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ABSTRACT

Waldenström macroglobulinemia (WM) is a rare IgM-secreting lymphoplasmacytic lymphoma with recurrent somatic mutations in *MYD88* and *CXCR4* observed in the malignant cells of >90% and 30-40% of the patients. Given its rarity, WM poses specific diagnostic and management challenges. The diagnosis of WM is clinicopathological and no pathognomonic findings exist. The combination of a monoclonal IgM paraproteinemia, lymphoplasmacytic lymphoma in the bone marrow or other organs, and the MYD88 L265P mutation makes a diagnosis of WM with a high specificity. Approximately, a third of the patients will be asymptomatic at diagnosis and the best approach is to observe, as these patients have similar survival rates than age, sex and year of diagnosis-matched individuals of the general population. Eighty percent of patients diagnosed with asymptomatic WM will need treatment within 10 years. Treatment is indicated in symptomatic patients in whom the symptoms affect the patients' activities and are likely to be caused by the disease process. Multiple standard treatment options are safe and effective in symptomatic patients, including rituximab in combination with alkylating agents or proteasome inhibitors, covalent BTK inhibitors, and BCL2 antagonists. Non-covalent BTK inhibitors have emerged as a novel treatment option. Second-generation BCL2 antagonists, BTK degraders, antibody-drug conjugates and bispecific T-cell engagers are being evaluated in clinical trials. Multinational collaborative consortia to accelerate clinical trial design and execution in WM have emerged in Europe and the United States.

INTRODUCTION

In 1944, Jan Gösta Waldenström described a small case series of patients with hyperglobulinemia, anemia, and coagulopathy with an “incipient myelomatosis” pattern in the bone marrow (1). Almost eight decades later, Waldenström Macroglobulinemia (WM) is defined as an indolent B-cell lymphoma characterized by the accumulation of malignant IgM-secreting lymphoplasmacytic lymphoma (LPL) cells in the bone marrow, lymph nodes, and other tissues (2).

Immunophenotypically, LPL cells express surface IgM, CD19, CD20, CD22, CD25, and variably CD38 or CD138, while being negative for CD5, CD10, CD23, and CD103 (3). Over 90% of WM cases harbor the MYD88 L265P mutation, promoting cell survival and proliferation (4). CXCR4 mutations are present in 30–40% of patients, and TP53 mutations in 5–10%, both of which contribute to disease progression and therapeutic resistance (5, 6). These features help distinguish WM from other lymphoproliferative disorders.

Clinically, WM presents heterogeneously, with many patients asymptomatic at diagnosis. These cases are managed with an observation strategy. Treatment is initiated in patients with symptomatic disease progression related to anemia, thrombocytopenia, extramedullary disease, constitutional symptoms, hyperviscosity, neuropathy, hemolytic anemia, amyloidosis, cold agglutinin syndrome, or cryoglobulinemia (7).

This review aims to provide guidance on optimizing the diagnosis of WM, managing asymptomatic patients, and treating symptomatic patients, including information on ongoing clinical trials.

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

WM has an estimated annual incidence of 1,000-1,500 cases in the United States, accounting for approximately 1% of all non-Hodgkin lymphomas (8). The median age at diagnosis is approximately 73 years, with a male-to-female ratio of 2:1 to 3:1, and a predominance in Caucasian individuals (8, 9). Familial predisposition is significant, with approximately 20% of patients having a close relative with WM or a related malignancy (10, 11).

The diagnosis of WM is clinicopathological, and there is no pathognomonic feature. With the detection of an IgM monoclonal paraprotein by serum protein electrophoresis and immunofixation, LPL bone marrow infiltration, and identification of the MYD88 L265P mutation, the diagnosis of WM can be made with high specificity (2, 12).

Genomically, WM features recurrent somatic mutations in MYD88 L265P (>90% of cases), CXCR4 (30-40%), and TP53 (5-10%). The MYD88 L265P mutation activates the NF-κB pathway, thereby enhancing tumor cell survival (4, 13). CXCR4 mutations correlate with higher serum IgM levels, increased marrow infiltration, hyperviscosity symptoms, and resistance to Bruton tyrosine kinase (BTK inhibitors (14, 15). TP53 mutations are associated with aggressive disease and inferior outcomes (5, 16).

MYD88 wild-type disease demonstrates a worse prognosis and independently predicts histological transformation to large-cell lymphoma (17, 18).

The differential diagnoses for WM include IgM monoclonal gammopathy of undetermined significance (MGUS), and IgM-secreting multiple myeloma (MM), marginal zone lymphoma (MZL), or chronic lymphocytic leukemia (CLL). The MYD88 L265P mutation is found in over 90% of WM patients, in approximately 50-60% of IgM MGUS, NOS, and in less than 10% of cases of MZL and CLL (19-21). Morphologically, IgM MM cells can closely mimic WM cells, sometimes expressing CD20 and adopting a lymphoplasmacytic phenotype (22). However, the positive expression of cyclin D1 and the detection of t(11;14) favor a diagnosis of IgM MM, as these are not expressed or detected in WM cells. Conversely, the MYD88 L265P mutation has not been detected in MM cells (23). Patients with IgM MM present with hypercalcemia, renal insufficiency, and lytic bone lesions, distinguishing them from WM. IgM MGUS, NOS, is characterized by an IgM monoclonal paraprotein and no lymphoplasmacytic aggregates**.** IgM MGUS, PC, on the other hand, also has an IgM monoclonal paraprotein but should have less than 10% bone marrow plasma cells. The MYD88 L265P mutation has not been detected in IgM MGUS, PC. In MZL, IgM secretion has been reported in 30% of cases, and the MYD88 L265P mutation in 5-10%. This makes it a less likely diagnosis in cases with concurrent IgM paraprotein and MYD88 L265P mutation. Furthermore, the presence of splenomegaly and lymphocytosis favors MZL over WM (20). Finally, CLL is typically characterized by CD5-positive B-cell lymphocytosis without plasmacytic differentiation. A summary of the differential diagnosis of WM is shown in **Table 1**.

Table 2 outlines the recommended tests for establishing a diagnosis of WM, as recommended by the National Comprehensive Cancer Network (NCCN) and the 8TH International Workshop for WM (IWWM-8) (24, 25). The basic diagnostic evaluation should include laboratory data (e.g., complete blood counts, comprehensive metabolic panel, serum protein electrophoresis and immunofixation [SPEP/SIFE], and serum immunoglobulin quantification), imaging studies for extramedullary disease assessment (e.g., computed tomography scan of the chest, abdomen and pelvis with intravenous contrast), and a bone marrow aspiration and biopsy for immunophenotyping (via flow cytometry and immunohistochemical studies) and mutational studies for MYD88 and CXCR4 mutations. Additional laboratory, imaging, and pathological tests can be obtained as clinically indicated.

THE MANAGEMENT OF ASYMPTOMATIC PATIENTS

Approximately 20-30% of patients with WM are asymptomatic at the time of diagnosis (26-28). These patients are often referred to as having asymptomatic or smoldering WM and can frequently be monitored without intervention for months or years (7, 26, 27). Early treatment does not lead to an improvement in survival, as the survival of patients with smoldering WM is comparable to that of age-, sex-, and calendar-year-matched individuals in the general population(29, 30). Most patients will ultimately require treatment, and the median time to progression from asymptomatic to symptomatic WM is 3.9 years, with a probability of disease progression within 2 years of diagnosis of 31% (27). Despite the risk of progression,

approximately 20-30% of patients continue to have stable disease without progression at ten years after diagnosis (26, 27) .

For patients who are asymptomatic or have minimal symptoms that do not meet the criteria for treatment, the asymptomatic WM scoring system can be applied. This scoring system was developed based on data from 439 patients over a 23-year period from 1992 to 2014 with a median follow-up of 7.8 years (27). During this time, 72% of patients progressed. Albumin levels ≤3.5 g/dL, beta-2-microglobulin ≥4 mg/dL, serum IgM ≥4500 mg/dL, and a lymphoplasmacytic infiltrate in the bone marrow of ≥70% were found to be independent predictors of disease progression. Using these data, a prediction model was developed that can risk-stratify asymptomatic patients into three groups: high risk, intermediate risk, and low risk, with a median time to progression of 1.8, 4.8, and 9.3 years, respectively. This AWM risk scoring tool is available online for clinicians and patients at www.awmrisk.com and can be used in patients who do not meet criteria for treatment of WM. Based on this study, the NCCN recommends follow-up once a year for low, once every 6 months for intermediate, and every 3 months for high-risk patients.

Similar data have been produced by other groups, such as a study of 143 patients with smoldering WM, with data collected from 1996 to 2013 (30). In this study, the rates of progression were 11% at 1 year, 38% at 3 years, and 55% at 5 years, with hemoglobin levels ≤12.3 g/dL and beta-2-microglobulin levels ≥2.7 µg/mL being predictors of a shorter time to progression. Additionally, this study demonstrated that patients with MYD88 wild-type WM had a shorter time to progression, with a median

of 1.7 years, compared with 4.7 years in those with MYD88-mutated disease. The presence of a CXCR4 mutation did not impact the time to progression. Another group confirmed the risk of progression from asymptomatic WM, noting that the cumulative probability of progression to symptomatic disease was 6% at 1 year, 39% at 3 years, and 65% at 10 years with 285 person-years of follow-up. A higher percentage of bone marrow infiltration, a higher serum M spike, and lower hemoglobin levels were predictors of progression to symptomatic WM (31).

The median age at the time of diagnosis of smoldering WM is approximately 63-64 years, and survival is measured in decades (26, 29, 32). Due to this prolonged survival, along with the potential toxicity and resistance associated with systemic therapies, treatment of asymptomatic patients is not recommended. Patients without symptoms should be monitored routinely with symptom assessment, physical exam, and laboratory evaluation to determine when symptoms develop and the criteria for treatment are met.

The criteria for treating WM were developed during IWWM-2 (7). These guidelines recommend therapy when patients develop constitutional symptoms, symptomatic anemia, symptomatic organomegaly or lymphadenopathy, symptomatic hyperviscosity, symptomatic sensory neuropathy, systemic AL amyloidosis, symptomatic cryoglobulinemia, or WM-related organ dysfunction.

Patients may meet these treatment criteria directly related to tumor infiltration and/or specific characteristics of the monoclonal IgM. Tumor infiltration in the bone marrow

can lead to symptomatic anemia, which is the most common indication for therapy. Treatment is recommended for patients with a hemoglobin level of 10 g/dL or less. Anemia may be hypoproliferative in the setting of bone marrow infiltration by the malignant WM cells or may be hemolytic, such as that related to the presence of cold agglutinins or warm autoantibodies. Although it is less common, some patients may develop thrombocytopenia, and treatment is recommended if the platelet count is less than 100 x 10^9/L. Tumor infiltration may also lead to constitutional symptoms, such as unexplained fevers, unintentional weight loss of 10% or more, drenching night sweats, or significant fatigue. Infiltration of the spleen, liver, or lymph nodes by malignant cells, causing symptomatic hepatomegaly, splenomegaly, or adenopathy, would also warrant therapy. Rarely, treatment is required for involvement of other organs, such as the kidneys and lungs. The manifestations of renal involvement vary, but most commonly include amyloidosis, IgM or free light chain deposition disease, cryoglobulinemia, and lymphoplasmacytic infiltration of the kidneys, which is most common (33). Infiltration of the central nervous system by malignant lymphoplasmacytic cells, also known as Bing-Neel syndrome, is a rare complication that occurs in approximately 1% of patients with WM and requires treatment if symptomatic.(34)

The monoclonal IgM may also have specific properties that can lead to disease complications. Peripheral neuropathy is a common manifestation of WM, typically leading to a length-dependent, symmetric peripheral sensory polyneuropathy, often caused by the presence of an anti-myelin-associated glycoprotein (anti-MAG) antibody(35). Other types of neuropathy, such as axonal neuropathy related to amyloidosis or cryoglobulinemia, may also occur. In patients with rapidly progressive

neuropathy or neuropathy significantly affecting a patient's functional ability or daily activities, treatment is recommended. Hyperviscosity is a complication associated with an increasing IgM level, with the risk of symptomatic hyperviscosity beginning at approximately 3000 mg/dL and continuing to rise with the IgM level. Hyperviscosity can result in retinal hemorrhages, vision changes, nose bleeds, cognitive changes, or other symptoms (36, 37). Patients with symptomatic hyperviscosity should be treated. The level of serum IgM alone is not typically an indication for therapy. However, in cases with IgM levels greater than 6000 mg/dL, in which the risk of symptomatic hyperviscosity is 370 times higher, treatment initiation can be considered, even in asymptomatic patients, due to the high risk of symptomatic hyperviscosity (37, 38). Other, less common IgM-related indications for therapy include end-organ damage associated with cryoglobulinemia and immunoglobulin light and/or heavy chain (AL and/or AH) amyloidosis (39, 40).

CURRENT STANDARD TREATMENT OF SYMPTOMATIC PATIENTS

Given the prolonged progression-free survival (PFS) and overall survival (OS) observed in WM, response assessment plays a crucial role in evaluating the efficacy of both standard and emerging therapies (41, 42). The current standard for defining response is based on the response criteria proposed by the IWWM-11 (43, 44). These criteria categorize patients based on the degree of reduction in serum IgM levels.

A complete response (CR), which is rare in WM, requires normalization of serum IgM, absence of monoclonal IgM by SPEP/SIFE, no evidence of extramedullary disease, and a bone marrow biopsy showing complete morphological remission without LPL involvement. A very good partial response (VGPR) is defined by a ≥90% reduction in serum IgM or normalization of IgM with persistent monoclonal spike in SPEP, a partial response (PR) by a ≥50% but <90% reduction, and a minor response (MR) by a ≥25% but <50% reduction. Stable disease (SD) is defined by changes of less than 25% in either direction. For progression, a ≥25% increase in serum IgM from nadir (with a minimum absolute increase of 500 mg/dL) must be confirmed by two consecutive measurements. Alternatively, the appearance of new lesions or a ≥50% increase in any axis of previously involved extramedullary sites also meets criteria for progressive disease.

The prognostic value of response depth has been validated. Studies with older treatment regimens demonstrated that patients achieving VGPR or CR experienced significantly longer PFS, while MR was associated with improved outcomes over stable or progressive disease (45, 46). More recently, a study of patients treated with ibrutinib monotherapy used landmark analyses to show that achieving a PR or better at 6 months was independently associated with prolonged PFS in two separate cohorts, reinforcing its utility as a surrogate endpoint (47). In a larger cohort of 440 patients treated with modern fixed-duration regimens, PR or better predicted longer PFS and OS (48). Moreover, Panel 4 of the IWWM-11 evaluated patients enrolled in the ASPEN trial and confirmed that the response criteria consistently predicted PFS across subgroups (44).

The standard treatment arsenal for WM is outlined in **Table 3**. Currently, the preferred frontline regimens endorsed by the NCCN include rituximab in combination with chemotherapy (chemoimmunotherapy, CIT) or with proteasome inhibitors and Bruton tyrosine kinase (BTK) inhibitors (49), selected based on patient characteristics, disease biology, risk of toxicity, and, importantly, patient preference.

Rituximab-containing regimens

CIT represents an established and historically effective approach for WM. Its rationale lies in the proven efficacy of combining rituximab, a CD20-targeting monoclonal antibody, with chemotherapy backbones known to be effective in B-cell lymphomas (50, 51). These regimens offer a time-limited treatment strategy (4-6 cycles) and induce deep and durable responses (52).

Earlier regimens, such as those incorporating nucleoside analogues (e.g., fludarabine, cladribine), achieved high response rates but are now discouraged due to long-term toxicity (53, 54). These include irreversible stem cell damage and association with secondary myeloid neoplasms and histological transformation to aggressive lymphomas such as diffuse large B-cell lymphoma (DLBCL) (55).

Therefore, when CIT is preferred, regimens based on alkylating agents are favored. In the pivotal StiL NHL1 trial, patients with indolent lymphomas were randomized to

receive bendamustine plus rituximab (Benda-R) or R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone) (56). Among the 40 WM patients, BR was associated with a significantly prolonged median PFS of 69.5 months versus 28.1 months with R-CHOP.

Dexamethasone, rituximab, and cyclophosphamide (DRC) is another commonly used regimen. While generally well tolerated and active, DRC lacks direct comparative randomized data and appears less potent than Benda-R. In a phase II study, DRC yielded an ORR of 83% and a CR rate of 7%, with a median PFS of 35 months (57, 58). Real-world data further underscore the inferior efficacy of DRC compared to Benda-R (59, 60). Despite these differences, DRC may be associated with a more favorable toxicity profile (61). These findings support Benda-R as the preferred chemoimmunotherapy for WM. However, DRC remains an effective time-limited option for patients who may not tolerate bendamustine or in settings where bendamustine or BTK inhibitors are unavailable.

Patients receiving CIT should be counseled on its potential for both short- and long-term hematologic toxicity. In the short term, risks include cytopenias and increased susceptibility to infections (56, 62, 63). Long-term concerns center on stem cell damage, which may contribute to clonal hematopoiesis and, potentially, secondary myeloid malignancies. Individual cohorts have reported higher rates of CHIP-associated mutations and secondary malignancies following CIT (63-65). These risks are particularly relevant for younger patients with WM, given their extended life expectancy.

Dose-modified and shortened Benda-R regimens have shown equivalent efficacy to full-dose treatment in retrospective studies (59, 60), with hypothetical suggestions of reduced hematologic toxicity and a lower risk of stem cell damage.

Combinations of rituximab and proteasome inhibitors are safe and effective treatment options for WM. The most extensive prospective experience involves combining bortezomib and rituximab with or without dexamethasone (66-69). Bortezomib-based regimens have been associated with deep and durable responses. However, there were early concerns for peripheral neuropathy when bortezomib was administered intravenously twice a week, with a high rate of treatment discontinuation (69). Bortezomib, administered subcutaneously once weekly, has been associated with lower rates of neuropathy (67). Intravenous carfilzomib and oral ixazomib are also safe and effective in WM (70-72). Both agents have lower rates of neuropathy compared with bortezomib. Carfilzomib therapy has been associated with cardiopulmonary toxicity, especially in the elderly, and ixazomib with gastrointestinal adverse events. Although the risk of infection is increased, and all patients on proteasome inhibitors should receive zoster prophylaxis, no stem cell toxicity has been reported. Proteasome inhibitor-based regimens are a good fit for patients who are not suitable for or would like to avoid chemotherapy exposure or BTK inhibitor therapy.

The addition of bortezomib to DRC (B-DRC) was evaluated in a randomized study versus DRC involving 204 patients with WM (73). Although B-DRC was associated

with faster responses (3 vs. 5.5 months), higher rates of PR or better (81% vs. 70%), and higher rates of VGPR or better (17% vs. 10%) than DRC at the end of treatment, there was no apparent benefit in terms of the 24-month PFS rate (81% vs. 73%). Two patients randomized to B-DRC reported grade 3 neuropathy.

An important consideration when using rituximab-based regimens in WM is the risk of IgM flare, a transient increase in serum IgM levels following rituximab initiation (74, 75). This phenomenon can be clinically significant, particularly in patients with baseline IgM levels >4,000 mg/dL, due to the heightened risk of symptomatic hyperviscosity, which may result in acute, organ-threatening, or even life-threatening events (76). To reduce this risk, it is common practice to delay rituximab administration until after the first 1–2 cycles of therapy.

Rituximab maintenance following induction is generally not recommended. The MAINTAIN trial, which evaluated rituximab maintenance after BR, found no significant benefit in the overall WM population. A potential advantage was observed in patients older than 65 years, for whom individualized discussions may be appropriate (77). However, these results remain unpublished and should be interpreted with caution.

Covalent BTK inhibitors

The discovery of the MYD88 L265P mutation, present in over 90% of patients with WM (78), provided the biological rationale for targeting BTK in WM. A pivotal study of 63 previously treated patients, most harboring the MYD88 mutation, demonstrated an ORR of 91%, with a 2-year PFS of 69% (79, 80). These findings led to the covalent BTK inhibitor ibrutinib becoming the first FDA-approved therapy for WM, offering an effective, oral, and non-myelotoxic alternative to CIT.

As observed in the pivotal trial, response to ibrutinib is tightly linked to MYD88 and CXCR4 mutational status. Lack of the MYD88 L265P mutation is a primary driver of resistance, while CXCR4 mutations, particularly nonsense, but also frameshift variants, are associated with slower and more superficial responses, as well as shorter PFS (5-year PFS rate of 70% vs. median of 4.5 years, wild-type vs. mutant) (79-81). A subsequent study in 30 treatment-naïve MYD88-mutated patients reported a 100% ORR and similarly prolonged PFS, supporting using ibrutinib as frontline therapy (82, 83).

The randomized phase III INNOVATE trial compared ibrutinib plus rituximab versus rituximab monotherapy and further demonstrated the benefit of BTK inhibition in WM. Patients receiving the ibrutinib-rituximab combination had superior outcomes, with a 30-month PFS of 82% versus 28% in the rituximab-alone group. The trial did not include an ibrutinib monotherapy arm, thus precluding a direct comparison of combination versus ibrutinib monotherapy (84-87). Notably, the PFS of the ibrutinib-rituximab regimen appeared unaffected by CXCR4 mutational status, a finding subsequently confirmed in a pooled analysis (88).

Despite its efficacy, ibrutinib requires continuous daily administration until disease progression or intolerance, which is particularly relevant in WM given its chronic course. Long-term toxicities can be burdensome and may lead to dose modifications or discontinuation. Atrial fibrillation is the most prominent, affecting approximately 20% of patients (80, 83, 84). Hypertension and bleeding events are also common with ibrutinib. Bleeding risk is significant given its implications for perioperative management, often necessitating the temporary discontinuation of the drug before and after surgical procedures. Additional adverse events, such as diarrhea, rash, and musculoskeletal pain, are less frequent but can impact long-term tolerability (80, 83, 84).

The combination of ibrutinib and venetoclax was studied in 45 patients with previously untreated WM (89). Although the combination induced deep responses, the study therapy was stopped early because of four events of ventricular arrhythmia, including two deaths. Therefore, the combination of ibrutinib and venetoclax is not recommended in patients with WM.

Zanubrutinib, a more selective covalent BTK inhibitor, was evaluated in the phase III ASPEN trial, which randomized 201 patients with MYD88-mutated WM to receive zanubrutinib or ibrutinib. Zanubrutinib demonstrated a numerically higher VGPR rate (36% vs. 25%) and superior 42-month PFS (78% vs. 70%), though these differences did not reach statistical significance. Importantly, zanubrutinib had a more favorable safety profile, with lower rates of atrial fibrillation (8% vs. 24%), hypertension,

bleeding, and treatment discontinuation (90, 91). A biomarker analysis indicated that zanubrutinib is more effective than ibrutinib in patients harboring high-risk mutations, including CXCR4 and TP53 (92). These findings support using zanubrutinib as the preferred BTK inhibitor, particularly for those with adverse genomic profiles. Retrospective data suggest that its efficacy may exceed Benda-R's in this population (93).

Importantly, BTK inhibitors have shown particular utility in clinical situations requiring rapid hematologic improvement, given an observed median IgM response and hemoglobin recovery often seen by week 4 (80, 83), and in BNS (94), where zanubrutinib is preferred (95, 96). BTK inhibitors are less preferred in patients with WM and amyloidosis (97).

BTK inhibitors have WM-specific considerations. Discontinuation often leads to an IgM rebound, typically peaking shortly after cessation (98). In addition, BTK inhibitors can cause a withdrawal syndrome in 20% of patients, characterized by flu-like symptoms, particularly in patients with prior similar reactions during treatment holds (99). As a class, a main disadvantage of BTK inhibitors is that they must be administered continuously until progression, distinguishing them from fixed-duration regimens. While this extended dosing may increase cumulative toxicity, it remains stem cell-sparing and is generally associated with fewer acute toxicities.

Relapsed or refractory disease

In the relapsed and refractory setting, rituximab-containing regimens and covalent BTK inhibitors are reasonable options if the patient has not yet been exposed to these agents. Prospective studies have shown that proteasome inhibitor-based regimens (100, 101) and covalent BTK inhibitors (80, 87, 91, 102) are safe and effective in previously treated WM. Retreatment with the same rituximab-containing regimens is an option in patients who experienced a durable response in a previous line of therapy, considering the cumulative risk of myeloid neoplasms with chemotherapy retreatment.

Several non-chemotherapy strategies have gained relevance in recent years, particularly for patients previously exposed to covalent BTK inhibitors, among whom ~50% harbor BTK C481 resistance mutations (103). Two emerging therapies with distinct mechanisms, venetoclax and pirtobrutinib, have demonstrated high efficacy in this context. Both agents are endorsed by the most recent version of the NCCN guidelines (25).

Venetoclax, a BCL2 inhibitor, has shown high activity in relapsed or refractory WM. In a multicenter phase II trial of MYD88-mutated patients, ORR was 84%, VGPR 19%, with a median PFS of 30 months. Responses were rapid (median 1.9 months) and unaffected by CXCR4 status. In covalent BTK inhibitor-pretreated patients, response remained high (ORR ~75%) but was slower (median 4.5 vs. 1.4 months). Neutropenia was the main toxicity (grade ≥3 in 45%), though no clinical tumor lysis syndrome was reported (104).

A recent multicenter retrospective study confirmed efficacy but noted frequent dose modifications (41%) and worse outcomes outside clinical trials (2-year PFS: 43% vs. 85%). TP53 mutations were associated with inferior outcomes, but CXCR4 mutations were not (105).

An additional non-chemotherapy option for patients relapsing after covalent BTK inhibitors is pirtobrutinib, a highly selective, non-covalent BTK inhibitor that, unlike covalent agents, does not bind the C481 site and thus retains activity in the setting of BTK C481S mutations. Its use is supported by results from the phase I/II BRUIN trial, which enrolled 80 patients with previously treated WM, including 79% with prior covalent BTK inhibitor exposure (106). The ORR was high across subgroups (88% in covalent BTK inhibitor-naïve and 78% in exposed patients) with a median PFS of 22.1 months. Importantly, pirtobrutinib demonstrated a highly favorable safety profile. Grade ≥3 atrial fibrillation, hypertension, and bleeding occurred in only 1%, 4%, and 4% of patients, respectively.

CLINICAL TRIALS AND FUTURE DIRECTIONS

Several trials evaluate the value of fixed-duration regimens using two or three agents in the frontline setting. The academic Canadian BRAWM study, which assesses the combination of bendamustine, rituximab, and acalabrutinib, has completed enrollment (107). It has shown early encouraging results, with VGPR and CR rates of 62% and 2% in the 50 patients who completed 6 months and 52% and 10% in the 42 patients who completed 1 year of treatment. Two academic phase II single-arm

studies, one in China (NCT05914662) and one in the United States (NCT06561347, through the WM-NET), evaluate the combination of zanubrutinib, bendamustine, and rituximab. Two academic studies evaluate using venetoclax in combination with rituximab (Ven-R). The SWOG Clinical Trial Group runs a randomized phase II study that compares Ven-R versus ibrutinib plus rituximab and aims to enroll 92 patients (NCT04840602). The European Consortium for WM (ECWM) runs a randomized phase II study comparing Ven-R versus DRC and aims to enroll 80 patients (NCT05099471). A company-sponsored study evaluates the combination of zanubrutinib and the second-generation BCL2 antagonist sonrotoclax in a cohort of previously untreated patients (NCT05952037). Of importance, the academic phase III RAINBOW study, which randomized patients to ibrutinib plus rituximab versus DRC, has completed its accrual of 148 patients, and the results are eagerly awaited (NCT04061512).

In the relapsed setting, two studies evaluate BTK inhibitors in combination with BCL2 antagonists. An academic phase II study combines pirtobrutinib and venetoclax, aiming to enroll 44 patients with previously treated WM (NCT05734495), which has shown early efficacy with a VGPR rate of 56% in the first 16 patients on treatment (108). A company-sponsored study evaluates the combination of zanubrutinib and the second-generation BCL2 antagonist sonrotoclax in previously treated patients (NCT05952037).

Several targeted agents with novel mechanisms of action are being actively studied as monotherapy in previously treated WM, especially in patients exposed to rituximab-containing regimens and BTK inhibitors. The second-generation BCL2

antagonist sonrotoclax has shown efficacy in venetoclax-resistant cells and is being evaluated as monotherapy and in combination with zanubrutinib in a company-sponsored study (109). BTK degraders inhibit the function of and degrade BTK, impacting scaffolding, a secondary cellular activation mechanism. Preclinically, BTK degraders degraded wild-type and mutant BTK, showing killing efficacy in cells resistant to covalent and non-covalent BTK inhibitors. Current BTK degraders under investigation in company-sponsored studies include BGB-16673 (NCT05006716), NX-2127 (NCT04830137), NX-5948 (bexobrutideg; NCT05131022), and ABBV-101 (NCT05753501). An initial experience in 22 patients treated with BGB-16673 reported an ORR of 90%, a major response of 81%, and a VGPR rate of 14%, with responses seen in patients exposed to covalent and non-covalent BTK inhibitors (110). An experience of NX-5948 on 13 patients with WM was reported at IWWM-12 with a 78% response rate, and all responses were observed within 8 weeks (https://ir.nurixtx.com/node/10496/pdf). The FDA granted NX-5948 breakthrough designation to NX-5948 in relapsed or refractory WM in December 2024.

Another area of interest in WM is immunotherapy. A WM-NET multicenter academic phase II study evaluates the anti-CD19 antibody-drug conjugate loncastuximab tesirine in patients with WM previously treated with rituximab-containing regimens and BTK inhibitors (NCT05190705). An early experience in seven patients showed encouraging results, with a VGPR rate of 43% and a PR rate of 43%, with expected skin toxicity and GGT elevation. Two multicenter phase II studies, one in the United States (NCT06510491, through the WM-NET) and one in Europe (through the ECWM), will evaluate the bispecific T-cell engager epcoritamab in patients with WM.

The therapeutic landscape for WM continues expanding, impelled by scientific curiosity, discovery, and the ultimate goal of improving patients' lives. Future studies will likely address several unmet needs. The first unmet need is to increase the rate of CR, which has been a *bona fide* gateway for durable remissions and cures in other hematologic cancers. In multiple myeloma (MM) and chronic lymphocytic leukemia (CLL), the CR rates exceed 90% and 50%, respectively, with standard treatment options (111, 112). In these diseases, minimal residual disease has emerged as a powerful predictor of disease progression and overall survival (113, 114). However, the CR rate in WM is lower than 10% with rituximab-containing regimens and is rarely observed with BTK inhibitors. It is essential to note that the attainment of CR is not the ultimate goal of the standard treatment of patients with WM, as minor or partial responses translate into durable periods in which patients feel well and can maintain their activities of daily living. Future treatments such as triplets, BTK inhibitor-immunotherapy combinations, or chimeric antigen receptor T-cell therapy might be able to induce deeper responses. Another unmet need is the identification of patients with high-risk disease, unlikely to benefit from current standard treatments. As in MM, CLL, and other hematologic malignancies, patients with *TP53*-mutated WM have poor prognoses {Christian, 2019 #601;Gustine, 2019 #602;Poulain, 2017 #603}.

Given the rarity of WM, multicenter collaboration is vital. For this purpose, two multinational consortia, the European ECWM and the United States-based WM-NET, have emerged. The formation of these consortia provides a unique opportunity to design and execute clinical trials in a collaborative manner across the Atlantic.

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Table 1. Differential diagnosis of Waldenström macroglobulinemia

	WM	IGM MGUS, NOS	IGM MGUS, PC	MM	MZL	CLL
IgM monoclonal paraprotein	+++ (95%)	+++	+++	+/- (1%)	++ (30%)	+/- (rare)
Bone marrow involvement	+++	-	+ (<10%)	+++	++	+++
MYD88 L265P	+++ (90%)	+++ (50-60%)	-	-	+ (5-10%)	+ (5-10%)
CXCR4 mutations	++ (30-40%)	++ (20-30%)	-	-	-	-
Cyclin D1 expression	-	-	+	++	-	-
t(11; 14)	-	-	+	++	-	-
Splenomegaly	+/-	-	-	-	++	++
Lymphocytosis	-	-	-	-	+	+++
Lytic lesions	-	-	-	+++	-	-

WM: Waldenström macroglobulinemia; MGUS: monoclonal gammopathy of undetermined significance; NOS: not otherwise specified; PC: plasma cell; MM: multiple myeloma; MZL: marginal zone lymphoma; CLL: chronic lymphocytic leukemia

Table 2. Recommended diagnostic workup for patients with Waldenström macroglobulinemia

Essential tests	**Useful in certain circumstances**
History and physical examination	Serum viscosity (if symptoms or IgM >4,000 mg/dL)
Complete blood count with differential	*CXCR4* and *TP53* mutation analysis (bone marrow preferred, PCR or NGS, if available)
Comprehensive metabolic panel	Hepatitis B, C, HIV testing (if rituximab planned)
Serum lactate dehydrogenase, beta-2-microglobulin level	Cryocrit and cold agglutinins (if clinically indicated)
Serum protein electrophoresis and immunofixation	Von Willebrand antigen, ristocetin cofactor and factor VIII assays (if excess bleeding reported, especially with serum IgM >5,000 mg/dl)
Quantitative serum IgG, IgA, IgM, kappa and lambda levels	Nerve conduction studies, anti-MAG titers, anti-ganglioside panel, and neurology consult (if neuropathy suspected)
Bone marrow aspiration and biopsy (immunohistochemistry and flow cytometry)	Abdominal fat pad biopsy for Congo Red staining, 24-hour urine protein quantification, troponin, NT-proBNP, echocardiogram (if amyloidosis suspected)
MYD88 L265P mutation analysis (bone marrow preferred, PCR or NGS)	Retinal evaluation (fundoscopy if hyperviscosity suspected)
CT scan of the chest, abdomen, pelvis with contrast	PET/CT scan (if aggressive transformation suspected)
	Brain and spine MRI and cerebrospinal fluid flow cytometry (if Bing-Neel syndrome suspected)

CT: computed tomography; MAG: myelin-associated glycoprotein; MRI: magnetic resonance imaging; NGS: next generation sequencing; PCR: polymerase chain reaction; PET: positron emission tomography

Table 3. Selected prospective studies in patients with Waldenström macroglobulinemia

Study	Treatment	Phase	Treatment naïve / Previously treated	ORR	PR or better	VGPR or better	PFS (median)	OS (median)
Rummel, 2013 (56)	Bendamustine, rituximab	III	40 (100%) / 0 (0%)	-	-	-	69.5 months	-
Kastritis, 2015 (58)	Dexamethasone, rituximab, cyclophosphamide	II	72 (100%) / 0 (0%)	83%	74%	VGPR (-) CR (7%)	35 months	95 months
Rummel, 2019 (77)	Bendamustine, rituximab	III	257 (100%) / 0 (0%)	-	-	-	65.3 months	78% at 5 years
Treon, 2009 (69)	Bortezomib (twice weekly IV), dexamethasone, rituximab	II	23 (100%) / 0 (0%)	96%	83%	VGPR (22%) CR (13%)	78% at 23 months	-
Gavriatopoulou, 2016 (67)	Bortezomib (weekly SQ), dexamethasone, rituximab	II	59 (100%) / 0 (0%)	85%	68%	VGPR (7%) CR (3%)	43 months	66% at 7 years
Treon, 2014 (70)	Carfilzomib, dexamethasone, rituximab	II	31 (100%) / 0 (0%)	87%	68%	VGPR (32%) CR (3%)	75% at 15 months	100% at 15 months
Castillo, 2020 (71)	Ixazomib, dexamethasone, rituximab	II	26 (100%) / 0 (0%)	96%	77%	VGPR (19%) CR (0%)	40 months	100% at 52 months
Kersten, 2022 (101)	Ixazomib, dexamethasone, rituximab	II						
Treon, 2021 (80)	Ibrutinib	II	0 (0%) / 63 (100%)	91%	73%	30%	54% at 5 years	87% at 5 years
Castillo, 2022 (82)	Ibrutinib	II	30 (100%) / 0 (0%)	100%	87%	30%	76% at 4 years	100% at 4 years

Owen, 2020 (102)	Acalabrutinib	II	14 (13%) / 92 (87%)	93%	79%	33%	82% at 24 months	90% at 24 months
Buske, 2022 (87)	Ibrutinib, rituximab	III	34 (45%) / 41(55%)	92%	77%	VGPR (29%) CR (1%)	68% at 54 months	86% at 54 months
Dimopoulos, 2023 (91)	Zanubrutinib	III	19 (19%) / 83 (81%)	95%	81%	36%	78% at 42 months	88% at 42 months
Castillo, 2022 (104)	Venetoclax	II	0 (0%) / 32 (100%)	84%	81%	19%	30 months	100% at 30 months
Palomba, 2024 (115)	Pirtobrutinib	I/II	0 (0%) / 80 (100%)	80%	71%	26%	22.1 months	-

ORR: Overall response rate; PR: partial response; VGPR: very good partial response; CR: complete response; PFS: progression-fre survival; OS: overall survival; IV: intravenous; SQ: subcutaneous