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Waldenström Macroglobulinemia: Review of Pathogenesis and Management

Seongseok Yun, MD PhD[1,2], **Ariel Johnson, BS**[3], **Onyemaechi Okolo, MD**[1], **Stacy J. Arnold, MD**[4], **Ali McBride, PharmD MS**[5], **Ling Zhang, MD**[6], **Rachid C. Baz, MD**[2], and **Faiz Anwer, MD**[7,†]

[1]Department of Medicine, Department of Medicine, University of Arizona, Tucson, AZ, 85721

[2]Hematology and Oncology, H. Lee Moffitt Cancer Center, Tampa, FL, 33612

[3]University of Arizona College of Medicine, Tucson, AZ, 85721

[4]Division of Pathology, Department of Medicine, University of Arizona, Tucson, AZ, 85721

[5]College of Pharmacy, University of Arizona, Tucson, AZ, 85721

[6]Department of Hematopathology and Laboratory Medicine, H. Lee Moffitt Cancer Center, Tampa, FL, 33612

[7]Division of Hematology, Oncology, Blood & Marrow Transplantation, Department of Medicine, University of Arizona, Tucson, AZ, 85721

Abstract

Waldenström macroglobulinemia (WM) is a low-grade B-cell clonal disorder characterized by lymphoplasmacytic bone marrow involvement associated with monoclonal immunoglobulin M (IgM). Although WM remains to be an incurable disease with a heterogeneous clinical course, the recent discovery of mutations in the MYD88 and CXCR4 genes further enhanced our understanding of its pathogenesis. Development of new therapies including monoclonal antibodies, proteasome inhibitors, and Bruton's tyrosine kinase inhibitors have made the management of WM increasingly complex. Treatment should be tailored to the individual patient while considering many clinical factors. The clinical outcomes are expected to continue to improve given the emergence of novel therapeutics and better understanding of the underlying pathogenesis.

[†]**Corresponding Author:** Faiz Anwer M.D., Department of Medicine, Division of Hematology Oncology, University of Arizona Cancer Center, 1501 N. Campbell Ave. AZ 85721, Phone: (520) 626 0662, Fax: (520) 626 8944, anwerf@email.arizona.edu.

AUTHOR CONTRIBUTION

SY, AJ, OO, SJA and FA designed the study.

SY, AJ, OO and FA searched for studies for the review.

All authors performed the study, contributed to data extraction, analyzed the data, and wrote the paper.

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Keywords

Waldenström macroglobulinemia; Lymphoplasmacytic lymphoma

INTRODUCTION

Waldenström macroglobulinemia (WM) is defined as Lymphoplasmacytic lymphoma associated (LPL) with monoclonal immunoglobulin M (IgM). WM represents approximately two percent of all hematologic malignancies with 1000–1500 new cases per year in the United States[1]. WM is more common in men, and Caucasians with a median age of 60–70 years[1]. WM is classified as an indolent disease with previous studies reporting a median survival about 5 years. Studies have evaluate mutations in WM cases and two candidate mutations were found including myeloid differentiation primary response 88 (MYD88) and/or C-X-C chemokine receptor type 4 (CXCR4) mutations[2]. As such, novel therapies are under development to target mutant proteins or their downstream effects to further improve treatment outcomes. A variety of factors should be considered for the treatment of WM patients including necessity for rapid cytoreduction, control of viscosity-related symptoms, adverse effects of treatment, comorbid conditions and eligibility for stem cell transplantation (SCT), and finally goal of treatment. We reviewed and summarized the current understandings of WM pathogenesis and treatment options in various clinical settings.

METHODS

We searched PubMed, EMBASE, and the Cochrane databases as well as annual meeting abstracts upto September 1, 2016 for randomized clinical trials (RCTs), phase I/II clinical studies and retrospective studies. Search key words included Waldenström macroglobulinemia, WM, Lymphoplasmacytic lymphoma, and LPL. Three reviewers (S.Y., R.C.B., F.A.) mutually agreed upon the selected articles. We focused on the prospective studies and emphasis was given to the regimens that are commonly used in daily practice.

CLINICAL PRESENTATION

WM can manifest with a variety of symptoms, which could be classified into two major categories: neoplasmic organ involvement- and IgM paraprotein-related symptoms. Patients may present with nonspecific B-symptoms such as fever, weight loss, fatigue, and drenching night sweat from BM involvement as well as lymphadenopathy or hepatosplenomegaly. BM involvement commonly causes anemia, which is exacerbated by hepcidin secretion by lymphoplasmacytic cells[3]. IgM paraprotein can cause various symptoms resulting from systemic amyloidosis, paraprotein depositions in the organs, cryoglobulinemia, peripheral neuropathy (PN) and hyperviscosity syndrome. About 20–25% of WM patients develop PN from sensory demyelination related to anti-myelin-associated glycoprotein (MAG) antibody. Hyperviscosity symptoms such as visual changes, neurologic and cardiovascular compromise commonly occurs when IgM protein level is above 30–40g/L[4–6].

DIAGNOSIS

The diagnosis of WM is based on clinicopathologic features[5,7–9]. BM examination in WM should demonstrate at least 10% of infiltration by small lymphocytes with lymphoplasmacytic features or lymphoplasmacytic lymphoma. Dutcher bodies which are intranuclear vacuoles containing IgM protein, are common in WM[5,7,8]. Elevated IgM should be present to diagnose WM. Immuno-phenotype in WM is typically positive for CD19, CD20, CD22, CD25, CD27, CD38, CD79a, FMC7, surface/cytoplasmic IgM, and negative for CD5, CD10, CD11c, CD23, and CD103 although there can be some variations[4]. These immuno-phenotypic features are important to differentiate WM from other hematologic malignances such as multiple myeloma (MM), mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL), and marginal zone lymphoma (MZL) (Table 1).

PATHOGENESIS

There are many cytogenetic abnormalities and mutations frequently found in WM patients. Common abnormalities are del(6q) (50%), somatic hyper-mutation in IGHV, t(9;14)(p13;q32) (50%), and trisomy 4 (20%). MYD88 and C-X-C chemokine receptor type 4 WHIM (CXCR4^{WHIM}) somatic mutations were found in more than 90% and 30–35% of WM patients, respectively, and have been shown to play a pivotal role in WM tumorigenesis.

MYD88 is an adaptor protein for toll-like receptor 4 (TLR-4) and interleukin-1 and -2 receptors (IL-1R and IL-2R). Once bound, MYD88 is either activated directly by these receptors, or is activated via interaction with TIR domain containing adaptor protein (TIRAP) and Bruton tyrosine kinase (BTK), leading to the activation of the NF-κB pathway[10,14,15]. A somatic point mutation of the MYD88 substituting amino acid leucine to proline at position 265 (MYD88^{L265P}) results in pro-survival “gain of function”[10]. Whole-genome sequencing in WM and non-IgM secreting LPL patients demonstrated MYD88^{L265P} to be the most common somatic variant (91%) followed by CXCR4 (27%)[2,11]. The MYD88^{L265P} mutation was rare or absent in the IgM MGUS (10–60%)[2,12], MZL (7%)[2], CLL (3%)[13], and MM (0%)[2,14], suggesting that MYD88^{L265P} as a potential biomarker that could be used to differentiate WM from other pathologies that share common morphologic and clinical features.

CXCR4 is a G-protein coupled receptor and was shown to play a pivotal role in cytokine release and chemotaxis[18]. CXCR4 mutations are similar to the WHIM (warts, hypogammaglobulinemia, infections, myelokathexis) syndrome, which result in permanent activation of CXCR4 by stromal derived factor 1 alpha (SDF-1a). WM cell migration and adhesions were shown to be inhibited by CXCR4 knockdown, CXCR4 inhibitor, and G_i protein inhibitor treatments in response to SDF-1, indicating the essential role that CXCR4 plays in homing of WM cells[18]. WM cells were also shown to express VLA-4, another chemokine receptor, which directly interacts with CXCR4 to activate AKT and MAPK pathways, leading to cell survival and evasion of apoptosis[18]. Whole genome sequencing identified CXCR4 somatic mutations (S344 frameshift, S339 frameshift, T311 frameshift, S338 nonsense) in 27% of WM patients[11]. These mutations include the regulatory carboxyl domain, resulting in the impairment of internalization and prolonged activation of

CXCR4[15,16] As such, patients harboring CXCR4 S338 mutations were shown to have inferior response to ibrutinib[17].

Although the majority of WM cases are of sporadic origin, familial WM also exists (about 20%)[18]. Kristinsson *et al.* showed that there is an excess risk among patients with first degree familial members with WM, suggesting an autosomal dominant or co-dominant inheritance pattern[18]. Familial WM has been correlated to an younger age and a higher BM involvement at the time of diagnosis[19]. In addition, familial disease has an increased risk of death (HR 1.3) compared to sporadic disease[20], and it was shown to be an independent risk factor for disease progression (HR 0.554)[21]. Patients with familial WM have inferior treatment responses, shorter time to progression, and shorter time to next therapy with rituximab therapy compared to sporadic WM; although they have improved outcomes with bortezomib-containing regimens[21].

MANAGEMENTS

Indications for treatment

WM is an insidious lymphoproliferative disease that shares many similarities with low grade NHLs. Its indolent manner therefore lends itself to close monitoring before any active treatment is needed[22].

Management of hyperviscosity

Hyperviscosity syndrome secondary to elevated IgM leads to decreased blood flow, compromising microcirculation including the central nervous system and heart. In patients with hyperviscosity related symptoms such as blurry vision, headache, papilledema, stupor/coma, chest pain, or ischemic changes, plasmapheresis should be initiated promptly for IgM removal from the serum. Red blood cell transfusion should be avoided since it can increase blood viscosity and precipitate symptoms[23]. Plasmapheresis is only a temporary measure and patients should proceed to systemic treatment to prevent the recurrence of symptoms[23].

Evidence in treatment-naïve patients

The paucity of randomized trials in WM limits the level of evidence supporting a particular approach. As a result, there is no standard care established for WM and the management options are mainly based on phase II clinical trials and expert opinion. Common treatment regimens include combination therapy utilizing anti-CD20 monoclonal antibodies, nucleoside analogs (fludarabine, cladribine, bendamustine), alkylating agents (cyclophosphamide, chlorambucil), proteasome inhibitors (bortezomib, carfilzomib) (Table 2).

Rituximab, anti-CD20 monoclonal antibody, is commonly used as first-line therapy based on clinical trials that showed ORR of 20–40% and 35–65% with standard (375mg/m^2/week for 4 weeks) and extended treatment (375mg/m^2/week for 4 weeks at week 1 and 12), respectively[24–27]. In a study by Gertz *et al.* with 34 treatment-naïve patients, rituximab treatment showed ORR 18% and OS rate 97.1%. Dimopoulos and colleagues evaluated 15 treatment-naïve patients, and rituximab treatment in this study showed ORR 44% and PFS

rate 33.3%. A follow up study examining extended rituximab treatment showed an ORR 35%, PFS rate 41.2%, and OS rate 94.1%[26] In a similar study with extended rituximab treatment, 29 WM patients (21 treatmentnaïve) achieved ORR 65% and PFS rate 89.5% with 29 months of median follow-up[27]. One of the caveats with rituximab use as monotherapy was the slower time to response. Accordingly, it is preferred in patients with minimal symptoms who do not need rapid response. A transient increase in IgM serum levels is common with monotherapy. IgM flare usually occurs in 1–4 months of treatment, and it could exacerbate anti-MAG neuropathy and hyperviscosity symptoms. Also, careful interpretation is needed to differentiate IgM flare from lack of response or disease progression. Plasmapheresis is suggested in patients with high IgM (>4000mg/dL) or hyperviscosity symptoms to prevent IgM flare[28]. Of note, late intolerance to rituximab occurs in 10–15% of cases. Ofatumumab, an anti-CD20 monoclonal antibody which binds to a distinct epitope from rituximab binding site, also showed ORR 67% in one study that included 9 (24%) treatment-naïve WM patients, indicating that ofatumumab may be an alternative option for rituximab intolerant patients[29].

Based on its efficacy as a single agent, rituximab was further evaluated in combination with other agents including alkylating agents, purine analogues, and bendamustine. In comparison to monotherapy, combination therapies were shown to rapidly reduce IgM level. As such, they are commonly used in patients who have hepatosplenomegaly or significant BM infiltration, requiring rapid cytoreduction. The most commonly used regimens are rituximab, cyclophosphamide, dexamethasone (RCyD); rituximab, bortezomib, dexamethasone (RVD); and bendamustine and rituximab (BR) although there are other combinations that have shown efficacy in WM.

In a prospective study with 72 treatment-naïve patients, RCyD showed ORR 83%, 2-yr PFS rate 67%, and 2-yr OS rate 81% with median follow-up of 23.4 months[30]. In the recent update of this study, time to treatment failure was 35 months, and many of the relapsing patients were still sensitive to rituximab based regimens. The 8-yr OS rates were 100%, 55%, and 27% for the low, intermediate, and high risk groups, respectively[31]. In a randomized trial with 48 treatment-naïve WM patients who were randomly assigned to either CHOP or R-CHOP, R-CHOP showed significantly higher ORR (91% vs. 60%, p=0.0188) and 2-year PFS rate (78% vs. 47%, p=0.0241)[32]. However, a phase III randomized trial comparing BR vs. R-CHOP in the indolent lymphomas including 41 of WM patients showed significantly longer median PFS (69.5 months vs. 28.1 months, HR 0.33, p=0.0033) and better safety outcomes in BR treated group[33]. In a study by Treon and colleagues with 43 WM patients (27 treatment-naïve and 16 treated patients), rituximab and fludarabine combination treatment significantly reduced median BM involvement (55% vs. 5%, p<0.001) and serum IgM protein level (3840mg/dL vs. 443mg/dL, p<0.001)[34]. ORR in treatment-naïve patients in this study was 96.3% and 2-year PFS rate was 67% with median follow-up of 40.3 months[34]. In an additional study with 43 treatment-naïve WM patients, a combination regimen of rituximab, FCR showed ORR and 2-year OS rate of 79% and 69.1%, respectively[35]. A recent retrospective study with FCR in 27 treatment-naïve WM patients showed ORR 76% and major response rate (MRR) 88% with 3-yr PFS and OS rates of 96%[36]. Despite its proven efficacy as front-line and salvage therapies, fludarabine containing regimens are preferably recommended for relapsed or refractory patients due to

prolonged cytopenia associated with fludarabine as well as high risk (10–15%) of secondary malignancies including myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML). However, nucleoside analogs, such as fludarabine or bendamustine, have an important role in central nervous system (CNS) involvement such as Bing-Neel syndrome since they have good CNS penetration compared to other classes of drug[37].

The efficacy of proteasome inhibitors has been extensively studied in MM patients[38]. In a study by Ghobrial *et al.* with 26 treatment-naïve WM patients, 6 cycles of bortezomib combined with rituximab showed ORR 100%, 1-year PFS and OS rates of 75% and 96%, respectively[39]. RCyD combination showed a median PFS of 35 months and 5-year OS rate of 62%[28,31]. Similar to RCyD, bortezomib, dexamethasone, and rituximab (BDR) combination in two studies showed ORR 90–96%, PFS rate 40–80%, and OS rate 80–100% with significant improvement in BM involvement and serum IgM levels[40,41]. In these studies, PN was the most common toxicity, rendering 8–61% patients to discontinue bortezomib[40,41]. Carfilzomib, a second generation proteasome inhibitor, was shown to have substantively low rate of PN compared to bortezomib in MM trials[42]. In a phase II trial with WM patients who received no more than one prior therapy, carfilzomib, rituximab, and dexamethasone (KRD) showed 87% of ORR regardless of MYD88 or CXCR4 mutational status, with no reported grade≥3 PN[43].

Evidence in relapsed or refractory disease

Anti-CD20 monoclonal antibodies were shown to be effective in WM patients with relapsed or refractory disease (Table 3). In two studies, patients with relapsed WM who received rituximab for four to eight cycles yielded an ORR 30–40%[25,44]. Similarly, relapsed WM patients achieved ORR 57% with ofatumumab treatment[29]. Anti-CD20 monoclonal antibodies in combination with bendamustine or fludarabine showed better efficacy compared to anti-CD20 monotherapy. In a retrospective study with 30 WM patients with relapsed or refractory disease, bendamustine combined with either rituximab or ofatumumab demonstrated ORR of 83.3% with significant improvement in serum IgM level (3980mg/dL vs. 698mg/dL)[45]. Also, rituximab combined with fludarabine showed ORR 93.8% and 2-yr PFS rate 38%[34]. In a recent retrospective study, FCR showed ORR 77.2%, MMR 82.4%, and 3-yr PFS and OS rates 73% and 89%, respectively[36].

Bortezomib also demonstrated clinical efficacy in refractory or relapsed WM patients. In a study by Dimopoulos *et al.*, 60% patients achieved PR with bortezomib[46]. Also, bortezomib significantly reduced the median serum IgM level (4460mg/dL vs. 2092mg/dL) as well as BM involvement (30% vs. 20%) as shown in a study by Treon *et al.*[47] In this study, ORR and MRR were 48% and 85%, respectively, and 6 of the 23 responding patients remained progression free (PFS rate 26%) with median follow-up of 18.2 months[47]. Moreover, bortezomib combined with rituximab in 37 relapsed patients showed ORR 62%, 1-year PFS 58%, and 1-year OS 94%[48].

Ibrutinib has also been studies in WM, as data with $MYD88^{L265P}$ leads to constitutively active BTK signaling[49]. In a recent phase II trial with 66 WM patients with prior treatments, ibrutinib showed ORR 73%, 2-year PFS rate 69.1%, and OS rates 95.2%[50] Also, the median BM involvement (60% vs. 25%) and serum IgM levels (3520mg/dL vs. 880mg/dL)

significantly improved upon ibrutinib treatment. The best serum IgM and hemoglobin responses were achieved in $MYD88^{L265P}$/$CXCR4^{WT}$ patients whereas the least responses in $MYD88^{WT}$/$CXCR4^{wt}$ patients[50]. Based on these results, FDA has approved ibrutinib for WM patients. Common adverse reactions associated with ibrutinib include cytopenia, fatigue, diarrhea, bruising, and rash[50]. It is also shown to increase the risk of atrial fibrillation and bleeding although the incidence is low[51].

Current studies are assessing the prognostic impact of MYD88 and CXCR4 mutations and correlative outcomes. A larger study evaluating 175 WM patients showed significantly higher BM involvement and serum IgM levels in patients harboring $MYD88^{L265P}$ and CXCR4 nonsense mutation compared to the ones with $MYD88^{L265P}$ and CXCR4 frameshift mutation or $MYD88^{L265P}$ and $CXCR4^{WT}$[52]. Surprisingly, patients with $MYD88^{L265P}$ showed significantly worse OS compared to $MYD88^{WT}$ patients despite their lower disease burden[52]. In a recent study comparing whole genome sequencing in 57 WM patients vs. healthy donors, MYD88 and CXCR4 expression levels were shown to be inversely correlated, which is also affected by mutation status[53]. In most of WM patients, DNTT, RAG1, and RAG2 that are involved in VDJ recombination and BCL2 were found to be highly upregulated, and BAX expression was low[53]. Further, in comparison to $MYD88^{L265P}$, $MYD88^{WT}$ patient showed increased expression of PI3K signaling genes, but low NFκB response genes as well as increase promoter methylation in PRDM5 and WNK2 genes[53]. Collectively, these findings suggest that BCL2, PI3K inhibitors and hypomethylating agents may be effective in WM.

Immunomodulatory agents and mTOR inhibitors have also been studied in WM. Combination therapy of lenalidomide and rituximab showed ORR 50% and PFS rate 25% with significant improvement in serum IgM level (2980mg/dL vs. 1775mg/dL, p=0.015)[54]. One of the caveats in the study was that tolerance was a limiting factor for treatment as lenalidomide causes noticeable toxicities including cytopenia from myelosuppression. The mTOR inhibitors were shown to be effective in NHLs[55–60], and preclinical study showed that PI3K/AKT/mTOR pathway is activated in WM[61]. In a phase II study with everolimus 10mg/day, 42% and 28% patients achieved PR and MR, respectively, with ORR 70%. The estimated PFS rates at 6 and 12 months were 75% and 62%, respectively, although 56% patients experienced grade≥3 toxicities, requiring dose reduction or treatment delay[62,63]. In a subsequent phase I/II trial with 46 patients, combination regimen of everolimus, bortezomib, and rituximab followed by everolimus maintenance therapy showed CR in 6% and MR in 89% patients[64]. In this study, 82% of patients completed 6 cycles of combination therapy; however, 52% of patients required everolimus dose reduction or interruption during treatment. In patients who did not have dose alteration and received the full dose during their treatment cycles, the median PFS was 21 months[64]. Of note, there are significant discordance between IgM and BM responses, indicating the importance of BM exam for the treatment response when treated with everolimus[64].

Stem cell transplantation

Although there is not enough data, SCT could be an option for patients with refractory disease as salvage therapy. Autologous SCT in European Bone Marrow Transplant Registry

(EBMTR) study with 155 WM patients showed 5-yr PFS and OS rates of 49% and 69%, respectively, and non-relapsed mortality (NRM) of 5.6%[65]. Allogeneic SCT reported by EBMTR showed 5-yr PFS and OS rates of 56% and 62% in patients who received myeloablative conditioning vs. 49% and 64% in reduced-intensity conditioning regimens[66].

RECOMMENDATIONS

Asymptomatic WM patients can be managed with watchful waiting, and only symptomatic patients need treatment. In patients with high IgM level (more than 4g/dL) or hyperviscosity symptoms, plasmapheresis should be immediately performed. Plasmapheresis should then be followed by cytoreductive treatment.

In treatment-naïve patients, rituximab mono- or combination-therapy provides a reasonable option for first-line therapy. Rituximab as a single agent can lead to IgM flare and the response rate is lower than combination therapy. Accordingly, it is contraindicated in patient with significantly high IgM levels, but can be considered in frail patients who cannot tolerate combination therapy. In rituximab-based combination regimens, RCyD and BR are both highly effective and well tolerated in elderly patients. Also, BR has lower myelosuppression compared to other purine analogs. Nucleotide analogs in general may increase the risk of secondary malignancies, therefore, it should be avoided in younger patients. Proteasome inhibitor based regimens are recommended in patients with paraprotein-related symptoms including hyperviscosity, cryoglobulinemia, cold agglutinemia, and amyloidosis. Although carfilzomib is favored as a neuropathy-sparing agent compared to bortezomib, it was shown to increase the risk of cardiac toxicity and it should be avoided in patients with underlying cardiovascular comorbidity. Ibrutinib is approved as the first-line therapy in treatment-naïve patients. Once treatment is started, patient should continue ibrutinib until they develop intolerance or disease progression. At this point, there is lack of long-term safety data. Therefore, it is favorably used in patients who are not able or not willing to receive cytotoxic therapy. Although there is no consensus regarding the role of maintenance therapy, rituximab was shown to have a PFS benefit in a retrospective study as a maintenance setting[67]. This still remains to be tested in the prospective study, and the optimal regimens also remains to be answered.

Previously treated WM patients with relapsed disease can be retreated with initial regimens as long as they had initial response more than two years. Rituximab late intolerance may occur in 10–15% patients, and ofatumumab can be an alternative option in these cases. Nucleotide analogs such as fludarabine based regimen can be considered in fit patients, and ibrutinib is a good option. mTOR inhibitors and immune modulatory agents could be an alternative option for treatment in the refractory setting. Lastly, autologous and allogeneic SCT can be an alternative option in select patients.

FUTURE PERSPECTIVE

There are a number of active clinical trials investigating the use of chemotherapy and other targeted therapy drugs. Therapies that are currently being investigated through phase II clinical trials include single or combination therapies of monoclonal antibodies, proteasome

inhibitors, immunomodulatory agents, PI3K/Akt/mTOR pathway inhibitors, BTK inhibitors, and a histone deacetylase inhibitor, while others are still in early developmental stages[28].

CONCLUSION

Traditionally, many of the WM treatment regimens have been adopted from those of MM and NHLs. MYD88^{L265P} and CXCR4 somatic mutations are newly identified in WM patients. Accordingly, new therapy such as ibrutinib was shown to be effective in WM patients, and currently there are many ongoing clinical trials with combination regimens. Given lack of randomized controlled trial, there is no standard care established and most of the recommendations are based on phase II clinical trials and expert opinion. The treatment choice should be tailored to individual patient considering necessity for rapid cytoreduction, presence of viscosity related symptoms, comorbidity, side effect of each agent, eligibility for SCT, and goal of treatment.

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TABLE1: Diagnostic Criteria of WM and Differential Diagnosis

Waldenstrom Macroglobulinemia[1]	**Smoldering Waldenstrom Macro globulinemia**[1]	**IgM MGUS**[1]	**Multiple Myeloma**	**Marginal Zone Lymphoma**
1. IgM monoclonal gammopathy of any concentration. 2. BM infiltration by small lymphocytes with plasmacytoid or plasma cell differentiation≥10% 3. Intertrabecular patterns of BM infiltration. 4. Surface marker - Positive: IgM, CD19, CD20, CD22, CD25, CD27, FMC7 - Negative: CD10, CD23, CD103, CD138 5. Presence of symptoms	1. Meet the criterial of WM 2. Absence of symptoms, anemia, organomegaly, lymphadenopathy, or hyperviscosity	1. Serum IgM monoclonal protein <3000mg/L 2. BM lymphoplasmacytic infiltration <10% 3. No evidence of end-organ damage, anemia, hyperviscosity, lymphoadenopathy, or hepatosplenomegaly from the underlying lymphoproliferative disorder.	1. Clonal BM plasma cell ≥ 10% or biopsy proven plasmacytoma and at least one of the myeloma defining events - Hypercalcemia with serum Ca >0.25mmol/L higher than the upper normal limit or >2.75mmol/L - Renal impairment with CrCl < 40ml/min or serum Cr > 2mg/dL - Anemia with Hb <100g/L or more than 20g/L below than lower normal limit - Osteolytic bone lesions on skeletal radiography, CT, or PET/CT	1. Polymophous small cell infiltration with associated reactive appearing follicles. 2. Positive for B-cell markers including CD19, CD20, CD22. 3. Negative for CD5, CD10, and CD23. 4. Presence of trisomy3 or t(11;18)

TABLE 2

Studies with Treatment-Naïve WM patients

Study	Regimen	No. of Pt	Med. Age (range)	Risk group	Treatment response (%)	Survival rates	Med F/U (mo)
Dimopoulos[8]⊖ 2002	R: 375mg/m^2/weekly IV infusion total 4 consecutive weeks, repeat 4 weeks courses of R in patients without disease progression at 3 months	27	72 (39–85)	NR	PR 12 (44) MRR 44% ORR 44%	PFS 33.3%	15.7
Gertz[9] 2004	R: 375mg/m^2/weekly IV infusion total 4 consecutive weeks	34	66.4 (44.8–81.4)	NR	MR 6 (18) MRR 0% ORR 18%	PFS NR OS 97.1%	NR
Dimopoulos[10] 2002	Extended R: 375mg/m^2/weekly IV total 8 cycles at weeks 1–4 and 12–16 (if no disease progression)	17	74 (39–84)	NR	PR 6 (35) MRR 35% ORR 35%	PFS 41.2% OS 94.1%	16–40
Treon[11]ǂ 2005	Extended R: 375mg/m^2/weekly IV total 8 cycles at weeks 1–4 and 12–16	29	65 (43–90)	NR	PR 14 (48) MR 5 (17) MRR 48% ORR 65%	PFS 89.5% OS NR	29
Furman[12] *P* 2011	Ofatumumab: ofatumumab 300mg for week 1 and 1000mg for weeks 2–4 (G1) or 2000mg for weeks 2–5 (G2). If stable disease or minimal response at 16th week, additional 300mg for week 1 and 2000mg for weeks 2–5	37	63 (43–85)	NR	PR 13 (35) MR 9 (24) ORR 66.7%£	NR	NR
Ghobrial[13] 2011	Bortezomib + R: Bortezomib 1.6mg/m^2 on days 1, 8, 15 every 28 days total 6 cycles with R 375mg/m^2/ weekly IV infusion on cycles 1 and 4	26	62.5 (43–85)	High 3(12) Int 11 (42) Low 10 (38) NA 2 (8)	CR 2 (8) PR 15 (58) MR 9 (35) MRR 65% ORR 100%	1yr PFS 75% 1yr OS 96%	14
Treon[14] 2009	BDR: B 1.3mg/m^2 IV, D 40mg on day 1,4, 8, 11, and R 375mg/m^2 on day 11,4 consecutive cycles for induction, then 4 cycles, each 3 months apart, for maintenance therapy	23	66 (48–86)	NR	CR 3 (13)/nCR 2 (9) VGPR 3 (13)/PR 11 (48) MR 3 (13) MRR 83% ORR 96%	PFS 78.3% OS 100%	22.8
Dimopoulos[15] 2013	BDR: B 1.3mg/m^2 IV on days 1,4, 8 and 11 followed by weekly B 1.6mg/m^2 IV on days 1, 8, 15, and 22 every 35 days for 4 cycles, followed by D 40mg and R IV 375mg/m^2 in cycle 2 and 5	60	70 (40–83)	Low 27 (45) † Int 24 (40) High 9(15)	CR 2 (3) VGPR 4 (7)/PR 38 (65) MR 10 (17) MRR 40 (73) ORR 54 (90)	3yr PFS 41% 3yr OS 82%	42
Treon[16] 2014	KRD: carfilzomib 20mg/m^2 IV for 1st cycle, then 36mg/m^2 for 2nd cycle and beyond) + R 375mg/m2 on days 2 and 9 every 3 weeks for 6 cycles + D 20mg IV on days 1,2, 8, and 9	31	61 (47–75)	Low 11 (36) Int 15 (48) High 5(16)	CR 1 (3) VGPR 10 (32) PR 10 (32) MR 6 (19) MRR 67.7% ORR 87.1%	PFS 64.5% OS 100%	15.4
Treon[16] 2014	KRD: carfilzomib 20mg/m^2 IV (cycle 1), 36mg/m^2 (cycle 2–6), D 20mg IV on days 1, 2, 8, and 9, R 375mg/m^2 on days 2 and 9 every 21 days, followed by	31	61 (47–75)	Low 11 (36) † Int 15 (48) High 5(16)	CR 1 (4) VGPR 10 (36)/PR 10 (36) MR 6 (21)	PFS 64.5% OS 100%	15.4

Study	Regimen	No. of Pt	Med. Age (range)	Risk group	Treatment response (%)	Survival rates	Med F/U (mo)
	maintenance with C 36mg/m^2 IV, D 20mg IV on days 1 and 2, R 375mg/m^2 on day 2 every 8 weeks for 8 cycles.				MRR 67.7% ORR 87.1%		
Dimopoulos[17,18] 2007	RCyD: D 20mg IV followed by R 375mg/m^2 IV on day 1. Cy 100mg/m^2 PO bid on days 1–5. Repeated treatment every 21 days for 6 cycles	72	69 (33–89)	NR	CR 5 (7) PR 48 (67) MR 6 (9) MRR 73.6% ORR 81.9%	2yr PFS 67% 2yr OS 81%	23.4
Treon[19]€ 2009	R + Lenalidomide: 48 weeks of lenalidomide 25 mg/day PO for 3 weeks and then1week off along with R 375 mg/m^2/wk IV dosed on weeks 2 to 5 and 13 to16	16	65 (49–85)	NR	PR 4 (25) MR 4 (25) MRR 25% ORR 50%	PFS 25%	31.3
Buske[20] 2009	CHOP: cyclophosphamide 750 mg/m^2 IV, doxorubicin 50 mg/m^2 IV, vincristine 1.4 mg/m^2 IV on day 1, prednisone 100 mg/m^2 PO on days 1–5, every 3 weeks, total 4–8 cycles	25	62 (37–74)	NR	CR 1 (4) PR 14 (56) MRR 60% ORR 60%	2yr PFS 47%	NR
	R + CHOP: R 375 mg/m^2/day on the day before the CHOP	23	58 (40–78)	NR	CR 2 (9) PR 19 (83) MRR 91.3% ORR 91.3%	2yr PFS 78%	NR
Treon[21]¥ 2009	R + Fludarabine: R 375 mg/m^2/week IV at weeks 1 to 4, 17, 18, and 30, 31 with 6 cycles of fludarabine 25 mg/m^2 daily for 5 days at weeks 5, 9, 13, 19, 23, and 27	43	61 (52–75)	NR	CR 2 (5) VGPR 14 (33)/PR 21(49) MR 4 (9) MMR 88.9%£ ORR 96.3%£	2yr PFS 67%	40.3
Tedeschi[22] 2012	R + Fludarabine + Cyclophosphamide: R 375 mg/m^2 IV on day 1, fludarabine 25 mg/m^2, cyclophosphamide 250 mg/m^2 IV on days 2–4, every 28 days, total 6 cycles	43	65 (36–77)	Low 14 (33) Int 16 (38) High 12 (29)	CR 8 (19) VGPR 6 (14)/PR 19 (44) MR 1 (2) MRR 76.7% ORR 79.1%	PFS NR 2yr OS 88.4% 4yr OS 69.1%	38.8
Souchet[23]Ω 2016	FCR: R 375mg/m2 IV on day 1, F 40 mg/m2 PO on days days 1–3, C 250 mg/m2 PO on days 1–3, every 4 weeks for total 6 course.	82	61 (NR)	NR	VGPR 10 (40)/PR 9 (36) MR 3 (12) MRR 76%£ ORR 88%£	3yr PFS 96% 3yr OS 96%	47
Rummel[24] 2013	RB: B 90 mg/m^2 on days 1–2 of a 4 week cycle + R 375 mg/m^2 on day 1 of each cycle	22λ	64 (56–69)	NR	NR	PFS HR 0.33 (95%CI 0.110–0.64)	45
	R-CHOP: cyclophosphamide 750mg/m^2, doxorubicin 50 mg/m^2, vincristine 1.4mg/m^2 (up to dose of 2mg) on day 1, and prednisone 100mg on days 1–5, every 3 weeks + R 375mg/m^2 on day 1 of each cycle	19λ		NR	NR		45
Tripsas[25] 2013	Everolimus: 10mg daily until progression or unacceptable toxicity	33	62 (41–80)	NR	VGPR 2 (6)/PR 18 (55) MR 4 (12) MRR 60.6% ORR 72.7%	NR	9

† Risk stratification by International Prognostic Scoring System for WM (ISSWM);

Θ A total of 15 patients (56%) had no prior therapy;

ǂ A total of 21 patients (41%) had no prior therapy;

Ψ A total of 23 patients (82%) had previous treatment;

Ρ A total of 9 patients (24%) had no prior therapy;

€ A total of 4 patients (25%) had previous treatment;

¥ A total of 27 (63%) had no prior therapy;

Ω A total of 25 (30%) had no prior therapy;

λ This study included total 514 patients with indolent lymphoma (follicular lymphoma (n=279), marginal zone lymphoma (n=67), WM (n=41), SLL (n=21), unclassified (n=12)) and mantle cell lymphoma (n=94);

£ Values with treatment native patients only;

κ Defined as at least 25% increase from the baseline.

Abbreviation: BDR (bortezomib, dexamethasone, rituximab), KRD (dexamethasone, rituximab, carfilzomib), RCyD (rituximab, cyclophosphamide, dexamethasone), BR (rituximab, bendamustine), FCR (fludarabine, cyclophosphamide, rituximab), MRR (major response rate), CR (complete response), nCR (near CR), PR (partial response), MR (minimal response), MRR (major response rate; defined as CR +VGPR+PR), ORR (overall response rate; defined as CR+VGPR+PR+MR), Int (intermediate), Pre (pre-treatment), Post (post-treatment), NR (not reported), CI (confidence interval), Tx (therapy), PFS (progression free survival), OS (overall survival), Mo (months).

TABLE 3

Studies of WM patients with Prior Therapy or Refractory/Relapsed Disease

Study	Regimen	No. of Pt	Med. age (range)	Med No. of prior Tx (range or %)	Risk group	Treatment response (%)	Survival rates	Med F/U (mo)
Byrd[26] 1999	R: 375mg/m^2/weekly IV infusion total 4 or 8 consecutive weeks	7	60 (50–75)	3 (1–4)	NR	PR 3 (43) MRR 42.9% ORR 42.9%	NR	NR
Treon[27] 2015	Ibrutinib: 420mg po daily	63	63 (44–86)	2 (1–9)	Low 14 (22) Int 27 (43) High 22 (35)	VGPR 10 (16) PR 36 (57) MR 11 (17) MRR 73.0% ORR 90.5%	2yr PFS 69.1% 2yr OS 95.2%	NR
Gertz[9] 2004	R: 375mg/m^2/weekly IV infusion total 4 consecutive weeks	35	70.3 (46.8–89.2)	NR	NR	MR 11 (31) MRR 0% ORR 31.4%	PFS NR OS 71.4%	NR
Furman[12] *P* 2011	Ofatumumab: 300mg for week 1 and 1000mg for weeks 2–4 (G1) or 2000mg for weeks 2–5 (G2). If stable disease or minimal response at 16th week, additional 300mg for week 1 and 2000mg for weeks 2–5	37	63 (43–85)	3 (1–5)	NR	PR 13 (35) MR 9 (24) ORR 57.1%£	NR	NR
Dimopoulos[28] 2005	Bortezomib: Bortezomib 1.3mg/m^2 IV on days 1,4, 8 and 11 in a 21 day cycle, total 4 cycles	10	78 (48–84)	3 (1–4)	NR	PR 6 (60) ORR 60% MRR 60%	NR	NR
Treon[29] 2007	Bortezomib: Bortezomib 1.3 mg/m^2 on days 1, 4, 8, and 11, total 8 cycles	27	62 (44–79)	2 (0–3)	NR	CR/PR 13 (48) MR 10 (37) ORR 48.1% MRR 85.2%	PFS 26%	18.2
Ghobrial[30] 2010	Bortezomib + R: Bortezomib IV 1.6mg/m^2 on days 1, 8, 15, every 28 days for 6 cycles, R 375mg/m^2/weekly IV on cycle 1 and 4	37	64 (42–81)	1: 11 (30) 2: 8 (22) 3: 7 (19) > 3: 11 (30)	Low 6 (16) Int 11 (30) High 18 (49) NA 2 (5)	CR 2 (5) PR 21 (57) MR 9 (24) ORR 62.2% MRR 86.5%	1yr PFS 58% 1yr OS 94%	16
Treon[31] 2011	B + R or ofatumumab: B 90 mg/m^2 IV on days 1, 2 total 6 cycles with R 375 mg/m^2 IV on day 1 or 2 every 4 weeks or ofatumumab 1g IV on day 1	30	68 (44–84)	2 (1–9)	NR	VGPR 5 (17)/PR 20 (67) MRR 83.3% ORR 83.3%	NR	7.5
Treon[21]¥ 2009	R + Fludarabine: R 375 mg/m^2/week IV at weeks 1 to 4, 17, 18, and 30, 31 with 6 cycles of fludarabine 25 mg/m^2 daily for 5 days at weeks 5, 9, 13, 19, 23, and 27	43	61 (52–75)	0 (0–2)	NR	CR 2 (5) VGPR 14 (33)/PR 21(49) MR 4 (9) MRR 81.3%£ ORR 93.8%£	2yr PFS 38%	40.3
Souchet[23]Ω 2016	R + Fludarabine + Cyclophosphamide: R 375mg/m2 IV on day 1, fludarabine 40 mg/m2 PO	82	61 (NR)	1 (1–4)	NR	CR 5 (9) VGPR 16 (37) PR 23 (40)	3yr PFS 73% 3yr OS 89%	47

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Study	Regimen	No. of Pt	Med. age (range)	Med No. of prior Tx (range or %)	Risk group	Treatment response (%)	Survival rates	Med F/U (mo)
	on days 1–3, cyclophosphamide 250 mg/m2 PO on days 1–3, every 4 weeks for total 6 course.					MR 3 (5) ORR 77.2%[£] MMR 82.4%[£]		
Ghobrial[32,33] 2014	Everolimus: 10mg daily	50	63 (43–85)	3 (1–11)	Low 11 (50) Int 7 (32) High 4 (18)	PR 21 (42) MR 14 (28) MRR 42% ORR 70%	6mo PFS 75% 12mo PFS 62%	11.5
Ghobrial[34]	Everolimus+Bortezomib+R (phase I): everolimus 5 or 10 mg with R at 375 mg/m2 or with R and bortezomib at 1.3 or 1.6 mg/m2 for the phase I. Everolimus+Bortezomib+R (phase II): Everolimus 10mg daily, bortezomib 1.6mg/m2 IV weekly on days 1, 8, 15 ever 28 days, and R IV 375mg/m2 weekly on days 1, 8 15, 22 every 28 days in cycle 1 and 4 only.	46	64 (48–84)	2 (1–9)	Low 18 (39) Int 21 (46) High 7 (15)	CR 2 (4) PR 21 (46) MR 17 (37) MRR 50% ORR 87%	1yr PFS 65% 2yr PFS 42%	15

[†]A total of 5 patients (18%) had no prior treatment in this study;

[¥]A total of 27 (63%) had no prior therapy;

[P]A total of 9 patients (24%) had no prior therapy;

[Ω]A total of 25 patients had no prior treatment in this study;

[£]Values with previously treated patients only.

Abbreviation: R (rituximab), B (bendamustine), MRR (major response rate), PPH (plasmapheresis), CR (complete response), PR (partial response), MR (minimal response), MRR (major response rate; defined as CR+VGPR+PR), ORR (overall response rate; defined as CR+VGPR+PR+MR), Int (intermediate), Pre (pre-treatment), Post (post-treatment), NR (not reported), Tx (therapy), PFS (progression free survival), OS (overall survival), MO (months).