Acta Haematologica

Review

Acta Haematol 2021;144:146–157
DOI: 10.1159/000509286

Received: April 28, 2020
Accepted: June 9, 2020
Published online: August 18, 2020

Current and Emerging Treatments for Waldenström Macroglobulinemia

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Keywords
Waldenström macroglobulinemia · Rituximab · Bendamustine · Bruton's tyrosine kinase inhibitors · Proteasome inhibitor · Ibrutinib

Abstract
Waldenström macroglobulinemia (WM) is a rare lymphoplasmacytic lymphoma. The primary goal of therapy is to reduce symptoms related to direct infiltration of the bone marrow and decrease monoclonal IgM-associated complications. Active agents in the management of WM can be broadly classified as rituximab-alkylator combination therapy, proteasome inhibitor-based therapy, and Bruton's tyrosine kinase inhibitor-based therapy. *MYD88*^{L265P} and *CXCR4* genetic status are pivotal for tailoring treatment options. Ibrutinib is a suitable treatment option for both treatment-naïve and relapsing WM patients. Recent advances in the intracellular B cell and cytokine signaling pathways have contributed to the development of novel therapeutic strategies. Current clinical trials are promising and may further advance WM-directed therapy.

Introduction

Waldenström macroglobulinemia (WM) is a rare, low-grade lymphoma in which lymphoplasmacytic cells infiltrate the bone marrow and produce a monoclonal IgM protein [1]. Other low-grade lymphoproliferative disorders may also present with IgM monoclonal protein and should be excluded (Table 1). Anemia, lymphadenopathy, and splenomegaly are typical clinical features of WM. Specific immunological characteristics of monoclonal IgM can result in neuropathy, hyperviscosity, and cryoglobulinemia.

According to the Surveillance, Epidemiology, and End Results database, approximately 1,000–1,500 new WM cases are diagnosed every year in the United States [2]. However, cancer registry data may be biased as there is no differentiation among IgM monoclonal gammopathy of undetermined significance, asymptomatic WM, and symptomatic WM [3–5]. The decision to initiate treatment is based on clinical and laboratory criteria. Treatment response in WM is primarily determined by a reduction in the serum IgM protein, in addition to the presence or absence of clinical manifestations of active and extramedullary disease [6]. However, serum IgM responses do not always correlate with bone marrow assess-

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Table 1. Differential diagnosis of WM

Disease	Clinical features	Histology/bone marrow biopsy	Immunophenotype/genetic
WM	hepatomegaly (20%), splenomegaly (15%), and lymphadenopathy (15%); fatigue due to anemia	plasmacytoid cells ≥10%; intertrabecular pattern	pan B cell markers and typically CD3 and CD103 negative; *MYD88*^{L265P} (90% of cases)
IgM MGUS	IgM level <3 g/dL; absence of end-organ damage	lymphoplasmacytic lymphoma of <10%	*MYD88*^{L265P} cannot be used to differentiate between WM
Multiple myeloma	end-organ damage (e.g., lytic bone lesions and renal dysfunction)	>10% infiltration of plasma cells	*MYD88* is not mutated in IgM multiple myeloma
Chronic lymphocytic leukemia	lymphocytosis, autoimmunity	small mature lymphocytes	always CD5+, CD23+
Marginal zone lymphoma	more likely to present with prominent lymphadenopathy, splenomegaly, or extranodal involvement	nodular nonparatrabecular infiltration pattern	differentiation between WM can be challenging; *MYD88* seen in 5–10%
Mantle cell lymphoma	involves lymph nodes and extranodal sites	monomorphous, small-medium lymphoid cells with irregular nuclei	CD5+, CD23–; t(11;14; q13:q32)

MGUS, monoclonal gammopathy of undetermined significance; WM, Waldenström macroglobulinemia.

ment. Owen et al. [6] proposed updated criteria to define clinical responses in patients with WM. The modified standard response criteria are predictive of overall outcome and are critical to the standardization of reporting in clinical trials.

WM remains incurable. The management of WM has been derived from therapeutic options available in the treatment of multiple myeloma and low-grade lymphoma. The decision to treat should consider a patient's clinical manifestations (i.e., fatigue, anemia, cryoglobulinemia, and hyperviscosity syndrome) [7], tolerance of medications, and the avoidance of short- and long-term toxicity. Recent advances in the understanding of the cytogenetic, intracellular B cell, and cytokine signaling pathways have contributed to the development of novel therapeutic strategies (Table 2).

Alkylating Agents

Alkylating agents including chlorambucil, melphalan, and cyclophosphamide were the first therapies utilized in the treatment of WM [8–10]. Single-agent chlorambucil may be effective in up to 40% of WM patients [11]. However, alkylating agents are limited by their toxicity profiles and adverse effect on future stem cell harvesting.

Nucleoside Analogs

The use of nucleoside analogs can lead to higher response rates. However, nucleoside analogs are not considered primary options for the first-line treatment of WM. In a large prospective observational multicenter clinical trial of 118 untreated and symptomatic WM individuals, fludarabine demonstrated an overall response rate (ORR) of 36% and a complete remission rate of 2% [12]. The WM1 trial, a large phase 3 randomized clinical trial, demonstrated that oral fludarabine had higher response rates (47.8 vs. 38.6%), progression-free survival (PFS) (36.3 vs. 27.1 months), and overall survival (OS) (70.3 vs. 61.4%) in newly diagnosed WM versus chlorambucil treatment [13].

Fludarabine has been investigated in combination with rituximab, with or without cyclophosphamide. In a study of 43 patients with symptomatic WM treated with fludarabine, cyclophosphamide, and rituximab, the ORR was 79% [14]. However, significant toxicities (mainly myelosuppression) occurred in 45% that led to discontinuation of treatment [14]. Fludarabine-based therapy remains an option for patients with relapsed/refractory (R/R) disease, but fludarabine-based combinations are not recommended for primary therapy.

Table 2. Novel approaches in WM

Ref. No.	Agent	Molecular target	Phase	Clinical trial information	Patients, *n*	Study population	ORR in WM	Most common adverse events
82	entospletinib	selective inhibitor of spleen tyrosine kinase	2	NCT01799889	17	R/R WM	24% (6% PR, 18% MRR)	fatigue, gastrointestinal, neutropenia, increased creatinine and ALT
68	idelalisib	PI3Kδ inhibitor	1	NCT00710528, NCT01090414	9	WM	55%	asymptomatic grade ≥3 serum transaminase elevations occurred in ~25%
69	idelalisib	PI3Kδ inhibitor	2	NCT01282424	10	LPL/WM	80% (70% PR, 10% MRR)	neutropenia, elevations in aminotransferase levels
83	idelalisib	PI3Kδ inhibitor	2	NCT01282424	p1 (n = 9), p2 (n = 10)	R/R WM (p1) + refractory disease to both rituximab and alkylating agent (p2)	56% (p1) and 80% (p2)	increased ALT/AST
70	idelalisib + obinutuzumab	PI3Kδ inhibitor + novel anti-CD20	2	NCT02962401	49	R/R WM	90% (76% MRR, 68% PR, 8% VGPR)	hepatotoxicity (20%), diarrhea (10%), and dermatologic complications (4%)
73	duvelisib	PI3Kδ and γ inhibitor	1	NCT01476657	4	WM/LPL	58%[a]	cytopenias, increased ALT (38.6%)/AST (37.6%), diarrhea (41.9%)[a]
84	everolimus	mTor inhibitor	2	NCT00436618	50	R/R WM	70% (42% PR, 28% MRR)	hematological toxicities, pulmonary toxicity (10%)
85	everolimus	mTor inhibitor	2	NCT00436618	60	R/R WM	73% (50% PR, 23% MRR)	hematological (67%), pulmonary toxicity (5%)
86	everolimus + bortezomib and rituximab	mTor inhibitor + PI + anti-CD20 inhibitor	1/2	NCT01125293	46	WM	87% (46% PR, 37% MRR)	fatigue, cytopenias, and sensory peripheral neuropathy (41%)
87	everolimus	mTor inhibitor	2	NCT00976248	33	symptomatic, previously untreated WM	72.7% (58% PR, 60.6% MRR)	mucositis (27.3%), infection (21.2%), and pneumonitis (18.2%)
88	ofatumumab	CD20 monoclonal antibody	2	NCT00811733	37	untreated WM and R/R WM	59% (41% PR, 19% MRR)	infusion-related reactions

[a] Includes all indolent non-Hodgkin lymphoma cases. ALT, alanine aminotransferase; AST, aspartate aminotransferase; LPL, lymphoplasmacytic lymphoma; MRR, major response rate; mTOR, mammalian target of rapamycin; ORR, overall response rate; p1, phase 1; p2, phase 2; PI, proteasome inhibitor; PI3K, phosphatidylinositol 3-kinase; PI3Kδ, phosphatidylinositol 3-kinase delta; PR, partial response; R/R, relapsed/refractory; VGPR, very good partial response; WM, Waldenström macroglobulinemia.

Rituximab as a Monotherapy

Currently, rituximab-based regimens are the primary recommended therapy for the majority of patients with WM. Rituximab is a selective chimeric anti-CD20 monoclonal antibody that lacks long-term toxicity and is relatively well tolerated.

As a monotherapy, rituximab has reduced response rates compared to other combination regimens. In a prospective phase 2 study, 27 individuals with WM were treated with rituximab intravenously for a total of 4 weeks [15]. Forty percent (6/15) of previously untreated WM patients achieved partial response (PR) [15]. A lower response to rituximab was reported in patients with high levels of serum monoclonal protein [15]. Similar findings were observed with the use of an extended rituximab dose with no evidence of myelosuppression [16]. However, a transient increase in IgM level during or shortly after treatment may be expected and worsen IgM-related morbidities. Therapeutic plasmapheresis is recommended as a short-term measure, followed by the initiation of systemic therapy. The IgM flare due to rituximab does not predict treatment failure, and in the majority of cases, IgM levels returned to baseline at 12 weeks [17].

In selected populations, single-agent rituximab may be useful as a treatment option for elderly patients who do not have a strong indication for cytotoxic therapy [18]. A population-based study of 1,310 Medicare beneficiaries (>65 years old) with WM demonstrated no difference in OS between patients receiving single-agent rituximab compared to combination with chemotherapy [19]. IgM levels and prophylactic measures were not recorded. However, no increased risk of plasmapheresis or hospitalization was observed.

Combination therapies have a synergistic activity that may provide a vital overlap to eradicate the entire WM clone [20]. The preferred frontline treatment options for WM can be broadly classified as rituximab-alkylator combination therapy, proteasome inhibitor-based therapy, and Bruton's tyrosine kinase (BTK) inhibitor-based therapy.

Rituximab with Alkylators (Chemoimmunotherapy)

One of the earliest combination chemotherapy regimens used with rituximab was dexamethasone and cyclophosphamide (DRC) [21]. The updated report of a phase 2 clinical trial in 72 newly diagnosed WM patients evaluating primary therapy with DRC showed a response rate of 83%, with 67% of patients achieving PR [21]. Disease progression at 3 years was 45%, and the median time to retreatment was 51 months [21]. The majority of cases retreated with a rituximab-based regimen achieved response rates of 82%. Solid tumors were the most common cause of WM-unrelated death. Secondary myelodysplastic syndrome occurred in 3% of WM patients, and 10% had transformation to diffuse large B cell lymphoma [21]. In the updated analysis, the 8-year and estimated 10-year OS related to WM were 64 and 53%, respectively [22]. The 8-year OS per the International Prognostic Scoring System for Waldenström Macroglobulinemia (ISSWM) was 100% for high-risk disease [22]. DRC is currently an alternative regimen for first-line treatment if the disease burden is low based on the Mayo Stratification of Macroglobulinemia and Risk-Adapted Therapy guidelines [23].

Bendamustine has been widely used since the 1970s in patients with lymphoid malignancies. In a phase 3, noninferiority trial of 514 patients with mantle cell or indolent lymphoma, a subset of 41 WM patients was analyzed [24]. Twenty-two patients received bendamustine-rituximab (Benda-R) and 19 patients received R-CHOP. The Benda-R arm demonstrated a significantly longer PFS (69.5 vs. 28.1 months, $p = 0.0033$) [25]. Benda-R treatment was better tolerated, with no alopecia, fewer hematological toxic effects, less frequent infections, and less peripheral neuropathy. Benda-R is the backbone regimen in the Study Group Indolent Lymphomas studies. At our institution, Benda-R is the preferred induction regimen for newly diagnosed WM [26].

In a retrospective study, the Benda-R regimen given every 4 weeks up to six cycles (bendamustine 90 mg/m^2 i.v. on days 1 and 2 in addition to rituximab 375 mg/m^2 on day 1) was compared to the DRC regimen (dexamethasone 20 mg i.v. on day 1, rituximab 375 mg/m^2 i.v. on day 1, and cyclophosphamide 100 mg/m^2 p.o. daily on days 1 through 5) given every 3 weeks for up to six cycles in all symptomatic WM patients ($n = 160$) [27]. In the treatment-naïve (TN) setting, the Benda-R and the DRC group had similar reductions in IgM, but the Benda-R cohort had a better median time to best response (6.1 vs. 11 months, respectively) [27]. Although the difference was not statistically significant, the 2-year PFS was improved in the Benda-R group (88 vs. 61%, $p = 0.07$) without associated toxicity [27]. Both regimens demonstrated remarkable activity and effectiveness independent of *MYD88*^{L265P} status [28]. In the setting of R/R disease, Benda-R therapy is well tolerated and has durable responses [29, 30].

Proteasome Inhibitor-Based Therapy

Bortezomib

Bortezomib is a selective proteasome inhibitor that has significant activity in the treatment of WM [31]. As a monotherapy, bortezomib was initially studied in 10 patients with R/R WM [32]. The number of cycles was limited since most of the patients had previously been exposed to other neurotoxic agents. Sixty percent of WM patients achieved PR after treatment with bortezomib. Bortezomib was well tolerated, but 3 patients developed peripheral neuropathy [32].

A subsequent phase 2 clinical trial of symptomatic WM patients demonstrated that 78% (21/27) of WM cases had a reduction in IgM of at least 25%, 26% achieved PR, and 70% had stable disease [33]. However, 74% of the patients developed new or worsening peripheral neuropathy with early discontinuation [33]. Similar results were demonstrated in a multicenter study that showed an ORR of 85% among individuals with R/R WM disease with a median time of response of 1.4 months [24]. In prior studies, the most concerning adverse event was sensory neuropathy, and caution is recommended in patients with preexisting peripheral neuropathy grade 2 or greater [34].

Various studies have been conducted to support the rationale for combining bortezomib with other agents. The combination of bortezomib, dexamethasone, and rituximab (BDR) was evaluated in 23 WM patients [35]. Bortezomib (1.3 mg/m^2 i.v. on days 1, 4, 8, and 11), dexamethasone (40 mg on days 1, 4, 8, and 11), and rituximab (375 mg/m^2 on day 11) therapy consisted of four consecutive cycles followed by a 12-week pause, and then four additional cycles of BDR spaced 12 weeks apart [35]. Prophylaxis against herpes zoster was added due to an unexpectedly high incidence of herpes zoster infection. A successful decline in the median IgM levels and bone marrow involvement was observed. The ORR and the major response rate (MRR) were 96 and 83%, respectively [35]. Twenty-two percent of the patients achieved complete response (CR) and 35% achieved very good PR (VGPR) or

better. Peripheral neuropathy was the most common adverse event, resulting in discontinuation of therapy in 60% of the cases. Similar findings were reported in 33 patients where ORR and MRR were 96 and 91%, respectively [36].

A phase 1/2 trial was conducted in the United Kingdom to determine the optimal schedule for bortezomib administration. In the phase 2 trial, 42 patients were randomized to receive two different doses and schedules of administration (twice weekly vs. weekly) of bortezomib plus rituximab (BR) [37]. Overall, the response rate (CR + PR) was similar in the two groups. In the subgroup analysis of 10 WM patients, the response rates were high (90%), and 4 of the patients who responded remained transfusion-free without progression between 2 and 2.5 years following completion of therapy [37]. BR combination appears promising, but further clinical studies are warranted. Neuropathy was the most commonly reported toxicity and may be a limiting factor to complete planned therapy. The higher incidence of bortezomib-related peripheral neuropathy in WM may be explained by underlying nerve damage. Nerve damage may be secondary to amyloid deposition and/or paraprotein-mediated demyelination [38].

In previously untreated WM patients, a phase 2 trial of the BR regimen displayed greater activity, with an improved toxicity profile and lower incidence of severe neurotoxicity related to bortezomib. Sixty patients from five European countries were included, and 45% were considered high-risk. The ORR was 85%; 65 and 68% achieved PR and MRR, respectively. Almost 40% of the patients had complete or partial resolution of their lymphadenopathy. The estimated median PFS was 42 months and the 3-year OS was 82% [39]. Furthermore, limited myelotoxicity was observed with the BR regimen. The BR regimen is an attractive option for patients who are candidates for an autologous stem cell transplant.

The efficacy of three combination regimens as primary therapy for symptomatic WM (Benda-R, BDR, and DRC), in addition to the role of maintenance rituximab following induction with rituximab-containing regimens, have also been evaluated [40]. No difference in response rates was observed between treatment groups. However, the time to best response was considerably longer with DRC when compared with Benda-R and BDR. Patients who received maintenance rituximab had a higher MRR (97 vs. 68%) compared to cases who did not, in addition to superior PFS and OS [40].

The use of maintenance rituximab in WM was studied by Rummel et al. [41]. A total of 257 patients received Benda-R (as first-line therapy) with up to six cycles of Benda-R plus two additional cycles of rituximab. Half of the patients (109/218) were then randomized to rituximab maintenance (every 2 months for 2 years) and half (109/218) to observation. The 2-year rituximab maintenance group had a better disease control compared to the observation group; however, it was not statistically significant (PFS 101 vs. 83 months, $p = 0.32$) [41]. There was no difference in OS. These results confirm Benda-R as an effective first-line treatment for WM, but 2-year rituximab maintenance was not demonstrated to be better than observation alone.

Carfilzomib

Carfilzomib is a second-generation proteasome inhibitor that is associated with low neuropathy risk (including those with baseline peripheral neuropathy), but associated with cardiotoxicity [42]. In preclinical models of multiple myeloma, carfilzomib exhibited potent antiproliferative and proapoptotic effects in myeloma cell lines [43]. In 2012, carfilzomib was approved for the treatment of R/R multiple myeloma, and subsequent trials in WM patients have been conducted.

A phase 2 prospective open-label study was conducted to evaluate carfilzomib, rituximab, and dexamethasone in symptomatic WM patients who never received bortezomib and rituximab. Median IgM levels and bone marrow involvement declined significantly. The ORR and MRR were 87.1 and 67.7%, respectively [44]. CR/VGPR was attained in 36% of the patients, with similar clinical responses to BDR regimens [35, 45]. Almost all patients expressed *MYD88*^{L265P} somatic mutation, and *CXCR4*^{WHIM} mutations were present in 36.7%, with an ORR of 90.9% in the latter group. Following therapy, CT-defined adenopathy resolved or remained stable. All patients were alive with a median follow-up of 15.4 months, and 64.5% remain free of disease progression [44]. Hyperglycemia and carfilzomib-related hyperlipasemia were the most commonly observed toxicities, and only 1 patient developed cardiomyopathy in the setting of smoking and heavy alcohol use.

In the standard of care setting, the carfilzomib-based combination showed a MRR of 67%, 50% PR, and a 100% resolution of B symptoms and anemia after treatment [46]. All patients had reduced levels of IgA and IgG, and only 2 required initiation of intravenous immunoglobulin with subsequent clinical improvement [46]. However, the data are limited by the small sample size and the retrospective nature of the study. The efficacy of carfilzomib-based combinations may offer a

neuropathy-sparing alternative to bortezomib-based protocols.

Novel Oral Proteasome Inhibitors

Alternative oral proteasome inhibitors have been accepted for use in patients with multiple myeloma [47]. Ixazomib is a proteasome inhibitor that blocks the chymotrypsin-like activity of the β5 subunit of the 20S proteasome [48]. Early-phase clinical studies of ixazomib in combination with dexamethasone and rituximab as primary therapy in WM have shown significant response rates and low toxicity. A phase 2 clinical trial of 26 patients with untreated WM was conducted. Patients received ixazomib 4 mg orally, dexamethasone 20 mg (on days 1, 8, and 15), and rituximab (375 mg/m^2 i.v. on day 1) that was administered for six 4-week cycles followed by maintenance (six 8-week cycles) for a total of 12 cycles [49]. Rituximab was administered after ixazomib and dexamethasone to reduce the risk of IgM flare. The ORR was 96%, VGPR was 15%, and PR was 62%. No CR was observed [49]. PFS was not reached at 2 years, which compares to data in the bortezomib- and carfilzomib-based regimens. Ixazomib in combination with dexamethasone and rituximab appeared to be well tolerated.

Effective, tolerable, and convenient proteasome inhibitors are highly desirable. Oprozomib, a chymotrypsin-like inhibitor (similar to carfilzomib), was evaluated as a single agent in a phase 1b/2 multicenter clinical study in previously treated WM patients [50]. However, gastrointestinal adverse events (primarily diarrhea) may limit its use in clinical practice.

BTK Inhibition

Ibrutinib

Ibrutinib is an oral agent that is a potent irreversible inhibitor of BTK and is highly effective, with the best treatment responses observed in patients with *MYD88*^{L265P} and *CXCR4*^{WT} mutations [51, 52]. Ibrutinib also can cross the blood-brain barrier and may be effective for Bing-Neel syndrome, a rare complication of WM [53]. However, ibrutinib is not specific and blocks several other kinases.

In a prospective study, 63 symptomatic WM patients who had been given at least one previous treatment received ibrutinib (at a dose of 420 mg) for twenty-six 4-week cycles until disease progression or unacceptable adverse events occurred [52]. At the time of best response, the median serum IgM levels and median bone marrow involvement were significantly decreased. ORR and MRR were 90.5 and 73%, respectively, and were the highest among patients with MYD88^{L265P} and CXCR4^{WT} genotype [52]. The 2-year PFS was 69.1% (95% CI 53.2 to 80.5), and the estimated OS rate was 95.2% (95% CI 86.0–98.4) [52]. Cytopenias (neutropenia and thrombocytopenia) were the most common related toxicities. Infections were mostly associated with preexisting hypogammaglobulinemia.

In 4 patients with R/R WM, oral ibrutinib induced profound and durable responses. Ibrutinib was administered between 560 mg/day and 12.5 mg/kg/day until progressive disease or unacceptable toxicity [54]. Three out of the 4 patients achieved durable PR with no evidence of progression (at 4 years) and sustained clinical improvement (hemoglobin levels and reduction in lymphadenopathy).

The safety and efficacy of ibrutinib in a population with rituximab-refractory WM disease was also evaluated [54]. Patients received oral ibrutinib 420 mg daily until disease progression, occurrence of unacceptable toxicity, or withdrawal of consent. ORR and MRR were achieved in 90 and 71% of WM cases, respectively. Response rates were similar in individuals with *MYD88*^{L265P} and *MYD88*^{WT}. Median PFS was not reached at the median follow-up (18.1 months), and OS was 97% at 18 months [54]. Additionally, ibrutinib had a clinically meaningful impact on quality of life that has not been previously reported.

The majority of nonhematological reported toxicities were diarrhea and infections (mainly respiratory tract infection) that occurred in 68% of patients [54]. Atrial fibrillation was seen in 6–11% of the patients receiving ibrutinib [54]. No events of IgM flare were reported, but close monitoring should be considered due to associated elevated IgM levels with ibrutinib cessation [55]. Withdrawal symptoms have been reported (20% of the patients) while holding ibrutinib to manage toxicities or in anticipation of surgery. Symptoms resolved after ibrutinib was restarted [56].

Based on preclinical data, the combination of ibrutinib and rituximab would be an ideal regimen. The ibrutinib-rituximab regimen was studied among TN WM patients and among those with disease recurrence. The iNNOVATE trial included a total of 150 patients that were randomly assigned in a 1:1 ratio to receive either oral ibrutinib (420 mg once daily) or placebo until disease progression or undesirable toxic effects [57]. Both groups also received prolonged i.v. rituximab (375 mg/m^2, with infusions at weeks 1–4 and 17–20). If disease progression was

confirmed, patients in the placebo group were permitted to cross over to receive ibrutinib. The 30-month PFS rate was higher in the ibrutinib-rituximab group compared to the placebo-rituximab group (82 vs. 28%), with an 80% lower risk of progression or death [57]. In the subgroup analysis, higher rates of PFS were seen in TN patients and those with relapsed disease at 24 months. Similar findings were consistent among high-risk ISSWM score patients. When response rates were assessed, the ibrutinib-rituximab group had higher ORR and VGPR (23 and 92% vs. 4 and 47%, respectively).

Moreover, IgM levels declined more rapidly, and hemoglobin levels showed a sustained rise. As reported in prior reports, the most common toxicities were diarrhea (28%), arthralgia (24%), and nausea (21%). Atrial fibrillation occurred in 12% of ibrutinib-rituximab cases and was treated with dose modification and supportive medications [57]. The rate of discontinuation between both groups (ibrutinib-rituximab and placebo-rituximab) was similar (5 and 4%, respectively). The response rates with ibrutinib-rituximab were similar across different CXCR4 genotypes, but slightly lower among patients without $MYD88^{L265P}$ activity. Combination therapy (ibrutinib-rituximab) is a viable treatment approach in WM patients, including WM patients who are TN, even if outcomes are not comparable to those seen in patients with relapsed WM disease.

Second- and Next-Generation BTK Inhibitors

Acalabrutinib (ACP-196) was developed to be more potent and selective than ibrutinib. Acalabrutinib is rapidly absorbed, has a short half-life, and lacks irreversible targeting to alternative kinases including the epidermal growth factor receptor, interleukin 2-inducible T cell kinase, and T cell X chromosome kinase [58]. In preclinical studies, acalabrutinib was initially evaluated in several B cell non-Hodgkin lymphoma animal models [59]. In clinical studies, acalabrutinib has been shown to be active and well tolerated in patients with relapsed chronic lymphocytic leukemia [60]. In a phase 2 multicenter study of 106 patients (14 TN and 92 R/R WM), oral acalabrutinib (100 mg) was administered twice a day in 28-day cycles until disease progression or toxic effects developed [61]. Dose modifications (100 mg once per day) were allowed for persistent drug-related grade 3–4 toxic effects [61]. The median follow-up was 27.4 months, and acalabrutinib was demonstrated to achieve an ORR of 93% in TN and R/R WM patients [61]. Major response was shown in 79 and 78% of TN and R/R WM patients, respectively. Treatment discontinuation occurred in 7 (50%) and 23 (25%) of TN and R/R WM patients, respectively. Overall, neutropenia (16%), pneumonia (7%), anemia (5%), lower respiratory tract infection (5%), increased alanine aminotransferase, and hyponatremia were the most common grade 3–4 adverse events documented [61]. Atrial fibrillation occurred in 5%, which is significantly lower than for ibrutinib as well as for ibrutinib and rituximab. Despite limited data on patients with *MYD88* mutation, clinically meaningful responses were also demonstrated. Combination therapy and further randomized trials are warranted to elucidate the efficacy of acalabrutinib. However, acalabrutinib can be safely administered and may be a potential treatment option for R/R WM patients.

Zanubrutinib is a potent irreversible next-generation BTK inhibitor. It has demonstrated excellent activity and tolerability in TN or R/R chronic lymphocytic leukemia/small lymphocytic lymphoma [62]. Preliminary data from the ASPEN trial (NCT03053440), a phase 3 multicenter clinical trial, compared zanubrutinib (160 mg twice daily) to ibrutinib (420 mg once a day). The ASPEN trial included two cohorts. Cohort 1 included 102 patients (19 TN and 83 R/R) and 99 patients (18 TN and 81 R/R) in the zanubrutinib and ibrutinib group, respectively. As of August 2019, the median follow-up was 19.4 months. In the overall patient population and R/R patients, VGPR and MMR rates were higher in the zanubrutinib versus the ibrutinib arm. Although there is no statistical significance, zanubrutinib demonstrated a substantial clinical benefit. The 1-year PFS rate was also higher in all patients and R/R WM patients in the zanubrutinib group (90 and 93%, respectively), compared to all patients and R/R WM patients in the ibrutinib group (87 and 86%, respectively) [63]. Zanubrutinib was found to be safe, with a lower rate of atrial fibrillation when compared to ibrutinib (2 vs. 15.3%). Minor bleeding was similar in both groups. However, neutropenia was higher in the zanubrutinib group compared to the ibrutinib group (30 vs. 13.3%). Overall, zanubrutinib is safe, and the rate of discontinuation due to adverse events is lower when compared to ibrutinib.

In some centers, based on *MYD88* and *CXCR4* genotype, BTK inhibitors have replaced Benda-R therapy. While BTK inhibitors are convenient due to oral administration, intolerable side effects and reduced efficacy in the $MYD88^{WT}$ cohort may limit its use. No randomized controlled trials comparing BTK and chemoimmunotherapy are available, and therapy should be individualized to the patient and mutational profile.

BCL2 Inhibitors

BCL2 is a protein that inhibits apoptosis and is overly expressed in primary WM cells [64]. Venetoclax (ABT-199) is a unique small molecule that selectively inhibits BCL2 and has demonstrated substantial efficacy in patients with R/R WM. In a phase 2 clinical trial (NCT02677324), venetoclax (at a maximum target dose of 800 mg daily) demonstrated an ORR and MRR of 87 and 80%, respectively [65]. The median time to response was 1.9 months, but a slower response was noted in 16 patients (52%) that had previously been exposed to BTK inhibitors. No tumor lysis syndrome or IgM flares were observed, and cytopenias and diarrhea were the most common adverse events. Interestingly, all patients had a *MYD88*^{L265P} mutation detected, and results may not be generalizable to the *MYD88*^{WT} subset. Venetoclax, when combined with ibrutinib, demonstrated a synergistic effect against WM cells, and a phase 2 clinical study in untreated WM is expected (NCT04273139).

Phosphatidylinositol 3-Kinase Inhibitors

The phosphatidylinositol 3-kinase (PI3K) pathway plays a significant role in the initiation and progression of malignancies, enhancing cell survival by stimulating cell proliferation and cell survival [66]. PI3Kδ inhibitors have been shown to induce cell death in WM cell lines [67], making it a potential target in patients with WM (Table 2).

Idelalisib (GS-1101, CAL-101) is a potent, highly selective, oral PI3Kδ/AKT inhibitor that promotes apoptosis. A phase 1b, dose escalation study evaluating idelalisib in patients with relapsed B cell malignancies demonstrated an ORR of 55% in 9 patients with WM. Overall, grade 3 serum transaminase abnormalities occurred in approximately 25% of patients [68]. Similar elevations in aminotransferase levels occurred in 13% of patients with R/R indolent non-Hodgkin lymphomas. In the subset of patients with WM, 8 of 10 patients reported responses to idelalisib with a median PFS of 22 months [69]. In an attempt to develop a "chemo-free" approach, a single-arm phase 2 study assessed the combination of obinutuzumab (anti-CD20 antibody) with idelalisib in patients with R/R WM (NCT02962401) [70]. Idelalisib was given continuously at a dose of 150 mg with intravenous obinutuzumab at 100 mg on day 1 followed by 900 mg on day 2 and 1,000 mg on days 8 and 15 during cycle 1 (induction phase), and subsequently at the same fixed dose of 1,000 mg on day 1 of cycles 2–6 of each 28-day cycle (maintenance phase). The median follow-up was 18.3 months, and 96% of the patients had *MYD88* mutation. ORR and MRR were 90 and 76%, respectively. The estimated PFS was 25 months with a 1- and 2-year PFS of 90 and 70%, respectively. Combination therapy had an effective response, but the low proportion of *MYD88*^{WT} patients and significant hepatotoxicity may limit its use [71].

The efficacy of other PI3K inhibitors which are less hepatotoxic, such as duvelisib and umbralisib (TGR-1202), is currently being evaluated in WM [72, 73]. In a phase 2b, multicenter, multicohort trial in patients with R/R marginal zone lymphoma, umbralisib monotherapy was effective and side effects were tolerable. The median time to initial response was 2.7 months, and 86% of patients had a reduction in tumor burden [74]. Phase III studies are planned in other indolent non-Hodgkin lymphoma subtypes.

Anti-CXCR4 Therapy

Patients with WM characterized by mutated *CXCR4* are less likely to respond to single-agent ibrutinib or ibrutinib/rituximab combination therapy than those who have *CXCR4*^{WT} disease [75]. A small number of drugs targeting *CXCR4* are currently under investigation.

Ulocuplumab (BMS-936564) is a fully human IgG4 monoclonal antibody which inhibits the binding of *CXCR4* to *CXCL12*, resulting in decreased WM cell proliferation [76]. Ulocuplumab (NCT03225716) is being evaluated in combination with ibrutinib in a phase 1/2 clinical trial for symptomatic patients who have *CXCR4*^{MUT} [77]. As of February 2020, 13 participants have been enrolled in daily oral ibrutinib plus intravenous ulocuplumab 2–4 times per cycle for cycles 1–6 [77]. The results of this trial are pending.

Mavorixafor (AMD-070) is a potent, noncompetitive antagonist of chemokine receptor *CXCR4*. Mavorixafor is a small molecule that is orally available and administered once daily. In warts, hypogammaglobulinemia, infections, and myelokathexis syndrome, a rare congenital immune deficiency, mavorixafor demonstrated a favorable safety profile and resulted in meaningful increases in neutrophils and lymphocyte biomarker counts along with a reduction in wart burden and infection rates [78]. A phase 1b trial designed to assess the safety and tolerability of mavorixafor and ibrutinib in patients with WM and *CXCR4* mutation (NCT04274738) is in progress [79].

Plerixafor (AMD3100) is a *CXCR4* antagonist that disrupts the CXCR4/SDF-1α bond. Plerixafor was approved by the Food and Drug Administration in combination with granulocyte colony-stimulating factor for hematopoietic stem and progenitor cell mobilization in patients with lymphoma and multiple myeloma [80, 81].

Conclusion

WM is a type of non-Hodgkin lymphoma, also known as lymphoplasmacytic lymphoma. Some patients with WM have a smoldering form that may be surveilled without intervention. For patients requiring treatment, Benda-R therapy can be considered the first-line treatment. Other chemoimmunotherapy combinations with DRC and BR provide effective and durable responses, but are limited by drug-specific toxicities. The success of ibrutinib in WM may change the current management of WM. Moreover, the recent and promising advances in the understanding of WM biology may expand future initial treatment options.

Conflict of Interest Statement

The authors have no conflicts of interest to declare related to this paper. M.A. Gertz: personal fees: Ionis/Akcea, Alnylam, Prothena, Celgene, Janssen, Spectrum, Annexon, Appellis, Research to Practice, Amgen, Medscape, Physicians Education Resource, and Abbvie; grants: Spectrum, Amyloidosis Foundation, and International Waldenström Foundation; speaker fees: Teva, Johnson and Johnson, Medscape, and DAVA oncology; advisory board: Pharmacyclics and Proclara; royalties: Springer Publishing; development of educational material: i3Health; stock options: Aurora Bio.

Funding Sources

The authors have no funding sources to declare.

Author Contributions

C.N. Grimont is the lead author who was responsible for critical review of the data and preparation of the manuscript. N.E. Castillo Almeida was responsible for the literature acquisition and review of the final manuscript. M.A. Gertz was responsible for the critical review of the final manuscript and mentorship.

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