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Advances in the Biology and Treatment of Waldenström's Macroglobulinemia: A Report from the 5th International Workshop on Waldenström's Macroglobulinemia, Stockholm, Sweden

The 5th International Workshop on Waldenström's Macroglobulinemia (IWWM5) was held on October 15-19, 2008, in Stockholm, Sweden. The meeting was co-organized by Drs. Eva Kimby (Sweden) and Steven Treon (United States), who served as Co-Chairs, and Christopher Patterson (United States) who served as Organizing Secretariat. During the four-day meeting, over 80 invited speakers and young investigator award recipients presented their latest findings on the genetic basis, pathogenesis, and treatment of Waldenström's macroglobulinemia (WM). A summary of those efforts appears in this edition of *Clinical Lymphoma & Myeloma*, for which Dr. Marvin Stone (United States) served as Senior Guest Editor. At the opening ceremonies of IWWM5, Dr. Robert A. Kyle presented the Robert A. Kyle Award, in recognition of outstanding contributions to WM, to Dr. Veronique LeBlond (France).

Some new important insights into the genetic basis of WM were made at IWWM5. Kyle et al¹ and McMaster et al² reported that monoclonal gammopathy of unknown significance (MGUS) of the IgM type is an important predisposition to symptomatic WM, with an estimated annual progression rate of 10.5% in the series presented by Kyle et al.¹ While the familial nature of WM has been previously reported, with up to 20% of patients with WM having a first degree relative with WM or a closely related B-cell disorder,³ Kristinsson et al⁴ reported that, among first degree relatives of patients with lymphoplasmacytic lymphoma (LPL)/WM, there was a 20, 3, 3.4- and 5-fold increased risk of developing LPL/WM, non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL), and MGUS, respectively. Hunter et al⁵ reported the interim findings of an International Waldenström's Macroglobulinemia Foundation (IWMF)-funded study, which detected an increased incidence of MGUS (predominantly IgM) among first and second degree rela-

tives of patients with a familial history of only WM versus other B-cell disorders. The findings of this study might suggest a different genetic basis for familial WM based on genetic predispositions leading to only WM, versus a more generalized risk for any B-cell disorder. In addition, the work of Landgren et al⁶ among US veterans suggests that chronic antigenic stimulation from hepatitis C, human immunodeficiency virus, and rickettsiosis may have a pathogenetic role for WM. A pathogenetic role for hepatitis C exposure in WM was also raised by the work of Giordano et al,⁷ though others have reported no such association.⁸

New insights reported at IWWM5 may offer important clues into the molecular basis for WM. The origin of the WM cell has long been thought to have emerged from a CD27-expressing memory B-cell. Sahota et al⁹ presented data suggesting that, in some patients with WM, VH immunoglobulin genes remain unmutated, a finding that contradicts a memory B-cell origin for WM. Moreover, malignant WM cells are found within CD27-negative fractions consistent with this hypothesis. Taken together, these studies suggest divergent pathways of origin for WM. Among patients displaying rearrangements in VDJH immunoglobulin genes, Garcia-Sanz¹⁰ reported that the most frequently used family and single segments were VH₃ and VH₃₋₂₃ in WM, which differs from the repertoire found in normal donor B-cells and tumor cells from patients with multiple myeloma. VH₃ and VH₃₋₂₃ are characteristically associated with inflammatory events or bacterial infections.

Braggio et al,¹¹ using high resolution array CGH and DNA sequencing, reported the inactivation of 2 negative regulators (TRAF3, A20/TNFAIP3) of the NFκβ pathway. Though these mutations were found in a few patients, this work underscores the importance of gaining a better understanding of the role that TRAFs and downstream regulators play in the systematic regulation of NFκβ, an important growth and survival factor that is also the target for proteasome inhibitors such as bortezomib. While structural alterations in the genome have long been sought after in WM, recent work suggests that epigenetic modifiers may play important roles in the pathogenesis of WM. Adamia et al¹² presented work on microRNAs, which are capable of regulating important growth, survival, and transcriptional pathways such as HOX, c-myc and Bcl-2, and demonstrated fundamental differences between healthy donors, patients

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with myeloma, and WM patients. Similar studies have recently also been reported by Roccaro et al,¹³ who provided an update of their work at IWWM5. Xu et al¹⁴ reported that inactivation of important growth suppressor genes occurred in WM through hypermethylation, and demonstrated that the use of 5-azacytidine, a hypomethylating agent, could suppress the growth and survival of WM cells. The role of histone deacetylases (HDAC) and the use of HDAC inhibitors (HDAC-I) in the treatment of WM was reported by a number of investigators¹⁵⁻¹⁷ at IWWM5, and raises the future prospect of incorporating HDAC-I such as vorinostat and LBH589 in the treatment of WM. The above studies lay the foundation for the exploration of agents targeting epigenetic modifications in the therapy of WM.

The influence of the microenvironment on WM growth and survival was also discussed at IWWM5. Hatjiharissi et al¹⁸ presented an update of gene expression profiling studies which showed a unique signature for microenvironmental cells from the bone marrow of patients with WM in comparison to healthy donors, including genes that mediate immune and inflammatory responses (ie, TLR 4,5,7,8, IL-6R, IL-10R, IL-8R), and genes encoding extracellular matrix components (ie, FN1 and HGF). Ansell et al¹⁹ presented data on elevated serum levels of Rantes (CCL5) in patients with WM. This cytokine induces secretion of IL-6 by bone marrow stromal cells. A role for IL-6 as a regulator of IgM production was demonstrated by these studies, suggesting a role for inhibitors of Rantes and IL-6, and their respective downstream pathways in the treatment of WM. The effect of the immune system in the regulation of WM was suggested by the studies of Joshua et al,²⁰ who observed an expansion of CD8+ CD57+ TCR V β -restricted cytotoxic T cells in patients with WM. Importantly, Joshua et al²¹ observed that this subset of regulatory T cells was depleted by nucleoside analogue therapy, a finding which may help shed light on the etiology for increased risk of disease transformation in WM patients treated with nucleoside analogues.^{21,22}

The significance of the 6q deletion was debated at IWWM5. Chang et al²³ extended on previous studies that had demonstrated the loss of 6q in up to 30%-50% of patients with WM,²⁴⁻²⁶ by demonstrating extension of this deletion from 6q21-q25 in up to one third of patients. However, the presence of the deletion had no bearing on disease presentation, time to treatment, or overall survival. Morel et al²⁷ presented an update on the International Prognostic Scoring System for Waldenström's Macroglobulinemia (ISSWM), a system based on the combination of age > 65 years, Hb < 11.5 g/dL, platelet count < 100 x 10⁹/L, B₂M > 3 mg/L, and M-protein > 7.0 g/dL. This scoring system had previously been validated in patients with newly diagnosed WM and was extended for prognostication in patients with advanced disease.²⁸ Kastiris et al²⁹ evaluated the effect of age on WM response and survival, and showed that, although clinical and laboratory features as well as response to treatment were similar among different age groups, the survival of older aged (> 75 years) patients was significantly shorter than those of middle aged (50-75 years) and very young (< 50 years) patients.

An important issue raised at the IWWM5 surrounded the complexities associated with assessing disease burden in patients with WM, particularly in this era of targeted therapies. While serum IgM levels have been the mainstay of assessment of WM response, discordance with overall disease burden can occur as was demonstrated

Figure 1 Patients and Faculty at IWWM5



WM patients joined the IWWM5 faculty at the Closing Ceremonies of the 5th International Workshop on WM, in the Nobel Hall of Stockholm City Hall, Stockholm, Sweden, on Saturday, October 19, 2008. A tribute to the life of Dr. Jan Gosta Waldenström was held during the closing ceremonies of the IWWM5.

by Owen et al³⁰ in patients treated with selective B-cell depleting agents such as rituximab and alemtuzumab, in whom residual IgM producing plasma cells are spared and continue to persist, thus potentially skewing the relative response and assessment to treatment. The assessment of response in WM patients experiencing a rituximab-related IgM flare or undergoing plasmapheresis was highlighted by the report of Yang et al,³¹ who demonstrated that measurement of soluble CD27, a TNF family member released by WM cells could be used as a more reliable surrogate marker of disease in such circumstances.

Strategies to optimize the use of rituximab were also presented at IWWM5. Buske et al³² presented the results of a randomized German Low Grade Study Group study demonstrating superior overall responses in WM patients treated with CHOP-R (cyclophosphamide/doxorubicin/vincristine/prednisone plus rituximab) versus CHOP. Interestingly, in a study by Ioakimidis et al,³³ similar response outcomes were observed among WM patients treated with CHOP-R, CVP-R and CP-R, with fewer adverse effects observed among CP-R-treated patients, particularly therapy-related neuropathy and febrile neutropenia. This study and those reported by Dimopoulos et al³⁴ with the combination of rituximab, dexamethasone and cyclophosphamide (RCD) suggest that high response rates and long progression-free survival (> 2-3 years) can be attained with doxorubicin- and vincristine-sparing regimens containing cyclophosphamide, steroids and rituximab.

The use of novel agents in combination with rituximab was also highlighted. Dimopoulos et al³⁵ provided a summary of studies

Figure 2 Presentation of the Waldenström Awards at the Closing Ceremonies of IWWM5, in the Nobel Hall, Stockholm, Sweden



Pictured from Left to Right: Dr. Eva Kimby (IWWM5 Co-Chair), and award recipients Dr. Meletios Dimopoulos; Dr. Giampaolo Merlini; Dr. Pierre Morel; Judith May, President of the International Waldenström's Macroglobulinemia Foundation; Dr. Deborah Dunsire, Millenium Pharmaceuticals, Inc.; Dr. Sol Barer, Celgene Corporation, Inc.; and Dr. Steve P. Treon (IWWM5 Co-Chair).

incorporating thalidomide and lenalidomide with rituximab in the treatment of WM. An overall response rate of 80% and time to progression exceeding 3 years was observed in WM patients treated with thalidomide and rituximab,³⁶ while the use of the thalidomide analogue lenalidomide proved to be prohibitive in one study due to aggravated anemia.³⁷ This later study underscores the need to conduct clinical trials in WM patients, even with agents which have shown good activity and tolerance in related populations. Morra et al³⁸ and Branagan et al³⁹ provided an update of combination strategies incorporating nucleoside analogues with rituximab, wherein high response rates (> 80%) were observed, but noted concerns over prolonged myelosuppression and long-term adverse effects, a finding supported by the studies reported by Leleu et al.²² Despite the findings of increased disease transformation and possibly myelodysplasia and acute leukemia in WM patients treated with nucleoside analogues, the importance of not abandoning these agents altogether, and taking a more balanced risk-versus-benefit approach was highlighted by Barlogie et al,⁴⁰ who reported an update of a SWOG study in which a 10-year event-free survival of 20% was observed among fludarabine-treated WM patients. The role of maintenance rituximab in the treatment of indolent NHL, and the application of this data to the care of WM patients, was discussed by Ghielmini.⁴¹ The importance of prospective clinical trials to address the impact and optimal schedule and duration of rituximab maintenance therapy in WM patients was highlighted in consensus discussions at IWWM5.

Chen et al⁴² presented an update of clinical studies involving bortezomib in relapsed and refractory WM, wherein overall response rates of 60%-80% were observed, and Treon et al⁴³ reported on their efforts combining bortezomib, dexamethasone, and rituximab (BDR) in the first-line treatment of WM, wherein an overall response rate of 96%, and complete or near complete response rate of 22% was observed. Close monitoring for bortezomib-related neuropathy, and prophylactic use of anti-viral therapy to prevent shingles in patients receiving bortezomib/steroid combinations was highlighted in the above studies.

The activity of several novel agents was also reported at IWWM5. Rummel et al⁴⁴ provided an update on the outcome of WM patients treated in a randomized clinical trial with bendamustine/rituximab versus CHOP-R and noted similar overall response outcomes, but with decreased toxicity in patients treated with the former. Ghobrial et al⁴⁵ reported encouraging results with the use of the Akt inhibitor perifosine, and the MTOR inhibitor RAD001 in the treatment of relapsed/refractory WM patients. Preclinical efforts in support of other novel agents such as the monoclonal antibodies SGN-40, SGN-70, HCD-122, and a novel proteasome inhibitor NPI-0052 were also presented at IWWM5.⁴⁶⁻⁴⁸

The role of transplantation therapy was discussed at IWWM5, including for those patients presenting with amyloidosis.⁴⁹ An important consideration for the performance of autologous stem cell transplantation (autoSCT) was raised by the studies of Thomas et al,⁵⁰ who observed a significant decrease in stem cell harvesting among patients treated with a nucleoside analogue. Kyriakou et al⁵¹ provided an update of data from the European Bone Marrow Transplant (EBMT) registry on the outcome of patients with WM who had undergone transplantation. Among 202 WM patients receiving an autologous SCT, which included primarily relapsed or refractory patients, the 5-year progression-free and overall survival rates were 61% and 33%, respectively. Chemosensitive disease at time of the autoSCT was the most important prognostic factor for response rate, progression-free survival, and overall survival, as well as for non-relapse mortality (NRM). The EBMT experience with 106 allogeneic transplantation, which included 44 patients who received a conventional myeloablative allogeneic SCT (alloSCT) and 62 patients who received a reduced intensity conditioning (RIC) alloSCT was also presented by Kyriakou et al.⁵¹ More advanced WM patients were included in this study, and the 3-year non-relapse mortality rate was 33%. The 5-year progression-free and overall survival rates were 48% and 63%. Among the 106 patients who underwent an alloSCT, 48 developed acute, and 16 and 11 patients developed limited and extensive chronic graft versus host disease, respectively. The potential role for RIC alloSCT to induce responses, including

complete responses, among patients with very advanced WM, was reported by Maloney and Anderson⁵² who observed 6 complete, 1 near complete, and 4 partial responses among 12 evaluable patients. In consensus discussions at IWWM5, the use of autologous, as well as RIC alloSCT were deemed appropriate modalities for the treatment of relapsed/refractory WM patients, though the risks and benefits of these modalities should be carefully weighed against other available treatment options.

The associated morbidities with WM were extensively discussed at IWWM5, and revealed not only advances in our understanding of the etiologies surrounding these morbidities, but also the paucity of knowledge that exists in some critical areas of WM care. Hochberg et al⁵³ revisited the Bing-Neel syndrome, an entity which has come to reflect a multiplicity of WM-related central nervous system (CNS) effects mediated by direct tumor or paraneoplastic processes. An important highlight of this presentation was the realization that direct CNS IgM deposition can contribute to morbidity as well radiographic findings, and systemic therapy may be of adjunct benefit in such patients. The antigenic targets for IgM-related peripheral neuropathies were discussed in the presentations of Nobile-Orazio et al,⁵⁴ and Levine et al,⁵⁵ and revealed considerable diversity for the determinants found on myelin sheaths. The use of rituximab alone and in combination therapy, as well as the role for plasmapheresis and intravenous gamma globulin for the treatment of IgM-related neuropathy in WM patients, were discussed by these investigators.

Augmenting experiences on the management of WM-associated morbidities was the work reported by Femand et al⁵⁶ on the cutaneous manifestations of WM, and noted their successes with pefloxacin and more so with anakinra, a selective interleukin-1 receptor antagonist in the treatment of WM-related Schnitzler's syndrome, a disorder mediated by cutaneous IgM deposition. Berentsen et al⁵⁷ presented studies on the prevalence of WM among patients with cold agglutinin disease, and observed that up to half of the patients in their single institutional experience had WM. The use of rituximab was also reported by this group to result in improvements in cold agglutinin-related hemolytic anemia in most patients. The impact of WM-related hyperviscosity on retinal changes in WM patients was the subject of a report by Menke et al,⁵⁸ who noted that retinal changes including hemorrhages could be seen at lower mean IgM levels (5400 mg/dL) and serum viscosity levels (3.1 cP) than previously thought to produce hyperviscosity changes in WM patients. Moreover, Stone⁵⁹ provided an extensive review on the systemic effects of hyperviscosity and cryoglobulinemia in WM patients, and noted that the presence of cryoglobulins could additionally aggravate serum viscosity levels by the complexing of serum IgM and IgG. The above studies could have important implications in the management of WM patients, particularly in advancing efforts aimed at better detection of WM-related hyperviscosity changes, as well as earlier intervention for those patients at greater risk for end organ damage due to hyperviscosity.

As part of the IWWM5, two consensus panels were held to address which basic and translational studies are needed to advance our understanding of the genetic basis of WM, and to update treatment recommendations for WM. Under the leadership of Drs. Linda Pilarski (Canada) and Mary McMaster (United States), the consensus panel on basic and translational studies received a number of recom-

mendations including expansion of efforts to utilize single-nucleotide polymorphisms in familial WM cohorts to define predisposing gene(s). Drs. Meletios Dimopoulos (Greece) and Steve Treon (United States) oversaw the consensus panel on treatment recommendations and clinical trial priorities. An update of consensus treatment recommendations made during IWWM4 were reviewed and adopted, which recently appeared in the *Journal of Clinical Oncology*.⁶⁰ Among the panel's forthcoming recommendations for changes in the treatment of WM will be a broadening of the use of bortezomib to include its use in up-front therapy; this is pending ongoing confirmatory studies in the United States and Europe. Moreover, the consensus panels also considered changing the recommendation for use of RIC allogeneic SCT from "only in context of clinical trials" to use in appropriate WM patients with high-risk relapsed/refractory disease. A number of clinical trial priorities were also discussed including randomized trials to address the up-front use of bortezomib in combination therapies with rituximab, and/or cyclophosphamide. A full report of these recommendations will be forthcoming.

Lastly, at the Closing Ceremonies of the IWWM5 (Figure 1), a ceremony was held in the Nobel Hall of Stockholm City Hall to honor the memory of Dr. Jan Gosta Waldenström. Dr. Waldenström, a Swedish physician, was remembered for his many contributions to medicine including the first description of "essential hyperglobulinemia,"⁶¹ which later would become known as "Macroglobulinemia of Waldenström," and thereafter "Waldenström's Macroglobulinemia." Dr. Anders Waldenström (son of Jan Waldenström), along with contemporary colleagues Drs. Gosta Gahrton, Ulric Ringborg, and Giampaolo Merlini paid tribute to the life and accomplishments of Dr. Waldenström. Capping the closing ceremonies, Drs. Eva Kimby and Steve Treon presented the Waldenström Awards which were awarded to Drs. Meletios Dimopoulos (Greece), Pierre Morel (France), Giampaolo Merlini (Italy), the International Waldenström's Macroglobulinemia Foundation, Millennium Pharmaceuticals, The Takeda Oncology Company, and Celgene Corporation for their contributions to the advancement of care for patients with WM (Figure 2).

A summary of the abstracts and proceedings for all the IWWM, and information on IWWM6 which will be co-chaired by Drs. Giampaolo Merlini (Italy) and Enrica Morra (Italy) in the Fall of 2010 in Venice, Italy can be found at www.wmworkshop.org.

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