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Treatment recommendations for patients with Waldenström's Macroglobulinemia (WM) and related disorders: consensus from the Seventh International Workshop on WM

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Running title : Treatment recommendations for WM

Abstract

Waldenström's macroglobulinemia (WM) is a distinct B-cell lymphoproliferative disorder for which clearly defined criteria for the diagnosis, initiation of therapy and treatment strategy have been proposed as part of the consensus panels of International Workshops on WM (IWWM). As part of the IWWM-7 and based on recently published and ongoing clinical trials the panels updated treatment recommendations. Therapeutic strategy in WM should be based on individual patient and disease characteristics (age, comorbidities, need for rapid disease control, candidacy for autologous transplantation, cytopenias, IgM-related complications (hyperviscosity, neuropathy). Mature studies show that rituximab combinations with cyclophosphamide/dexamethasone (DRC), or bendamustine (BR) or bortezomib/dexamethasone (BDR) provided durable responses and are indicated for most patients. New monoclonal antibodies (ofatumumab), second generation proteasome inhibitors (carfilzomib), mTOR inhibitors and BTK inhibitors, are promising and may expand future treatment options. A different regimen is typically recommended for relapsed or refractory disease. In selected patients with relapsed disease after long lasting remission re-use of a prior effective regimen may be appropriate. AutoSCT may be considered in young patients with chemosensitive disease and in newly diagnosed patients with very high-risk features. Active enrollment of patients with WM in clinical trials is encouraged.

Introduction

Waldenström's macroglobulinemia (WM), is, according to WHO classification,alymphoplasmacyticlymphoma[1] in which the bone marrow is infiltrated by IgM-producing clonal lymphoplasmacytic cells. The Second International Workshop on WM(IWWM-2) proposed criteria for the clinicopathological diagnosis and for initiation of therapy in WMpatients[2-3].The IWWM consensus panels have provided treatment recommendations[4-5],which were last updated in 2008 (IWWM-4)[6].As part of its last consensus deliberations(IWWM-7, Newport, Rhode Island, August 2012), the panel considered the results from phase II studies of several chemoimmunotherapy regimens, novel drugs (alone or with rituximab)and of emerging novel targeted agents (ofatumumab, everolimus, perifosine, enzastaurin, panobinostat, carfilzomib, ibrutinib),examined these data and updated its recommendations, which are presented herein.

The consensus panels have recommended that individual patient considerations should be weighed for the choice of therapy, including the need for rapid disease control, age, candidacy for autologous transplantation, co-morbidities, presence of cytopenias, hyperviscosity, lymphadenopathy, IgM-related end-organ damage and patients' preferences. Based on available data, the panel provides guidance on the management of patients with WM adjusted to specific conditions and complications of the disease both for the initial therapy and for relapsed or refractory disease.

Major changes since the last published recommendations

Rituximab-based regimens remain a recommended primary therapy for most patients with WM. As per the previous recommendations of IWWM-4[6], DRC remains a primary choice but, combinations such as R-CHOP are no longer considered a first line choice; instead bendamustine-rituximab (BR) is now a primary treatment option, especially for patients with high tumor bulk. In the current recommendations bortezomib-rituximab combinations may also be considered a primary option for patients with specific high risk features (i.e. hyperviscosity) or in younger patients for whom avoidance of alkylator therapy is sought. Fludarabine-based combinations are not recommended for primary therapy but remain an option for patients with relapsed/refractory disease with adequate performance status. In patients who may be candidates for single agent oral therapy, oral fludarabine (if available) is recommended over chlorambucil(table 3).

Risk stratification

The importance of a prognostic system for the risk stratification of patients with WM and as a tool for study comparisons has been emphasized[6]. In IPSSWM five covariates (age >65

years, hemoglobin≤11.5 g/dl, platelet counts≤100x10^9/L, β2-microglobulin>3 mg/L, serum monoclonal protein >70 g/L) defined three risk groups (low, intermediate and high risk respectively)[7]. IPSSWM has been validated externally and its prognostic significance has been confirmed[8-10]. Results per IPSSWM risk category are increasingly reported and are used for stratification in randomized clinical trials. However, the use of IPSSWM in making treatment decisions remains to be delineated.

Justifying treatment initiation

Not all patients with a diagnosis of WM need immediate therapy. Criteria for the initiation of therapy (proposed in the IWWM-2 consensus panel and confirmed in IWWM-7) are presented in Table 1. For patients who do not fulfill the criteria in table 1 and in whom only laboratory evidence may indicate a possible development of symptomatic disease (such as a minor decrease in hemoglobin level, but >10 gr/dl, or mild increases in IgM or mild increase of lymphadenopathy or splenomegaly without discomfort for the patient), close observation is recommended[3].

Risk assessment for progression to symptomatic disease and follow up recommendations

IgM-MGUS or asymptomatic WM are increasingly diagnosed because more individuals undergo a serum protein electrophoresis as part of a routine laboratory assessment. The diagnosis of asymptomatic WM requires the demonstration of infiltration of the bone marrow by at least 10% clonal lymphoplasmacytic cells on trephine biopsy, or a monoclonal IgM above 3 gr/dl, and no end-organ damage or symptoms[11].

The median time to initiation of therapy for asymptomatic patients in the SWOG-S9003 study exceeded 7 years[12].In the series by Kyle et al, the cumulative probability of progression for patientswith asymptomatic WM was 6%, 39%, 59%& 68% at 1, 3, 5 &10 years respectively[11]and 75% required therapy during a median of 15 years of follow-up. Lower hemoglobin[11-12], extensive bone marrowinfiltration[11], size of serum M-spike[11]and β-microgobulin levels[12]were significant predictors of an eventual need for therapy.

There are no data to justify early initiation of treatment and patients with asymptomatic WM should be followed without therapy, preferably every 3 months for the first year in order to evaluate the pace of disease progression and, if stable, at more extended intervals thereafter. The risk of progression remains and individuals with asymptomatic WM should be followed lifelong.

Evaluation of response to therapy

The consensus-based uniform response criteria for WM, based mainly on the degree of M-protein reduction, were recently updated[5-6, 13](Table 2).Caution is advised in the early

evaluation of response during rituximab-based therapy (or other anti-CD20 monoclonal antibodies), because of the common "IgM flare"[14-16]which does not necessarily imply disease progression; in most cases will resolve but, if necessary, additional tests maybe performed to discriminate from disease progression. In patients treated with agents such as bortezomib or everolimus, tumor reduction in the bone marrow may not be proportional to the suppression of IgM levels[17-20]. Thus, the variability of the IgM kinetics with various therapies should be taken into account and in discordant cases additional investigations should be considered.

New treatment options for patients with WM

Bendamustine

In the StiL NHL 1-2003 study, 513 newly diagnosed patients with follicular, marginal zone, small lymphocytic, mantle cell lymphoma and WM received bendamustine with rituximab (BR)or R-CHOP: of 41 patients with WM, 22received BR and 19 R-CHOP)[21]. Responses were similar (95% in both arms) but BR was superior in terms of PFS (median 69.5 vs 28.1 months, p=0.0033) and tolerability. After a median follow up of 45 months a difference in overall survival was observed after the 5th year, but further follow up is needed. Regarding stem cell harvest, after 6 cycles of BR the CD34 yield was similar to that after R-CHOP.

As part of a large study investigating rituximab-maintenance in patients with previously untreated low-grade lymphomas (including WM), BR induction was given in 162 patients with WM(116 were evaluable for response)and 86% achieved ≥PR[22]. Responding patients(≥PR) were randomized to either observation or 2 years of rituximab maintenance; updated results are awaited.

Bendamustine is also active in patients with relapsed or refractory WM; either with rituximab, ofatumumab or as monotherapy(VGPR in 17%, PR in 67%;median PFS13.2 months) but prior nucleoside-analog exposure was associated with prolonged myelosuppression[23].

Thus, available data indicate that BR is at least as effective as R-CHOP, may be associated with longer PFS and less toxicity, and probably does not compromise stem cell collection. However, R-CHOP is not a standard first line regimen for WM[24] but less intensive and less toxic regimens like DRC are more often used. No increased incidence of secondary malignancies after bendamustine-rituximab was observed but longer follow-up is needed[21]. Bendamustine/Rituximab is a primary option for patients with newly diagnosed WM, especially those in need for rapid disease control or with bulky disease[25].

Bortezomib

Single agent bortezomib is associated with responses in ~40% of patients with relapsed or refractory WM, including fludarabine and rituximab refractory patients. Bortezomib with

rituximab(+/-dexamethasone) are active and in the frontline setting, three phase II studies of bortezomib/rituximab combinations showed response rates(≥PR) between 66% to 83%and rapid times to first response (2-3 months). Treon et al[26], treated 23 previously untreated patients with 4 consecutive cycles of BDR using twice-weekly, intravenous bortezomib, followed by4 additional cycles given at 3 month intervals (≥PRs in 83% and CRs/nCRs in 22%);61% of patients discontinued bortezomib due to neurotoxicity while two patients developed symptomatic "IgM flare". In order to reduce neurotoxicity, Ghobrial et al used weekly bortezomib with rituximab (6 cycles-no maintenance) in 26 patients[27] (58% achieved ≥PR, 8% CRs/nCRs and 1-year EFS was 79%). "IgM flare" developed in 40% and54% of patients developed peripheral neuropathy but in none was grade≥3. Dimopoulos et al, in order to avoid "IgM flare" used an induction cycle of bortezomib(i.v.1.3 mg/m^2 days 1,4,8 & 11),followed by four cycles of weekly bortezomib(i.v.1.6 mg/m^2 for 4 weeks) with rituximab and dexamethasone on cycles 2 and 5. Among 59 previously untreated patients 68% achieved ≥PR(3% CRs, 7% VGPRs); "IgM flare" occurred in 11% but plasmapheresis was not required, probably due to the initial bortezomib-induction. After a median follow up of 42 months responses were durable (median PFS was 42 months and 3-year PFS for those with ≥PR was 70%) despite the lack of maintenance. Peripheral neuropathy was observed in 46% (grade≥3 in 7%) but only 5(8%) patients discontinued bortezomib due to neuropathy.
Neurotoxicity is the major concern with bortezomib because underlying IgM-related neuropathy or neuropathies due to age-related co-morbidities (such as diabetes) are common. Weekly dosing[28-30] and subcutaneous administration may reduce rates and severity of neuropathy and is explored in a clinical trial(NCT01592981). Bortezomib is not stem cell toxic and long-term follow-up in myeloma patients does not suggest a risk for secondary malignancies[31].Prophylaxis against herpes zoster is strongly recommended. Primary therapy with bortezomib is recommended for patients with high levels of IgM, with symptoms of or, at risk of developing hyperviscosity syndrome, symptomatic cryoglobulinemia or cold agglutinemia, amyloidosis and renal impairment.

Carfilzomib, a second generation proteasome inhibitor, is associated with a low risk of neurotoxicity in myeloma patients and was recently evaluated in combination with rituximab and dexamethasone(CaRD), mainly in untreatedWMpatients[32]. The schedule of carfilzomib was attenuated (days 1,2 &8,9) compared to myeloma dosing, and maintenance therapy (days 1,2 only) was given every 8 weeks for 8 cycles. Overall response rate was87% (≥VGPR in 35%),and no grade≥3 neuropathy was observed. With a median follow-up of 15.4 months, 20/31(65%) patients remain progression-free. CaRD therefore represents a novel neuropathy-sparing option for proteasome-inhibitor based therapy for WM.

Everolimus

Mature data from a phase II study of the oral mTOR inhibitor everolimus(10 mg daily)showed a ≥PR in 50% (additional 23% MRs) of previously treated patients. Responses were rapid, occurring at a median of 2 months, and the median PFS was 21 months[33]. Grade ≥3 toxicities occurred in 67% of patients. Among previously untreated patients(N=33), everolimus induced a ≥PR in 61% (plus 12% MRs)[20], though discordance between serum IgM levels and bone marrow disease burden was commonly observed. Six(18%) patients discontinued therapy due to toxicity. Myelosuppression with everolimus was common, and significant non-hematological toxicities included diarrhea, fatigue and stomatitis(8%-27%).Additionally, 5%-15% developed pulmonary toxicity, frequently resulting in interruption or discontinuation of therapy. Everolimus may therefore be considered for selected patients with relapsed or refractory disease and limited options.

Fludarabine

Nucleoside analogues have been used extensively in the treatment of WM, either alone or in combinations. In the large WM1 randomized phase III study, oral fludarabine was superior to chlorambucil in terms of response rates, PFS and OS in newly diagnosed WM/LPL[34]. Fludarabine has been studied in combination with rituximab, with or without cyclophosphamide (FR or FCR).Tedeschi et al[35] published mature data (median follow-up 37 months) with FCR in either previously untreated or patients relapsing after 1 line of alkylator-based (chlorambucil or cyclophosphamide) therapy. A ≥PR was observed in 74.4% (CR in 11.6% and VGPR in 20.9%) with an improvement of the quality of responses observed during follow-up, to a final 18.6% of CRs. Median EFS was 50 months and estimated 4-year OS was 69%. Myelosuppression, especially neutropenia, was the main reason for treatment discontinuation, including episodes of long lasting neutropenia after the end of treatment, while three patients developed myelodysplastic syndrome. In retrospective studies fludarabine-based therapy was associated with an increased risk of secondary malignancies[36], although the frequency was not greater than with chlorambucil in the WM1 study[34]. Nevertheless, response rates with fludarabine combinations are high, even in patients with relapsed or refractory WM and the duration of response is long. Fludarabine-based combinations should be considered in patients with relapsed/refractory WM, in good performance status. In young patients who are ASCT eligible it is preferable that stem cells be collected before fludarabine administration.

Oral Alkylating agents

Alkylators as single agents have been associated with relatively low rates and delayed responses. Single agent chlorambucil may induce responses in up to 40% of patients; however, the randomized WM1 study indicated that chlorambucil is inferior to single agent oral fludarabine[34].

IMiDs

Thalidomide has clinical activity in pretreated or previously untreated patients with WM, either alone[37] or with rituximab[38]. Primary therapy with thalidomide/rituximab induced PRs in 70%and the median time to progression was 35 months. However, doses up to 200 mg/day were poorly tolerated (mainly due to neurotoxicity). Because of the advanced age of many patients (who are less tolerant to thalidomide) and the co-existence of WM–related neuropathy, thalidomide is not a primary choice. Nevertheless, the minimal myelotoxicity of thalidomide may be important for selected patients with severe cytopenias (especially those with severe thrombocytopenia). Lenalidomide with rituximab was associated with significant hematologic toxicity[39]; thus it should only be considered in the context of a clinical trial. Pomalidomide is under investigation.

Monoclonal antibody therapy

Rituximab

Single agent rituximab is moderately active (responses rates of~30%);more extended administration is associated with higher response rates. Rituximab-based combinations (with alkylating agents, nucleoside analogs, proteasome inhibitors, IMiDs) are the mainstay of WM therapy. Rituximab has a favorable toxicity profile, is neither myelosuppressive nor stem cell toxic. However, rituximab is associated with a potentially clinically significant complication, “IgM flare”: this surge of IgM levels may be observed with either single agent rituximab or with rituximab combinations with alkylating agents, nucleoside analogs or proteasome inhibitors (bortezomib or carfilzomib), and has also been observed with other monoclonal anti-CD20 antibodies (such as ofatumumab). “IgM flare” may require immediate institution of plasmapheresis. Furthermore, response to rituximab may be affected by polymorphisms in the Fc-gamma-III receptor.

Dimopoulos et al reported updated results of the DRC regimen phase II study with a minimum follow-up >6 years[40]. Median PFS was 35 months and median time to next treatment was 51 months. Forty patients received second line treatment, 28(70%) patients were retreated with either rituximab alone or rituximab-based regimens and 82% achieved ≥MR. Thirty-five(49%) patients have died (including 15 patients from unrelated causes). One patient, who received further therapy with fludarabine, developed MDS and 2 patients

developed diffuse large-B cell lymphoma. Five-year OS was 62% and median OS was 95 months.

Rituximab maintenance improves duration of response in patients with other low-grade lymphomas, especially follicular lymphoma[41]. A retrospective comparison indicated that maintenance rituximab may improve quality of responses and prolong PFS and time to next therapy in both previously untreated and pretreated WM patients[42], though at the expense of increased infections (mainly grade≤2).An ongoing prospective, randomized study examines the impact of maintenance rituximab following BR[22]. Due to the lack of prospective data the use of maintenance rituximab is not routinely recommended.

Ofatumumab

Ofatumumab is a fully human monoclonal anti-CD20 antibody approved for the treatment of patients with CLL. Ofatumumab was given to37 patients (28 with relapsed/refractory and 9 with untreated WM)[43] at two dose levels (four weekly infusions of 1000 vs 2000 mg) following a dose of 300 mg on the first week– non progressing patients received a second cycle at week 16. After the first cycle, 11(30%) achieved PR and 7(19%) a MR; twelve patients received a second cycle. The ≥MRs after both cycles were 59%(PR in 38%), somewhat higher with higher doses(47% vs 68%), in therapy-naïve(6/9, 67%) and rituximab-naïve(9/12, 75%) than in rituximab-exposed patients(13/25, 52%). Infusion-related reactions were common especially during the first dose; mild infections were also common and “IgM flare” was observed. Ofatumumab has promising activity, may be active in patients with prior exposure to rituximab and may be considered for patients intolerant to rituximab, however, more data is needed in rituximab-refractory disease. Combinations of ofatumumab with other agents in WM are under investigation.

Alemtuzumab

CD52 is highly expressed in lymphoplasmacytic cells; however, the toxicity of the anti-CD52 antibody alemtuzumab is high, especially infectious complications, most notably CMV reactivation. Mature results (median follow-up 64 months)[44]from 28 patients(23 previously treated and 12(46%) refractory to the most recent therapy)indicated the activity of alemtuzumab (≥PR in36% and 39% MRs, median TTP14.5 months) but toxicity was significant, including deaths of patients while on therapy. CMV reactivation occurred in 18% and new-onset autoimmune thrombocytopenia occurred in 4(14%) patients. Based on the above results, the toxicity of the drug must be weighed against available treatment options and on an individual and restrictive basis.

1. Management of newly diagnosed patients who require therapy for WM

The data on therapy of WM come mainly from non-randomized studies since only few randomized studies have been conducted in the field. Based on the available data as well as the experience from the treatment of patients with low grade lymphomas, specific recommendations can be made based on individual patient needs (Table 4).

A. Patients with WM related cytopenias or organomegaly or bulky lymphadenopathy

Most patients with WM require therapy because of cytopenias, most commonly anemia, and/or organomegaly with or without constitutional symptoms. Toxicity and efficacy are very important considerations. Rituximab-based combinations are recommended for patients with moderate to severe symptomatology. Rituximab in combination with cyclophosphamide and steroids (DRC[45])or bendamustine(BR)are primary options. When rapid disease control is needed (as in patients with bulky symptomatic lymphadenopathy), BR or fludarabine/rituximab combinations may be considered. However, given the increased toxicity (early and late) of nucleoside analogues and the potential impact on stem cell collection, their use should be avoided in most, especially in younger patients.

B. *Patients with symptomatic hyperviscosity, cryoglobulinemia or cold agglutinemia*

Morbidity due to paraprotein-mediated hyperviscosity, cryoglobulinemia or cold agglutinemia is common. Rituximab-associated “IgM flare” may worsen paraprotein-related symptoms. Plasmapheresis should be considered for patients with symptomatic hyperviscosity and/or severe cryoglobulinemia and cold agglutinemia. “Preemptive” plasmapheresis before rituximab may be considered for patients with IgM≥4 g/dLin order to avoid symptomatic “IgM flare”. In patients without symptomatic hyperviscosity, bortezomib may rapidly reduce IgM levels; induction with single-agent bortezomib can be considered before institution of rituximab (as in BDR)[29]. Weekly and/or subcutaneous administration of bortezomib is preferred. In patients at high risk for neuropathy bendamustine can be considered; FCR is very effective but toxic. For patients with cold agglutinin disease requiring therapy, fludarabine/rituximab combination is superior over rituximab alone[46]; however, toxicity should be weighed against combinations such as DRC, BDR or bendamustine/rituximab.

C. *Patients with paraprotein-related neuropathy*

The treatment of IgM-related neuropathy may initially involve a course of plasmapheresis, particularly in patients with an aggressive course of progressing neuropathy. Plasmapheresis should not be used as a permanent modality. Systemic chemotherapy with rituximab resulted in improvement in sensory function in several studies, including a placebo

controlled trial[47]. Single agent rituximab can be considered as the first intervention in patients with mild, slowly progressive neuropathy. In patients with moderate to severe IgM-related neuropathy data indicate more rapid improvement with fludarabine-rituximab combination than with rituximab alone[48]. Thus, in patients with more severe or a more aggressive course of the IgM neuropathy, a rituximab-based combination appears reasonable. Fludarabine-rituximab is effective but toxic, DRC is safe; bendamustine/rituximab may achieve robust paraprotein reductions but there is limited experience in IgM-related neuropathy. Patients who experience a rituximab related "IgM flare" may also develop a flare in their neuropathy. Symptomatic treatment should also be considered (i.e with gabapentin, pregabalin, duloxetine)[49]. Bing-Neel syndrome is a rare complication of WM characterized by direct infiltration of the CNS by malignant cells with or without cerebrospinal fluid hyperglobulinemia. There are limited reports on the management of these patients with aggressive chemotherapy, which may also require intrathecal therapy[50-51].

D. Patients with IgM-associated amyloidosis

IgM-associated AL amyloidosis is a rare condition with distinctive clinical characteristics[52-53]. These patients are fragile, due to systemic amyloid organ involvement and require a dedicated approach. Treatment should aim at the rapid elimination of the amyloidogenic light chains, with monitoring of the free light chains and cardiac biomarkers. There is limited evidence on the applicability and outcome of treatment with regimens designed for WM to IgM-AL amyloidosis[53-57]. In selected patients, ASCT may be considered. Given the activity in patients with non-IgM AL amyloidosis and in WM, bortezomib-based therapy could be used in carefully selected patients[29, 56].

2. **Salvage therapy**

The panel encourages the participation of patients with relapsed or refractory WM in clinical trials exploring novel agents or strategies. Outside clinical trials treatment options depend on the duration and response to prior therapies, the patient's overall condition and age, and candidacy for ASCT.

Administering the same regimen used for primary treatment is reasonable in patients who achieved responses that lasted for at least 12 months; otherwise, use of an alternate single agent or combination is recommended. Updated results from the phase II DRC study indicate that this is an effective strategy for many patients[40].

For patients with short-lasting remissions (<12 months) or with progressive disease/resistance to a first-line regimen, second-line treatment should include agents of a

different class, either alone or in combination. Exposure to stem cell damaging agents should be avoided in patients who are candidates for autologous-SCT; especially if stem cells have not been harvested.

All regimens discussed under primary treatment options are effective salvage therapies. Bortezomib in combination with rituximab and/or dexamethasone is reasonable but neurotoxicity is of concern. Bendamustine-based therapy is effective mostly in combination with rituximab. FCR is effective but toxic. Ofatumumab for rituximab-intolerant or resistant patients maybe considered. Everolimus or alemtuzumab may be considered for selected patients with very limited treatment options, which should be followed closely for toxicity.

Stem cell transplantation (SCT) for patients with WM

High dose therapy with autologous-SCT is an option for salvage therapy in selected patients with chemosensitive disease; patients with several lines of prior therapies (≥3 lines) appear to have limited benefit from autologous-SCT[58]. As part of primary therapy autoSCT could be considered in selected young patients with high risk IPSSWM and elevated LDH. The use of myeloablative or non-myeloablative allogeneic SCT is less defined. Younger patients with slowly progressing disease may be better candidates for allo-SCT. However, in view of the increasing treatment options and the high morbidity and mortality associated with allo-SCT, the opinion of the panel is that this therapy should preferably be considered in the context of a clinical trial.

Management of Patients Intolerant to Rituximab

Rituximab is a chimeric (mouse/human) monoclonal antibody and may be intolerable in some patients, mainly due to major infusions reactions. Ofatumumab is a fully human monoclonal antibody and has been successfully administered in patients with prior rituximab-resistant disease and in patients intolerant to rituximab.“IgM flare” is also observed with ofatumumab therefore similar precautions as with rituximab should be considered.

Future perspectives

The identification of the common somatic mutation in MyD88 offered the opportunity for a more targeted approach. This mutation results in tonic MYD88-IRAK signaling which activates the NF-κB and MAPK pathways to support growth and survival of WM cells. BTK has a critical place in signaling transduction through this signaling pathway[59] and ibrutininib, a selective BTK inhibitor, has shown high activity in MyD88 mutated cell lines and very promising results in patients with relapsed/refractory WM. Recently, ibrutinib was approved for the treatment of patients with relapsed or refractory mantle cell lymphoma or chronic lymphocytic leukemia. Ixazomib is an orally available proteasome inhibitor which has shown

efficacy in myeloma patients and is under investigation in phase I/II studies in relapsed/refractory WM. Oprozomib,an orally available epoxyketone class proteasome inhibitor, is under investigation in myeloma and in WM. Obinutuzumab (GA-101) a new monoclonal anti-CD20 antibody was recently approved for the treatment of patients with previously untreated chronic lymphocytic leukemia in combination with chlorambucil. A phase III study is comparing chemotherapy (CHOP) plus obinutuzumab or rituximab followed by maintenance with obinutuzumab or rituximab in patients with advanced untreated indolent non-Hodgkin's lymphoma, including WM. HDAC inhibitor panobinostat showed activity in patients with relapsed/refractory WM indicating a potential role for HDAC inhibition in WM[60].

An important advancement is the initiation of phase III studies designed specifically for patients with WM, either in newly diagnosed or in the relapsed/refractory setting, through multicenter collaborations such as the European WM Consortium (EWMC). Such studies will define the treatment strategies based on high quality data and offer the opportunity of high quality translational research.

Authorship:

M.A.D, E.K. & S.P.T drafted the first version of the manuscript, all authors reviewed the manuscript, provided comments and suggestions and all authors approved the final manuscript.

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Table 1: Indications for initiation o therapy in patients with WM

Clinical and laboratory indications for initiation of therapy
• Recurrent fever, night sweats, weight loss, fatigue
• Hyperviscosity
• Lympadenopathy which is either symptomatic or bulky (≥5cm 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
• Hemoglobin ≤10g/dL
• Platelet count $<100x10^9$/L

Table 2. Consensus-based uniform response criteria for WM developed by the International Workshop on WM , updated in the Sixth IWWM and published by Owen et al [13]

Response category Definition	
Complete response (CR)	Absence of serum monoclonal IgM protein by immunofixation Normal serum IgM level Complete resolution of extramedullary disease, i.e., lymphadenopathy and splenomegaly if present at baseline Morphologically normal bone marrow aspirate and trephine biopsy
Very good partial response (VGPR)	Monoclonal IgM protein is detectable ≥90% reduction in serum IgM level from baseline* Complete resolution of extramedullary disease, i.e., lymphadenopathy/splenomegaly if present at baseline No new signs or symptoms of active disease
Partial response (PR)	Monoclonal IgM protein is detectable ≥50% but<90% reduction in serum IgM level from baseline* Reduction in extramedullary disease, i.e., lymphadenopathy/splenomegaly if present at baseline No new signs or symptoms of active disease
Minor response (MR)	Monoclonal IgM protein is detectable ≥25% but<50% reduction in serum IgM level from baseline* No new signs or symptoms of active disease
Stable disease (SD)	Monoclonal IgM protein is detectable <25% reduction and <25% increase in serum IgM level from baseline* No progression in extramedullary disease, i.e., lymphadenopathy/splenomegaly No new signs or symptoms of active disease
Progressive disease (PD)	≥25% increase in serum IgM level* from lowest nadir (requires confirmation) and/or progression in clinical features attributable the disease

*Sequential changes in IgM levels may be determined either by M-protein quantitation by densitometry or total serum IgM quantitation by nephelometry.

**An absolute increase of >5 g/L (0.5 g/dL) is required when the increase of IgM component is the only applicable criterion.

Table 3: summary of changes from the previous recommendations from the Fourth International Workshop on Waldenstro¨m's Macroglobulinemia, published in 2009

Clinical condition	New recommendation (2014)	Old recommendation (2009)
Cytopenias	DRC, Bendamustine-Rutuximab, Bortezomib-Rituximab	DRC, Thalidomide+Rituximab
High M-protein, transplant candidate	Bendamustine-Rutuximab, Bortezomib-Rituximab	R-CHOP, DRC
High M-protein, non-transplant candidate	Bendamustine-Rutuximab, Bortezomib-Rituximab	Nucleoside analogs + rituximab; nucleoside analogs + rituximab + cyclophosphamide
Co-morbidities and cytopenias	Rituximab	Rituximab
Older age, slow progression, candidate for oral therapy	Oral fludarabine	Cladribine

Table 4: Recommendations for initial therapy of patients with WM, based on the individual patient characteristics

	Primary choice(s)	Alternative (s)
Patients with WM related cytopenias or organomegaly	Rituximab-based combination • DRC • Bendamustine/R	• Bortezomib/rituximab
Patients with symptomatic hyperviscosity, cryoglobulinemia or cold agglutinemia	• Bortezomib followed by bortezomib/rituximab • Bendamustine / Rituximab	• Fludarabine/rituximab+/- cyclophosphamide
Patients with paraprotein related neuropathy	• Rituximab alone • DRC	• Fludarabine/R • Bendamustine / Rituximab
Elderly patients with poor PS	• DRC • Oral fludarabine	• Rituximab monotherapy • Chlorambucil
Elderly patients not eligible for systemic IV therapy	• Oral fludarabine	• Chlorambucil
Young patients eligible for ASCT	• DRC • Bortezomib/Rituximab	• Bendamustine/Rituximab • R-CHOP