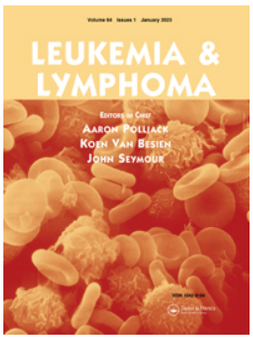

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REVIEW

Treatment of relapsed and refractory Waldenstrom Macroglobulinemia

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ABSTRACT

Waldenström's Macroglobulinemia (WM) is a rare type of indolent non-Hodgkin lymphoma (NHL) that remains incurable. Several effective agents such as monoclonal antibodies (in combination with chemotherapy), Bruton's tyrosine kinase inhibitors, proteasome inhibitors, and BCL2 inhibitors are (becoming) available for the treatment of relapsed and refractory WM. There is however no consensus on a preferred treatment in the relapsed setting. Choice of therapy in relapsed WM should be individualized by taking several treatment and patients characteristics into account, such as treatment duration, toxicity, age, comorbidities and *MYD88*^{L265P} and *CXCR4* mutational status. Due to better understanding of WM biology and the arrival of novel anti-lymphoma agents, the therapeutic options are increasing. Non-cytotoxic and fixed duration regimens, such as those explored in other indolent NHLs should be the focus of future clinical trials in WM.

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Waldenstrom's Macroglobulinemia; relapsed or refractory disease; treatment recommendations

Introduction

Despite great advances in the treatment of Waldenström's Macroglobulinemia (WM), the disease is still incurable and patients will ultimately relapse. WM is rare and accounts for approximately 1 to 2% of all non-Hodgkin lymphoma (NHL) with an annual incidence rate of approximately 3-10 per million person-years in western countries [1–3]. With a median age of 70 years at diagnosis, WM is primarily affecting the elderly [2,3].

The World Health Organization (WHO) defines WM as bone marrow (BM) involvement by lymphoplasmacytic lymphoma (LPL) accompanied by an IgM monoclonal gammopathy [4]. LPL is defined as a neoplasm of small B lymphocytes, plasmacytoid lymphocytes and plasma cells, usually with BM involvement and occasionally localization in lymph nodes and spleen, that does not meet the criteria for other small B cell lymphomas with plasmacytoid differentiation [4]. WM is preceded by IgM monoclonal gammopathy of undetermined significance (MGUS), a premalignant phase wherein the small B cell clone is less than 10% and does not cause symptoms.

Compared to other lymphomas, WM is unique due to a wide variety of symptoms that can occur at presentation potentially involving almost all organ systems. Symptoms can be caused by the immunological properties of the pathogenic IgM itself, including hyperviscosity syndrome in 15% of patients, neuropathy, and cryoglobulinemia [5–7]. Symptoms resulting from the LPL clonal cells include anemia (which is the commonly presenting symptom) thrombocytopenia, constitutional symptoms, lymphadenopathy, hepatosplenomegaly or other end-organ damage [8]. However, extramedullary disease at initial diagnosis is less common (15-20%) and is primarily seen at relapse in up to 60% of patients [9]. Still, many patients can remain asymptomatic for years without the need for treatment [10].

Histopathological involvement of the BM is a prerequisite of WM diagnosis wherein two criteria currently coexist: the WHO defines WM as a combination of IgM monoclonal gammopathy of any level combined with >10% BM infiltration by LPL with WM-related symptoms, while the International Workshop on WM (IWWM) defines WM as IgM paraproteinemia combined with BM infiltration of any level with WM related symptoms. The clonal population in the BM consists of B-cells with a phenotypical profile with expression of mature B-cell markers [11,12].

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Biology of WM

The identification of a highly recurrent somatic mutation in the myeloid differentiation primary response 88 gene (*MYD88*^{L265P}) in over 90% of WM vastly improved the genomic understanding of WM [13]. This mutation harbors a single nucleotide change (position 38182641 in chromosome 3p22.2) resulting in an amino acid change from leucine to proline. The *MYD88* protein participates in toll-like receptor and interleukin-1 receptor-associated kinases (IRAK) signaling, which in turn activate Bruton tyrosine kinase (BTK). BTK activation results in downstream activation of nuclear factor kappa B (NFKB) promoting B cell survival and growth.

The C-X-C chemokine receptor type 4 (*CXCR4*) mutation is the second most commonly occurring mutation in WM and has been described in up to 40% of patients [14]. Over 40 different mutations of two classes (nonsense (NS) and frameshift (FS) mutations) have been described in the C terminal domain of which amino acid S338X at position 1013 is the most frequently mutated region. The NS and FS mutations impair the ability of the G-protein coupled receptor to internalize leading to enhanced AKT and subsequent MAPK 1/2 signaling upon activation by its ligand CXCL12 [14,15].

Other less commonly occurring mutations in WM include ARID1A in 17% and *CD79A/CD79B* in 8-12% of patients [16].

TP53 mutations are even more rarely described in WM occurring in 2-3% of patients and while only few data are available seem associated with an aggressive disease course [17–19].

Current treatment options for relapsed/refractory WM

In the event of a symptomatic recurrence, therapy should be initiated [20]. In the absence of a treatment indication, i.e. in the case of asymptomatic biochemical recurrence, a wait-and-see approach is recommended [20]. For symptomatic relapsed or refractory patients (R/R), the most important factors for determining the second-line therapy are patient characteristics, duration of response to the first-line therapy as well as previous toxicities. Although there is a wide variety of available treatment options, there is no consensus on a preferred regimen in the relapse setting given the lack of randomized controlled trials. Many RR WM patients are managed outside clinical trials. A large retrospective study with 454 European WM patients demonstrated that monotherapy (43%) was the most applied treatment strategy in the frontline setting between 2000-2014 followed by chemoimmunotherapy (36%). After first-line treatment, median PFS was 29 months and 10-year OS was 69%. PFS was shorter in patients treated with monotherapy compared to immunochemotherapy or other combination treatments [21].

Current treatment options for relapsed patients include different types of drugs including immunochemotherapy, proteasome inhibitors, and BTK-inhibitors [22]. An overview of the current treatment options for R/R WM along with their efficacy and toxicity will be discussed below and is summarized in Table 1.

Alkylating agents

Alkylating agents such as cyclophosphamide were among the first applied agents in WM in the frontline setting. The dexamethasone-rituximab-cyclophosphamide (DRC) regimen, the most commonly applied first-line treatment, is still highly effective in the relapsed setting. In second- and subsequent therapy lines, DRC proved feasible as 71% of patients completed 6 cycles resulting in an overall response rate (ORR) of 87% including 4% very good partial response (VGPR), 64% partial response (PR), and 19% minor response (MR) [23, 25].

Bendamustine is widely used in patients with lymphoid malignancies [55]. A retrospective analysis of bendamustine combined with rituximab (R-Benda) to establish optimal dose and schedule in WM demonstrated a major response rate (MRR) in 74% of 111 R/R WM patients. After a median follow-up (FU) of 37 months, 48 R/R patients (43.2%) progressed [28]. In another retrospective analysis of 30 R/R WM patients who had a median of 2 prior treatments, bendamustine monotherapy, R-Benda or bendamustine combined with ofatumumab resulted in an ORR of 83.3% and median progression-free survival (PFS) of 13.2 months after a median of 5 cycles [27]. Another study with 71 R/R WM patients with a median of 2 prior treatments demonstrated an ORR and MRR of 80.2% and 74.6%, respectively. Grade 3/4 adverse events were mostly neutropenia (13%). After a median FU of 19 months, PFS was not reached. Paludo et al. compared R-Benda versus DRC in 160 R/R? WM patients of which 43 and 60 R/R patients received R-Benda and DRC, respectively. In R/R WM patients, the ORR was 95% and the median PFS was 58 months. *MYD88* status did not affect depth of response. Although toxicity of R-Benda and DRC were comparable, a trend toward longer PFS was observed with R-

Table 1. Current treatment regimens for patients with R/R WM.

Regimen	Study	Type of study	Median FU, months	*N*	ORR, %	MRR, %	MedianPFS, months	Adverse events (grade ≥3)
DRC	Paludo et al. [23]	Retrospective	51	50	87	68	32	Neutropenia (20%), thrombocytopenia (7%) and infections (3%)
CAP	Leblond et al. [24]	Prospective	52	45	NR	11	8	>2 Infections (2%), ≥1 mucositis (4%)*and* ≥1 alopecia (5%)
R-Benda	Paludo et al. [25]	Retrospective	32	43	95	81	58	Neutropenia (11%), infections (5%), thrombocytopenia (2%)
R-Benda	Tedeschi et al. [26]	Retrospective	19	71	80.2	74.6	NA	Neutropenia (13%)
Benda ± Rituximab ± Ofatumumab	Treon et al. [27]	Retrospective	13.2	30	79	79	13.2	Myelosupression (13%), infection (7%) and hypersensitivity (7%)
R-Benda	Arulogun et al. [28]	Retrospective	37	250 (111 R/R)	NR	73.9	NR	NR
Fludarabine	Leblond et al. [24]	Prospective	52	45	NR	14	8	>2 Neutropenia (32%), >2 infections (1%)
R-2CDA	Laszlo et al. [29]	Prospective	50	29	89.6	79	60.3	Neutropenia 37%), anemia (0.3%)
FCR	Tedeschi et al. [30]	Prospective	37.2	43 (15 R/R)	79	32	NR	Neutropenia (88.3%), thrombocytopenia (4.6%)
FCR	Tedeschi et al. [31]	Retrospective	51	40	80	80	77	Neutropenia (87%)
FCR	Souchet et al. [32]	Retrospective	47	82	85.4	76.8	48	Neutropenia (43%), thrombocytopenia (13%), and anemia (9%)
OFC	Gavriatopoulou et al. [33]	Prospective	23	12	92	84	75% after 23 months	Neutropenia (91.6%), lymphopenia (42%), thrombocytopenia (8.3%), and aneima (8.3%)
Bortezomib	Treon et al. [34]	Prospective	18.2	27	85	48.1	6.6	Sensory neuropathies (22.2%), leukopenia (18.5%), neutropenia (14.8%)
Bortezomib	Chen et al. [35]	Prospective	NR	27	78	44	16.3	Neuropathy (56%), infections (48%)
R-bortezomib	Ghobrial et al. [36]	Prospective	16	37	81	51	15.6	Neutropenia (12%), anemia (8%), thrombocytopenia (8%)
Bor-dex	Leblond et al. [37]	Prospective	42.5	34	75	43	15.3	Thrombocytopenia (35%), anemia (29%), and neutropenia (15%)
IRD	Kersten et al. [38]	Prospective	24	59	71	85	61	anemia (12%), thrombocytopenia (12%), neutropenia (21%)
CaRD	Treon et al. [39]	Prospective	15.4	31 (3 R/R)	87.1	67.7	64.5% at 15.4 months	Dexamethasone-related hyperglycemia (22.6%), carfilzomib-related hyperlipasemia (16.1%), and neutropenia (6.5%)
Carfilzomib	Vesole et al. [40]	Retrospective	13-27 months	7	≥MR	NR	19.4	Cytopenia, neuropathy
Ibrutinib	Treon et al. [41]	Prospective	NR	63	90.5	73	2-year: 69.1% 5-year:54%	Neutropenia (22%), thrombocytopenia (14%), and postprocedural bleeding (3%)
Ibrutinib	Dimopoulos et al. [42]	Prospective	18.1	31	90	71	82% at 18 months	Neutropenia (13%), hypertension (10%), anemia (6%)
R-Ibrutinib	Dimopoulos et al. [43]	Prospective	26.5	75 (41 R/R)	92[a]	72[a]	80% at 30 months	Atrial fibrillation (12%), Hypertension (13%)
Acalabrutinib	Owen et al. [44]	Prospective	27.4	92	93	78	82% at 24 months	Neutropenia (16%), pneumonia (7%), bleeding (3%)
Zanubrutinib	Trotman et al. [45]	Prospective	36	77 (53 R/R)	96	82	80% at 3 years	Neutropenia (18.2%), hemorrhage (3.9%), and atrial fibrillation (5.2%)
Zanubrutinib	Tam et al. [46]	Prospective	18	102 (83 R/R)	94	78	86% at 18 months	Neutropenia (20%), upper respiratory infection (24%), diarrhea (21%)
Zanubrutinib	An et al. [47]	Prospective	33	44	76	70	61% at 24 months	Neutropenia (31.8%), thrombocytopenia (20.5%), pneumonia (20.5%)
Zanubrutinib (in $MYD88^{WT}$)	Dimopoulos et al. [48]	Prospective	18	28 (23 R/R)	81	50	68% at 18 months	Neutropenia (11%), anemia (11%), thrombocytopenia (7%)
Tirabrutinib	Sekiguchi et al. [49]	Prospective	8.3	27 (9 R/R)	88.9	100	89% at 24 months	Neutropenia (11.1%), lymphopenia (11.1%), and leukopenia (7.4%)
Orelabrutinib	Zhou et al. [50]	Prospective	10.5	47	87.2	74.5	NR	Thrombocytopenia (27.7%), neutropenia (14.9%), leukopenia (10.6%), upper respiratory infection (14.9%)
Venetoclax	Castillo et al. [51]	Prospective	33	32	84	81	30	Neutropenia (45%)
Idelalisib + obinutuzumab	Tomowiak et al. [52]	Prospective	25.9	48	71.4	65.3	25.4	Neutropenia (9.4%), diarrhea (8.6%), and liver toxicity (9.3%)
Daratumumab	Castillo et al. [53]	Prospective	NR	13	23	15	2	Febrile neutropenia, bacteremia, infusion reaction (all 8%)
Ulocuplumab + ibrutinib	Treon et al. [54]	Prospective	22.4	13 (4 R/R)	NA	100	90% at 24 months	Grade ≥2 Thrombocytopenia, rash, and skin infections

R: rituximab; R/R: relapsed/refractory; DRC: dexamethasone, rituximab and cyclophosphamide; CAP: cyclophosphamide, doxorubicin, and cisplatin; R-Benda: rituxmab and bendamustine; 2CDA: 2-chloro-2′-deoxyadenosine; OFC: ofatumumab, fludarabine and cyclophosphamide; Bor-Dex: bortezomib and dexamethasone; IRD: ixaxomib, rituximab and dexamethasone; CaRD: Carfilzomib, rituximab, and dexamethasone; NR: not reported/not reached.
[a]In both TN and R/R patients.

Benda [25]. A retrospective study in 71 R/R WM patients treated with R-Benda demonstrated that R-Benda is feasible since 66% of patients completed all six planned cycles. In 14% of patients, R-Benda was discontinued after the 4th cycle due to response achievement and unsatisfactory responses [26]. A dose reduction (70 mg/m^2) is often recommended in frail and/or elderly patients although there is no evidence-based exact guidance for this.

Purine analogs

In a prospective trial of fludarabine, cyclophosphamide, and rituximab (FCR) in 43 WM patients (15 R/R WM) no difference in response was observed between treatment-naïve and pretreated patients with an ORR of 79%. However, FCR was discontinued in 45% of patients mainly due to myelosuppression [30]. Another trial investigating cladibrine combined with rituximab demonstrated no difference in response between newly and R/R patients with an ORR of 90% [29]. Fludarabine monotherapy resulted in longer duration of response and a higher event-free survival rate in the salvage setting compared to cyclophosphamide-doxorubicin-prednisone (CAP) [24]. The FCR regimen (fludarabine-rituximab-cyclophosphamide) as salvage treatment resulted in an ORR of 80-85% with a PFS at 36 months of 7% and a median event-free survival of 77 months in retrospective studies [31,32]. Although purine analogs result in higher response rates, they are not considered preferred options due to their toxicity profile [56–58].

Proteasome inhibitor-based therapy

The proteasome inhibitor (PI) bortezomib has significant activity in the first-line treatment setting of WM [59]. The WMCTG Trial in R/R patients, treatment with bortezomib monotherapy resulted in fast responses (median time to response (TTR) of 1.4 months) and an ORR of 85% [34]. The most common occurring adverse event was grade 3/4 peripheral neuropathy and median time to progression was 7.9 months. In another phase 2 trial with over half of R/R WM patients, bortezomib monotherapy resulted in an ORR of 78% with no significant difference between treatment-naïve and R/R patients. Median PFS was 16.3 months and 74% of patients experienced neuropathy or worsening of existing neuropathy [35]. Bortezomib in combination with rituximab was assessed in a phase 2 trial with 37 R/R WM patients and resulted in an ORR of 81% and a median PFS of 15.6 months [36]. Grade 1/2 anemia (81%), fatigue (68%), neuropathy (41%), and diarrhea (37%) were the most frequently occurring adverse events. Grade 3 neuropathy occurred in 5% of patients.

Peripheral neuropathy is the most concerning adverse event of bortezomib, especially in patients with preexisting neuropathy, often leading to discontinuation of treatment [60]. Weekly as opposed to twice per week and subcutaneous instead of intravenous administration can reduce the incidence of bortezomib-related neuropathy [61].

The novel and oral PI ixazomib was well tolerated and resulted in less neurotoxicity in multiple myeloma (MM) [62]. A total of 59 patients with R/R WM were treated with oral ixazomib in combination with rituximab and dexamethasone (IRD) during a phase 1/2 trial. The ORR was 71% and after a median FU of 24 months PFS and overall survival (OS) were 56% and 88%, respectively. Neurotoxicity was mostly grade 1 or 2, with no occurrence of grade 3 toxicity and no increase in neuropathy-associated symptom burden. The IRD regimen was well tolerated with manageable toxicity [38].

A phase 2 study with another less neurotoxic PI carfilzomib demonstrated an ORR of 87.1% and PFS was 65% after a median FU of 15.4 months in 28 treatment-naïve WM patients and 3 patients previously treated with everolimus. Since carfilzomib is a neuropathy-sparing PI, treatment-related neuropathy occurred in only 1 patient and discontinuation of therapy due to neuropathy did not occur [39]. Carfilzomib has not been prospectively assessed in R/R WM patients with the exception of the 3 abovementioned patients. In a case series with 7 R/R WM patients with a median of 2 prior treatments and of whom 2 were bortezomib refractory treated with carfilzomib a PFS of approximately 19 months was demonstrated [40].

BTK inhibitors

The BTK inhibitor Ibrutinib is an oral agent with substantial activity in WM. Highest response rates are seen in patients with *MYD88*^{L265P} but without *CXCR4*^{WT} mutations, followed by those with both mutations. Ibrutinib seems much less effective in patients with MYD88 wild-type disease [41]. In a prospective study, 63 R/R WM patients, of whom 40% were refractory to last treatment, were treated with ibrutinib monotherapy. The ORR was 90.5% (95% CI 80.4 – 96.4) and the MRR was 73% (95% CI, 60.3 – 83.4) in all patients; the ORR and MRR were 100% and 91.2% in patients with *MYD88*^{L265P}/*CXCR4*^{WT}, 85.7% and 61.9% in *MYD88*^{L265P}/

CXCR4^{WHIM}, and 71.4% and 28.6% in *MYD88*^{WT}/*CXCR4*^{WT}, respectively. The median time to minor response was 4 weeks and prior lines of therapy or refractory disease did not significantly affect response. After 2 years the PFS and OS were 69.1% (95% CI 53.2 to 80.5) and 95.2% (95% CI 86.0–98.4), respectively. Grade 2 and higher adverse events were neutropenia (22%), thrombocytopenia (14%), post-procedural bleeding (3%) and atrial fibrillation (5%) [41]. Ibrutinib was also assessed in rituximab refractory disease [42]. A total of 31 WM patients with a median of 2 prior treatments were treated with 420 mg ibrutinib daily until progression, intolerable toxicity or withdrawal. After a median FU of 18 months, the ORR and MRR were 90% and 71%, respectively. In patients with *MYD88*^{L265P}/*CXCR4*^{WT} ($n = 17$), ORR and MRR were 88% and 82% compared to 100% and 71% in *MYD88*^{L265P}/*CXCR4*^{WHIM} ($n = 7$) patients. After 18 months, the PFS was 86% [42].

In the iNNOVATE trial, a total of 150 WM patients were assigned to receive either ibrutinib-rituximab or placebo-rituximab [43]. About 55% of these patients were previously treated. Major response rates were higher in the ibrutinib-rituximab group (72% vs 32%). Grade 3 or higher toxicities more frequent in the ibrutinib-rituximab arm and consisted of atrial fibrillation (12% vs 1%) and hypertension (13% vs 4%). Major bleedings were equal in the two groups (4%). At 30 months, the PFS was 82% in the ibrutinib-rituximab arm and 28% in the placebo-rituximab arm [43].

Second- and next-generation BTK inhibitors

Acalabrutinib (ACP-196) is a 2nd generation BTK inhibitor [63]. A phase 2 multicenter study included 106 patients (14 treatment-naive and 92 R/R WM) who were treated with oral acalabrutinib until disease progression or toxicity occurred [44]. The ORR in R/R WM was 93% (IQR 86–98) and the MRR 78% (IQR 68–86). Responses in the *MYD88*^{WT} patients were lower with an ORR of 79% and MRR of 57% compared to an ORR of 94% and MRR of 78% in *MYD88*^{L265P} patients, though clearly better than in the aforementioned ibrutinib study. At 24 months the PFS was 82% for R/R WM patients. The median time to best response was 4.6 months (IQR 1.9-9.2). Adverse events consisted mainly of headache, diarrhea, dizziness, fatigue, nausea, joint pain, and upper respiratory tract infections. The most common grade 3-4 adverse events were neutropenia (16%) and pneumonia (7%). Treatment discontinuation occurred in 25% of R/R WM [44]. The long-term data from this study demonstrated a median PFS of 68 months in R/R WM after a median of 63.7 months of follow-up and an estimated 66-month OS of 71%. Of the R/R patients, 16% discontinued treatment due to adverse events and 22% progressed while on acalabrutinib treatment. Eleven R/R patients experienced grade 5 AEs [64].

Zanubrutinib, another 2nd generation BTK inhibitor, has been studied in four prospective clinical trials. In a phase 2 study in 77 WM patients (24 treatment-naïve and 53 R/R) an ORR of 96% (ORR of 94% in the R/R group) and high VGPR/Complete response (CR) rates in the treatment-naïve (33%) and R/R (51%) groups. ORR and MRR were 97% and 87% in *MYD88*^{L265P}/*CXCR4*^{WT} ($n = 39$), 100% and 91% in *MYD88*^{L265P}/*CXCR4*^{WHIM} ($n = 11$), and 100% and 63% in *MYD88*^{WT} cases ($n = 8$). After a median FU of 36.8 months, the median PFS was not reached [45]. In another phase 2 trial zanubrutinib was investigated in 44 R/R WM patients and resulted in an ORR of 77%, a MRR of 70% and VGPR/CR rates of 33%. Similar to the abovementioned study, patients with *MYD88*^{L265P}/*CXCR4*^{WT} ($n = 32$) had a higher response rate (26% ORR, 24% MRR) compared to *MYD88*^{L265P}/*CXCR4*^{WHIM} ($n = 5$) (3% ORR, 3% MRR) and *MYD88*^{WT} ($n = 6$) (4% ORR, 3% MRR). After 33 months the median PFS was not reached [47]. In a phase 3 multicenter clinical trial zanubrutinib was compared to ibrutinib in 201 WM patients (37 treatment-naïve and 164 R/R). The ORR and MRR were similar; 93% and 78% in the ibrutinib arm versus 94% and 77% in the zanubrutinib arm. However, deeper responses were more prevalent in the zanubrutinib arm (28% VS 19% VGPR; p=.09). No CRs were observed in either arm. MRR was similar for *MYD88*^{L265P}/*CXCR4*^{WHIM} vs *MYD88*^{L265P}/*CXCR4*^{WT} patients across both treatment arms; (63% vs 64% in the ibrutinib arm and 80% vs 79% in the zanubrutinib arm, respectively). After 18 months of FU, the median PFS was not reached. The one-year PFS rate was higher in R/R WM patients treated with zanubrutinib vs R/R patients treated with ibrutinib (93% vs 86%). Zanubrutinib was found to be a safe agent considering atrial fibrillation/flutter which was more prevalent in the ibrutinib arm (15% vs 2%). However, neutropenia was most frequently observed in the zanubrutinib arm (30% vs 13%). Grade $\geq$3 hypertension and pneumonia were more frequent in patients treated with ibrutinib. The number of infections (around 67%) was similar in both arms. Grade $\geq$3 neutropenia had a 5% higher incidence among zanubrutinib-treated patients. Overall, compared to ibrutinib, zanubrutinib was proven safe with lower rates of discontinuation due to adverse events. A separate cohort within this trial consisted of 28 *MYD88*^{WT} patients treated with

zanubrutinib of whom 23 were R/R. The ORR was 81%, MRR was 50% and the PFS at 18 months was 68% [46]. Long-term data from this study (after a median of 43 months of FU) confirmed the higher CR/VGPR rates for zanubrutinib (36% for zanubrutinib vs 22% for ibrutinib; $p=.02$). Only 1 CR occurred in the separate single-arm cohort with *MYD88*^{WT} patients. Median PFS and OS were not yet reached [65].

Of note, the great variability with regards to the used MYD88 mutation detection methods between the various trials with BTK inhibitors, might influence the sensitivity of MYD88 detection and could partially explain the differing responses in MYD88^{L265P}/MYD88^{WT} patients.

Tirabrutinib was assessed in 27 WM patients (18 treatment-naïve and 9 R/R) in a phase 2 study. The ORR was 94–100%. The most frequently observed adverse events were rash (44.4%) and neutropenia (25.9%) [49].

Orelabrutinib is currently being investigated in a phase 2 clinical study with 47 R/R WM patients. Preliminary results demonstrate an ORR and MRR of 87.2% and 74.5%, respectively after a median FU of 10.5 months. PFS and OS were 88.0% and 92.3% at 12 months, respectively. The MRR was higher in patients with *MYD88*^{L265P}/*CXCR4*^{WT} (79.5%). Grade $\geq$ 3 AEs were reported in 34% of patients [50].

Although covalent BTK inhibitors such as ibrutinib, acalabrutinib and zanubrutinib are effective in WM, resistance to these BTK inhibitors can occur due to acquired BTK mutations [66]. Therefore, there was an interest for the development of non-covalent BTK inhibitors such as pirtobrutinib that bind an alternate site. In a phase 1/2 study in previously treated patients with B-cell malignancies including 26 WM patients, pirtobrutinib was found safe and active even in patients who were previously treated with covalent BTK inhibitors [67].

Stem cell transplant (SCT)

No prospective clinical trials on autologous SCT have been conducted in WM and evidence is based on retrospective studies conducted before widespread implementation of rituximab [68–71]. In the largest retrospective study with 158 R/R WM patients in the pre-rituximab era, ASCT was mainly effective in young and fit patients with chemosensitive disease after early relapse and an aggressive disease course [72]. The conditioning regimens used varied; however, BEAM (carmustine, etoposide, cytarabine, and melphalan) was most commonly applied (46%). At 1 year, the nonrelapse mortality (NRM) was 3.8% and 5-year PFS and OS were 39.7% and 68.5%, respectively. In total, 22% of patients achieved a CR after ASCT. Multivariate analyses demonstrated that chemorefractory disease at the time of transplantation, at least 3 lines of therapy prior to transplantation, age $>$ 50 years and male gender were all associated with poorer OS [72]. Currently, there is no international consensus on the role of autologous SCT (ASCT) in WM [73]. ASCT can be considered in younger and fit patients with an aggressive disease course; e.g. early relapse after rituximab-containing immmunochemotherapy, and who are resistant to BTK inhibitors. Also, if transformation to a high grade lymphoma occurs, application of consolidative high dose chemotherarpy and ASCT can be considered as in conventional DLBCL treatment [10].

Data on allogeneic SCT (alloSCT) are also derived from retrospective studies only. A retrospective series in 144 WM patients demonstrated an OS of 74% after 1 year and 52% after 5 years with PFS of 68% and 46%, respectively. The 1- and 5-year NRM was 15% and 30%, respectively [74]. Comparative results were found in another series with 86 WM patients; 5 year OS was 64%, PFS 56% and an NRM of 33% after myeloablative conditioning and 5 year OS of 64%, PFS of 49% and an NRM of 23% after reduced-intensity conditioning [75]. AlloSCT is rarely recommended in WM due to high toxicity where less toxic treatment options are increasingly available. International guidelines recommend alloSCT in very limited cases; either in the context of clinical trials or in selected younger patients with aggressive clinical course and resistance to BTK inhibitors [10, 20, 76,77].

Other emerging treatments

BCL2 inhibitors

BCL2 is an inhibitor of apoptosis, and is overexpressed in WM [78]. Venetoclax is a selective BCL2 inhibitor that is highly effective in a range of hematological malignancies. In a phase 2 clinical trial, 31 R/R WM patients received 200-800mg venetoclax daily for a fixed duration of 2 years, of whom 50% were previously treated with a BTK inhibitor. The median FU was 33 months and ORR and MRR were 87 and 80%, respectively. The median PFS was 30 months [51]. CXCR4 mutation status had no effect on response or PFS. Neutropenia (45%) was the only occurring grade $\geq$3 AE. Grade $\geq$ 2 adverse events were seen in 94% of patients and consisted mostly of anemia, lymphopenia and neutropenia. Temporary drug hold occurred in 14 patients and was mostly due to neutropenia,

infections, and diarrhea. Currently, a phase 2 trial assessing the combination of venetoclax with ibrutinib in treatment-naïve WM is in progress [79].

Phosphatidylinositol 3-kinase (PI3Kδ) inhibitors

The PI3Kδ inhibitor Idelalisib, although effective, has not been further developed or recommended in WM due to excess toxicity [52].

Anti-CXCR4 monoclonal antibodies

Since CXCR4 mutations can impact the clinical outcome of WM patients treated with ibrutinib or ibrutinib-rituximab, agents targeting CXCR4 are currently assessed in phase 1/2 clinical trials. Ulocuplumab, a CXCR4 antagonist, has shown activity in NHL *via* antibody-induced apoptosis [80] and has been assessed combined with ibrutinib in a phase 1/2 clinical trial in 13 WM patients (4 R/R) with mutated CXCR4 [54, 81]. Ulocuplumab in combination with ibrutinib resulted in a MRR of 100% and after a median FU of 22.4 months, the 2-year PFS was 90%. A phase 1 study with mavorixafor, a CXCR4 antagonist, combined with ibrutinib in 9 WM patients with *MYD88* and $CXCR4^{WHIM}$, demonstrated an ORR (minor response or better) in all (100%) patients. Also this combination resulted in durable decrease in IgM levels and increase in Hb levels. A total of 9 out of 107 AEs (79% grade 1) were attributable to mavorixafor only of which two grade 2 AEs led to drug interruption. One dose-limiting toxicity (grade 3 hypertension) occurred and was attributed to the combination therapy [82].

Antibodies

Expression of CD38, a marker of plasmacytoid differentiation, is seen in a subset of WM patients [83]. Daratumumab is an anti-CD38 monoclonal antibody that is highly active and has become standard of care in patients with plasma cell dyscrasias including multiple myeloma and light chain amyloidosis [84–86]. A phase 2 study with daratumumab monotherapy in 13 R/R WM patients however yielded disappointing results as ORR was 23%, MRR was 15% and median PFS of 2 months [53].

T-cell therapies

T-cell-directed therapies are an attractive option in WM since T-cell composition and functionality is mostly intact, even in R/R patients [87].

In chimeric antigen receptor (CAR) T-cell therapy, the patient's autologous T-cells are collected from the peripheral blood and engineered to express a tumor-specific CAR (for example against CD19), followed by cell expansion and re-infusion [88]. CAR T therapy is highly efficacious in several B-cel NHL such as DLBCL and follicular lymphoma (FL). It is however an intensive therapy with specific (potentially serious) side effects [89]. Only 3 WM patients were treated with CAR T therapy in two different phase 1 clinical trials in CLL/indolent NHLs. CAR T therapy was safe and induced responses in these three heavily previously treated WM patients [90]. Further prospective research in this field will have to demonstrate the role of CAR T therapy in the treatment of R/R WM.

Other emerging T-cell targeted immune therapies such as bispecific antibodies are active in indolent NHLs including WM [91]. In a phase I trial with a CD20xCD3 bispecific antibody in relapsed/refractory B-NHL including 3 R/R WM, the most commonly reported grade $\geq$3 AEs were anemia, decreased lymphocytes/lymphopenia, infections and infestations, and decreased neutrophils/neutropenia. Bispecific antibodies may be an attractive option in R/R WM due to their favorable toxicity profile and availability as off-the-shelf products [87]. This will have to be further explored in prospective clinical trials.

Current ongoing clinical trials in WM include daratumumab in combination with ibrutinib in ibrutinib naïve patients [92], ibrutinib combined with ixazomib in newly diagnosed and RR WM patients [93], loncastuximab (a CD19 antibody) in RR WM [94], and iopofosine I 131 (CLR 131), a targeted radiotherapeutic, in RR WM [95].

Mutational status related to BTK inhibitors

Currently, mutational analysis as a potential tool to tailor treatment options is on the rise in WM. Limited data reveals that *MYD88* mutational status does not impact outcomes of WM patients treated with immunochemotherapy or PIs as response rates were similar between *MYD88* mutated and *MYD88* wild-type patients [25, 39]. It is especially important in the case of BTK inhibitors and other novel targeted therapies such as anti-CXCR4 antibodies given that ibrutinib demonstrated less activity in $MYD88^{WT}$ and $MYD88^{L265P}/CXCR4^{MUT}$ genotypes [41]. Patients with $MYD88^{WT}$ or $CXCR4^{MUT}$ had shorter PFS and no major responses occurred in $MYD88^{WT}$ patients. Although major responses were observed in $MYD88^{L265P}/CXCR4^{MUT}$ patients, the time to these major responses was increased compared to $CXCR4^{WT}$ patients [96]. On the contrary, major responses are achieved In $MYD88^{WT}$ patients treated with acalabrutinib or zanubrutinib. Assessment of mutational status for the

determination of therapy should also include sequencing the whole gene to detect non-L265P *MYD88* mutations when the *MYD88*^{L265P} mutation is absent. In addition, rare non-L265P *MYD88* mutations that are also associated with good responses to BTK inhibitors can sometimes be present and will be missed when using AS-PCR techniques [97]. Physicians should be aware of this and have a dialogue with their molecular laboratory when using *MYD88* mutational testing for clinical decision-making.

Determining type of therapy

If a treatment indication arises, type of therapy should be individualized. Certain treatment attributes should be considered in the selection of salvage treatment such as duration (fixed duration vs ongoing), toxicity and the duration of response after last treatment. Furthermore, patient's age, comorbidities and patient and physician perceived treatment goals could further aid in selecting the most fitting treatment. WM patients seem to prefer fixed duration treatment with the highest efficacy with however the lowest risk of secondary malignancy [98].

In the selection of salvage therapy, it is recommended to encourage participation in clinical trials when possible. While each case should be individually assessed, in case of a late relapse after immunochemotherapy (± 3 years based on expert opinion), an alternative immunochemotherapy regimen compared to first-line, prior effective regimen or a PI can be considered [10]. Monotherapy with BTK-I is also a valid option [10]. In patients with a long therapy-free interval after immunochemotherapy, the same regimen or an alternate regimen can be repeated. Treatment with a PI is also an option and BKT-I can be considered.

Patients with an early relapse (< 6-12 months), especially after rituximab-containing first-line therapy, are preferably managed with a BTK inhibitor [42]. Bortezomib or bendamustine are also options that can be considered after early relapse. Younger and fit patients with early relapse after rituximab-containing therapy and who are resistant or intolerant to BTK inhibitors can be considered for SCT.

Future directions

The currently available treatment options for WM have varying properties in terms of mode of administration, duration of reponse and toxicity. Chemoimmunotherapy has the advantage of a fixed duration and a treatment-free interval of several years, compared to BTK inhibitors which should be administered daily until progression or intolerable side effects occur. However, chemoimmunotherapy is accompanied by a different toxicity profile compared to a targeted agent such as ibrutinib, including the potential of secondary malignancies. However, the risk of secondary malignancies for regimens such as DRC and R-Benda remains unclear. Taking patients' preferences into account, future clinical trials in WM patients should focus on nontoxic treatments with fixed duration [98]. This is already successfully explored in CLL in which patients were treated with a fixed duration combination of Ibrutinib-venetoclax, which results in long PFS and deep responses [99]. For the future, smart combinations of novel agents and the introduction of bispecific antibodies to make use of the vital T-cell compartment seen in WM will hopefully lead to a regimen that is highly efficacious, fixed duration and low in toxicity.

Conclusion

Several effective agents are currently available for the treatment of relapsed and refractory WM. There is however no consensus on a preferred treatment strategy in the relapsed setting. Selection of salvage therapy should be individualized by taking several treatment and patient characteristics into account. Due to better understanding of WM biology, novel agents are on the rise and patients' treatment preferences should be incorporated in the direction of future clinical trials.

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