In this issue of ONCOLOGY, Dr. Robert Kyle and colleagues provide their clinical and epidemiological perspective on monoclonal gammopathy of undetermined significance (MGUS) and smoldering myeloma (SMM)—a perspective that is based on more than three decades of experience.

Benign monoclonal protein was first described by Waldenström in 1960 after abnormal narrow hypergammaglobulinemia bands were noted in the serum of healthy individuals on serum protein electrophoresis.[1] In 1978, Kyle coined the term “monoclonal gammopathy of undetermined significance (MGUS)” after observing that asymptomatic patients with monoclonal protein have a higher risk of developing multiple myeloma, Waldenström macroglobulinemia, light-chain amyloidosis, and related disorders.[2] Since then, definitions of MGUS have undergone several revisions. Today, three distinct clinical subtypes of MGUS (non-IgM MGUS, IgM MGUS, and light-chain MGUS) have been delineated.[3,4] The review by Kyle et al discusses these subtypes and their epidemiological relationships with corresponding malignancies. In addition, the paper sheds light on recent discoveries regarding etiologic risk factors, complications, and clinical predictors of transformation from a precursor state to full-blown malignancy.

In 1980, Kyle and Greipp were the first to describe SMM as a distinct entity: as an “illness that met the criteria of multiple myeloma but has not had a progressive course”—a corollary to smoldering leukemia.[5] In their case series of six patients, all six patients had ≥ 10% bone marrow plasma cells and ≥ 3 g/dL of monoclonal (M) protein without progression to multiple myeloma for at least 5 years.[5] Following this initial description, several other studies of SMM were completed using criteria that ranged from inclusion of patients with mild anemia, to the requirement that the M protein be < 4.5 g/dL and the marrow plasma cells > 15% with the percentage of marrow plasma cells ignored entirely, to the requirement that Bence Jones proteinuria be present.[6-8]

In 2003, the International Myeloma Working Group (IMWG) developed consensus definitions of the known monoclonal gammopathies.[9] MGUS was defined as the presence of serum M protein < 3 g/dL with fewer than 10% monoclonal plasma cells in the bone marrow; SMM was defined as either serum M protein ≥ 3 g/L or ≥ 10% monoclonal plasma cells in the bone marrow. In contrast to these laboratory-based definitions, a diagnosis of multiple myeloma is based on the clinical assessment of myeloma-related end-organ impairment in the presence of an M protein and/or monoclonal plasma cells. In the 2003 IMWG criteria, end-organ damage was defined using the classic “CRAB” criteria of hypercalcemia (serum calcium level > 11.5 mg/dL), renal failure (defined by a creatinine level >1.95 mg/dL with no other cause of the renal failure identified), anemia (hemoglobin level <10 g/dL), or skeletal lesions (lytic lesions by skeletal survey, osteoporosis with pathologic fractures, or cord compression).[9] In the updated 2010 IMWG diagnostic criteria, plasma cell MGUS is defined as having serum M protein < 3 g/dL, clonal plasma cell population in bone marrow < 10%, and absence of end-organ damage (CRAB criteria of multiple myeloma).[10] The CRAB criteria have also been slightly revised in the 2010 version; these now include: hypercalcemia with calcium level > 11.5 mg/dL, renal insufficiency with serum creatinine level > 2.0 mg/dL or estimated creatinine clearance < 40 mL/minute, normochromic normocytic anemia with a hemoglobin value < 10 g/dL (or a hemoglobin value more than 2 g/dL below the lower limit of normal), and bone lesions (lytic lesions, severe osteopenia, or pathological fractures).[10] Reflecting its greater disease burden, SMM is distinguished from MGUS by higher cut-off values, although a lack of end-organ damage remains one of the criteria. IMWG diagnostic criteria from 2010 define SMM as having serum M protein > 3 g/dL and/or clonal plasma cell population in bone marrow > 10%, and lack of end-organ damage (CRAB criteria).[10] Based on retrospective data from the Mayo Clinic, risk of progression from SMM to
multiple myeloma is 10% per year for the first 5 years, 3% per year for the next 5 years, and 1% for the subsequent 10 years.[11] The entities analogous to SMM with respect to IgM and light chain monoclonal gammapathies are smoldering Waldenström macroglobulinemia and idiopathic Bence Jones proteinuria, respectively.[3]

Based on available clinical markers, two major schools of thought have surfaced regarding the establishment of models for predicting the risk of progression from MGUS/SMM to multiple myeloma—that of the Mayo Clinic and that of the Spanish PETHEMA study group. The Mayo Clinic model emphasizes clonal plasma cell burden with monoclonal protein values and skewed free light chain ratios.[12,13] The Spanish study group utilizes multiparametric flow cytometry techniques to identify aberrant plasma cell populations.[14] Both these risk models are discussed in the paper by Kyle et al.

A lot of impressive work has been done in this field in the last three decades; however, much more remains to be done. For example, the conventional clinical markers that are used to stratify MGUS and SMM patients into clinical risk groups[12, 13] are not reliable tools for predicting prognosis for individual patients, since they do not account for molecular heterogeneity. Clearly, we need future prospective studies based on clinical monitoring and extensive correlative science.[15-17]

Indisputably, we need to improve our understanding in key areas, including pathogenesis and early oncogenic events, early bone marrow changes (including both tumor cells and bone marrow microenvironment), molecular imaging and its role in the detection of early myeloma disease, flow cytometry of peripheral blood and bone marrow aspirates to detect minimal residual disease and to predict outcome, characterization of early osteoclast and osteoblast changes in myelomagenesis, and improvements in molecular and clinical markers used to track disease progression beyond conventional M protein. We also need to develop early treatment strategies, based on rationale science, for high-risk myeloma precursor disease.[15-17]

In our opinion, the ultimate goal for the future should be to develop better molecular markers. Such markers would allow clinicians to identify high-risk and low-risk precursor patients so that these patients might receive more tailored clinical management; these markers would provide insights into the individual patient’s disease biology that in turn could be used to delineate targeted and more individualized treatment strategies.[15-17] In the near future, it seems reasonable to believe that high-risk precursor patients will likely become candidates for early treatment strategies. It is important that future studies assess the role of early treatment in relation to overall survival and quality of life. High response rates among SMM patients receiving treatment may not correlate with survival. One may speculate that prolonged “stable disease” will provide clinical benefit to patients; future studies will provide the answers to this and other important questions.

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