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Smoldering Multiple Myeloma: Changing the Management Paradigm or Just the Definition ?

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The time has come for Smoldering Multiple Myeloma (SMM) as we know it, to become a treatable disease in some cases. SMM accounts for approximately 15% of myelomas. Since its first description, thirty-four years ago, observation has been the gold standard, until myeloma-related end-organ/tissue injury occurs and symptomatic or Clinical Multiple Myeloma (CMM) develops. However, SMM may be considered as a "hinge disease", positioned between Monoclonal Gammopathy of Uncertain Significance (MGUS) and CMM. Virtually all cases of CMM are preceded by an asymptomatic phase, including both MGUS or SMM. Furthermore, SMM can behave stably (MGUS-like), but also as a slowly or rapidly progressive disease.

In recent years, several studies have attempted unsuccessfully to demonstrate a benefit of different treatment strategies for MMS, in terms of overall survival. A recent trial [1] by the Spanish Myeloma Group (PETHEMA/GEM), for the first time, has challenged the paradigm of observation, showing that early treatment of high-risk (HR) patients with lenalidomide and dexametasone, followed by maintenance with lenalidomide, significantly delayed the time to progression to symptomatic disease and resulted in an Overall Survival (OS) benefit. The study emphasizes the need to properly select patients with HR-SMM, but unfortunately, some limitations [2,3] prevent firm conclusions.

Attempts have been made to establish the characteristics of HR-SMM, but to date, there is no consensus about which criteria must fulfil these patients with the highest risk of progression to symptomatic MM. Several prognostic factors have been implicated and recently reviewed, including involved/ uninvolved serum free light chain (sFLC) ratio ≥ 100 [4], molecular cytogenetic abnormalities [5], phenotipically aberrant bone marrow plasma cells ≥ 95% [6], high levels of peripheral blood circulating plasma cells [7], monoclonal component ≥ 2,5 g/dl [8], bone marrow plasma cell count ≥ 60% [9], and others, or some combination of them.

The percentage of patients considered as HR-SMM varies depending on the method and definition used for this purpose. The two most widely used models for predicting the risk of progression of SMM are based on multiparameter flow cytometry (the Spanish model) or sFLC ratio (the Mayo Clinic model) but a high level of discordance between both clinical models have been observed [10], warranting the search for new biomarkers to help clinicians to determine if early treatment is beneficial for HR-SMM.

On the other hand, the role of modern imaging techniques is crucial because some patients with HR-SMM or even MGUS could be upgraded to CMM, based on the findings of magnetic resonance imaging (MRI) [11,12] or ^{18}F-fluorodeoxyglucose (^{18}F-FDG) positron emission tomography / computed tomography (PET/CT) [13].

Collectively, these reports provide an useful set of tools to predict the risk of progression of SMM, but still there is no consensus on how to use it. The definition of HR-SMM is controversial and even the current definition of SMM could be probably improved. From a practical point of view, in real-world clinical practice, a prognostic score for SMM should be based on easy, standardized, inexpensive and widely available tests. Furthermore, new prognostic scores should be tested in the context of a prospective trial and subsequently validated. The first prospective evaluation of clinical, genomic and imaging features of SMM and MGUS has just been reported [14], showing that integration of gene expression profiles data (score > -0.26, based on a 70-gene signature) with sFLC ratio > 25 and serum monoclonal spike > 3 g/dl, led to a risk model with high predictive level. It is currently difficult to ascertain if gene expression profiles will be moved, in the short run, from bench to bedside.

The clinical management of SMM is currently influenced by a high level of uncertainty, giving room for an unsuitable clinical variability. So how should we face real-world SMM patients today? The first step should be performing a diagnostic workup as comprehensive and exhaustive as possible, according to current guidelines and the best local available resources, including modern imaging techniques. Secondly, a prognostic evaluation is mandatory, to identify HR-SMM. The method of choice depends on the availability of each center, but sFLC ratio seems a good basic option, given that other methods are not standardized or widely available. Treatment should be probably offered to patients with sFLC ratio ≥ 100, bone marrow plasmocytosis ≥ 60% or positive imaging, since these patients could be reclassified as CMM. At present, enter a clinical trial is probably the best choice.

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