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Report of consensus panel 1 from the 11th International Workshop on Waldenstrom's Macroglobulinemia on management of symptomatic, treatment-naïve patients

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ABSTRACT

Consensus Panel 1 (CP1) of the 11th International Workshop on Waldenstrom's Macroglobulinemia (IWWM-11) was tasked with updating guidelines for the management of symptomatic, treatment-naïve patients with WM. The panel reiterated that watchful waiting remains the gold standard for asymptomatic patients without critically elevated IgM or compromised hematopoietic function. For first-line treatment, chemoimmunotherapy (CIT) regimens such as dexamethasone, cyclophosphamide, rituximab (DRC), or bendamustine, rituximab (Benda-R) continue to play a central role in managing WM, as they are effective, of fixed duration, generally well-tolerated, and affordable. Covalent BTK inhibitors (cBTKi) offer a continuous, generally well-tolerated alternative for the primary treatment of

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WM patients, particularly those unsuitable for CIT. In a Phase III randomized trial updated at IWWM-11, the second-generation cBTKi, zanubrutinib, was less toxic than ibrutinib and induced deeper remissions, thus categorizing zanubrutinib as a suitable treatment option in WM. While the overall findings of a prospective, randomized trial updated at IWWM-11 did not show superiority of fixed duration rituximab maintenance over observation following attainment of a major response to Benda-R induction, a subset analysis showed benefit in patients >65 years and those with a high IPPSWM score. Whenever possible, the mutational status of *MYD88* and *CXCR4* should be determined before treatment initiation, as alterations in these 2 genes predict sensitivity towards cBTKi activity. Treatment approaches for WM-associated cryoglobulins, cold agglutinins, AL amyloidosis, Bing-Neel syndrome (BNS), peripheral neuropathy, and hyperviscosity syndrome follow the common principle of reducing tumor and abnormal protein burden rapidly and deeply to improve symptoms. In BNS, ibrutinib can be highly active and produce durable responses. In contrast, cBTKi are not recommended for treating AL amyloidosis. The panel emphasized that continuous improvement of treatment options for symptomatic, treatment-naïve WM patients critically depends on the participation of patients in clinical trials, whenever possible.

Introduction

In a modern era of widening global access to covalent Bruton tyrosine kinase inhibitors (cBTKi), several questions arise about using fixed-duration chemoimmunotherapy (CIT) regimens versus using these oral therapies of indefinite duration in the first-line treatment of WM. For those receiving rituximab-chemotherapy, we assess updated data on the 2 commonly used and highly effective regimens, Bendamustine-Rituximab (Benda-R) and Dexamethasone, Cyclophosphamide, and Rituximab (DRC), and review the role of rituximab maintenance. We discuss the patient populations in whom cBTKI might be suitable and preferred agents based on long-term data from phase II studies and a phase III randomized clinical trial comparing ibrutinib and zanubrutinib. We address the impact of our emerging understanding of genetic alterations of WM on treatment selection. We consider what agents to choose, and as importantly avoid, in specific first-line clinical situations. Even with these efficacious and well tolerated first-line treatment options, we reiterate the ongoing central role of watch-and-wait (W&W) for those with smoldering disease. As we move into a more "endemic" albeit still unpredictable phase of COVID-19, a nuanced, evidence-based approach to each patient with WM remains essential. Notwithstanding the data, cost implications result in differing access to WM therapies worldwide, and these first-line treatment guidelines endeavor to provide therapeutic options for all patients globally.

What are the preferable treatments for treatment naïve, symptomatic WM patients?

Rituximab-chemotherapy and the covalent BTK inhibitors (cBTKi), ibrutinib alone or with rixtuximab, and zanubrutinib are reasonable first-line treatment options for patients with WM [1]. A large, multicenter, retrospective study of treatment-naïve WM patients who received ibrutinib or Benda-R showed similar outcomes in PFS and overall survival with a median follow-up of 4.2 years suggesting that CIT with Benda-R or a cBTKi are similarly effective in treatment-naïve patients [2].

Chemoimmunotherapy

Benda-R is the CIT of choice for patients requiring rapid debulking or with a high tumor burden. No prospective data have compared Benda-R and DRC in WM. However, a retrospective analysis suggested a trend to longer PFS with Benda-R than DRC, and patient-derived data supports a longer time-to-next treatment (TTNT) with Benda-R [3,4]. For less fit patients with lower tumor burden, particularly those with a gradual progression to treatment initiation, DRC is an effective and well-tolerated treatment option [5,6].

For patients treated with Benda-R, the pivotal STiL trial used six four-weekly cycles of bendamustine at a dose of 90 mg/m^2, demonstrating high efficacy and manageable toxicity for WM [7]. Doses as low as 70mg/m^2 and/or as few as 4 cycles may be sufficient in some cases [8]. However, no prospective study has analyzed 4 vs 6 cycles of Benda-R in WM.

Alternative regimens such as R-CHOP, R-CVP, fludarabine, or cladribine-based therapies are not preferred in WM because of higher toxicity, particularly neurological and hematological, without evidence of long-term efficacy benefit compared to Benda-R or DRC.

cBTKI

Where available, cBTKi should be preferentially used in patients with significant comorbidities or frailty predicting increased risk of chemotherapy-associated toxicity. In addition, cBTKi are an important treatment option in young patients, in whom alkylator exposure with its long-term consequences pertaining to second hematologic malignancies may not be desirable. However, there is no formal definition of what constitutes medically unfit patients in WM ineligible for CIT. Thus, the decision to offer a cBTKi instead of CIT must be made by each clinician based on individual patient characteristics. Individual co-morbidities should guide the use of first vs second-generation cBTKis (eg, cardiac toxicity of ibrutinib). The 1:1 randomized comparison between ibrutinib and zanubrutinib in patients with MYD88^{Mut} that was updated at IWWM-11 demonstrated a lower rate of atrial fibrillation (8% vs 25%) and hypertension (15% vs 26%) for zanubrutinib compared to ibrutinib [9,10]. A higher rate of neutropenia for zanubrutinib versus ibrutinib was also reported, but this did not translate into a higher rate of infections for patients on zanubrutinib with 45 months of median follow-up. Fewer patients in the zanubrutinib arm had an adverse event (AE) leading to treatment discontinuation (9% vs 20%) or dose reductions (14% vs 23%) [9,10]. This update charted a numerical trend of deeper, earlier, and more durable responses on zanubrutinib compared with ibrutinib [10]. Zanubrutinib provided faster and deeper responses in patients with *CXCR4*^{MUT}, and responses to zanubrutinib were also seen in a single arm observational cohort of *MYD88*^{WT} patients who showed continued deepening of categorical responses over time [10]. Overall, no difference in PFS or OS between the zanubrutinib and ibrutinib arms was observed, though patients with CXCR4^{MUT} disease showed a trend towards superior PFS with zanubrutinib [10]. Thus, both cBTKi are valid treatment options, and individual patient co-morbidities and MYD88 and CXCR4 mutation status can be considered when selecting between these 2 cBTKi. Phase II data on acalabrutinb suggest

Table 1
Selected data from prospective studies in treatment-naïve patients with Waldenström Macroglobulinemia.

Study	Regimen	N	PR or better	VGPR or better	PFS
Dimopoulos et al.[43]	Dexamethasone	72	74%	7%	35 mo (median)
Kastritis et al.[5]	Rituximab				
	Cyclophosphamide				
Rummel et al.[27,44]	Bendamustine	257	88%	4%	65 mo(median)
	Rituximab				
Treon et al.[45]	Bortezomib	23	83%	35%	66 mo(median)
Treon et al.[46]	Dexamethasone				
	Rituximab				
Dimopoulos et al.[47]	Bortezomib weekly	59	68%	10%	42 mo(median)
Gavriatopoulou et al.[18]	Dexamethasone				
	Rituximab				
Treon et al. [14]	Carfilzomib	28	68%	36%	46 mo (median)
Meid et al.[48]	Dexamethasone				
	Rituximab				
Castillo et al.[49]	Ixazomib	26	77%	19%	40 mo (median)
Castillo et al.[15]	Dexamethasone				
	Rituximab				
Buske et al.[7]	Bortezomib	102	81%	17%	81% at 24 mo
	Cyclophosphamide				
	Dexamethasone				
	Rituximab				
	Cyclophosphamide	100	70%	10%	73% at 24 mo
	Dexamethasone				
	Rituximab				
Treon et al.[50]	Ibrutinib	30	87%	30%	76% at 4 y
Castillo et al.[51]					
Dimopoulos et al.[52]	Ibrutinib	34	76%	27%	70% at 4.5 y
Buske et al.[53]	Rituximab				
	Rituximab	34	41%	9%	32% at 4.5 y
Tam et al.[9]	Zanubrutinib	19	74%	36%	78% at 42 mo
Dimopoulos et al.[10]					
	Ibrutinib	18	67%	22%	70% at 42 mo
Owen et al.[11]	Acalabrutinib	14	79%	NR	86% at 66 mo
Owen et al.[54]					

N = number of patients; NR = not reported; PFS = progression-free survival; PR = partial response; VGPR = very good partial response.

this cBTKi is also well tolerated in WM patients. However, only 14 patients were treated first-line in this trial with 106 patients [11] (Table 1).

Data on other second-generation cBTKis, orelabrutinib and tirabrutinib, in first-line treatment are limited, but show encouraging activity with sustained responses. Whenever possible, treatment with cBTKi should be continued until second-line treatment is initiated to minimise IgM rebound and "cytokine response" side effects that are seen in up to 20% of patients following withdrawal [12,13].

Is there a role for proteasome inhibitor-based therapy in treatment-naïve, symptomatic WM patients?

Bortezomib, the first in class proteasome inhibitor (PI), has shown activity in combination with rituximab with or without dexamethasone, or combined with DRC [6]. An early analysis of the ECWM Phase II comparison of B-DRC vs DRC in 202 patients showed that adding bortezomib was deliverable with a trend towards faster and deeper responses. However, there was increased neurotoxicity (18%) and a possible signal of increased infections. PFS, the primary study end point, was comparable between the quadruplet and DRC [7]. Carfilzomib or ixazomib in combination with rituximab and dexamethasone has shown high levels of activity and durability in treatment-naïve WM patients [14,15]. In front-line therapy, a PI-based regimen may be appropriate for patients with AL amyloidosis, light chain deposition disease, and renal compromise. While PIs may produce treatment-related neuropathy, subcutaneuous bortezomib, carfilzomib or ixazomib may be less neuropathic in patients with peripheral neuropathy [16-18]. Carfilzomib should be avoided in patients with cardiopulmonary disease [14].

Is there a role for Rituximab monotherapy in treatment-naïve, symptomatic WM patients?

In 2023, there is a more limited role for rituximab monotherapy in the first-line treatment of WM, given major response rates of only 20% to 40% and median PFS of 16 to 18 months [19,20]. Patients being unfit for CIT may benefit from rituximab single agent treatment. Generally, however, if a patient is unfit for chemotherapy, a cBTKi is recommended. Single-agent rituximab may be an option in settings where cBTKi is unavailable. However, the time to response is long, the efficacy is moderate, and there is a risk of IgM flare in ~50% of patients [1,21,22]. Based on the latter, rituximab monotherapy should be avoided in patients with serum IgM levels >40 g/L, and apheresis facilities should be available for critically elevated IgM levels after treatment [22].

Role of COVID-19 and primary therapy of WM

As we move into the fourth year of the COVID-19 pandemic, it is recognized that WM patients show poor serological response to COVID-19 vaccination if they are on a cBTKi or had recent rituximab therapy [23-25]. Covid-specific T cell responses are preserved. Boosters may be of particular benefit in augmenting serological response to vaccination [25]. In this context, the impact of COVID-19 probably does not justify a compromise in therapy choice; patients should be offered the best treatment option, while optimizing immunization and pre-exposure prophylaxis in parallel, as well as education about the importance of seeking medical assessment and use of antiviral therapy, such as nirmatrelvir/ritonavir (Paxlovid). A discussion about the benefits and risks of treatment of COVID-19 infection should be considered for all patients, and in particular for those who are unvaccinated or who have not received updated

boosters for COVID-19 (see also CP5 report in this edition of Seminars in Hematology) [26].

Given the CYP3A inhibition of nirmatrelvir/ritonavir and the increase of the plasma concentration of cBTKis, a dose pause or 4-fold reduction in dosing is recommended while on and 48 hours immediately after the use of nirmatrelvir/ritonavir (see CP5 report in this edition of Seminars in Hematology). Both CIT and cBTKi are immunosuppressive and justify pre-exposure prophylaxis with anti-COVID-19 antibodies for WM patients, as long as variants remain sensitive to a given passive antibody combination.

In which patient should rituximab maintenance be used as part of frontline therapy of WM? Also, in light of the COVID-19 pandemic, should rituximab maintenance be held or shortened, and in what patient?

Based on prospective data, there is no general role for rituximab maintenance after first-line induction. In an update of the MAINTAIN study, which randomized >200 patients who attained at least a partial response to Benda-R induction to 2 years of maintenance vs observation, there was no significant difference in the PFS or OS between arms after a median of 7 years of follow-up. Of note, the median PFS in the observation arm was 84 months [27]. Based on these data, rituximab maintenance is not generally recommended for all WM patients who attained a major response after induction CIT. However, some WM patients may benefit since patients >65 years and those with high IPPSWM score showed an improved PFS, in a subset analysis. Maintenance rituximab after CIT may also be considered in patients with a minor response to induction or disease manifestations that might benefit from more profound responses (eg, renal involvement).

Which molecular characteristics have an impact on our treatment choice? MYD88? CXCR4? TP53?

The mutational status of MYD88, and increasingly CXCR4, guide treatment decisions in WM and should be determined whenever possible, particularly when considering BTK-inhibitor use (see above). Disruption or mutations of TP53 occur in up to 10% of treatment-naïve WM patients [28]. However, the precise impact of TP53 alterations on treatment outcomes in the primary treatment setting of WM is not currently known.

Additional questions submitted to consensus panel from the audience at IWWM-11

How should we manage asymptomatic treatment naïve patients in WM, including patients with high-risk disease?

W&W with serial evaluation of IgM levels, complete blood count, and patient symptoms remains the gold standard for asymptomatic patients with WM. Monitoring intervals should be individualized according to the dynamic of the disease in a given patient. The risk of progression can be estimated by a patient risk calculator (Patient AWM Risk Calculator; available at www.awmrisk.com) dividing patients into high, intermediate, and low-risk groups with median estimated time to therapy of 1.8, 4.8, and 9.2 years, respectively [29]. Follow-up frequency can be adopted according to the risk of progression. Low-risk patients can be seen every 6 to 12 months, intermediate-risk every 4 to 6 months, and high-risk every 2 to 3 months. A high-risk category does not constitute a need to initiate treatment.

Should we use covalent BTK inhibitors for WM-related amyloidosis?

Data on the efficacy and safety of cBTKi in WM-related AL amyloidosis are scarce and limited to case series; these have demonstrated high toxicity rates and less efficacy [30,31]. In addition, cBTKi should not be used in patients with cardiac amyloidosis, given the potential increased risk of arrhythmia. Thus, cBTKI are not the preferred treatment option for WM patients with AL amyloidosis (see CP6 report inthis edition of Seminars in Hematology).

What is our treatment approach for cryoglobulins, cold agglutinins, amyloidosis, BNS, peripheral neuropathy and HV syndrome in WM?

Treatment approaches for WM-associated cryoglobulins, cold agglutinins, AL amyloidosis, Bing-Neel syndrome (BNS), peripheral neuropathy (PN), and hyperviscosity syndrome (HV) follow the common principle of reducing tumor burden and production of abnormal proteins as rapidly and deeply as possible. In BNS, ibrutinib can be highly active and produce durable responses [32]. In case of ibrutinib failure, CNS-penetrating compounds such as methotrexate, cytarabine, fludarabine and bendamustine show varying levels of activity [33]. Neurotoxic agents such as bortezomib, ixazomib, and vincristine should be avoided in WM-associated PN. Rituximab with or without chemotherapy could be an option according to the severity of anti-MAG neuropathy [34]. For symptomatic HV, plasmapheresis followed by systemic treatment is the recommended approach. WM patients with AL amyloidosis were shown to benefit from treatments including PIs or CIT such as Benda-R [35]. Cryoglobulins and cold agglutinins can be efficiently treated by CIT, PI-based treatment, or cBTKi [35].

Should the risk of therapy-associated secondary malignancies be factored in for selecting first-line treatment?

Several independent retrospective analyses have shown an increased risk for secondary malignancies (SM) in WM patients compared to the general population [36]. However, data quantifying the risk of therapy-induced SM in WM are still mounting. The risk of inducing SM by chemotherapy, especially treatment-related myeloid neoplasms and myelodysplasia, should be discussed with the patient. In addition, screening for SM should be part of the regular follow-up program in patients with WM (see also CP2 recommendations in this edition of Seminars in Hematology).

Should the "tempo of symptom progression" be factored in for decision-making on initiating treatment?

The dynamic of symptom progression is an important factor in tailoring follow-up intervals in the asymptomatic, W&W patients and the decision to initiate treatment. However, there is no formal assessment available categorizing the tempo of symptom progression. Thus, disease dynamics must be judged on a case-by-case basis. The decision to start, and choice of treatment should be based on individual patient characteristics, genomics, comorbidities, and disease dynamics.

When is plasmapheresis appropriate and how long should a patient be plasmapheresed?

Plasmapheresis is indicated in symptomatic hyperviscosity (HV) and should be considered in patients without symptomatic HV when a CD20-directed antibody containing regimen is planned for patients with serum IgM levels above 40 g/L to prevent an IgM flare [21,22]. Alternatively, to reduce the risk of IgM flare, the chemotherapy component may be administered without rituximab for 1 to 3 cycles until the IgM level is <40 g/L. Two to 3 plasmapheresis sessions, each performed ideally every other day can lower the IgM level by 30% to 60% and should continue until symptoms associated with HV are relieved. Plasmapheresis should always be followed by systemic "definitive" treatment as the effect of plasmapheresis on lowering IgM is transient. Avoidance of red

cell transfusions is recommended in this setting, and if necessary, this should be timed to follow plasmapheresis.

How should we "bridge" WM patients coming off BTK inhibitors?

An IgM rebound is a common occurrence following the discontinuation or withholding of a cBTKi [37]. Whenever possible, treatment with cBTKi should be continued until subsequent treatment is initiated and shows activity to avoid serum IgM rebound. Caution with even temporary combinations should be exercised, particularly with venetoclax, due to the unexpected risk of ventricular arrhythmias reported in combination with ibrutinib [38]. Oral prednisone might help mitigate the risk of withdrawal symptoms characterized by fever, body aches, night sweats, arthralgia, headache, and fatigue, which have been reported in approximately 20% of patients who stop cBTKi therapy [13]. The choice of subsequent therapy should be directed by the patient's symptoms, comorbidities, genomic profile, and previous therapy history (see also CP2 report in this edition of Seminars in Hematology). CIT, proteasome inhibitor-based therapy, venetoclax, noncovalent BTKi such as pirtobrutnib or clinical trials are reasonable options after progression on a cBTKi [12,39]. A switchover from ibrutinib or acalabrutinib to zanubrutinib without any bridge may also be considered for patients with intolerance to ibrutinib [40].

How should prognostic factors be incorporated into treatment recommendations?

The International Prognostic Scoring System for WM (IPSSWM) or revised IPSSWM (rIPSSWM) allows robust categorization of patients into different risk groups, separating patients with good prognosis from those with poor long-term outcomes. However, it is not recommended to stratify treatment according to the IPSSWM or rIPPSWM in routine clinical practice, as prospective data identifying the superiority of specific treatments in distinct risk groups is lacking. CXCR4 mutations and the lack of MYD88 mutations impact cBTKi efficacy and thus should be incorporated as predictive factors into treatment decisions (see above). TP53 mutations are associated with inferior outcomes, but prospective data analyzing their impact on outcome after CIT or cBTKi are lacking in the primary therapy of WM (see CP2 recommendations in this edition of Seminars of Hematology as well) [28].

Discussion

Since the publication of the last consensus treatment recommendations from the 10th IWWM, the dramatic impact of the COVID-19 pandemic reminds us of the vulnerability of WM patients caused by treatment-associated or disease-inherent immunosuppression. The quote of Jan Gosta Waldenström to "*let well alone*" remains central to our decisions to initiate treatment or to apply dose intense or continuous regimens. W&W remains the gold standard in 2023 in asymptomatic patients despite the emergence of well-tolerated chemotherapy-free approaches.

The class of cBTKIs has gained relevance in the first-line treatment of WM, being now approved in many parts of the world as single agents or in combination with rituximab. We now have prospective, long-term data demonstrating that the second-generation cBTK-inhibitors zanubrutinib and acalabrutinib are highly effective in WM, with zanubrutinib showing less cardiac toxicity as compared to ibrutinib. However, the sequencing of cBTKi remains unclear, with scant data on the efficacy of subsequent CIT in patients who progress after first-line cBTKi.

CIT remains a central first-line treatment approach, and a common regimen used in the frontline setting in Europe, North America, Asia-Pacific and Latin America [2,41,42]. CIT has the advantage over cBTKi of being a less costly fixed-duration treatment with the capacity to induce deep and durable remissions and comparable PFS to cBTKIs in the case of Benda-R.[2] Prospective, randomized clinical trials comparing CIT with fixed-duration chemotherapy-free treatments are needed though to clarify the role of CIT in an era with rapidly emerging novel treatment concepts.

Although there is consensus that the mutational status of *MYD88* and *CXCR4* should be determined in all WM patients, technical challenges in identifying *CXCR4* mutations and the relative impact of different *CXCR4* mutations hinder the introduction of widespread, reliable testing in clinical practice and a genotype-driven therapeutic approach in WM. It is also accepted that other molecular alterations in WM, such as TP53, will likely impact treatment outcome, but little prospective data currently exists on the impact of these on treatment response and duration in the primary therapy of WM.

We appreciate the extraordinary progress made in the initial clinical management of WM since our last consensus statement. Expanded first-line treatment options are ensuring more patients achieve longer first remissions. Nonetheless, major challenges lie ahead for our ambitious goal to establish well-tolerated, molecularly and clinically guided personalised fixed-duration chemotherapy-free approaches to ensure long-lasting quality remissions. The greatest challenge will be to ensure such approaches are accessible and affordable for all patients globally. Finally, we advocate for the thoughtful design of clinical trials in the frontline setting and strongly encourage patient participation.

Authors' Contributions

CB, JT, JJC, RGS, JSM, and SPT prepared, reviewed and submitted key questions for Consensus Panel 1 (CP1). Questions were reviewed in an open general assembly by attendants of IWWM-11, and additional questions for CP1 deliberations were formulated and submitted. CB wrote the first draft of CP1 responses, and draft was reviewed and modified by CB, JT, JJC, RGS, JSM, and SPT. Final draft was submitted to CP1 general panel for review and commentary. CP1 general panel was composed of individuals with experience in the care of WM patients who attended IWWM-11 and volunteered to be on CP1 panel.

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