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REVIEW ARTICLE

Updates in prognostication and treatment of Waldenström's macroglobulinemia

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Abstract
Waldenström's macroglobulinemia (WM) is a rare, incurable hematologic disorder with a relatively indolent course in a majority of the patients. Despite this, a significant proportion of patients require treatment because of hypersecretion of immunoglobulin M and the invasion of bone marrow and peripheral organs by neoplastic lymphoplasmacytic lymphoma cells. Historically, there has been a dearth of research and therapeutic advancements in the field of WM, with most understanding based on other, related B-cell lymphoid malignancies, including multiple myeloma, chronic lymphocytic leukemia, and non-Hodgkin lymphoma. Recently, there has been an increase in dedicated work to better explain the pathobiology of WM, which has identified several clinical and genetic markers that serve to prognosticate disease course and patient outcomes. Furthermore, this has led to dedicated clinical trials and the development of novel drugs/regimens including the first Food and Drug Administration-approved agent for this diagnosis, ibrutinib. This review aims to document some of the recent advancements with respect to prognostic markers and therapeutic options for patients with WM, as well as certain selected novel treatments with unique mechanisms of action, that are currently under development.

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Introduction

Waldenström's macroglobulinemia (WM) is a rare lymphoproliferative malignancy, with an estimated 1,500 new cases diagnosed per year in the United States and an incidence of three to five cases per million persons per year [1—3]. Of all B-cell neoplasms, WM accounts for approximately 1—2% of diagnoses and is an indolent disease with a median survival quoted anywhere from 5 years to greater than 10 years [4,5]. The diagnostic criteria for WM have evolved over time; current guidelines, as determined by the 7th International Workshop on Waldenström's Macroglobulinemia, broadly define it as a lymphoplasmacytic lymphoma (LPL) that manifests with hypersecretion of immunoglobulin M (IgM) and the invasion of bone marrow and peripheral organs by neoplastic B cells [6]. The median age at diagnosis is 64 years; however, WM has been known to occur in younger patients, with a slight female preponderance [3,7,8]. Whites are more commonly affected than Blacks, and it is rare in individuals with Mexican ancestry [3]. The most important risk factor for developing the malignancy is a preexisting diagnosis of IgM-type monoclonal gammopathy of undetermined significance (MGUS), which transforms to WM at a rate of 1.5% per year [9]. Compared to the general population, individuals with IgM-MGUS have a 46-fold higher relative risk to develop WM [9,10]. Data collected by the National Cancer Institute from a large cohort of WM patients with unaffected siblings suggest that patients have a higher incidence of autoimmune diseases, infections, exposure to pesticides, organic solvents, and farming as compared to their unaffected kin [11].

Pathogenesis and disease biology

Although the precise etiology of WM remains unclear, it is believed that most frequently the malignant WM clone arises from a postgerminal center B-lymphocyte, which has encountered antigenic exposure, undergone somatic hypermutation, and is transformed prior to isotype switching [12]. This clone is perceived to originate from a mature, memory-like B lymphocyte that displays lymphoplasmacytoid morphology and secretes IgM [13]. Immunophenotype of the WM clone varies but is generally composed of surface IgM+, CD5—, CD10—, CD19+, CD20+, CD23—, CD79a+, and PAX5+ cells and as such, the malignant cells share considerable resemblance with those of related malignancies such as multiple myeloma (MM) and chronic lymphocytic leukemia (CLL) [14]. Through the use of next-generation sequencing and allele-specific polymerase chain reaction techniques, it is well established that >90% of WM patients harbor an L265P mutation in the myeloid differentiation primary response gene 88 (*MYD88*) [15—17]. The L265P mutation in *MYD88* ($MYD88_{L265P}$) leads to spontaneous and enhanced assembly of IRAK1 and IRAK4 with constituent activation of the nuclear factor-kappa B (NF-κB) and Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathways, which inevitably lead to cellular proliferation [18]. Mutant $MYD88_{L265P}$ protein can also associate with Brutons tyrosine kinase (BTK) protein, which is a proximal component of the B-cell receptor (BCR) pathway and together, the $MYD88_{L265P}$/BTK protein complex further contributes to this cellular pathway activation, regulating the expression and stability of several tumor promoting genes (including c-MYC, interleukin [IL]-6, Bcl-xL, Gadd45b, and inhibitors of apoptosis) [17—19]. The net effect of the mutant $MYD88_{L265P}$ protein is unchecked growth of WM cells, and recognition of this has exposed WM cells to therapeutic BTK targeting through ibrutinib [1].

Clinical presentation

Although it is generally an indolent disease, there is considerable heterogeneity in the clinical presentation of WM. Approximately 25% of WM patients are asymptomatic at diagnosis, with nearly 40% and 70% developing symptomatic disease within 3 years and 10 years of diagnosis, respectively. Patients may present with constitutional symptoms including fatigue, malaise, fever, and/or weight loss [20].

More than a third of patients will have anemia–a result of insufficient erythropoiesis because of marrow infiltration, decreased erythrocyte survival secondary to IgM-associated hemolysis, low erythropoietin levels, or concomitant iron deficiency [21,22]. Lymphadenopathy and/or hepatosplenomegaly are noted in approximately 25% of patients. As IgM forms sizable pentamers, which are primarily localized within the vascular compartment, a hyperviscous state may be seen in up to a third of WM patients. Hyperviscosity syndrome generally manifests with headache, dizziness, ataxia, visual disturbances, nystagmus, tinnitus, deafness, mucocutaneous bleeding, and rarely impaired cognitive function or altered mental status. Neurologic complications may also occur, with distal peripheral neuropathy, typically sensory and symmetric, noted in 25—50% of WM patients. As IgM can pathologically behave as an autoantibody, resulting in a wide range of autoimmune-like symptoms, the underlying cause of the neuropathy and nerve damage in some patients may be associated with specific antigenic targets of IgM, including myelin-associated glycoprotein (MAG). Additionally, precipitation of IgM can lead to cryoglobulinemia and cold agglutinin syndrome in about 10% of patients, which may manifest as Raynauds phenomenon, acrocyanosis, or hemolytic anemia.

Prognostic factors and risk stratification

The median survival of WM patients is approximately 7.4 years (95% confidence interval [CI], 6.8—8.2), and with the advent of newer, more tolerable therapies, survival is expected to increase [23]. It is important to note that WM-related mortality is associated with symptomatic disease, whereas asymptomatic WM patients have an overall survival (OS) similar to that of the general population. To date, earlier intervention in asymptomatic patients has shown no benefit in extending survival [24]. Thus, an active surveillance strategy is typically used so as to maintain quality of life and avoid unnecessary exposure to anticancer therapy. As such, various clinical and genomic characteristics have been examined for their ability to identify patients who might have poor prognosis and perhaps require definitive therapy.

Clinical aspect

Several groups have examined the association of clinical characteristics and manifestations with clinical outcome of WM patients. The International Prognostic Staging System for WM (IPSS-WM) is the most well developed and validated tool for risk stratification of symptomatic WM patients requiring treatment, established using 587 patients from seven different institutions [5] (Table 1). The staging system relies on five common clinical characteristics, with low-risk disease (27% incidence) defined by the presence of one or less adverse characteristic and age $\leq$65 years; intermediate-risk disease (38% incidence) defined as two adverse characteristics and age >65 years; and high-risk disease (35% incidence) categorizes as having three or more adverse factors. OS was 87%, 68%, and 36% in the low, intermediate, and high-risk groups, respectively. Kastritis et al. [25] independently validated the IPSS-WM and additionally, demonstrated that combining with lactate dehydrogenase (LDH) levels further improved the ability of the system to delineate high-risk patients with a median survival <3 years. Sex, presence of B symptoms, IgM value, performance status, presence of hyperviscosity, bone marrow infiltration, and cytogenetic changes have also been reported as risk factors by other investigators [26].

Investigators from the Southwest Oncology Group tested the prognostic ability of a three-covariable system including serum β2-microglobulin, hemoglobin concentration, and IgM levels, with a median follow-up of 10 years [27] (Table 1). This system divided patients into low (β2-microglobulin <3 mg/L and hemoglobin $\geq$12 g/dL), intermediate (β2-microglobulin <3 mg/L and hemoglobin <12 g/dL or β2-microglobulin $\geq$3 mg/L and serum IgM $\geq$4 g/dL), and high-risk groups (β2-microglobulin $\geq$3 mg/L and IgM $\geq$4 g/dL) with 5-year OS rates of 87%, 63% and 53% (for the two distinct intermediate-risk categories), and 21%, respectively [27]. At a 10-year follow-up, elevated LDH was an independent additional risk factor associated with compromised survival [28]. As this model was developed in the context of a clinical trial, extrapolation of its prognostic significance, especially to patients who are ineligible for clinical trial enrollment, is questionable.

Table 1 Clinical Prognostic Models for Patients with Waldenstrom's Macroglobulinemia (WM).

	IPSS-WM[a5]	SWOG [27]	Mayo Clinic [29]	French Group [30]
Number of patients	587	231	337	318
Variables/risk factors	• Age > 65 years • Hemoglobin $\leq$ 11.5 g/dL • Platelets $\leq 100 \times 10^9$/L • β2M > 3 mg/L • Serum IgM > 7 g/dL	• β2M • Hemoglobin level • IgM level	• Age > 65 years • Presence of organomegaly • β2M	• Age $\geq$ 65 years • Serum albumin < 4 g/dL • Presence of $\geq$ 1 cytopenias
High risk criteria	>3 adverse risk factors	β2M $\geq$ 3 mg/L and IgM $\geq$ 4 g/dL	Presence of both risk factors and β2M $\geq$ 4 mg/L	Presence of all 3 adverse risk factors
Survival outcome for high risk disease	5-year OS: 36%	5-year OS: 21%	10-year OS: 5%	5-year OS: 25%

Note. β2M = beta-2-microglobulin; IgM = immunoglobulin M; IPSS-WM = International Prognostic Staging System for WM; LDH = lactate dehydrogenase; OS = overall survival; SWOG = Southwest Oncology Group.
[a]Modified IPSS-WM as reported by Kastritis et al. [25] also includes LDH as a variable/adverse risk factor.

In another prognostic model reported from 337 WM patients with symptomatic disease, age and presence of organomegaly were the reported variables [29] (Table 1). Presence of any one risk factor correlated with a 10-year estimated survival rate of 16%, whereas having both risk factors decreased the OS to 5%. Conversely, patients without either risk factor were found to have a survival rate of 57%. Additionally, the investigators observed that β2-microglobulin ≥4 mg/L was linked to an increased risk of death by three-fold. Prior to these studies, earlier models using similar clinical characteristics have been reported as well. Another one of the larger prognostic models used patient age, serum albumin, and the presence of one or more cytopenias as the major risk factors for poor survival, with the 5-year OS going from 87% to 25% with the risk factors ranging from ≤1 to ≥3 [30] (Table 1). Gobbi et al. [31] independently noted that age >70 years, hemoglobin <9 g/dL, and the presence of weight loss or cryoglobulinemia were the most important prognostic features.

Thus, the IPSS-WM or similar clinical prognostic models have been reported and validated in large patient datasets to suggest prognosis in symptomatic WM patients.

Genomic aspect

Deletion 17p or loss of TP53

The significance of abnormalities in chromosome 17 is largely attributed to the fact that the p53 tumor suppressor gene (*TP53*) resides in its p13 locus. Deletion or functional loss through mutation in *TP53* leading to deregulation of cellular proliferation, cell-cycle checkpoint, DNA repair, and apoptosis is well established in cancer biology [32–34]. Deletion 17p (Del 17p) was initially reported at a low frequency in heterogeneous WM cohorts and was found to be associated with significantly shorter progression-free survival (PFS) [34,35]. However, the exact relationship between TP53 mutation, p53 activity, and the genomic landscape of WM remains understudied. In a recent study of 125 WM patients, somatic *TP53* mutations were observed in 7.3% of patients [36]. No mutation was observed in IgM MGUS patients. No association was observed between mutations in *TP53* with *MYD88*, *CD79A*/*CD79B*, or *CXCR4*. Overall, the study showed that *TP53* alteration, irrespective of *TP53* mutation or Del17p, defines a high-risk population in WM characterized with significantly shorter time to progression (TTP) for symptomatic WM or time to treatment (TTT) for indolent WM, and subsequently OS. The median OS was significantly shorter in WM with *TP53* alteration (9 years; 95% CI, 6–11) compared to patients without these genomic abnormalities (18 years; 95% CI, 6–29; $p = .003$). Clinically, patients with *TP53* alterations were noted to have β2-microglobulin >3 mg/L (89% vs. 40%, $p = .012$), and a higher (≥2) IPSS-WM score (50% vs. 30%, $p = .041$, respectively). In indolent WM patients with *TP53* alteration ($n = 9$), a shorter median TTT was observed (2 years; 95% CI, 1–3) relative to *TP53* wildtype (WT) patients (5 years; 95% CI, 4–6; $p = .001$).

MYD88

Presence of the $MYD88_{L265P}$ gene mutation is now considered an essential biomarker for distinguishing WM from IgM MM or splenic marginal-zone lymphoma (MZL), as it is observed at a much lower frequency (5–7%) in patients with the latter diseases. In a series by Treon et al. [37] approximately 30% of cases suspected to be $MYD88^{WT}$ WM were subsequently found to be IgM MM, MZL, DLBCL, CLL, or IgM MGUS. It is interesting that in patients with IgM MGUS, $MYD88_{L265P}$ is also observed in >50% of cases and thus might represent an early event in the transition from normal to neoplastic. Although possibly prognostic, *MYD88* mutation status alone does not explain the slow rate of IgM-MGUS transformation to overt WM. More recently, data have begun to emerge on both the biological and clinicopathologic characteristics of $MYD88^{WT}$ WM/LPL cases. Transcriptome profiling shows heterogeneous gene expression in $MYD88^{WT}$ cases that differ from $MYD88_{L265P}$ WM cases [38]. $MYD88^{WT}$ patients show no major responses to ibrutinib, and increased risk of death versus $MYD88_{L265P}$ patients [15,39]. Histologically, patients with $MYD88^{WT}$ show similar features to $MYD88_{L265P}$ patients but may present with significantly lower bone marrow involvement and relatively uncommon *CXCR4* mutations as compared to $MYD88_{L265P}$ cases [40]. In terms of impact on survival outcome, in one series, the estimated 10-year survival was reported to be 73% (95% CI, 52–86%) and 90% (95% CI, 82–95%) for $MYD88^{WT}$ and $MYD88_{L265P}$ patients, respectively (log-rank $p < .001$) [37]. Intriguingly, the incidence of transformation to DLBCL at 20 years in $MYD88_{L265P}$ patients was 8% (95% CI, 1–39%) versus 29% (95% CI, 12–58%) in $MYD88^{WT}$ patients (hazard ratio = 19.8; 95% CI, 4.08–95.8; $p < .001$) [37].

CXCR4

In addition to $MYD88^{WT}$, truncating mutations in the C-X-C chemokine receptor type-4 (*CXCR4*) gene may act as potential modifiers of drug response in WM, particularly toward ibrutinib [15,41]. In a large study evaluating 418 patients with B-cell lymphoproliferative disorders, *CXCR4*-associated mutations (primarily *C1013G*/*CXCR4*) were seen in 28.2% patients with WM as compared to only 7% in other B-cell lymphomas [41]. CXCR4 is known to modulate cell trafficking in clonal B cells and homing of $CD34^{+}$ cells to the bone marrow niches [42]. Specifically, the *C1013G* mutation was noted to have an activating role in WM cells showing increased tumor proliferation and association with extramedullary organ involvement, resulting in decreased OS. It has been reported that WM patients who are $MYD88_{L265P+}$/*CXCR4*-mutated (38% patients) exhibit suboptimal response versus 62% of $MYD88_{L265P+}$/*CXCR4-WT* patients who demonstrate major responses to the BTK inhibitor, ibrutinib [15].

Management

A variety of algorithms have been developed to triage patients toward the most appropriate course of clinical management with the three most widely used systems being the Mayo Clinic M-SMART guidelines, the National Comprehensive Cancer Network (NCCN) recommendations, and those from the Eighth International Workshop for WM [43–45]. However, it is generally agreed that owing to its indolent and so far incurable nature, control of symptoms and reducing organ damage are the more immediate

objectives of therapy. Overall, the goals of treatment should be to maintain long-term disease control, balancing the risks and benefits of therapy so as to limit drug-related toxicity, enhance OS, and improve quality of life.

Newly diagnosed

Low-risk symptomatic WM patients without bulky disease, profound cytopenias, or hyperviscosity syndrome and with mild–moderate anemia, symptomatic cryoglobulinemia, or hemolytic anemia that does not respond to steroids, are recommended per mSMART guidelines to receive anti-CD20 monoclonal antibody (mAb) therapy with single-agent rituximab [44]. As a single agent, rituximab has been reported to have a median PFS of 16–29 months, and an overall response rate (ORR) of 25–40% from a single 4-week cycle and 65% with an extended course of two 4-week cycles administered 8 weeks apart [44]. Rituximab use can be associated with an IgM flare in approximately 50% of patients (defined as $\geq$25% increase above baseline serum IgM level), and thus, it should be introduced when the IgM level has decreased, using plasmapheresis or other techniques [46]. A second-generation anti-CD20 mAb, ofatumumab, may be considered in patients intolerant to rituximab [47]. Rituximab monotherapy is considered suboptimal for patients requiring immediate disease control, where rituximab-based chemoimmunotherapy regimens are recommended. In patients with low disease burden, six cycles of the DRC (dexamethasone, cyclophosphamide, rituximab) regimen are acceptable [48,49]. In a multicenter, Phase II study of 72 treatment-naïve patients DRC demonstrated an ORR of 83%, with a favorable toxicity profile (Grade 3/4 adverse events in 9% of patients) [49]. For patients with higher disease burden, severe cytopenias (hemoglobin <10 g/dL or platelets <100,000/L), and constitutional symptoms, the BR (bendamustine and rituximab) regimen is recommended for four to six cycles. If hyperviscosity symptoms are evident, plasmapheresis is first recommended prior to initiation of BR therapy. The rationale for this treatment regimen is based on data from the Phase III Study Group Indolent Lymphomas (StiL) trial, in which a subset consisted of WM patients (n = 41) [50]. In this same trial, 22 WM patients received R-CHOP (rituximab plus cyclophosphamide, doxorubicin hydrochloride, vincristine sulfate, and prednisone). With both regimens, ORR was approximately 95%; however, BR was better tolerated with lower rates of infections, hematologic toxicities, neuropathy, stomatitis, and alopecia. Although no significant survival benefit was observed between patients receiving BR versus R-CHOP, a longer PFS (median 69.5 months; interquartile range, 36.6–73.0 months) was noted in the BR cohort. Additionally, if the patient is $\leq$70 years of age and has low tumor burden after initial therapy, stem cells should be harvested if autologous stem cell transplant (ASCT) is to be considered for future management of disease.

The use of bortezomib-based regimens has also been examined in the frontline setting for WM. The BDR regimen (bortezomib, dexamethasone, rituximab) has been investigated across three Phase II studies and demonstrated an ORR ranging from 81% to 96%, with generally a rapid time to response [51–53]. An important limitation of bortezomib use in WM has been its well-studied association with peripheral neuropathy, which may be attributable to the disease itself and possibly further compounded by bortezomib [54]. In the WMCTG05-180 trial, the overall incidence of all grade peripheral neuropathy was 69%, with Grade 3 levels seen in 30% of patients, leading to early discontinuation in 61% of patients [53]. Subsequently, decreased dose-density strategies for BDR with once weekly bortezomib were used, showing a significant reduction in neurotoxicity (Grade 3, 0–7%), albeit also at the expense of a lower response rate (major response rate, 65%–68%) [51,52]. Subcutaneous administration of bortezomib, the standard of care in MM, is now being studied in the frontline setting in WM, to further improve peripheral neuropathy, while maintaining efficacy (NCT01592981). Carfilzomib and ixazomib, newer generation proteasome inhibitors, have overcome the issues of neuropathy associated with bortezomib. A Phase II study of the IDR regimen (ixazomib, dexamethasone, rituximab) showed an ORR of 96% with a major response rate of 77% (VGPR + PR) and an 18-month PFS of 90% [55]. Major responses were observed in 69% of patients with *CXCR4* mutations versus 82% in those who were CXCR4-WT (p > .05). Importantly, Grade 1/2 neuropathy was noted in only 19% of patients with Grade $\geq$3 observed in only one patient [56]. Similarly, the combination of carfilzomib, with rituximab and dexamethasone (CaRD) has been reported as highly effective in WM, with no significant treatment-related peripheral neuropathy [57]. In a Phase II trial of 31 patients, given six cycles of induction followed by a less intensive maintenance regimen using the same agents, an ORR of 87% was observed, with a combined VGPR+CR rate of 36% [57]. *MYD88* and *CXCR4* mutations were noted in 96% and 36.7% of the patients, respectively, with the ORR being similar in patients who were *CXCR4-WT* or carried the *CXCR4 WHIM* mutation (85% and 90.9%, respectively). Overall, median time to first response was 2.1 months (range, 0.7–14.7 months), with median time to best response being 12.8 months (range, 2.1–25 months). The median PFS for all patients was 46 months (range, 2–63 months), with significantly longer PFS noted for patients with a deeper response (VGPR+CR). The adverse event profile was manageable, with only one patient experiencing Grade 2 peripheral neuropathy (3.2%) with no Grade 3/4 neuropathy-associated events reported.

Maintenance

Maintenance therapy with rituximab has been examined in other B-cell lymphomas and shows improvement of clinical outcome; however, definitive data have been lacking in WM. In a single-center study, the outcome of 248 patients who were rituximab-naïve and had subsequently received a rituximab containing induction therapy in which at least an minimal response was achieved, the role of maintenance was looked at retrospectively [58]. Of these patients, 34% (n = 86) received maintenance therapy following induction treatment, whereas the remaining patients (n = 162, 65%) were monitored without any maintenance treatment. Significantly better response rates (CR, VGPR, and PR) were seen among patients who received maintenance therapy as compared to those who did not (p < .001). Both PFS and

OS were significantly longer in patients on the maintenance arm (56.3 months and not reached, respectively) versus the observational arm (28.6 and 116 months, respectively, $p = .009$). Of note, the maintenance regimen reported in this analysis was not uniform, and there was prolonged immunosuppression noted in some cases. In another retrospective study from the same group, response and survival outcome were compared in WM patients who received induction treatment with DRC, BDR, or BR regimens, followed by maintenance with rituximab versus those who received induction therapy alone [59]. From a total of 182 patients, 116 (64%) received maintenance therapy and had significantly higher rates of major response (97% vs. 68%), better median PFS (6.8 years vs. 2.8 years) and 10-year OS rate (84% vs. 66%) compared to patients who did not receive maintenance.

Owing to the lack of prospective randomized studies showing benefit of maintenance with rituximab, this is not a universal recommendation among all the treatment guidelines for WM. The significance and impact of maintenance rituximab is currently being assessed in a prospective randomized trial in Germany (NCT00877214) where 2 years of rituximab maintenance is being compared with observation alone following induction therapy with BR regimen.

Salvage treatment

Although most patients tend to have durable responses to frontline therapy with the aforementioned treatments, minor subsets experience disease relapses. The grounds for initiating treatment in relapsing patients are mostly the same as those for previously untreated patients. Biochemical progression alone generally does not warrant initiation of treatment, until the onset of symptoms. The most appropriate forward strategy for these patients is contingent on several factors such as the depth and duration of first remission with initial therapy, the patient's level of tolerability to the prior regimen, candidacy for ASCT, and the possible effects on the ability to receive future alternative treatments. Retreatment of patients with the first-line therapy they received is an option if the time-to-next-treatment (TTNT) was $\geq$3 years from the initiation of the previous therapy [44]. In the relapsed/refractory patients, BR (or bendamustine combined with ofatumumab) therapy yields an ORR of 83% with a median PFS of 19 months but may be associated with prolonged myelosuppression in patients who had formerly received a purine-nucleoside analog [60,61]. In patients who do not have preexisting peripheral neuropathy of Grade $\geq$2, the BDR regimen is also an acceptable alternative with responses in 85—96% of patients [51,53].

Several studies have now demonstrated the importance of ASCT in maintaining long-term disease control in WM [62,63]. A strategy recommended within the mSMART guidelines is to utilize cryoperserved cells as early as possible in chemosensitive, relapsed patients as the efficacy of ASCT may be much lower in patients treated with three or more lines of prior therapy. Although CR rates in the order of 61—66% have been noted with ASCT, toxicity associated with the process may be significant with a 1-year treatment-related mortality rate reported up to 44% [62]. The role of allogeneic SCT (alloHCT) in WM has been reported in a study that included 144 patients registered with the CIBMTR who underwent alloHCT for WM/LPL between 2001 and 2013 [64]. Five-year PFS, OS, relapse, and nonrelapse mortality were 46%, 52%, 24%, and 30%, respectively. Factors associated with improved OS included chemosensitive disease and better pre-transplant disease status.

Although the regimens mentioned so far are routinely used and are recommended per NCCN guidelines, none have gained formal Food and Drug Administration (FDA) approval. In 2015, the BTK inhibitor, ibrutinib, was the first drug to be approved by the FDA for treatment of patients with symptomatic WM. In a Phase II study of patients with relapsed/refractory disease ($n = 63$), ibrutinib monotherapy was associated with an ORR of 95.5%, with the highest responses seen in $MYD88_{L265P}$/*CXCR4* WT patients [65]. Although a rapid decrease in IgM (median time to response, 1.2 months) and increase in hematocrit was observed, interestingly, no patient experienced CR. Comparable to other salvage regimens, the 2-year PFS and OS with ibrutinib were shown to be 69% and 95%, respectively. Serious adverse events that can occur with ibrutinib comprise neutropenia (Grade 3, 19%), thrombocytopenia (Grade 3, 13%), and atrial fibrillation in patients with a history of arrhythmias (10.7%). Of note, despite the broad indication/approval for ibrutinib, studies and efficacy data in treatment-naïve patients are lacking and thus mSMART guidelines recommend its use in the salvage setting [44]. As per current guidelines, ibrutinib therapy should be continued indefinitely, until disease progression or onset of treatment-related toxicity. This places patients at risk for cumulative drug toxicity and potentially, ibrutinib-resistant disease. A recent single-center analysis of 189 WM patients (73% of whom were relapsed/refractory) treated with ibrutinib, showed that after a median treatment duration of 13 months (range, 0.3—60), 51 patients (27%) had discontinued ibrutinib–with the most common reason for treatment discontinuation being disease progression (14%), followed by toxicity (8%), nonresponse (3%), and other unrelated reasons (2%). In alignment with the outcomes observed in CLL and mantle cell lymphoma, patient who progress on ibrutinib have compromised OS (21 months). Thus, treatment of ibrutinib-resistant disease presents a formidable challenge to treating physicians, for which alternative or novel treatment strategies are warranted, including clinical trial options.

Novel treatment approaches

Immunolodulating drugs (IMiDs) are a class of therapeutics approved for the treatment of MM, and have shown some benefit in patients with WM. The thalidomide—rituximab combination has been investigated in a Phase II clinical trial in symptomatic WM patients. The combination yielded a 72% ORR, and responding patients exhibited a 38-month median time to progression. Thalidomide is known to be associated with peripheral neuropathy, and this was observed at Grade $\geq$2 in 44% of WM patients on this regimen [66]. Compared to this, lenalidomide plus rituximab resulted in a lower ORR of 50% [67], with Grade 2/3 anemia as its major adverse effect (56%). Notably, peripheral neuropathy was observed in only

one patient. Some ongoing clinical trials with novel agents including the newer IMiD, pomalidomide, are summarized in Table 2.

Preclinical data with studies using everolimus (mTOR inhibitor) showed its ability to decrease WM cell proliferation and induce WM cell death. In a Phase II trial, 50 relapsed/refractory WM patients were treated with 10 mg everolimus daily, and their tumor burden was evaluated after Cycles 2 and 6 with subsequent assessment every three cycles until disease progression. An ORR of 42% was achieved along with an estimated 12-month PFS of 62%. The most common Grade $\geq$3 adverse events were hematologic toxicities (anemia, leukopenia, thrombocytopenia, and neutropenia) seen in 52% of patients. Subsequently, alternative dosing (5 mg daily or every other day) was used, with maintained responses [68].

One of the limitations of ibrutinib or rituximab therapy has been that as agents that primarily target monotypic B cells (CD19+/CD20+), they spare a significant portion of malignant cells with a more plasmacytoid (CD20−/CD19−) phenotype [69]. Thus, strategies to target both populations of cells are actively being investigated. Preclinical studies have shown that cotargeting of BTK and CD38 (with daratumumab), which is readily expressed on the plasmacytic fraction of WM cells, induces significant WM cell death through both immune-mediated and direct apoptotic mechanisms [70]. Considering this, a Phase II trial of single-agent daratumumab for the treatment of WM is underway (Table 2).

With *CXCR4* mutations now known to be of major biologic importance in WM, they have become a focus as a therapeutic target as well, utilizing the anti-CXCR4 mAb ulocuplumab in WM patients with the *CXCR4* mutation. Increased expression of Bcl-2 pathway and its disruption is lethal to WM cells [38]. A Phase I clinical trial utilizing the first-in-class Bcl-2 inhibitor, venetoclax, had four WM patients who demonstrated major responses. This has led to a dedicated trial of this agent in patients with WM [71] (Table 2). Similar to several other hematologic malignancies, the role of chimeric antigen receptor T cells has been explored in WM as well. The preclinical activity of second generation CD19−CD28 (19-28z) CARTs has been studied in a xenograft model of WM [72]. 19−28z CARTs were administered to WM-bearing mice and when compared to nontreated or irrelevant (MUC16) antigen-directed CART-treated mice, 19−28z CART-treated mice demonstrated delayed disease progression with double the median survival time (p = .001). This has paved the way for a dedicated clinical trial for this CAR-T formulation in patients with relapsed/refractory WM.

Table 2 Selected Novel Therapeutic Approaches for Waldenstrom's Macroglobulinemia, Currently in Clinical Development.

Agent(s)	Regimen	Mechanism of action	Phase of clinical trial	NCT number
Daratumumab	Single-agent	Anti-CD38 MoAb	II	NCT03187262
Ulocuplumab	+ Ibrutinib	Anti-CXCR4 MoAb	I/II	NCT03225716
Venetoclax	Single-agent	Bcl-2 inhibitor	II	NCT02677324
Pomalidomide	Single-agent	Immunomodulatory	I	NCT01198067
Pomalidomide	+ Rituximab and Dexamethasone	Immunomodulatory	I	NCT01078974
CD19-CD28 (19-28z)	Single-agent	CAR-T cells	I/II	NCT00466531
Umbralisib	Single-agent	PI3K delta inhibitor	II	NCT03364231
BGB-3111	+ Ibrutinib	BTK inhibitor	III	NCT03053440
Nivolumab	+ Lenalidomide	Immunomodulatory	I/II	NCT03015896
Pembrolizumab	+ Ibrutinib	Anti-PD-1 MoAb	I	NCT02950220
Ixazomib	+ Rituximab	Proteosome inhibitor	II	NCT02339922
Pembrolizumab	+ Idelalisib or Ibrutinib	Anti-PD-1 + PI3K inhibitor + BTK inhibitor	II	NCT02332980
Cyclophosphamide	+ Fludarabine + CAR-T cells	CAR-T cells	I/II	NCT03277729
Selinexor	+ R-CHOP	Exportin inhibitor	I/II	NCT03147885
Idelalisib	Single-agent	PI3K inhibitor	II	NCT03133221
ARQ 531	Single-agent	Reversible BTK inhibitor	I	NCT03162536
SD-101	+ BMS 986,178	TLR9 agonist + Anti-OX40 Ab	I	NCT03410901
Entospletinib	+ Obinutuzumab	Syk inhibitor	I/II	NCT03010358
Vecabrutinib (SNS-062)	Single-agent	BTK inhibitor	I/II	NCT03037645
Lenalidomide	+ DA-EPOCH-R	Immunomodulatory	I/II	NCT02213913
ADCT-301	Single-agent	Anti-CD25 ADC	I	NCT02432235
CLR-131	Single-agent	Radioisotope	II	NCT02952508
Romidepsin	+ 5-Azacitidine	HDAC1/HDAC2 inhibitor	I/II	NCT01998035
Pralatrexate	+ Romidepsin	Antifolate + HDAC inhibitor	I/II	NCT01947140
Dasatinib	Single-agent	Tyrosine Kinase Inhibitor	I/II	NCT01643603
Dasatinib	Single-agent	Tyrosine Kinase Inhibitor	I/II	NCT01609816
XmAb13676	Single-agent	Anti-CD20/CD3 MoAb	I	NCT02924402
Rituximab	+ ALT-803	Anti-CD20 MoAb + IL-15 superagonist	I/II	NCT02384954

Note. ADC = antibody drug conjugate; BTK = Brutons tyrosine kinase; CAR = chimeric antigen receptor; MoAb = monoclonal antibody.

Conclusion

Although patients with WM typically have an indolent disease course and most may not require treatment for prolonged periods, a better understanding of disease biology, more activity in drug discovery, and availability of safer, targeted therapeutic options are translating into even better outcomes including for those patients who do require treatment for their disease. Ongoing work in this direction will surely continue to improve outlook for patients in this, so far incurable malignancy.

Declaration of Competing Interest

None of the authors have any relevant conflicts of interest to report related to this work.

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