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EDITORIAL

Will the real myeloma please stand up?

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Epidemiological studies over the past several decades have contributed significantly to our understanding of monoclonal plasma cell disorders. It has become clear that symptomatic multiple myeloma is preceded in all patients by a precursor condition, the monoclonal gammopathy of undetermined significance (MGUS).[1–4] Patients with MGUS have a fixed risk of approximately 1% per year of progressing to symptomatic myeloma or another related condition, and various risk factors have been described to identify those at the highest risk of progression.[5–9] Equally important in this equation is the fact that 70–80% of these patients will never suffer a deleterious effect of the monoclonal process and eventually die of unrelated conditions. We are barely starting to understand the molecular underpinnings of the transition from a 'benign' clonal proliferation of plasma cells to a malignant state, capable of inducing the various end-organ effects associated with symptomatic myeloma. It is likely a multistep process, with the initial event leading to clonal proliferation of plasma cells with the associated increase in monoclonal protein: patients we diagnose as having MGUS. It is likely that additional clones with more malignant characteristics develop over time, either as a result of a critical event or a series of events, which confer the clonal cell with distinct survival advantages. One can hypothesize that this clone acquires additional changes over time and will gradually become the dominant clone, at which time the symptoms and signs of myeloma ensues.[10,11] Unfortunately, we do not have any molecular markers that can be reliably used to distinguish the malignant plasma cell from the benign, yet clonal, plasma cell. However, we have been able to use indirect markers of this clonal evolution to make crude estimates of the risk of development of myeloma.[5–9] Most of these factors directly or indirectly relate to the clonal burden and the impact of the malignant clone on the body systems.

At the time of the initial detection of the monoclonal protein, it is clear that there are a proportion of patients in whom development of symptomatic myeloma is incipient. From a clinical perspective, it is imperative that we identify these patients ahead of time, so that we can observe them closely and intervene appropriately. The categorization of patients as having 'smoldering multiple myeloma' (SMM) is the result of such an exercise.[12,13] The designation of SMM, originally defined using rather arbitrary cutoffs for bone marrow plasmacytosis of 10% and monoclonal protein values of 3.0 g/dl, allowed us to group these patients together for closer observation and clinical studies. Patients with smoldering myeloma have clearly a greater risk of developing multiple myeloma in the short term, with nearly half of them requiring therapy for myeloma in the first 5 years following diagnosis.

Careful analysis of the kinetics of progression in patients with SMM offers important insights. Nearly 30% of patients progress in the first 2 years, 20% in the next 3 years and another 20% in the ensuing 5 years.[12] However, the progression curves beyond 10 years suggest that the remaining patients have no higher risk of progression than the fixed risk seen among the MGUS patients.[4] In essence, this tells us that rather than being a unique biological entity, SMM is an arbitrary grouping of patients based purely on their clonal burden. This arbitrary group of patients clearly have those patients in whom the 'malignant switch' of the clonal plasma cells has occurred but the proportion of the malignant cells have not yet reached the tipping point, and those patients who really have a clonal proliferation of 'benign' plasma cells. This paradigm is very similar to many other clinical situations we deal with everyday. Take the patient with a fever of unknown origin, in whom the diagnosis is a temporary label given until a specific cause can be discovered, which typically occurs as the underlying condition evolves and makes itself obvious. Further refinement of this classification would require identification of molecular markers that can be applied to the clonal cells to differentiate the malignant plasma cell from the 'benign' one. An analogous situation would be that of colon polyps, where the majority of the polyps identified on routine examinations are benign collections of the colonic epithelial cells and have no implications for patient outcomes. However, in a small proportion of polyps, the pathologist can identify specific dysplastic features, which marks the presence of malignant transformation. Unfortunately, it is not possible to differentiate histopathologically clonal yet benign plasma cells from clonal malignant myeloma cells. Clearly, the ongoing efforts at molecular characterization of myeloma cells will lead us to that point in future.

Unfortunately, we cannot wait for the day where we can molecularly characterize the plasma cell as being malignant before making therapeutic decisions. There is a renewed urgency today to identify these patients early on in their clinical course, not because the natural history of this condition has changed over time, but because we have better tools that can be potentially used to intervene early. The current approach is to observe patients with SMM closely and institute therapy when they develop CRAB (hypercalcemia, renal failure, anemia and bone lesions) features.[14] This approach to SMM was developed during a time when limited therapeutic options were available and they were associated with significant toxicity and impaired quality of life. This together with lack of any data supporting improved survival with early intervention cemented the current thoughts regarding management of SMM. So, what has changed? It has become clear that even a very close follow-up of these patients will not preclude the development of catastrophic complications as the first evidence of CRAB, such as spinal cord compression from fractures or renal failure requiring dialysis.[15] It has been shown that patients with myeloma presenting with renal failure have a poor survival, with reversal of renal failure leading to improvement in outcomes but never to the level of those with no renal failure at diagnosis.[16] Although this may reflect biology, one cannot discount permanent renal damage as an explanation of this discrepancy. Another important change has been the availability of newer therapies, which are more effective and less toxic than what were available a decade ago.[17] We feel more confident and comfortable starting patients with myeloma on therapy today, given the improvements we have seen in outcome over the last decade. So, the key is identifying those patients who will develop myeloma in the immediate future, so that we can initiate therapy before they suffer irreversible complications from myeloma-related end-organ damage. That begs the question, how immediate is immediate? We would argue that if you can reliably identify patients who have an 80–90% risk of developing symptomatic myeloma within 2 years of their initial diagnosis

of SMM, it would be appropriate to initiate them on therapy. In a survey of myeloma experts by the International Myeloma Working Group, the majority felt that this degree of risk will be enough rational for initiating therapy instead of waiting for CRAB features to develop. Given the lack of molecular markers that can do this reliably, we need to develop clinical parameters that can serve as surrogate markers of early progression.

The two studies being published in this issue of *Leukemia* represent the efforts of the myeloma community to reach this goal. The current studies, one from the Mayo Clinic and the other from the Greek Myeloma group, provide remarkably congruent messages regarding the utility of serum-free light chain as such a surrogate marker. Although it has been known for some time that abnormal serum free light chain (FLC) ratios can predict progression in patients with MGUS and SMM, these studies demonstrate the use of very high levels of involved FLC and high involved to uninvolved FLC ratios to predict risk of early progression.[6,18] These studies come on the heels of two other recent publications, where we showed that the degree of plasmacytosis and presence of circulating plasma cells could be utilized in a similar fashion to identify the patients for early therapy.[19,20] It is clear that none of these clinical surrogate markers is likely to identify all the patients at risk of early progression and, hence, merit initiation of therapy. However, the development of a panel of markers, each with a high degree of specificity, will allow us to achieve that goal, while awaiting the development of specific and sensitive molecular markers.[11,21]

It is also very important that we do not confuse this exercise with the ongoing efforts at understanding the role of therapeutic intervention to prevent progression from SMM to symptomatic myeloma.[22] Although these two concepts overlap in terms of the patients being targeted, there is a fundamental difference. With the current exercise, we are not attempting to prevent progression, but rather redefining a small subset of patients with smoldering myeloma as patients who have multiple myeloma that requires therapy. This represents the tip of the iceberg. We still need prospective randomized control trials for the remaining majority of patients with smoldering myeloma to determine if current therapies can successfully prevent or delay progression, or achieve eradication of the malignant clone (cure), which is typically possible only by early intervention, or meaningfully alter the natural history of the disease. With all the advances in genomic technology, the day where we can examine the plasma cell and decide if the patient has myeloma or MGUS clearly cannot be too far, but until that happens, we can use the available tools to further reduce the morbidity in patients with myeloma and potentially improve their survival.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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