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Defining Waldenstrom's Macroglobulinemia

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NEARLY 60 YEARS have passed since Jan Gosta Waldenström (Fig 1) first described two patients with oronasal bleeding, lymphadenopathy, anemia and thrombocytopenia, elevated erythrocyte sedimentation rate, high serum viscosity level, normal bone radiographs, and bone marrow demonstrating predominately lymphoid cells.[1] These seminal observations provided the foundation for the widely recognized, though uncommon, clinical diagnosis of Waldenstrom's macroglobulinemia (WM). Likely hampered by its uncommon presentation, estimated at 1.7 (for females) and 3.4 (for males) per million person-years at risk,[2] WM remained a loosely defined clinical diagnosis that encompassed patients with an elevated serum IgM level and a monoclonal IgM gammopathy. Many interpretations of what was considered WM existed, which differed largely on the basis of arbitrarily established serum IgM level cutoffs, while no underlying histopathological diagnosis existed to provide a firm pathological basis for the disease. With improvements in the diagnosis of lymphoid malignancies introduced by successive pathological classification systems, a pathological accounting for patients with WM was attempted. The most recent of these classification schemes, the World Health Organization and (WHO) and Revised European and American Lymphoma (REAL) classifications, attempted to define "real" disease entities among the lymphoid neoplasms by reconciling morphological, immunophenotypic, genetic, and clinical features.[3,4] Within the WHO and REAL classifications, WM was recognized as a clinical syndrome that largely corresponded to the "real" disease entity of "lymphoplasmatic lymphoma." Although the WHO and REAL classification systems provided a pathological basis to diagnose many patients with WM, they left open the possibility that patients with WM could have any of the recognized IgM-secreting lymphoid neoplasms as their underlying diagnosis, thereby hampering the conduct or interpretation of clini-

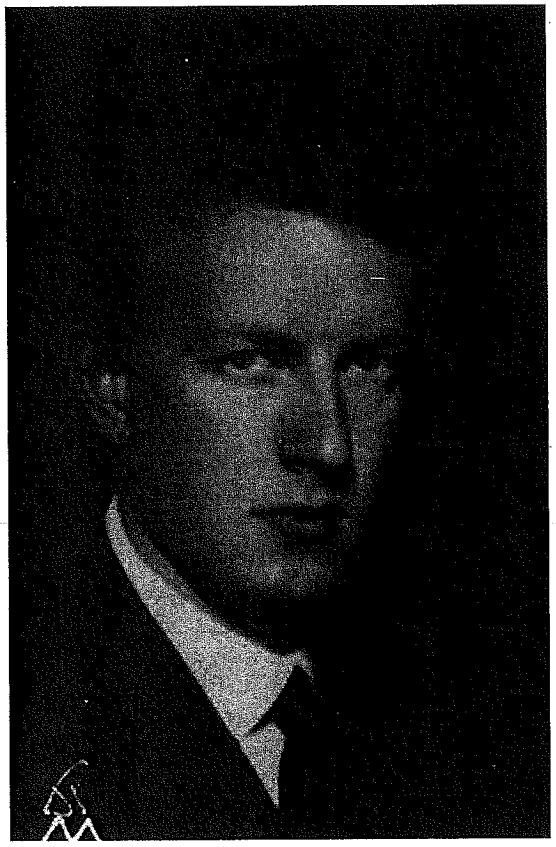

Fig 1. Dr Jan Gosta Waldenström in 1944.

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cal trials involving WM patients. In view of the above, a consensus panel of experts focused on WM was organized as part of the Second International Workshop on Waldenstrom's Macroglobulinemia, which was held in Athens, Greece in September, 2002. Consensus Panel One, chaired by Drs Meletios Dimopoulos (Greece) and Roger Owen (United Kingdom) was charged with formulating a clinicopathological definition for WM. The highlight of this consensus panel summary, as reported in this issue of *Seminars in Oncology*, was the recognition that WM is a defined clinicopathological entity represented by the underlying pathological diagnosis of lymphoplasmacytic lymphoma, as defined by the WHO and REAL classification systems.[5] Moreover, the consensus panel concluded that since the IgM "macroglobulin" was a significant component of the morbidity of WM, the diagnosis of WM should be limited to patients with IgM-secreting lymphoplasmacytic lymphoma, and that serum IgM levels, per se, should not form a a basis for establishing the diagnosis of WM. In addition to providing a clinicopathological definition for WM, Consensus Panel One formulated criteria to distinguish apart patients with an IgM monoloclonal gammopathy in whom there was no histological evidence for disease, thereby discerning the categories of "IgM monoclonal gammopathy of undetermined significance" (MGUS) and IgM-related disorders, the latter recognizing those patients in whom the IgM monoclonal antibody is pathologically relevant.

In this issue of *Seminars*, the recommendations of Consensus Panel Two, charged with identifying prognostic criteria and developing criteria to initiate therapy in WM, are also presented.[6] Co-chaired by Drs Robert Kyle (United States) and Veronique Leblond (France), Consensus Panel Two identified serum β_2-microglobulin and hemoglobin levels at the time of diagnosis as important prognostic determinants for overall survival in WM patients, though they stressed that no data existed at this time to validate the use of these or other factors in deciding the initiation, or choice of treatment for a particular patient. Consensus Panel Two, however, considered that initiation of therapy was appropriate for patients who demonstrated a hemoglobin of $\leq$10 g/dL, or a platelet count of less than 100×10^9/L due to marrow infiltration. Certain complications, such as hyperviscosity syndrome, symptomatic sensorimotor peripheral neuropathy, systemic amyloidosis, renal insufficiency, or symptomatic cryoglobulinemia, were also considered as potential indications for therapy.

The outcome of deliberations from Consensus Panel Three, charged with providing treatment recommendations in WM are also presented here.[7] Co-chaired by Drs Morie Gertz (United States) and Steven Treon (United States), Consensus Panel Three considered that alkylating agents, nucleoside analogues, and the monoclonal antibody rituximab represented reasonable choices for the first-line therapy of WM. The panel also recognized the paucity of randomized clinical trials in WM, and concluded that it was not possible to recommend the use of one first-line agent over another, and that individual patient considerations, including the presence of cytopenias, need for rapid disease control, age, and candidacy for autologous transplant therapy, should be weighed in making the choice of a first-line agent. The panel also considered options for the treatment of relapsed disease, and recommendations on the use of alternate first-line agents, re-use of a first-line agent, use of combination myelotoxic chemotherapy, and thalidomide as a single agent or in combination therapy. Importantly, Consensus Panel Three affirmed for eligible patients, a role for high-dose chemotherapy with autologous peripheral blood cell transplantation in primary refractory or relapsed disease, while stressing that allogeneic or "nonmyeloablative allogeneic" transplant procedures should be cautiously approached in view of the associated high mortality and/or morbidity risks, and ideally should be undertaken in context of a clinical trial.

A confounding factor for therapeutics trials in WM has been a lack of uniformity in the clinical response criteria used. Current response criteria for WM rely on various adaptations of low-grade non-Hodgkin's lymphoma and multiple myeloma response criteria, thereby complicating interpretation and comparison of clinical trial outcomes. The recommendations of Consensus Panel Four, co-chaired by Drs Donna Weber (United States) and Eva Kimby (Sweden), are also summarized in this issue, in which uniform response criteria are proposed for evaluating therapeutic responses in WM.[8]

While the above consensus panel efforts represent a defining moment for the diagnosis and man-

agement of WM, considerable progress has also been made in characterizing and defining WM at the chromosomal and molecular level. These efforts, which were presented at the Second International Workshop on WM, are detailed in large part in reports appearing in this issue. Highlights of these studies include the identification of 6q21 deletions in 42% of WM patients by Schop et al,[9] while translocations involving the immunoglobulin heavy chain (IgH), which are typically present in IgM myeloma patients,[10] were not found in WM.[9,10] The latter finding may be particularly critical to differentiating patients with WM from those with IgM secreting multiple myeloma. Lastly, the outcomes of studies by Pilarksi et al[12] and Sahota et al[13] using IgH VDJ sequencing in WM patients are reported. Their studies have helped characterize the clonal origin of the WM malignant cell to a post-germinal, but pre-immunoglobulin heavy chain–switched mature IgM^+ B cell, which should greatly facilitate further studies aimed at identifying the oncogenetic event(s) that contribute to malignant transformation in WM.

Lastly, to facilitate the ongoing clinical and basic science progress into WM, a Third International Workshop on WM has been planned for October, 2004 in France.

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