

## Report From the Sixth International Workshop on Waldenström's Macroglobulinemia

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When the First International Workshop on Waldenström's Macroglobulinemia (IWWM1) took place in Washington DC a decade ago, it was clear that WM was an orphan disease. The 19 participants who met during that fateful meeting had an easier time agreeing what was unknown for WM despite having first been described by Jan Gosta Waldenström some 56 years earlier.<sup>1</sup> Importantly, the participants of IWWM1 established priorities for the recognition and advancement of WM. These included establishing consensus diagnostic and treatment criteria; WM-specific treatment recommendations; and formulation of response criteria. By the time IWWM2 concluded in Athens, Greece two years later, consensus criteria for the diagnosis and management for WM would emerge and were subsequently published.<sup>2-5</sup> Eight years later, nearly one hundred investigators would come together to present their research at IWWM6, held in Venice, Italy from October 6-10, 2010 (Figure 1). This edition of *Clinical Lymphoma, Myeloma & Leukemia* is dedicated in part to the advancements in WM that emerged from this workshop.

So what have we learned in the past 10 years, and what still needs to be learned? Despite a functional clinicopathologic definition for WM, which was reviewed by Harris and is now part of World Health Organization (WHO) criteria, no underlying genetic defect specific to WM has been identified.<sup>6</sup> This is an important consideration because many pathologic entities have overlapping morphologic, immunophenotypic, and clinical characteristics but potentially different clinical management and outcome. The presence of t(11;14) may aid in the clarification of IgM myeloma from

WM as was pointed out by Mikhael, though delineation of WM from marginal zone lymphoma (MZL) remains problematic.<sup>7</sup> Arcaini reported on a large series of splenic MZL (SMZL) and WM patients, and contrasted their clinical, histologic, and molecular features.<sup>8</sup> Their studies showed more prevalent hepatitis C serology, paratrabeular versus intertrabeular bone marrow histology, expression of CD23, preferred use of IGHV1, IGHV4, IGHV1-2, and IGHV4-34 heavy chain repertoire, and a higher incidence of unmutated immunoglobulin rearrangements in SMZL versus WM. The strong expression of CD138 on WM lymphoplasmacytic cells was also reported to delineate WM from SMZL by Kyrtonis et al<sup>9</sup> and Morice.<sup>10</sup>

Risk factors for development of WM were extensively discussed at IWWM6. IgM monoclonal gammopathy remains a risk factor, as pointed by Kyle,<sup>11</sup> in whose studies progression to WM or another B-cell disorder occurred in 24% of patients with IgM monoclonal gammopathy of unknown significance (MGUS) with 15 years of follow-up, or 1.5%/year of follow-up. Similar results were reported by Morra in asymptomatic IgM MGUS patients, with an estimated risk of progression to WM or related B-cell disorder of 16 times higher than general population.<sup>12</sup> A strong familial link for WM was reported by several investigators. In a large Swedish-based registry study, Landgren reported that first-degree relatives of WM/LPL patients had a 20-, 3-, 3.4-, and 5.0-fold increased risk for developing WM/LPL, other non-Hodgkin lymphoma, chronic lymphocytic leukemia, and MGUS, respectively.<sup>13</sup> Importantly, these studies as well as those by McMaster et al in families with multiple cases of WM and mixed WM/B-cell disorders, showed a significantly higher incidence of autoimmune disorders and infections suggesting shared susceptibility for these events with WM predisposition.<sup>14</sup> Hunter et al reported the results of comprehensive SNP studies that showed significantly higher copy number loss of genes effecting glutathione S-transferases in patients with a familial WM history, and their kin.<sup>15</sup>

Braggio and colleagues reported results of copy number abnormalities in WM cells using array-based comparative genomic hybridization which showed more prevalent abnormalities in regulators of the nuclear factor kB (NF-kB) pathway (TNFAIP3, REL,

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**Figure 1** Dr. Robert Kyle addresses panel members during a discussion session of the 6th International Workshop on WM, Venice, Italy



TRAF3, and MALT1) in WM, non-IgM lymphoplasmacytic lymphoma and MALT lymphoma patients.<sup>16</sup> Genome-wide SNP array analysis of bone marrow lymphoplasmacytic cells were also reported by Poulain et al that showed copy number loss involving a minimized area of 6q22-25 as the most common abnormality in WM, with deletion of TNFAIP3 in all with this deletion, and gain of 4q as the second most common abnormality.<sup>17</sup> Zhou and colleagues reported that the Ets family member Spi-B was overexpressed in primary WM cells, and showed in lentiviral transfection models that overexpression of Spi-B led to suppression of the transcription factors BLIMP-1, XBP-1 spliced and IRF4, which mediate plasma cell differentiation.<sup>18</sup>

Considerable progress on the effect of the microenvironment on WM cell growth and survival, as well as immune function in WM patients was reported at IWWM6. Ansell and colleagues elaborated on their studies showing RANTES induced IL-6 support of WM cell growth, survival, and IgM release and reported that inhibition of the JAK-STAT pathway modulated both RANTES and IL-6 secretion.<sup>19</sup> Several investigators reported T-cell abnormalities in WM patients, including that TH1, TH2, and TH17 helper T-cell subsets were deficient in WM patients.<sup>20-23</sup> Differences in T-cell function studies (for Treg and TH17 cells) between myeloma and WM patients were presented suggesting succinct immunodysregulatory mechanisms for these plasma cell disorders. Rawstron et al discussed progressive humoral immune suppression that occurs in WM, though characterized this as a late event occurring 2-3 years after normal peripheral B-cell depletion in individuals with IgM MGUS.<sup>23</sup>

Significant advances in the development of novel treatments for WM were also reported at IWWM6. Owen and colleagues reported the outcome of a joint UK-French phase III study that included 337 WM patients and compared the primary therapy of WM with chlorambucil versus fludarabine.<sup>24</sup> Their study showed a higher overall response rate, improved progression-free survival and time to treatment failure for patients who received fludarabine. Rummel et al reported the outcome of a large randomized phase III study that compared bendamustine and rituximab (Benda-R) versus CHOP-R in patients with indolent NHL and included 40

patients with WM.<sup>25</sup> Improved PFS (80% vs. 15% at 4 years) in favor of patients who received Benda-R was observed in this study. Studies examining the primary therapy of WM with bortezomib-based therapy were also updated at the IWWM6. Treon and colleagues reported an overall response rate of 95% and an updated PFS of > 56 months using a twice-a-week bortezomib schedule with dexamethasone and rituximab.<sup>26</sup> An overall response rate of 88% and PFS of over 12 months was reported by Ghobrial using a once-a-week schedule for bortezomib with rituximab, and no grade 3 or 4 neuropathy.<sup>27</sup> High rates of responses, including attainment of complete remissions, and prolonged PFS were reported with the combination of nucleoside analogues and rituximab in studies by Tedeschi et al<sup>28</sup> (using fludarabine, cyclophosphamide, and rituximab) and by Laszlo et al<sup>29</sup> (using subcutaneous cladribine and rituximab) in untreated and previously treated WM patients. Two episodes of myelodysplasia were reported in the Tedeschi series which occurred in previous alkylator recipients, though no transformation events were observed in either study.<sup>28</sup> These experiences were in contrast to those of Leleu et al who reported increased risk of disease transformation and myelodysplasia in nucleoside analogue-treated WM patients.<sup>30</sup> In addition, clinical studies examining the MTOR inhibitor everolimus as primary and salvage therapy, and panobinostat as salvage therapy were reported with encouraging results.<sup>26,31</sup> Ioakimidis et al reported on a study that examined the outcome of 245 WM patients who were observed or maintained with rituximab, and observed improvements in categorical response and PFS in those patients who received maintenance rituximab therapy.<sup>32</sup> The importance of achieving a better categorical response was the subject of a Dana Farber Cancer Institute study that showed improved PFS among patients with rituximab-naive WM who received treatment with a rituximab-containing regimen and achieved at least a very good partial response.<sup>33</sup> Central to these findings was the fact that polymorphisms in the FcγRIIIA (CD16) receptor predicted depth of response in these patients. Importantly, the gains made in the therapy of WM were reflected in a study by Kristinsson, who examined the outcome of 1555 Swedish WM patients who were diagnosed from 1980-2005 and showed significant improvements in survival in recent years.<sup>34</sup>

Several novel agents in preclinical development were also presented. Yang et al presented data on the novel CD20-directed antibody GA101, which showed improved ADCC-directed activity, as well as induction of direct apoptosis when compared to rituximab in primary WM cells.<sup>35</sup> Importantly, their studies demonstrated that GA101 overcame limitations imposed by polymorphisms in the FcγRIIIA (CD16) receptor. Mitsiades et al reported encouraging preclinical results in WM studies with MLN4924, a selective ubiquitin inhibitor that acts upstream of proteasome inhibitors such as bortezomib and carfilzomib.<sup>36</sup> Dual targeting of the PI3K/Akt and MTOR pathways by NVP-BE235 was reported by Sacco et al to result in selective WM cell killing, as well as inhibition of bone marrow stromal cell adhesion.<sup>37</sup>

The diagnosis and management of various morbidities associated with WM were discussed at IWWM6. Sheehy and colleagues presented data on 900 consecutive WM patients, with a finding of disease-related neuropathy in 22% of patients.<sup>38</sup> Myelin-associated glycoprotein (MAG) is a frequent target of IgM in WM patients

with neuropathy as pointed out by Nobile-Orazio, though the target in most patients remains to be delineated.<sup>39</sup> The use of rituximab was shown to be of benefit in patients with IgM-related peripheral neuropathy, though higher dosed rituximab or combination therapy with rituximab may produce more optimal results.<sup>38,40,41</sup> The diagnostic and treatment challenges facing patients with CNS involvement with WM (ie, Bing Neel Syndrome) was discussed by Hochberg, whose studies suggest two subtypes: type A, mediated by WM lymphoplasmacytic cell infiltration, and type B, mediated by paraprotein deposition or autoantibody activity.<sup>42</sup> Distinguishing the subtype of Bing Neel syndrome is important because treatment approach can be very different; ie, chemotherapy with high-dose methotrexate (with or without radiotherapy) in type A, versus plasmapheresis for type B.

Amyloidosis is an infrequent complication in WM patients, though diagnostic testing has been problematic in many centers. Fat pad aspirations with congo red staining can be helpful if done in centers of excellence, as pointed out by Merlini and Palladini with 82% sensitivity, though in and of itself does not resolve amyloid typing which is needed to direct proper therapy.<sup>43</sup> A novel advance using protein identification by mass spectrometry can be useful for such resolution. A higher incidence of peripheral neuropathy (32% vs. 11%) among IgM versus non-IgM amyloid patients was reported by Gertz, suggesting that IgM amyloid proteins may have a higher affinity for peripheral nerves.<sup>44</sup> Fermand presented the experiences of a center in France involving renal manifestations of WM, and pointed to the multiple causes for renal pathology including immunoglobulin, amyloid, and cryoglobulin deposition, as well as lymphoplasmacytic cell infiltration underscoring the value for a renal biopsy to help delineate etiology and directed therapy.<sup>45</sup> Stone discussed the diversity of autoantibody syndromes that contribute to morbidity in WM patients including cold agglutinin disease, mixed cryoglobulinemias and immune-related polyneuropathies, with a conservative estimation of 10-20% of all WM patients manifesting clinically significant autoantibodies.<sup>46</sup> Stone also pointed to the fact that for most patients, the antigenic determinant for the paraprotein remains to be defined.<sup>46</sup> Such insights may now be possible as reported by Bogen, who shared preliminary results from studies using random combinatorial libraries to reconstruct the epitope to which the paraprotein binds and showed distinct patterns in WM versus MM patients.<sup>47</sup> Dammacco and Sansonno reported on the presence of "rheumatoid macroglobulinemia" in patients with HCV-related macroglobulinemia, in whom a serum IgM monoclonal component showing RF activity with a tendency to cryoprecipitate is seen.<sup>48</sup>

Presentations on two problematic areas in the clinical management of WM patients were reviewed at IWWM6. The use of prognostic factors, including the WM International Scoring System (WM ISS) and how prognostic scoring can be used to make treatment-related decisions was discussed. The WM ISS, which predicts overall survival after first-line treatment is based on age, hemoglobin levels, platelet counts, beta-2-microglobulin and M-protein levels and can stratify patients into low, intermediate, and high risk.<sup>49</sup> While no consensus on the use of WM ISS exists, and other prognostic factors are now in place to dictate treatment usage, Morel et al encouraged the adoption of WM ISS in more

**Figure 2** Recipients of the Jan Gosta Waldenstrom Awards: Drs. Eva Kimby (Sweden), Jean-Paul Fermand (France), and Steve Treon (USA) at the 6th International Workshop on WM, Venice, Italy



front-line studies so as to clarify its role in the management of WM patients, particularly those with high-risk disease.<sup>50</sup> Kastiris elaborated on the experience with Greek WM patients, and pointed out that 10% of WM patients survived for < 2 years, a finding that was associated with lack of response to initial treatment that they considered should be viewed as an additional poor prognostic indicator.<sup>51</sup> Owen et al discussed the difficulties encountered in assessing response in WM patients, particularly in this era of novel biological drugs that often can lead to discordance between IgM levels and underlying tumor response.<sup>52</sup> The use of confirmatory bone marrow biopsies in clinical trials, as well as the assessment of patients when the clinical circumstances warrant clarification of an individual patient's response was advised during consensus discussions on updating WM response criteria.

Lastly, the future and past of WM were acknowledged at the IWWM6. Fifteen young investigators were awarded a fellowship supported by the International Waldenstrom's Macroglobulinemia Foundation to present their basic and clinical studies at IWWM6, which included gene expression studies in WM and microenvironmental cells, Spi-1 transactivation in WM, novel prognostic and response markers, role of metalloproteinases in the release of soluble CD27 by WM cells, the development of a novel WM cell line, and advances in diagnostic and treatment strategies for WM. At the Opening Ceremonies of IWWM6, Dr. Irene Ghobrial (United States) received the Robert A. Kyle Award, given for important scientific contributions to WM. Finally, the lifetime contributions to WM were acknowledged for three investigators at the Closing Ceremonies of IWWM6 with the awarding of the Jan Gosta Waldenstrom Awards (Figure 2) to Drs. Jean-Paul Fermand (France), Eva Kimby (Sweden), and Steven Treon (United States). The next workshop for the IWWM will be held in Newport, RI on August 23-26, 2012. Current and past IWWM proceedings and information for IWWM7 can be found at [www.wmworkshop.org](http://www.wmworkshop.org).

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