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Issue Introduction

Highlights of the 11th International Workshop on Waldenstrom's Macroglobulinemia: What we learned, and how it will impact scientific discovery and patient care

The 11th International Workshop on Waldenstrom's Macroglobulinemia (IWWM-11) was held in Madrid, Spain from October 27 to 30, 2023. Drs Ramon Garcia Sanz (Spain), Jesus San Miguel (Spain) and Steven P. Treon (USA) served as workshop chairs, and Christopher J. Patterson (USA) as the meeting secretariat (Fig. 1). IWWM-11 represented the largest workshop devoted to Waldenstrom's Macroglobulinemia with over 650 attendees. There were several important revelations at this meeting including novel genomic findings on WM predisposition, the role of *MYD88* as the primary oncogenetic event in WM, the importance of *MYD88* and *CXCR4* in the clinical management of patients, limitations and new approaches for *MYD88* and *CXCR4* mutations testing, and the importance of TP53 mutations in relapsed WM. In previous work, McMaster et al [1] identified loci at 6p25.3 and 14q32.13 as independent SNPs for WM/lymphoplasmacytic lymphoma (LPL) risk. In a larger study, McMaster et al re-affirmed these previously identified predisposition SNPs, as well as other potentially new loci which await validation. The identification of such loci may herald efforts to identify patents at risk for WM/LPL, particularly in clusters of families with familial WM/LPL disease. Paiva et al described groundbreaking work alluding to the presence of mutated MYD88 ($MYD88^{Mut}$) in phenotypically normal B-cells suggesting that $MYD88^{Mut}$ by itself is not sufficient to drive oncogenesis. Consistent with this, transgenic models presented by several investigators at IWWM-11 suggested that $MYD88^{Mut}$ was insufficient to drive oncogenesis, and that other hits such as mutations in CXCR4 ($CXCR4^{Mut}$), loss of chromosome 6q' and BCL2 overexpression were required. Given the latency for transgenic modeling, the impact of these and other secondary hits remain to be discerned. The importance of a receptive microenvironment was further suggested by Jose A. Martinez-Climent et al in their work with $MYD88^{Mut}$ expressing B-cell transgenic mice. The importance of the microenvironment for supporting clonal expansion of WM was alluded by the work of Sperling et al, who focused on clonal hematopoeisis (CH) as a driver of WM progression. Approximately 14% of IgM MGUS and asymptomatic WM patients carried mutations associated with CH such as *DNMT3A, TET2, and ASXL1*. The rate of progression was significantly higher in IgM MGUS and asymptomatic WM patients who exhibited CH. The mechanistic insights remain to be clarified for CH's role as a contributor to progression in WM, but as Sperling et al suggest CH may be valuable in the risk stratification of IgM MGUS and asymptomatic WM.

An important highlight at IWWM-11 was the first reporting of the "300" project by Zachary Hunter et al. Using multiomic sequencing that included whole genome, transcriptome, methylome and ATAC sequencing for 300 treatment-naive patients, they showed that WM was likely composed of 4 distinct clusters entailing early and late B-cell, as well as early and late plasma cell like disease subtypes. The identified subtypes showed distinct clinical, genomic, transcriptomic, and epigenomic characteristics which may lend to the development of targeted treatments. Importantly, these studies permitted pseudotime analysis that compared early vs late WM disease and provided a biological model for WM disease evolution. The transcriptional alterations accompanying WM disease evolution may well offer targets to prevent disease progression. Cristina Jimenez et al presented seminal findings using single cell analysis to detail linear and branching clonal evolution of disease in WM patients undergoing treatment. In these studies, $MYD88^{Mut}$ was the most clonal alteration at diagnosis supporting its role as a driver event. Secondary oncogenic events following $MYD88^{Mut}$ included $CXCR4^{Mut}$, deletions of chromosome 6q, *TRAF3*, and 17p, amplification of chromosome 3q, and acquired uniparenteral disomy of 3p (the locus for $MYD88^{Mut}$). The role of these secondary alterations to treatment resistance was also alluded by their work. Chohan et al presented data integrating microRNA and gene expression findings that differentiated WM from IgM monoclonal gammopathy of unknown significance. Their study identified several differentially expressed microRNAs with a known oncogenic role including miR-4532, miR-20, and miR-1260.

Illuminating single cell RNA findings were also presented by Bagratuni et al who showed that MYD88 wild-type ($MYD88^{WT}$) patients had a distinct transcriptional profile compared to those carrying $MYD88^{Mut}$, which was most distinct among switched memory B-cells. Gene expression among $MYD88^{Mut}$ clones was notable for expression of the SRC family member *HCK*, as well as *CCND2, MAN1A1, FBXW7* and *PLD4*. HCK has emerged as a novel treatment target for $MYD88^{Mut}$ driven WM, given its transcriptional upregulation by $MYD88^{Mut}$ and its role as a driver of BTK/NFKB, ERK and SYK pro-survival signaling. At IWWM-11, Guang Yang et al reported on the development of an HCK inhibitor (KIN-8194) that showed preclinical activity in $MYD88^{Mut}$ lymphoma models, including WM and could overcome ibrutinib resistance in mutated BTK^{Cys481} expressing cells. Novel treatment approaches including use of IRAK1, IRAK4 and CXCR4 inhibitors to augment BTK-inhibitor activity were also presented.

A key affirmation at IWWM-11 was the importance of *MYD88* and *CXCR4* mutation status in discerning disease presentation and treatment outcome. Updated findings of the ASPEN trial that randomized $MYD88^{Mut}$ WM patients to either ibrutinib or zanubrutinib (cohort 1), and to single agent $MYD88^{WT}$ WM patients (cohort

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Fig. 1. Organizers of the 11th International Workshop on Waldenstrom's Macroglobulinemia. Drs Ramon Garcia Sanz of Spain (left), Jesus San Miguel of Spain (second from the right) and Steven P. Treon of the USA (right) served as co-chairs of the workshop, and Christopher J. Patterson of the USA (second from the left) as the workshop secretariat.

2) were presented by Dimopoulos et al. In cohort 1, *CXCR4*^{Mut} WM patients showed better outcomes with zanubrutinib with shorter time to major response attainment; deeper responses; and longer progression free survival. In addition, major responses were observed with single agent zanubrutinib in 65% of *MYD88*^{WT} WM patients, a remarkable finding given that no major response activity was observed in the pivotal trial in this patient population with single agent ibrutinib [2]. The mechanism(s) surrounding the improved performance of zanubrutinib in *CXCR4*^{Mut} or *MYD88*^{WT} WM patients remain to be clarified but may be related to differences in "off" target effects and/or pharmacokinetics. In addition to differences by *MYD88* and *CXCR4* mutation status, updated safety data for ASPEN study presented at IWWM-11 affirmed a significantly lower incidence of atrial fibrillation and hypertension with zanubrutinib. Conversely, a significantly lower incidence of neutropenia including Grade 3 or higher neutropenia was observed with ibrutinib, though no differences in rates of infection were observed between the two arms of cohort 1.

An important revelation at IWWM-11 came about from the corollary biomarker studies presented by Tam et al as part of the ASPEN study. Previous studies in treatment-naïve WM patients suggested that *TP53* alterations including mutations, deletions and copy-neutral loss of heterozygosity were uncommon with an incidence of 5% to 7% [3,4]. Akin to previous studies, the incidence of *TP53* alterations was low in treatment-naïve WM patients treated on ASPEN in *MYD88*^{Mut} patients in cohort 1 (3.2%), and *MYD88*^{WT} patients enrolled in cohort 2 (5%). However, in previously treated patients the incidence of *TP53* alterations was much higher at 22.1% and 15% in cohorts 1 and 2, respectively. Notably, among previously treated patients, 85% and 23% had received alkylator agents and/or nucleoside analogues, respectively. Previous studies suggested that WM patients with *TP53* alterations had more aggressive disease and/or shorter survival but responded to ibrutinib [3,4]. In the update of the ASPEN study presented at IWWM-11, patients who received ibrutinib showed fewer major and very good partial response (VGPR) responses, and a lower event-free rate at 42 months if they carried *TP53* alterations (57.9% vs 72.1% for *TP53* altered and wild-type patients, respectively; $P = .027$). Conversely, those on zanubrutinib had similar major and very good partial response (VGPR) responses. The event-free rate was also impacted in zanubrutinib treated patients with *TP53* alterations (62 vs 84.6 months for *TP53* altered and wild-type patients, respectively; $P = .120$) though such differences were not significant possibly because of the small study cohort. While further study of *TP53* alterations in WM is warranted, these findings may have important practice implications. As discussed in the Consensus Panel (CP) 3 recommendations that appear in this edition of *Seminars in Hematology*, *TP53* mutation testing including examination for deletions of 17p is now recommended as part of the molecular workup of WM patients, particularly in those patients who relapse and require therapy. In relapsing WM patients requiring therapy, the use of zanubrutinib may offer an advantage over ibrutinib based on the ASPEN biomarker analysis, though the findings are based on small study numbers and should be interpreted with some caution. The findings however are provocative given the important question on how to sequence BTK-inhibitors relative to alkylator therapy. While many institutional or national guidelines prioritize alkylator regimens such as dexamethasone, rituximab and cyclophosphamide (DRC) or bendamustine and rituximab (Benda-R) before BTK-inhibitors, the relatively high incidence of acquired *TP53* alterations that may follow alkylators may be a reason to re-think such a strategy. Indeed, as reported by Abeykoon et al at IWWM-11 in a large, multinational, and retrospective study, progression-free (PFS) and overall survival (OS) was not significantly different for *MYD88*^{Mut} WM patients who received either Benda-R or ibrutinib with a 4.2 year median study follow-up. As such, a BTK-inhibitor first strategy may offer a more optimal approach to avoiding acquired *TP53* alterations while providing effective frontline therapy. Prospective, randomized studies that compare clinical and genomic outcomes including emergence of acquired *TP53* alterations for alkylator and BTK-inhibitors, and clarify their clinical importance are needed.

An effort to improve outcome of patients and provide definitive duration therapy was reported by Castillo et al who investigated the combination of ibrutinib and venetoclax (IVEN). As single agents, both ibrutinib and venetoclax are highly active and well

Fig. 2. Recipients of the Robert A. Kyle Award at the 11th International Workshop on Waldenstrom's Macroglobulinemia. The Robert A. Kyle Award is given to honor outstanding contributions to scientific and medical advancements in WM. The recipients selected by previous award recipients were Drs Ramon Garcia Sanz (Spain), Jorge J. Castillo (USA), and Stephen M. Ansell (USA) who are pictured left, center, and right, respectively.

tolerated in WM patients. Castillo et al administered the combination utilizing dose and schedule for the combination of ibrutinib and venetoclax previously used in chronic lymphocytic leukemia and mantle cell lymphoma patients. While the combination produced high rates of major responses in 93% of treatment-naïve patients, including a very good partial response (VGPR) ate of 40%, study treatment was terminated due to an unexpectedly high rate of ventricular arrythmias (9%), including 2 grade 5 events. While the etiology for these events is not clear, particularly since the dose and schedule used was previously investigated and deemed safe in patients with chronic lymphocytic leukemia and mantle cell lymphoma, they do point to fundamental differences in outcomes that may result for WM patients. Previous examples include the rituximab related IgM flare; a higher than expected incidence of bortezomib related treatment neuropathy; an increased incidence of disease transformation related to fludarabine; late onset idiopathic thrombocytopenia with alemtuzumab; moderate to severe anemia with lenalidomide; and a high incidence of autoimmune pneumonitis with the MTOR-inhibitor RAD001 in treatment-naïve WM patients. These findings together with those for IVEN reported by Castillo et al reinforce the necessity for devoted WM clinical studies, and the avoidance of "basket trials" that may draw safety and efficacy conclusions from a limited number of WM patients. While the safety findings from IVEN study were a setback for efforts to develop a fixed duration approach for BTK-inhibitor use, they nonetheless showed that high very good partial response (VGPR) rates could be obtained with combinations of BTK- and BCL-inhibitors. A trial examining the combination of the noncovalent BTK-inhibitor pirtobrutinib and venetoclax (PV) is being initiated in previously treated WM patients (NCT05734495) given safety findings to date with pirtobrutinib suggesting very low incidence of arrythmias. Importantly, as reported by Palomba et al at IWWM-11, pirtobrutinib was active in WM patients including those previously exposed to and/or resistant to a covalent BTK-inhibitor.

Rummel et al presented an important update of the Study group indolent Lymphomas (StiL) study at IWWM-11 that investigated the role of maintenance rituximab following major response attainment in patients receiving induction with Benda-R. While a retrospective study in the pre-Benda-R era suggested benefit in terms of PFS and OS in WM patients receiving maintenance rituximab, prospective data was lacking until the Study group indolent Lymphomas (StiL) study [5]. In the Study group indolent Lymphomas (StiL) study, patients received 6 cycles of Benda-R, and had to be major responders (partial response or better) to be randomized to observation or maintenance rituximab (1 infusion every 2 months for 2 years). While the findings showed no benefit of maintenance rituximab, an unplanned analysis showed that patients over 65 years of age, or with a high WM International Prognostic Scoring System score had significantly longer PFS on maintenance rituximab. The inclusion of only major responders in the Study group indolent Lymphomas (StiL) study also contrasted with the earlier retrospective study wherein patients who achieved a minor response or better were included. As such, the role of maintenance in those who do not attain a major response remains to be further clarified.

The use of proteosome inhibitors (PI) in WM remains an important mainstay of therapy, particularly in those with WM related amyloidosis. Treatment related neuropathy and cardiomyopathy (with carfilzomib) have relegated PI to third tier status with the adoption of Benda-R and BTK-inhibitors. At IWWM-11, Amaador et al presented the final results of the HOVON 124/ECWM-R study in relapsed WM patients. In this study, patients underwent induction therapy with ixazomib, dexamethasone and rituximab (IDR) followed by 2 years of maintenance rituximab. The overall response rate was 85% with 24% of patients achieving a very good partial response (VGPR). Improvements in categorical response attainment was observed in 22% of patients following maintenance rituximab. Significant improvements in hemoglobin and IgM levels accompanied treatment. With a median study follow-up of 45.6 months, the median PFS was 23.6 months and median OS was not reached. Importantly, by using a peripheral blood digital droplet polymerase chain reaction (ddPCR) to detect $MYD88^{Mut}$, Amaador et al showed that patients who became negative after treatment showed significantly longer PFS. Yi et al also presented data at IWWM-11 on a novel PI combination using zanubrutinib, ixazomib

Fig. 3. Recipients of the Jan Gosta Waldenstrom Award at the 11th International Workshop on Waldenstrom's Macroglobulinemia. The Jan Gosta Waldenstrom Award honors a lifetime of contributions and achievements for improving the lives of patients with WM. Drs Christian Buske of Germany (A), Irene M. Ghobrial of the USA (B), and Jesus San Miguel of Spain (C) are pictured with their award. Drs Ken Anderson (USA), Eva Kimby (Sweden), and Veronique Leblond (France) are depicted who presided over the award ceremony.

Fig. 4. Recipients of the Peter S. Bing Humanitarian Award at the 11th International Workshop on Waldenstrom's Macroglobulinemia. The Peter S. Bing Humanitarian Award honors individuals for extraordinary humanitarian service and activism on behalf of patients with WM. Drs Shirley D'Sa (UK), Mary McMaster (USA), and Judith Trotman (Australia) are pictured with their awards. Previous award recipients of the Peter S. Bing Humanitarian Award Christopher J. Patterson, Karen Lee Sobel, and Ranjana Advani MD presented the awards at IWWM-11.

and dexamethasone in symptomatic, treatment-naïve WM patients. Treatment was well tolerated, and all patients responded, with 95% and 42% of patients attaining a major and very good partial response (VGPR) response, respectively.

The emerging role of ddPCR as a more reliable and efficient means to detect *MYD88*^{Mut} and nonsense *CXCR4* variants was raised in several studies presented at IWWM-11. In previous studies, CD19-selection of bone marrow (BM) and peripheral blood mononuclear cells was utilized to increase allele-specific PCR sensitivity. While CD19-selection is feasible in academic laboratories, its utilization in most clinical laboratories is prohibitive. Moreover, the use of next generation sequencing which is commonly used in the clinical setting to detect *MYD88* and *CXCR4* mutations is associated with high rates of false negative results, particularly among patients with low volume bone marrow (BM) disease burden [6,7]. Ferrante et al as part of the BIOWM Trial of the Fondazione Italiana Linfomi showed that ddPCR could be used in cell-free DNA samples collected from the plasma to detect *MYD88*^{L265P} with high concordance to findings with parallel CD19-selected bone marrow (BM) samples. Fernandez de Larrea et al reported on the feasibility and higher sensitivity of ddPCR testing in unsorted bone marrow (BM) and cell-free DNA samples against allele-specific PCR for *MYD88*^{L265P} and nonsense *CXCR4*^{S338X} variants. Particularly revealing was the successively increasing *MYD88*^{L265P} burden in collected samples from IgM MGUS, Asymptomatic WM, and Symptomatic WM patients using ddPCR. The mutation burden of *MYD88*^{L265P} and nonsense *CXCR4*^{S338X} variants was shown by Fernandez de Larrea et al to associate with disease progression in IgM MGUS and asymptomatic WM patients.

A highlight of the meeting were the spirited debates moderated by Jesus San Miguel (Spain) and Eva Kimby (Sweden) covering timely and controversial topics on (1) observation vs initiation of treatment in asymptomatic, high risk smoldering WM; (2) use of Benda-R or BTK-inhibitors as the standard for frontline treatment; (3) choice of covalent BTK-inhibitor; (4) management of the ibrutinib intolerant patient; and (5) what the endpoint of treatment should be in WM. The meeting concluded with CP discussions moderated by Meletios Dimopoulos (Greece) and Steve Treon (USA) that addressed the key questions in WM management. A heavily attended session that included active audience participation formulated the key questions for 7 CPs that updated frontline (CP1) and relapsed/refractory (CP2) treatment approaches for WM; use of molecular diagnostics for WM (CP3); diagnostic and response criteria for WM (CP4); COVID prophylaxis and management of the COVID infected WM patient (CP5); management of WM related amyloidosis (CP6); and priorities for novel clinical trials in WM (CP7). A globally diverse panel of experts was empaneled for each CP to deliberate the key management questions and provide insightful recommendations. Their findings represent the most comprehensive changes made since IWWM-2 and are reported in this edition of *Seminars in Hematology*.

Honored at IWWM-11 were 10 Young Investigators that included Drs Vaishali Bhardwaj (USA); Karan Lal Chohan (USA); Martina Ferrante (Italy); Alexandros Gkiokas (Greece); Joshua Gustine (USA); Melanie Khamyath (France); Jahanzaib Khwaja (UK); Quentin Lemasson (France); Patrizia Mondello (USA); and David Moreno (Spain). Their awards were sponsored by the International Waldenstrom's Macroglobulinemia Foundation, and each YIA was competitively chosen for their submitted work to IWWM-11. Drs Stephen Ansell (USA), Jorge Castillo (USA), and Ramon Garcia Sanz (Spain) received the Robert A. Kyle Award to honor outstanding contributions to scientific and medical advancements in WM (Fig. 2). To honor a lifetime of contributions and achievements for improving the lives of patients with WM, Drs Christian Buske (Germany), Irene Ghobrial (USA), and Jesus San Miguel received the Jan Gosta Waldenstrom Award (Fig. 3). For extraordinary humanitarian service and activism on behalf of patients with WM, Drs Shirley D'Sa (UK), Mary McMaster (USA), and Judith Trotman (Australia) received the Peter S. Bing Humanitarian Award (Fig. 4). Finally, it was announced that IWWM-12 will be held in Israel, and will be led by Moshe Gatt (Hadassah University Medical Center) and Merav Leiba (Assuta Ashdod University Hospital). The IWWM-11 program and abstracts cited in this report can be found at http://www.waldenstromsworkshop.org/.

Declaration of Competing Interest

RGS declares honoraria from Amgen, Takeda, Janssen, Incyte, Astellas, BeiGene, AstraZeneca, Pfizer; and research funding from Novartis, Gilead, Astellas, Janssen; and participation in advisory boards for Amgen, Pharmacyclics, Takeda. JSM declares participation on advisory boards and consulting services, on behalf of my Institution, for Abbvie, Amgen, BMS, Celgene, GSK, Haemalogix, Janssen-Cilag, Karyopharm, MSD, Novartis, Pfizer, Takeda, Regeneron, Roche, Sanofi, and SecuraBio. SPT received research funding, and/or consulting fees from Abbvie/Pharmacyclics Inc, Janssen Oncology Inc, Beigene Inc, Eli Lilly Pharmaceuticals, and Bristol Myers Squibb. CJP has no disclosures.

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Supplementary material

Supplementary material associated with this article can be found, in the online version, at doi:https://doi.org/10.1053/j.seminhematol.2023.05.001.

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