Lymphoma & Myeloma International Congress

Smoldering Multiple Myeloma: Who and When to Treat

María-Victoria Mateos, Verónica González-Calle

Abstract

Smoldering multiple myeloma (SMM) is an asymptomatic plasma cell disorder characterized by the presence of ≥ 3 g/dL serum M-protein and/or 10% to 60% bone marrow plasma cell infiltration with no myeloma-defining event. The risk of progression to active multiple myeloma (MM) is not uniform, and several markers are useful for identifying patients at high risk of progression. The definition of the disease has recently been revisited and asymptomatic MMs at 80% to 90% of progression risk at 2 years are now considered to be active MM candidates for treatment. In the future, more precise biomarkers are necessary for accurate risk stratification to plan an optimized follow-up according to the risk of progression, as well as to expand the group of patients that can obtain a benefit if they receive early treatment. A phase 3, randomized trial in high-risk patients with SMM comparing early treatment versus observation has shown a significant benefit in terms of time to progression and overall survival for early intervention and confirmatory clinical trials will definitively contribute to establish the early treatment as standard of care in high-risk SMM.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 17, No. 11, 716-22
Key words: Asymptomatic, Biomarkers, Early treatment, Risk factors, Smoldering multiple myeloma

Introduction

Smoldering multiple myeloma (SMM) is an asymptomatic plasma cell disorder defined in 1980 by Kyle and Greipp[1] on the basis of a series of 6 patients who met the criteria for multiple myeloma (MM) but whose disease did not have an aggressive course.

At the end of 2014, the International Myeloma Working Group (IMWG) updated the definition and SMM was defined as a plasma cell disorder characterized by the presence of ≥ 3 g/dL serum M-protein and/or 10% to 60% bone marrow plasma cells (BMPCs), but with no evidence of myeloma-related symptomatology (hypercalcemia, renal insufficiency, anemia, or bone lesions [CRAB]) or any other myeloma-defining event (MDE).[2] According to this recent update criteria, the definition of SMM excludes asymptomatic patients with BMPCs of 60% or more, serum free light chain (FLC) levels of ≥ 100, and those with 2 or more focal lesions in the skeleton as revealed by magnetic resonance imaging (MRI).

Kristinsson et al,[3] based on the Swedish Myeloma Registry, has recently reported that 14% of patients diagnosed with myeloma had SMM and, accordingly, the age-standardized incidence of SMM would be 0.44 cases per 100,000 people.[3]

Hematology Department, Complejo Asistencial Universitario de Salamanca/Instituto Biosanitario de Salamanca (CAUSA/IBSAL), Salamanca, Spain

Submitted: Apr 21, 2017; Accepted: Jun 8, 2017; Epub: Jun 23, 2017

Address for correspondence: María-Victoria Mateos, MD, PhD, Hematology Department, Complejo Asistencial Universitario de Salamanca/Instituto Biosanitario de Salamanca, Paseo San Vicente, 58-182, 37007 Salamanca, Spain
E-mail contact: mvmateos@usal.es

Differential Diagnosis With Other Entities

SMM must be distinguished from other plasma cell disorders, such as monoclonal gammopathy of undetermined significance (MGUS) and symptomatic MM (Table 1). The MGUS entity is characterized by a level of serum M-protein of < 3 g/dL plus < 10% plasma cell infiltration in the bone marrow, with no CRAB and no MDE. Symptomatic MM must always have CRAB symptomatology or MDE, in conjunction with ≥ 10% clonal BMPC infiltration or biopsy-proven bony or extramedullary plasmacytoma.[2]

End-organ damage often needs to be correctly evaluated to distinguish myeloma-related symptomatology from some signs or symptoms that could otherwise be attributed to comorbidities or concomitant diseases.[4]

Due to the updated IMWG criteria for the diagnosis of MM, there are some specific assessments to which physicians must pay attention to make a correct diagnosis of SMM.[2]

(1) For evaluation of bone disease, the IMWG recommends performing in all patients with suspected SMM one of the following procedures: skeletal survey, 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT), or low-dose whole-body CT be carried out, with the exact modality determined by

2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2017.06.022

availability and resources. The aim is to exclude the presence of osteolytic bone lesions, currently defined by the presence of at least 1 lesion ($\geq$ 5 mm) revealed by radiograph, CT, or PET-CT. In addition, whole-body MRI of the spine and pelvis is a mandatory component of the initial workup. It provides detailed information about not only bone marrow involvement but also the presence of focal lesions that predict more rapid progression to symptomatic myeloma. Hillengass et al[5] reported in 2010 that the presence of more than 1 focal lesion in whole-body MRI was associated with a significantly shorter median time to progression (TTP) to active disease (13 months), as compared with patients without focal lesions. Kastritis and colleagues[6] reported similar results after the analysis of a subgroup of patients who underwent spinal MRI and were followed for a minimum of 2.5 years. The median TTP to symptomatic disease was 14 months when more than 1 focal lesion was present.[6] Therefore, if more than 1 focal lesion in MRI is present in a patient with SMM, this entity should no longer be considered as SMM but as MM, according to the current IMWG criteria. It is important to emphasize that they should be unequivocal focal lesions larger than 5 mm.

(2) With respect to bone marrow infiltration, the Mayo Clinic group evaluated BMPC infiltration in a cohort of 651 patients and found that 21 (3.2%) had an extreme infiltration ($\geq$ 60%).[7] This group of patients had a median TTP to active disease of 7.7 months, with a 95% risk of progression at 2 years. This finding was subsequently validated in a study of 96 patients with SMM, in whom a median TTP of 15 months was reported for the group of patients with this extreme infiltration.[8] In a third study, 6 (5%) of 121 patients with SMM were found to have $\geq$ 60% BMPC, and all progressed to MM within 2 years.[9] Therefore, if $\geq$ 60% of clonal plasma cell infiltration is present either in bone marrow aspirate or biopsy, the diagnosis of SMM should be replaced by MM. Additional assessments, for example, by flow cytometry or by identifying cytogenetic abnormalities in patients with SMM, are not mandatory but can help to estimate the risk of progression to active disease.

(3) With respect to the serum FLC (sFLC) assay, Larsen et al[10] studied 586 patients with SMM to determine whether there was a threshold FLC ratio that predicted 85% of progression risk at 2 years. They found a serum involved/uninvolved FLC ratio of at least 100 in 15% of patients and their risk of progression to symptomatic disease was 72%. Similar results were obtained in a study by Kastritis and colleagues[8] from the Greek Myeloma Group. In their study of 96 patients with SMM, 7% had an involved/uninvolved FLC ratio of $\geq$ 100 and almost all progressed within 18 months. In a third study, the risk of progression within 2 years was 64%.[9] Therefore, physicians must perform the sFLC assay at the moment SMM is first suspected and, if the involved/uninvolved ratio is $\geq$ 100, a diagnosis of active MM instead of SMM should be established.

If, after considering the specific assessments mentioned previously (Table 2), a diagnosis of SMM is finally made, the serum and urine M-component, hemoglobin, calcium, and creatinine levels should be reevaluated 2 to 3 months later to confirm the stability of these parameters. The frequency of the subsequent follow-up examinations should be adapted on the basis of risk factors for progression to symptomatic MM (see the next section).

How to Evaluate the Risk of Progression to MM?

The annual risk of progression from SMM to symptomatic MM is 10% per year for the first 5 years, 5% per year during the following 5 years, and only 1% per year after 10 years.[11] Although most patients diagnosed with SMM will progress to symptomatic MM and will need to start treatment, SMM is not a uniform disorder.

Several groups have reported possible predictors of progression to symptomatic MM, and this information could be useful for physicians and can help to explain to patients their risk of progression to active MM (Table 3).

Size of Serum M-Protein and the Extent of Marrow Involvement

The Mayo Clinic group[11] proposed 3 SMM subgroups according to BMPC infiltration and the size of the serum M-protein. Group 1 was characterized by $\geq$ 3 g/dL of M-protein and $\geq$ 10% of plasma cells in bone marrow, with a median TTP to symptomatic MM of 2 years. Group 2 featured $\leq$ 3 g/dL of M-protein and $\geq$ 10% BMPCs M-protein with a median TTP of 8 years. Group 3 had $\geq$ 3 g/dL of M-protein but $<$ 10% BMPC infiltration, resulting in a median TTP of 19 years.

sFLC Ratio

The Mayo Clinic group also evaluated the previously described patient population to identify the risk of progression to symptomatic myeloma on the basis of an FLC assay. A kappa/lambda FLC ratio between 0.125 and 8 was found to be associated with an increase in the risk of progression to symptomatic MM. This parameter was added to their previous score, which considered the size of serum M-protein and BMPC infiltration, to refine the Mayo risk stratification model. This yielded 3 groups, with a median TTP of 1.9 years for the high-risk group, whose members exhibited all 3 defined risk factors.[12]

The Danish Myeloma Group did not find in the analysis of Danish National Multiple Myeloma Registry any significant threshold for the sFLC ratio, therefore they do not support the recent IMWG proposal that identifies patients with an FLC ratio above 100 as having ultra-high risk of transformation to MM.[13]

Immunophenotyping and Immunoparesis

Multiparameter flow cytometry (MFC) to identify the immunophenotypic profile of plasma cells in SMM has been evaluated by the Spanish Myeloma Group. We reported that the presence of an aberrant BMPC phenotype in the vast majority of plasma cells (PCs) ($\geq$ 95% phenotypically abnormal plasma cells from total PCs) determined by MFC (defined as the overexpression of CD56 and CD19, CD45 negative and/or decreased reactivity for CD38) was the most important predictor of early progression from SMM to active MM.[14] The presence of immunoparesis (ie, a decrease in 1 or