Proceedings of the Seventh International Workshop on Waldenström Macroglobulinemia

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On August 23-26, 2012, more than 200 delegates met in Newport, Rhode Island, for the Seventh International Workshop on Waldenström Macroglobulinemia (IWWM7). Key advances on the genetic basis, pathogenesis, clinical management, and response assessment of Waldenström macroglobulinemia (WM) were presented at this meeting. Highlighting the meeting was the revelation that whole genome sequencing had revealed a somatic mutation present in most patients with WM, a finding confirmed by the presentations of multiple investigators. Since the initial description of macroglobulinemia by Dr Jan Gosta Waldenstrom, in 1944, the genetic basis for WM has been elusive. The discovery of a point mutation in MYD88 that results in a change of leucine to proline at amino acid position 265 (L265P) was the most common single mutation found in patients with WM by whole genome sequencing.

The discovery of a mutation in MYD88 was a surprise to many investigators at IWWM7. MYD88 is an adapter molecule in Toll-like receptor and interleukin (IL) 1 receptor (IL-1R) signaling. After Toll-like receptor or IL-1R stimulation, MYD88 is recruited to the activated receptor complex as a dimer, which then complexes with interleukin-1 receptor associated kinase 4 (IRAK4) and activates IRAK1 and IRAK2 and leads to nuclear factor kappa beta (NF-κB) activation via IκBα phosphorylation. The role of NF-κB has previously been established as an important purveyor of growth and survival for WM, although the trigger has remained elusive. By confirming the dependence of WM tumor survival on MYD88 signaling, Dr Guang Yang and colleagues presented data that showed that NF-κB signaling and tumor survival were impacted by MYD88-dependent pathways in WM cell lines expressing the L265P mutation. Importantly, their work also identified Bruton tyrosine kinase (BTK) as a binding partner for MYD88 in WM cells with dual but independent NF-κB signaling facilitated by IRAK as well as BTK-dependent pathways. These findings are of particular relevance given the advanced development of inhibitors for both IRAK and BTK signaling.

An important dilemma in prior WM workshops has been the diagnostic discrimination of WM from other overlapping B-cell disorders, including marginal zone lymphoma and immunoglobulin (Ig) M multiple myeloma. Dr Nancy Harris, showed data on the potential use of MYD88 L265P as a molecular tool to support the WM diagnosis given its high prevalence in WM/lymphoplasmacytic lymphoma (LPL) and rare presence or absence in marginal zone lymphoma and IgM multiple myeloma. An important revelation at IWWM7 was also the finding of MYD88 L265P in IgM monoclonal gammopathy of unknown significance (MGUS). IgM MGUS is a recognized precursor condition to WM, with an approximate 2% annual rate of progression to the malignant state, most commonly WM. By Sanger sequencing, MYD88 L265P was present in a minority of cases of IgM MGUS. By allele-specific polymerase chain reaction capable of identifying point mutations at considerably lower limits of detection than Sanger sequencing, several investigators at IWWM7 reported finding the MYD88 L265P in up to half of patients with IgM MGUS. Their findings frame MYD88 L265P as an early oncogenic event in WM pathogenesis and suggest that other mutations may play a role in facilitating progression. Such a possibility was eluded to by the work of Dr Zachary Hunter, who reported on other common somatic mutations in patients with WM, including in the *CXCR4, ARID1A, MUC16, TRAF2*, and *TRRAP* genes. Dr Nikhil Munshi, compared whole genome findings in tumor cells from patients with WM vs. patients with myeloma and showed distinct profiles in recurring somatic mutations in the *CCND1, DTX1, and KRAS* genes in patients with myeloma.

Chromosome 6q deletions represent the most frequent structural abnormality observed by fluorescence in situ hybridization and are present in up to half of patients with WM although absent in patients with IgM MGUS. Dr Rafael Fonseca and colleagues reported on 2 minimal deleted regions on 6q, including 6q21 and 6q23.3-24.1, which encompass the *PRDM1* and *TNFAIP3* genes, respectively. Partial or whole gains on chromosome 18 and 6p were also identified in up to 20% of patients with WM in their work, whereas gains in 4q13.1-35.2 were observed in 12% of patients. The importance of TNFAIP3 was discussed by Dr Xavier Leleu and colleagues, al-

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though, in their work, no cryptic losses in this gene were observed by high-resolution single nucleotide polymorphisms arrays in patients without 6q deletions. The role of epigenomic dysregulation in WM pathogenesis was raised by Dr Aldo Roccaro and colleagues who observed dysregulation in microRNA (miRNA)-155 and miRNA-9, thereby providing the rationale for testing miRNA-based therapeutic approaches for WM.

Dr Bruno Paiva and colleagues presented work on the use of multicolor flow as a tool to characterize the early B-cell clone in IgM MGUS. Their work showed that a CD22 dim clone identified by multicolor flow cytometry increased with progression from IgM MGUS to asymptomatic WM and then to symptomatic WM. The use of 8-color flow cytometry to discern and sort out IgM MGUS cells could help advance genomic discovery into mutations that permit disease progression. The distinct molecular signature in early IgM MGUS vs. later WM clones was eluded to by the work of Dr Alessandra Trojani and colleagues who showed that a distinct gene expression signature exists for these clones. Dr Robert Kyle updated his findings on factors that predict evolution of smoldering WM to active disease. By multivariate analysis, the percentage of lymphoplasmacytic cells in the bone marrow, size of the serum M-spike, and hemoglobin were independent risk factors for progression. Similarly Dr Antonino Greco and colleagues showed that IgM MGUS and smoldering WM represented distinct clinical entities with similar overall survival but a different probability of transformation to lymphoid malignancies. These findings, therefore, may help to delineate a population of patients with smoldering WM and at high risk who may be candidates for early treatment intervention, particularly with the onset of new targeted and potentially safer agents currently in development for symptomatic WM.

The genetic predisposition to WM was discussed by several investigators. Dr Ola Landgren showed that first-degree relatives had significantly increased risks of developing WM/LPL (20-fold), other non Hodgkin lymphoma (3-fold), chronic lymphocytic leukemia (3.4-fold), and IgM MGUS (5-fold). When taken into context with reports offered by Drs Mary McMaster and Olga Ogmundsdottir, there appears to be a shared susceptibility gene(s) that predisposes to familial WM and other lymphoproliferative disorders. Whereas MYD88 L265P represents a common somatic mutation in WM, no differences for its presence were observed between patients with familial and sporadic disease to account for familial predisposition. Ongoing efforts that use genome-wide association studies and whole genome sequencing were reported to be underway to identify germline predisposing genes. Dr Enrica Morra reported an increased risk of solid cancers, including brain cancer, as well as predisposition for diffuse large B-cell lymphoma and myelodysplasia/acute myelogenous leukemia, which suggests that shared genetic risks may transcend lymphoplasmacytic disorders for some patients.

The importance of microenvironmental and cytokine interactions in the growth, survival, and prognostication of WM was raised by several investigators. Activated T-cell secretion of IL-21 in the bone marrow of patients with WM was shown by Dr Lucy Hodge and colleagues to trigger proliferation and IgM secretion through signal transducer and activator of transcription 3 (STAT3), whereas use of a STAT3 inhibitor abrogated these events. Dr Evangelos Terpos and colleagues showed that macrophage inflammatory protein 1 alpha (MIP-1α) (chemokine ligand 3) is produced by WM cells and that high levels of serum MIP-1α are associated with inferior progression-free survival in patients with WM. Dr Stathis Koulieris also showed that higher levels of transforming growth factor-beta were associated with improved overall survival in patients with WM.

The identification of novel targets for the therapy of WM was discussed by several investigators. Drs Yu-Tzu Tai and Guang Yang discussed the role of BTK inhibitors in plasma cell malignancies, citing constitutive activity for this target in both myeloma and WM primary cells. Ibrutinib, a BTK inhibitor was noted to have direct antimyeloma and WM activity, and to block tumor–bone marrow stromal interactions and elaboration of growth supportive cytokines. Dr Guang Yang further showed the potentiation of WM cell killing with a combination of BTK and IRAK inhibitors. The role of novel proteasome pathway inhibitors for WM was also discussed by Dr Constantine Mitsiades, who showed encouraging preclinical work in WM with MLN4924, a novel E3 ligase inhibitor. Dr Claudio Sette provided a stimulating discussion on the development of potent inhibitors of MYD88 pathway signaling by using peptidomimetics developed for inflammatory disorders.

There were many clinical trial updates at IWWM7. Foremost was the presentation of the largest randomized clinical trial ever performed in WM. The WM1 study, a trial that compared chlorambucil with fludarabine in patients with advanced WM was undertaken in 101 centers in 5 European countries and enrolled 339 patients with WM. Drs Véronique Leblond and Roger Owen presented data from this study, which showed superior outcomes in terms of responses, progression-free survival, and overall survival as well as a lower incidence of secondary malignancies for patients treated with fludarabine vs. chlorambucil. Dr Meletios Dimopoulos provided an update of the European Network study of bortezomib, dexamethasone, rituximab in WM and showed high rates of activity and reduced peripheral neuropathy with the adoption of a weekly dosing strategy with bortezomib. The promising early results and neuropathy sparing activity of carfilzomib in combination with rituximab and dexamethasone was also presented at IWWM7. Dr Alessandra Tedeschi presented an update of a prospective clinical trial of fludarabine, cyclophosphamide, and rituximab as salvage therapy in patients with WM, including those with refractory disease. Up to 80% of patients attained a response in this study, which included complete responders. Dr Irene Ghobrial updated several trials conducted by her group, including use of novel signal inhibitors (everolimus, panobinostat) as well as a trial by using the combination of everolimus, bortezomib, and rituximab, which showed high rates of response in patients who relapsed and/or were refractory. The activity of the BTK inhibitor ibrutinib in phase I and early phase II trials was also presented at IMMW7 by Dr Ranjana Advani, with encouraging activity, including fast time to IgM reduction and recovery of anemia in patients with relapsed and/or refractory WM. Dr Sheeba Thomas presented work from an M.D. Anderson study on the use of pomalidomide, a novel immunomodulatory drugs agent in patients with relapsed and/or refractory WM, which demonstrated tolerance at a 1 mg daily dose, and encouraging preliminary activity. The positioning of bendamustine and nucleoside analogues in the treatment of patients with WM as well as the role of maintenance rituximab, autologous and allogeneic stem cell transplantation ther-

Figure 1 Delegates of Seventh International Workshop on Waldenstrom Macroglobulinemia, Patients With Waldenstrom Macroglobulinemia, and Family Members Attend the Closing Ceremony Held at the Marble House, Newport, Rhode Island, on August 25, 2012

apy were the subject of intense debates held at IWWM7. Investigators presented both pro and con positions on the utilization of these modalities in WM therapy.

Special topics that covered the diagnosis and management of WM-related complications, including amyloidosis, peripheral neuropathy, hyperviscosity, and cryoglobulinemia, were addressed at IWWM7. Drs Fred Hochberg and Michael Lunn addressed deficiencies that surround the diagnosis and management of the Bing-Neel syndrome as well as peripheral neuropathy and emphasized urgency for the development of better diagnostic tools and treatments for these WM-related complications. Dr Giampaolo Merlini pointed to differences that surround the presentation of amyloidosis in patients with WM vs. other plasma cell dyscrasias, whereas Drs Morie Gertz and Ashutosh Wechalekar discussed the outcome of autologous transplantation efforts in patients with WM and with symptomatic amyloidosis. Dr Marvin Stone addressed the appropriate use of plasmapheresis in the treatment of IgM-related morbidities in patients with WM and with symptomatic hyperviscosity and cryoglobulinemia.

Finally, there were many presentations on response assessment in WM. Dr Roger Owen presented the revised WM response criteria, which were updated to include a category recognizing very good partial responses and adoption for the use of either serum IgM (sIgM) or sIgM monoclonal protein for serial response assessment. Drs Sacha Uljon and Christina Tripsas discussed limitations associated with use of both sIgM and sIgM monoclonal protein in patients with WM. A presentation on the use of allele-specific quantitative polymerase chain reaction to measure MYD88 L265P copy number as a response tool in WM was made by Dr Zachary Hunter, whereas Dr Ramon Garcia Sanz delivered a paper on the use of multicolor flow cytometry to more stringently define complete responses in patients with WM. Use of more stringent response criteria was emphasized at IWWM7 in recognition of deeper categorical responses being achieved with novel, more targeted therapeutics for WM. Abstracts as well as disclosures for all presentations made at IWWM7 can be found at http://www.wmworkshop.org.

At the IWWM7, Dr Pierre Morel of France received the prestigious Robert A. Kyle Award in recognition of important medical and scientific advancements made for WM, and Dr Véronique Leblond received the Jan Gosta Waldenstrom Lifetime Achievement Award in recognition of the scientific and medical accomplishments made by her to WM. At the closing ceremony held at the Marble House, Newport, Rhode Island (Figure 1), delegates, patients with WM and family members were addressed by the organizers (Drs Shirley D'Sa, Chara Kyriakou, and Roger Owen) of the next WM workshop, IWWM8, which will be held in London, United Kingdom, from August 13-17, 2014. Details for this meeting can be also be found at http://www.wmworkshop.org.

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