 64 patients with relapsed/refractory indolent lymphoma [60], the ORR in LPL/WM patients was 55 % (5/9 patients). In a phase I study on 44 patients with relapsed/refractory indolent lymphoma, GDC-199 induced a response in 3 out of 4 WM patients (ORR 75 %), including one CR [61]. Promising agents with greater efficacy, novel mechanisms of action, and better safety profiles are likely the future of WM therapy.

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