

Review

# First-Line Treatment of Waldenström's Macroglobulinaemia: Considerations Based on the Dutch National Guideline

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**Abstract:** Waldenström macroglobulinemia (WM) is a rare B-cell Non-Hodgkin Lymphoma. There are only few prospective randomized clinical trials to guide treatment recommendations and there is no international consensus on a preferred first line treatment approach. In the recently revised Dutch guideline for WM, we describe recommendations for practice based as much as possible on the known data. Here, we summarize the considerations for first-line treatment based on these Dutch guidelines. Available evidence is summarized, including efficacy and toxicity data. Combinations of Rituximab with chemotherapy, proteasome inhibition or BTK-inhibition are all valid first line treatment options. The Dutch WM working group considers Dexamethasone/Rituximab/Cylofosfamide (DRC) a suitable first-line treatment for many WM patients, given the efficacy, the relatively mild toxicity profile and the extensive experience with this regimen. However, the long-term toxicities of DRC are unclear and need further clarification. Other regimens such as R-bendamustine, R-Bortezomib-dexamethasone are also effective options, however with specific toxicities. BTK-inhibitors are not a preferred option in first line for most patients in the Dutch WM guidelines because of the need for longterm treatment and toxicities. Based on patient preferences research, future clinical trials should focus on effective fixed-duration regimens with non-cytotoxic therapies that have a favorable toxicity profile. Further development of (combinations with) BCL-2 inhibitors, novel proteasome inhibitors and BTK-inhibition could be interesting. In addition T-cell-directed treatments including bispecific antibodies as a monotherapy or combined with other novel agents deserve further study in WM.

**Keywords:** Waldenström's Macroglobulinemia; guideline; ibrutinib; zanubrutinib; DRC; bendamustine

## 1. Introduction

Waldenström's Macroglobulinemia (WM) was first described by the Swedish physician Jan Gösta Waldenström (1906–1996) in 1941. According to the World Health Organization's classification, WM is defined as lymphoplasmacytic lymphoma (LPL) involving bone marrow (BM) and a monoclonal gammopathy of the immunoglobulin "M (IgM) type" [1]. LPL is defined as "a neoplasm of small B lymphocytes, plasmacytoid lymphocytes and plasma cells, usually with bone marrow involvement and sometimes of lymph nodes and spleen, that does not meet the criteria for any of the other small cell malignant B cell lymphomas with plasmacytic maturation".

WM is rare and accounts for only about 2% of all B-cell Non-Hodgkin lymphoma (NHL) cases. The genomic understanding of WM vastly improved following the identification of the MYD88<sup>L265P</sup> mutation in over 90% of patients [2]. The CXCR4 mutation, which is the second-most commonly occurring mutation in up to 40% of WM patients, together with the MYD88 mutation, determines the clinical presentation and has an effect on the prognosis in WM cases [3–5]. The most common clinical presentation and treatment indication of WM is anemia. However, one of the striking aspects of WM compared with other malignant lymphomas is the very diverse symptomatology that can involve almost all organ systems. This is mainly due to the circulating IgM protein, which can lead to damage via several routes (for example, hyperviscosity syndrome, deposition diseases such as amyloidosis, or autoimmune activity such as in anti-MAG neuropathy). Therefore, patients with IgM monoclonal gammopathy of unknown significance (MGUS) with <10% BM infiltration may also have symptoms related to the pathologic IgM. These diseases are referred to as IgM monoclonal gammopathy of clinical significance (MGCS) [6].

Because WM is rare, there are few prospective randomized phase III trials. Indeed, there is no international consensus on a specific regimen for first-line treatment. Population-based data from the Netherlands show that the 5-year relative survival improved for patients diagnosed during 2011–2018, as compared with those diagnosed during 1989–1995: 93% versus 75%, 85% versus 65%, and 79% versus 46% based on three age groups ( $\leq 65$  years, 66–75 years,  $\geq 75$  years, respectively) [7].

In the recently revised Dutch guideline for WM, we describe recommendations for practice based as much as possible on the known data. Here, we summarize the considerations for first-line treatment [8].

## 2. Indications for Starting Treatment

First of all, as in other indolent NHLs for which there are no curative treatments, treatment only needs to be started if a treatment indication arises (symptomatic disease). Otherwise, patients can be observed, as smoldering WM can remain without need for treatment for many years in a large proportion of patients.

Established treatment indications based on international consensus are shown in Table 1 [9]. However, a recent publication suggested that treatment should be started at an IgM above 60 g/L due to the high incidence of hyperviscosity syndrome above this level. This generated some discussion as to whether the IgM level alone should be a treatment indication in otherwise asymptomatic WM patients.

Recently, two groups investigated whether there is a cut-off point above which the risk of hyperviscosity syndrome (HVS) is greatly increased. HVS is a potentially life-threatening complication. Gustine et al. found that in a cohort of 825 untreated WM patients, 14% developed HVS [10]. They reported a median time to develop HVS of 3 months and an incidence rate of HVS of 67% when the total IgM was 60 g/L or higher, while at an IgM of 50–60 g/L HVS developed later (36 months) and the incidence rate was 32%. Serum viscosity measurements were not mentioned. Based on these data, the authors advised that an IgM of 60 g/L or higher should serve as a cut-off for the initiation of treatment. Abeykoon et al. described 997 WM patients, of whom 13% developed HVS [11]. In this series, for patients with an IgM > 60 g/L at diagnosis ( $n = 13$ ) who were managed expectantly, the median time to initial therapy was 6.9 years, and only 15% subsequently developed hyperviscosity-related symptoms. Serum viscosity was the only factor correlated with the onset of HVS. In both series, there was no relationship between the occurrence of HVS and survival. There is no good explanation for the discrepancy in the results of both cohorts in these retrospective analyses. In the recent ESMO guideline, an IgM of 60 g/L or higher is included as a treatment indication, but two other recent guidelines (IWWM-8 consensus guideline and “How I Treat”) do not suggest IgM level alone as a treatment indication [9,12–14].

**Table 1.** WM consensus-based treatment indications.

WM Treatment Indications * Proposed in the IWWM-2 Consensus Panel and Updated in IWWM-8
Hemoglobin $\leq$ 10 g/dL
Platelet count $<$ $100 \times 10^9$ /L
Recurrent fever, night sweats, weight loss, fatigue
Hyperviscosity
Lymphadenopathy that is either symptomatic or bulky ( $\geq$ 5 cm in maximum diameter)
Symptomatic hepatomegaly and/or splenomegaly
Symptomatic organomegaly and/or organ or tissue infiltration
Peripheral neuropathy due to WM
Symptomatic cryoglobulinemia
Cold agglutinin anemia
Immune hemolytic anemia and/or thrombocytopenia
Nephropathy related to WM
Amyloidosis related to WM

\* only if WM related; WM, Waldenström Macroglobulinemia; IWWM, International Workshops on WM.

In conclusion, there are conflicting data regarding a serum IgM  $\geq$  60 g/L as a treatment indication. We therefore do not consider it obligatory to start treatment based only on a serum IgM  $\geq$  60 g/L. However, we do advise that in this situation, the existence of HVS should be investigated very closely, not only by medical history but also by physical examination and ophthalmic examination (fundoscopy), and that treatment should be initiated if there are any signs of HVS. If treatment is not initiated immediately, the patient should be monitored closely, and the ophthalmic examination should be repeated regularly, e.g., every 3–6 months depending on the dynamics of the IgM level.

Finally, we want to emphasize that HVS is a potentially life-threatening hematologic emergency that needs a swift diagnosis and immediate treatment with plasmapheresis, together with the initiation of fast-acting WM therapy. For details on the diagnosis and treatment of HVS, we refer to recent guidelines on this topic [15].

### 3. First-Line Treatment

The moment of treatment initiation must be chosen carefully, with the aforementioned treatment indications serving as a guideline. In addition, it is important to note that the median age at diagnosis is about 65–70 years, and many patients do not ultimately die from WM but rather with WM. In WM, a partial response often leads to a normalization of the hemoglobin level and a good clinical improvement. Quality of life, toxicities and progression-free/disease-related survival, as well as needed depth-of-response, must therefore be taken into account in the choice of treatment, especially in the elderly and/or frail patients.

Due to the fact that WM is still incurable, there is no consensus about the best first-line treatment, and as the further reduction of (late) toxicity of conventional chemotherapy is desired, it is recommended that patients be treated in a clinical trial whenever possible to allow for the development of novel treatment modalities.

Table 2 summarizes a selection of relevant studies on first-line WM treatments regarding the most commonly used and recommended treatment regimens.

**Table 2.** Summary of the literature on various treatments in the first-line.

Regimen	Study	Type of Study	Median Follow-Up	N	ORR (%)	MRR (%)	Median PFS	Toxicity $\geq$ Grade 3
DRC	Kastritis et al., 2015 [16] (update of Dimopoulos et al. JCO 2007 [17])	Prospective	8 years	72	83	74	35 months	Neutropenia (9%)
DRC	Paludo et al, 2017 [18]	Retrospective	30 months	50	96	87	34 months	Neutropenia (20%), thrombocytopenia (7%) and infections (3%)
DRC	Castillo 2018 [19]	Retrospective	5 years	38	89	84	59 months	NR
R-benda	Rummel 2013 [20]	Prospective	45 months	22	96		69 months	Leucocytopenia (37%), neutropenia (29%) and lymphocytopenia 74%
R-benda	Castillo 2018 [19]	Retrospective	36 months	57	97	93	66 months	NR
R-benda	Laribi 2018 [21]	Prospective	23 months	69	97	96	87% after 2 years	Cytopenias ( $n = 10$ ), infections ( $n = 8$ ) and toxidermia ( $n = 1$ )
R-benda	Paludo 2018 [22]	Retrospective	30 months	16	93	86	not reached	neutropenia (11%), infections (5%), thrombocytopenia (2%), and nausea/vomiting (2%)
R-mono	Santos 2016 [23]	Meta-analysis		317	44	38		NR
R-mono	Dimopoulos 2018 [24,25]	Prospective randomized	50 months	34	53	41	20.3 months 20% after 4 years	Infusion-related reaction (16%), anemia (17%), thrombocytopenia (5%)
R-Bort-dex	Treon, update 2015 [26]	Prospective	8,5 years	23	96	91	66 months	Peripheral neuropathy ( $n = 16$ ); neutropenia ( $n = 13$ ); infections without neutropenia ( $n = 13$ ); thrombocytopenia ( $n = 10$ )
R-Bort-dex	Gavriatopoulou 2017 [27]	Prospective	6 years	59	85	68	43 months	Peripheral neuropathy (7%)
R-bort	Ghobrial 2010 [28]	Prospective	14 months	26	88	66	Not reached	Neutropenia (16%), anemia (11%), thrombocytopenia (14%), and peripheral neuropathy (5%)
Ibrutinib	Treon 2018 [29,30]	Prospective	50 months	30	100	83	76% after 4 years	Atrial fibrillation (10%), and hypertension (13%)

Table 2. Cont.

Regimen	Study	Type of Study	Median Follow-Up	N	ORR (%)	MRR (%)	Median PFS	Toxicity $\geq$ Grade 3
R-Ibrutinib	Dimopoulos 2018 [24,25]	Prospective randomized	50 months	34	92	72	84% after 2 years 71% after 4 years	Atrial fibrillation (12%) and hypertension (13%)
Zanubrutinib	Trotman 2020 [31]	Prospective	36 months	24	96	82	80% at 3 years	neutropenia (15.6%), anemia (9.1%), basal cell carcinoma and cellulitis (each 5.2%)
Zanubrutinib	Tam 2020 [32]	Prospective randomized	18 months	19	94	78	86% at 18 months	Neutropenia (20%), thrombocytopenia(6%), hypertension (6%)
Chlorambucil	Leblond 2013 [33]	Prospective randomized	36 months	339	46		27 months	Neutropenia (17.8%), infections (6%)
CaRD (not approved as first-line)	Treon 2014 [34]	Prospective	15.4 months	31	87		65% at 15.4 months	Anemia (3.2%), neutropenia (6.5%)
IRD (not approved as first-line)	Castillo 2020 [35]	Prospective	52 months	26	96	77	40 months	Infections ( $n = 2$ , unrelated to IDR), hyperglycemia ( $n = 2$ ), infusion reactions ( $n = 2$ ), and neuropathy ( $n = 1$ )

R, rituximab; DRC, dexamethasone, rituximab and cyclophosphamide; R-Benda, rituximab and bendamustine; R-mono, rituximab monotherapy; Bort-Dex, bortezomib and dexamethasone; CaRD, Carfilzomib, rituximab and dexamethasone; IRD, Ixazomib, dexamethasone and rituximab; NR, not reported.

Recent international guidelines from the IWWM, NCCN and ESMO list Dexamethasone-Rituximab-Cyclophosphamide (DRC), R-Bendamustine and R-bortezomib-dexamethasone (R-Bor-Dex) as the preferred first-line options [9,13,36]. The data on these three regimens are summarized in Table 2. The responses are deepest and longest with R-bendamustine, followed by R-Bor-Dex, followed by DRC, although the differences are small and these regimens were not directly compared in prospective RCTs. There seems to be no difference in survival. No data are available to make an evidence-based choice of therapy based on patient characteristics.

The addition of rituximab to the treatment regimens is based on a subgroup analysis within a basket trial of the STiL group, in which for WM, R-CHOP was superior to CHOP in both response and time to treatment failure [37]. In addition, retrospective data from various patient registries show that rituximab as a first-line treatment is associated with a longer survival [38,39]. A large American cohort study of 1310 WM patients aged 65 years or older showed that a treatment containing rituximab was associated with a significantly longer survival and less need for transfusions [40]. In the following section, the various first-line treatment options for WM will be discussed in more detail. Agents that were assessed for, but not yet approved as, first-line treatment options will also be discussed.

#### 4. Immuno-Chemotherapy

Rituximab monotherapy has a modest major-response rate (~40%) and PFS (~20 months) [23]. This option can be used in vulnerable patients when no rapid or prolonged response is required and no problems are expected regarding IgM flare.

DRC is an effective, well-tolerated regimen. DRC was introduced on the basis of a prospective study and subsequently evaluated in various retrospective series [16,18,19]. In practice, it appears that patients often experience nausea with the original 100 mg/m<sup>2</sup> orally twice daily for 5 days schedule. Therefore, administering cyclophosphamide 1000 mg/m<sup>2</sup> iv on day 1 instead may be considered to. Furthermore, a lower dose of cyclophosphamide 750 mg/m<sup>2</sup> iv as in the R-CVP course, is used. Based on clinical data and pharmacology, there is no preference for either schedule. While six cycles were given in the original trial, eight cycles are also often used (based on the similar R-CVP protocol).

Adding vincristine (as in R-CVP or R-CHOP) to cyclophosphamide/prednisone/rituximab (R-CP) leads to high rates of neuropathy in WM patients: up to 50–70%. The responses obtained with the vincristine-containing regimens versus the regimens without vincristine are comparable, as has been analyzed in a large retrospective series [41]. In addition, R-CHOP was found to be inferior to R-bendamustine in a subset analysis of a prospective randomized trial [20]. Based on this, vincristine should be avoided in WM patients and R-CHOP/R-CVP are not considered preferred first-line treatment options in WM.

Rituximab-bendamustine was introduced as a treatment for WM based on a sub-study in a large, randomized basket trial for indolent lymphomas, where it was more effective than R-CHOP for WM [20]. The effectiveness of R-bendamustine was subsequently confirmed in a French prospective trial and in two retrospective series [19,21,22]. For patients in whom a rapid response is desired, when there is a need for a longer PFS or with extensive lymphadenopathy, R-bendamustine as first-line therapy can be considered. It is also an option for the treatment of IgM-related AL amyloidosis, considering the deep and long-lasting responses that can be achieved with this regimen [6]. In clinical practice, the bendamustine dose is often reduced, especially in elderly patients. This can then be carried out either by giving four instead of six cycles, and/or by reducing the dose to 70 mg/m<sup>2</sup> instead of 90 mg/m<sup>2</sup>. The advantages and disadvantages of these reduced regimens with regard to toxicity and effectiveness have not been studied prospectively. Based on the published data, not many patients complete six full-dose courses. In case of a rapid response and/or excessive toxicity, it is recommended to consider limiting the treatment to four courses. When R-Bendamustine is given to elderly and/or frail patients, a reduced dose of 70 mg/m<sup>2</sup> is also advised, although here also the evidenced-based guidance is lacking.

Chlorambucil monotherapy has been studied in three prospective and one large retrospective series. In the largest prospective series, it was remarkable that 19% of the patients developed grade-three or higher neutropenia, and a high percentage (20%) of patients developed secondary malignancies [33]. The ORR was approximately 50%, and the PFS 27 months. Altogether, due to the balance between efficacy and toxicity, chlorambucil is no longer considered a preferred option in first-line treatment. There are no data available on the combination of rituximab with chlorambucil in WM.

Purine analogues (fludarabine, cladribine) are highly effective in WM but are associated with relatively high rates of short-term (cytopenia/infections) and long-term (secondary malignancies and transformation) toxicity, and are therefore not considered as preferred first-line treatment options.

## 5. Proteasome Inhibitors

Rituximab-Bortezomib-Dexamethasone (BDR) showed good results as a first-line treatment based on three prospective studies, but the risk of neurotoxicity (severe peripheral neuropathy (PN)) is higher than observed with other indications such as multiple myeloma (MM), making it a less attractive option in WM [26–28,42]. It does lead to a fast response, so it can be used in patients for whom R-bendamustine is considered not feasible. An alternative for BDR is ibrutinib. Treatment with bortezomib is also an option for IgM-related AL amyloidosis, although again treatment-related (worsening of) neuropathy can be a major issue in this population. The incidence and severity of bortezomib-related neuropathy can probably be reduced by subcutaneous administration in a once weekly schedule.

Regarding Ixazomib-Rituximab-Dexamethasone, Castillo et al. [43] published a prospective trial in which the combination of ixazomib (an oral proteasome inhibitor that is associated with less neurotoxicity) combined with rituximab and dexamethasone (IRD) was given to 26 treatment-naïve WM patients. Six induction cycles (every 4 weeks) were followed by six maintenance cycles (every 8 weeks). An ORR of 96% was achieved and with a median follow-up of 22 months, the median PFS was 40 months [35]. There were no grade-four AEs, and 19% grade-one neuropathy. The only event with >1 grade-one neuropathy was grade-three neuropathy related to uncontrolled diabetes. IRD could therefore be an effective, non-cytotoxic, time-limited treatment option for WM in the first-line. However, ixazomib is currently not approved for the treatment of WM.

Regarding Rituximab-carfilzomib-dexamethasone, in 2014, a prospective study in 31 WM patients was published, of which 91% concerned first-line treatment. The overall and major response rates were 87% and 67%, respectively, and the PFS after 15 months was 64%. Grade  $\geq 2$  toxicities included asymptomatic hyperlipidemia (41.9%), reversible neutropenia (12.9%) and cardiomyopathy in one patient (3.2%) with multiple risk factors, and grade-two PN in one patient (3.2%) [34]. Carfilzomib is currently not approved for the treatment of WM.

## 6. BTK-Inhibitors

### 6.1. Ibrutinib

Ibrutinib monotherapy is an effective treatment for WM in the first-line setting. Ibrutinib is most effective in patients who have a MYD88 mutation but no CXCR4 mutation [44], followed by patients who have both genes mutated and is least effective in patients that are wildtype for both mutations (<5–10% of all WM patients) [29]. CXCR4 mutations prevent CXCL12-induced CXCR4 receptor internalization and result in rescue from ibrutinib-triggered apoptosis [45]. As opposed to immunochemotherapy, BTK inhibitors, including ibrutinib, have to be used indefinitely until progression or intolerable toxicity. In very frail elderly patients it is important to realize that older age is a risk factor for ibrutinib toxicity [46]. The main side effects are the risk of bleeding (a history of serious bleeding or double anticoagulation can be considered a contraindication), atrial fibrillation (AF) (highest risk in patients with age >65 and a history of AF) and hypertension (e.g., relevant for patients with poorly controlled hypertension).

Rituximab-ibrutinib: In the randomized “Innovate trial” [24], rituximab monotherapy was compared with R-ibrutinib. About 45% of the patients were treated in the first-line. The PFS at 2 years in this group was 84% with R-ibrutinib and 58% with rituximab monotherapy. Overall survival was not different (92–94% at 30 months). Across the entire trial (first-line and relapse), the ORR was 92% vs. 47% and the major response was 72% vs. 32%. Unfortunately, this trial did not provide data on how useful it is to add rituximab to ibrutinib therapy, as ibrutinib monotherapy was not an experimental arm. We conclude there is insufficient evidence that R-ibrutinib should be recommended in first-line treatment, especially as the added value and toxicity of adding rituximab to ibrutinib (which is already known to be highly efficacious as monotherapy) is currently unknown.

### 6.2. Zanubrutinib

Four prospective clinical trials with zanubrutinib for WM have been published. In a phase-II study, an ORR of 97% was achieved in 77 (24 untreated, 53 relapsed) patients, with a relatively high percentage of deep responses (44% VGPR, one CR) [31]. The median PFS at 2 years was not reached. In a large phase-III study, zanubrutinib was randomized versus ibrutinib for the treatment of WM [32]. A total of 201 patients were randomized (164 relapsed/refractory, only 37 were treatment-naïve). The ORR/major response rate was similar: 93%/78% (ibrutinib) versus 94%/77% (zanubrutinib). There was a non-significant trend towards deeper responses with zanubrutinib (28% VGPR) versus ibrutinib (19%). No CR was achieved in either group. The median PFS was not reached at 18 months of follow-up in both arms. Toxicity was significantly different for atrial fibrillation/flutter, which was more common in the ibrutinib arm (15.3% vs. 2%), whereas neutropenia was more common in the zanubrutinib arm (29.7% vs. 13.3%). The number of infections was similar in both groups (~67%).

Within the Aspen study, there was a separate non-randomized cohort in which only MYD88 wild-type WM patients were enrolled and treated with zanubrutinib [47]. In 28 patients (23 relapsed/refractory, 5 treatment-naïve), the ORR was 81%, the major response rate was 50% and the PFS at 18 months was 68%. These results seem quite favorable compared with the low response rates seen with other BTK-I in MYD88-wildtype diseases, but this comparison is not straightforward as there are few data available.

Zanubrutinib is considered by the Dutch WM working group as an equivalent alternative to ibrutinib; the choice should be made individually based mainly on the toxicity profile.

### 6.3. Other BTK-Inhibitors

Owen et al. performed a phase-II trial with acalabrutinib treatment in 106 WM patients, of whom only 14 were treatment-naïve [48]. The ORR for the treatment-naïve patients was 93% (IQR 66–100%) and the major response rate was 79% (IQR 49–95%). The 24-month PFS for the treatment-naïve group was 90% (IQR 47–99%). The main adverse events (for the total patient group) were headache, diarrhea, dizziness, fatigue, nausea, joint pain and upper respiratory tract infections. The most common Grade-three–four adverse reactions were neutropenia (16%) and pneumonia (7%). A small phase-II study was performed with the BTK inhibitor Tirabrutinib in 27 WM patients (18 previously untreated, 9 relapsed/refractory). The ORR was 94–100%. The major adverse events were a rash in 44% and neutropenia in 26% [49]. Both acalabrutinib and tirabrutinib are currently not approved for WM.

## 7. Maintenance Therapy

There are no published randomized or prospective studies on the benefits of rituximab maintenance. There is one publication with a retrospective analysis that suggested benefit of rituximab maintenance. Although the baseline characteristics of the groups from this large comparative retrospective study are similar, these data could be biased by factors that may influence the choice to start maintenance treatment, for example because patients who responded well to R-chemotherapy may have had a greater probability to receive the

maintenance treatment [19]. This could have led to selection of a group of patients with an inherently better prognosis. A prospective randomized study investigated the effect of 2-year R-maintenance for WM patients that achieved a response to R-bendamustine induction. The data have thus far only been published as an abstract [50]. No statistically significant difference in PFS or OS was found after 6 years of follow-up. On theoretical grounds, CD20 expression could decrease, and thus the sensitivity to rituximab would also decrease. However, there are no data on the response to next treatments in WM patients on long-term rituximab maintenance. Maintenance treatment with rituximab use may lead to toxicity (immunosuppression/infections). Altogether, we do not currently recommend the use of maintenance treatment with rituximab.

### 8. Other (Emerging) Options

The oral BCL2-inhibitor venetoclax was used in a prospective trial in 32 relapsed/refractory WM patients, and showed promising effectivity with a time-limited (2 years) treatment in a heavily pretreated population [51]. A clinical trial combining venetoclax and ibrutinib is currently ongoing. Whether venetoclax (-based) treatment becomes a preferred option for first-line treatment remains to be determined.

### 9. Stem Cell Transplant (SCT)

Currently, the role of autologous SCT (ASCT) in WM is undetermined. Prospective clinical trials on ASCT in WM are absent, and the current evidence is based on retrospective studies prior to the widespread use of rituximab [52–55]. There is, however, international consensus that ASCT is not appropriate as a first-line therapy for patients who do respond to induction treatment [56]. ASCT is an option in younger and fit patients with an aggressive disease course; e.g., early relapse after rituximab-containing immunochemotherapy and who are resistant to BTK-I, or patients who transform to a high-grade lymphoma [57]. Data on allogeneic SCT (alloSCT) also consists of retrospective studies only. AlloSCT is discouraged in the international guidelines; it is only recommended either in the context of clinical trials or in a group of highly selected younger patients with aggressive clinical course and resistance to BTK inhibitors, but never in the first-line [9,13,58,59].

### 10. Conclusions and Discussion

There is no international consensus on a preferred first-line treatment. Indeed, it is not possible to select an evidence-based preferred first-line regimen. In general, immunochemotherapy regimens are considered the preferred treatment in the first-line, but ibrutinib monotherapy or rituximab monotherapy are also options. Based on the data from clinical studies and international guidelines that we discussed, the Dutch WM working group considers DRC a suitable first-line treatment for many WM patients, given the efficacy, the relatively mild toxicity profile and the extensive (inter)national experience with this regimen. Intravenous (instead of oral) administration of cyclophosphamide should be considered, as this seems to result in less nausea and vomiting. The long-term toxicities (secondary malignancies) of DRC are unclear and need clarification.

In recent years, various prospective and retrospective studies have been published on R-Bendamustine as a first-line treatment in WM. While it is more effective (deeper responses/longer PFS) compared with DRC, it is also more toxic (cytopenias, sometimes long-lasting, risk of infections), although the latter is difficult to compare as head-to-head studies have not been performed. It is often advised to use a reduced dose (70 mg/m<sup>2</sup>) or a limited number of cycles (four instead of six). The long-term toxicities (secondary malignancies) compared with, for example, DRC are unclear and need clarification. The same applies to stem cell toxicity and the potential for stem cell harvesting after bendamustine treatment. Internationally, R-bendamustine is considered a valid first-line option when a rapid response is needed and when there is bulky lymphadenopathy, although the latter is not strictly based on evidence.

R-bortezomib-dexamethasone is also an effective regimen. It is, however, associated with neurotoxicity, and this appears to be a larger problem in WM than in MM patients. The first studies in WM used bortezomib intravenously and 2x/week. The occurrence of neurotoxicity can probably be at least partially prevented by applying subcutaneous administration once weekly. Internationally, it is considered a valid first-line treatment option, but if this regimen is chosen we advise very strict monitoring for neurotoxicity. Meanwhile, less neurotoxic PIs such as ixazomib and carfilzomib have also proven effective in WM, but are not approved for this indication.

Treatment with purine analogs is not recommended in the first-line setting. Although these drugs are effective, they are associated with relatively high short-term toxicity (cytopenias, infections). There are also concerns about long-term toxicity (secondary malignancies), although published results on this matter are lacking.

DRC, R-Bendamustine in adjusted doses and R-bortezomib-dexamethasone can be used in patients up to an old(er) age. For patients who are nevertheless considered to be too vulnerable for these treatments, rituximab monotherapy can be considered if the disease burden is limited. An alternative is ibrutinib or zanubrutinib monotherapy, although the risk of adverse effects might also be increased in older patients. Chlorambucil monotherapy has a relatively low effectiveness and (partly dependent on dosage) still quite some toxicity, and is not advised as a preferred option in the first-line.

The Dutch working group considers the role for ibrutinib/zanubrutinib in first-line treatment limited for most WM patients. On the one hand, BTK-inhibition is very effective, especially in cases that have a MYD88 mutation but no CXCR4 mutation. It also has the advantage of being a non-cytotoxic drug which can be delivered orally. However, the major disadvantage is the need for long-term treatment (until progression or toxicity). Furthermore, toxicities may be an issue mainly in elderly/frail patients. Finally, the follow up of ibrutinib-treated patients is still relatively short, meaning unknown long-term risks may currently not be fully clarified. There is insufficient evidence to recommend the combination of rituximab and ibrutinib. Prospective studies combining BTK-inhibitors with other novel agents aiming for a fixed-duration chemo-free regimen are ongoing [60,61]. In particular, the results of a randomized trial in the United Kingdom comparing rituximab-ibrutinib with DRC as a primary therapy are highly awaited [62].

With regard to the other treatments mentioned (combinations with carfilzomib, Ixazomib and venetoclax), data are still limited, and approval is lacking. Finally, stem cell transplant (autologous/allogeneic) is not recommended in the first-line treatment of WM.

Of note, specific clinical presentations, including IgM paraproteinemia-related AL amyloidosis, and other deposition diseases such as light-chain deposition disease, central nervous system involvement (Bing-Neel syndrome) and IgM-related disorders such as cold agglutinin disease or IgM-related neuropathy have their own considerations for treatment that are not within the scope of this review [6,63–66].

## 11. Discussion & Future Perspectives

Overall, a great improvement in the survival of WM patients has been achieved in recent years, mainly attributable to the introduction of rituximab-based regimens [7]. The selection of an appropriate treatment regimen can be challenging due to the great variety of options. It is therefore vital to individualize treatment choices and actively involve patients in shared decision making when deciding on a treatment plan. A better understanding of what patients prefer and expect from a treatment can result in satisfaction and improved adherence. Based on a discrete choice experiment (DCE) in Dutch patients, WM patients preferred a treatment with high efficacy that is not associated with an increased risk of secondary malignancies. Furthermore, a fixed-duration IV/SC treatment with a targeted agent and the lowest risk of neurotoxicity was preferred over an oral treatment administered indefinitely [67]. This may serve as guidance for future clinical trials that should focus on effective fixed-duration regimens with non-cytotoxic therapies that have a favorable toxicity profile. Further development of (combinations with) BCL-2 inhibitors, novel

proteasome inhibitors and BTK-inhibition could be interesting. In addition, we found that WM patients, even in the relapsed setting, maintain well preserved T-cell numbers and functionality [68]. Therefore T-cell-directed treatments including bispecific antibodies as a monotherapy or combined with other novel agents deserve further study in WM.

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