Smoldering Multiple Myeloma

María-Victoria Mateos, MD, PhD

University Hospital of Salamanca/IBSAL, Salamanca

Smoldering Multiple Myeloma (SMM) is an asymptomatic disorder characterized by the presence of ≥ 3 g/dL serum M-protein and/or 10-60% bone marrow plasma cell infiltration with no myeloma-defining event. Kristinsson et al., through the Swedish Myeloma Registry, recently reported that 14% of patients diagnosed with myeloma had SMM and, taking the world population as a reference, that the age-standardized incidence of SMM was 0.44 cases per 100,000 people. The risk of progression to active MM is not uniform, and several markers are useful for identifying patients at high risk of progression, approximately 50% at 2 years. The definition of the disease has recently been revisited and asymptomatic MMs at 80-90% of progression risk at 2 years are now considered to be MMs. The biomarkers for the identification of this subgroup of patients are: 1) the presence of more than one focal lesions in magnetic resonance imaging, 2) more than 60% of plasma cells within the bone marrow, or 3) a ratio of involved versus uninvolved serum free light ratio equal to or higher than 100. For the rest of patients, the standard of care is observation, although a randomized trial in high-risk SMM patients comparing early treatment versus observation has shown early intervention to provide a significant benefit in terms of time to progression and overall survival. These findings highlight the need to follow a correct diagnosis by accurate risk stratification in order to plan an optimized follow-up according to the risk of progression: if ultra high-risk of progression, patients should be called myeloma

and treated; if low or intermediate risk of progression, it would be necessary to do follow-up every year or twice-year; and if high-risk of progression to myeloma is present, the best option is the patients to be refered to a center specialized in myeloma and include them in a clinical trial if available.

Introduction

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

At the end of 2014, the International Myeloma Working Group (IMWG) updated the definition and SMM is now defined as a plasma cell disorder characterized by the presence of one or both of the features of ≥ 3 g/dL serum M-protein and 10-60% 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, the definition of SMM excludes asymptomatic patients with BMPCs of 60% or more, serum free-light chain (FLC) levels of ≥ 100, and those with two or more focal lesions of the skeleton as revealed by magnetic resonance imaging (MRI).

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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 plasacytoma[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].

Diagnostic work-up

Initial investigation of a patient with suspected SMM should include the tests shown in Table 2, which are coincidental with those used for a correct diagnosis of symptomatic MM[5]. However, due to the updated IMWG criteria for the diagnosis of MM, there are some specific assessments to which physicians have to pay attention in order to make a correct diagnosis of SMM[2].

1) With respect to the evaluation of bone disease, the IMWG recommends that one procedure from skeletal survey, ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT), or low-dose whole-body CT be carried out in all patients with suspected SMM, with the exact modality determined by availability and resources. The aim is to exclude the presence of osteolytic bone lesions, currently defined by the presence of at least one lesion (≥ 5 mm) revealed by X-ray, CT or PET-CT. In addition, whole-body MRI of the spine and pelvis is a necessary component of the initial work-up. 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. reported in 2010 that the presence of more than one focal lesion in whole-body MRI was associated with a significantly shorter median time to progression (TTP) to active disease of 13 months, compared with the period when no focal lesions were present[6]. Kastritis

and colleagues reported similar results after the analysis of a subgroup of patients who underwent spinal MRI and were followed up for a minimum of 2.5 years. The median TTP to symptomatic disease was 14 months when more than one focal lesion was present[7]. Therefore, if more than one focal lesions in MRI are present in SMM patients, this entity should no longer be considered as SMM but as MM, according to the current IMWG criteria.

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 (≥ 60%)[8]. 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[9]. In a third study, six of 121 patients (5%) with SMM were found to have ≥ 60% BMPC, and all progressed to MM within 2 years[10]. Therefore, if ≥ 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 SMM patients, are not obligatory but can help estimate the risk of progression to active disease.

3) With respect to the serum free-light chain (FLC) assay, Larsen et al. 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 a risk of progression to symptomatic disease of 72%[11]. Similar results were obtained in a study by Kastritis and colleagues from the Greek Myeloma Group. In their study

of 96 SMM patients, 7% had an involved/uninvolved FLC ratio of ≥ 100 and almost all progressed within 18 months[9]. In a third study, the risk of progression within 2 years was 64%. Therefore, physicians must consider the sFLC assay at the moment SMM is first suspected and, if the involved/uninvolved ratio is ≥ 100, they should discount a diagnosis of SMM because MM is the correct diagnosis under these circumstances.

Once a diagnosis of SMM has been made, considering the specific assessments mentioned above, the serum and urine M-component, hemoglobin, calcium and creatinine levels should be re-evaluated 2-3 months later to confirm the stability of these parameters. The subsequent follow-up involves the same evaluation but the frequency should be adapted on the basis of risk factors for progression to symptomatic MM (see below).

Risk factors predicting progression to active MM

Most patients diagnosed with SMM will progress to symptomatic MM and will need to start treatment. However, SMM is not a uniform disorder and once the diagnosis has been confirmed, the doctor should evaluate the risk of progression to symptomatic disease in order to plan an appropriate, risk-based follow-up, and to optimize the management of the SMM patient. 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[12].

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

Management of SMM patients

The standard of care for the management of SMM patients has been observation until MM develops. However, several groups evaluated the role of early intervention in this group of patients using conventional and novel agents.

There have been different trials evaluating the role of early treatment with melphalan and prednisone (MP), or novel agents, such as thalidomide or even bisphosphonates.

None of these trials provided evidence favoring the early treatment of patients with SMM. However, they were conducted without considering the differences in the risk of progression to active disease, and while the high-risk subgroup of patients may have benefited, this could have been counterbalanced by the absence of benefit in low-risk patients. The Spanish myeloma group (GEM/Pethema) has conducted a phase 3 randomized trial in 119 SMM patients at high risk of progression to active disease (according to the Mayo and/or Spanish criteria) that compared early treatment with lenalidomide plus dexamethasone as induction followed by lenalidomide alone as maintenance versus observation. The primary end-point was TTP to symptomatic MM, and after a median follow-up of 40 months, the median TTP was significantly longer in patients in the early treatment group than in the observation arm (not reached *vs.* 21 months; hazard ratio, HR = 5.59; $p < 0.001$). Secondary end-points included response, OS and safety. The PR or better after induction was 82%, including 14% of cases of stringent complete response (sCR) plus CR, and after maintenance the sCR/CR rate increased to 26%. The safety profile was acceptable and most of the adverse events reported were grade 1 or 2. The OS analysis showed that the 3-year survival rate was also higher for the group of

patients who received early treatment with lenalidomide-based therapy (94% *vs.* 80%; HR = 3.24; p = 0.03)[13]. A recent update of this trial confirmed the efficacy of early treatment in terms of TTP (HR = 6.21; 95% CI: 3.1-12.7, p<0.0001) and the benefit to OS was even more evident with longer follow-up (HR = 4.35, 95% CI: 1.5-13.0, p=0.008)[14]. This study showed for the first time the potential for changing the treatment paradigm for high-risk SMM patients based on the efficacy of early treatment in terms of TTP to active disease and of OS. Moreover, several trials currently underway are focusing on high-risk SMM patients using novel agents.

Managing SMM patients in clinical practice

Given the extensive background to this disease described above, the first step in clinical practice is to identify the risk of progression to active disease for each newly diagnosed SMM patient. The key question is which risk model is better for evaluating the risk of progression to symptomatic disease for each individual SMM patient. The Mayo Clinic and Spanish models enable initial risk stratification of SMM and, in fact, both were validated in a prospective trial. However, new risk models are emerging that incorporate new clinical and biological features[10,12,15-20](Table 4). The components of these models are not identical, and each patient's risk should probably be defined on the basis of all the available data rather than through the use of a restricted model (Table 3).

SMM patients should be classified as follows:

1) Patients at low risk of progression who are characterized by the absence of the aforementioned high-risk factors (using the validated Mayo and Spanish risk models), with a probability of progression at 5 years of only 8%. The patients in this group behave similarly to MGUS-like patients and should be followed

annually.

2) The second group includes patients at intermediate risk of progression and they only display some of the aforementioned high-risk factors. These are probably the true SMM patients. They have a risk of progression at 5 years of 42%, and they must be followed up every 6 months.

3) The third group includes high-risk patients classified on the basis of one of the risk models mentioned above. Half of them will progress during the 2 years following diagnosis. These group of patients need a close follow-up every 2-3 months. The key question is whether this high-risk group should be treated. Although the Spanish trial showed significant benefit from the early treatment in high-risk SMM patients, there are some limitations that prevent the results being generally applicable at present; these may be resolved when the results of the ongoing clinical trials become available. The best approach for these patients should be to refer them to centers that specialize in MM therapy and to include them in clinical trials to better understand their biology and to confirm the survival benefit of early treatment in this cohort[21].

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Table 1. Differential diagnosis of MGUS, SMM and symptomatic MM

Feature	**MGUS**	**SMM**	**MM**
Serum-M protein	< 3 g/dL and	≥ 3 g/dL and/or	
Clonal BMPC infiltration	< 10%	10-60%	≥ 10% or biopsy-proven plasmacytoma
Symptomatology	Absence of CRAB*	Absence of MDE** or amyloidosis	Presence of MDE**

* CRAB includes (1) hypercalcemia: serum calcium > 0.25 mmol/L (> 1 mg/dL) higher than the upper limit of normal or > 2.75 mmol/L (> 11 mg/dL); (2) renal insufficiency: serum creatinine > 177 μmol/L (2 mg/dL) or creatinine clearance < 40 ml/min; (3) anemia: hemoglobin value of > 2 g/dL below the lower normal limit, or a hemoglobin value < 10 g/dL; (4) bone lesions: one or more osteolytic lesion revealed by skeletal radiography, CT, or PET-CT.

**MDE: Myeloma-defining events include CRAB symptoms (above) or any one or more of the following biomarkers of malignancy: clonal bone marrow plasma cell percentage ≥ 60%; involved/uninvolved serum free light-chain ratio ≥ 100; > 1 focal lesions revealed by MRI studies.

Table 2. Work-up for newly diagnosed SMM patients

• Medical history and physical examination
• Hemogram
• Biochemical studies, including of creatinine and calcium levels; Beta2-microglobulin, LDH and albumin
• Protein studies - Total serum protein and serum electrophoresis (serum M-protein) - 24-h urine sample protein electrophoresis (urine M-protein) - Serum and urine immunofixation • Serum free light-chain measurement (sFLC ratio)
• Bone marrow aspirate ± biopsy: infiltration by clonal plasma cells, flow cytometry and fluorescence *in situ* hybridization analysis
• Skeletal survey, CT, or PET-CT
• MRI of thoracic and lumbar spine and pelvis; ideally, whole-body MRI

FLC: free light chain; CT: computed tomography; PET-CT: ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT; MRI: magnetic resonance imaging

Table 3. Smoldering MM: markers predicting progression to symptomatic MM

Features for identifying high-risk SMM patients: 50% at 2 years
• **Tumor burden:** ▪ - ≥ 10% clonal plasma cell bone marrow infiltration plus - ≥ 3 g/dL of serum M-protein and - serum free light-chain ratio between 0.125 and 8 ▪ Bence Jones proteinuria positive from 24-h urine sample ▪ Peripheral blood circulating plasma cells > 5 x 10^6/L
• **Immunophenotyping characterization and immunoparesis:** ▪ - ≥ 95% of aberrant plasma cells by flow within the plasma cell bone marrow compartment plus - immunoparesis (> 25% decrease in one or both uninvolved immunoglobulins relative to the lowest normal value)
• **Cytogenetic abnormalities:** - Presence of t(4;14) - Presence of del17p - Gains of 1q24 - Hyperdiploidy - Gene Expression Profiling risk score > -0.26
• **Pattern of serum M-component evolution** - Evolving type: if M-protein ≥ 3 g/dL, increase of at least 10% within the first 6 months. If M-protein < 3 g/dL, annual increase of M-protein for 3 years - Increase in the M-protein to ≥ 3 g/dL over the three months since the previous determination
• **Imaging assessments** - MRI: Radiological progressive disease (MRI-PD) was defined as newly detected focal lesions (FLs) or increase in diameter of existing FL and a novel or progressive diffuse infiltration. - Positive PET/CT with no underlying osteolytic lesion

MRI: magnetic resonance imaging; PET-CT: ^{18}F-fluorodeoxyglucose (FDG) positron-emission tomography (PET)/CT

Table 4. Risk models for the stratification of SMM

Risk Model	Risk of progression to MM	
Mayo Clinic		**Median TTP**
- ≥ 10% clonal PCBM infiltration	1 risk factor	10 years
- ≥ 3 g/dL of serum M-protein	2 risk factors	5 years
- serum FLC ratio between < 0.125 or > 8	3 risk factors	1.9 years
Spanish Myeloma		**Median TTP**
- ≥ 95% of aberrant PCs by MFC	No risk factor	NR
- immunoparesis	1 risk factor	6 years
	2 risk factors	1.9 years
Heidelberg		**3- year TTP**
- Tumor mass using the Mayo Model	T-mass low + CA low risk	**15%**
- t(4;14), del17p, or +1q	T-mass low + CA high risk	**42%**
	T-mass high + CA low risk	**64%**
	T-mass high + CA high risk	**55%**
SWOG		**2-year TTP**
- Serum M-protein ≥ 2 g/dL	No risk factor	30%
- Involved FLC > 25 mg/dL	1 risk factor	29%
- GEP risk score >-0.26	≥ 2 risk factors	71%
Penn		**2-year TTP**
- ≥ 40% clonal PCBM infiltration	No risk factor	16%
- sFLC ratio ≥ 50	1 risk factor	44%
- Albumin ≤ 3.5 mg/dL	≥2 risk factors	81%
Japanese		**2-year TTP**
- Beta 2-microglobulin ≥ 2.5 mg/L	2 risk factors	67.5%
- M-protein increment rate > 1 mg/dL/day		
Czech & Heidelberg		**2-year TTP**
- immunoparesis	No risk factor	5.3%
- serum M-protein ≥ 2.3 g/dL	1 risk factor	7.5%
- involved/uninvolved sFLC > 30	2 risk factors	44.8%
	3 risk factors	81.3%
Barcelona		**2-year TTP**

- evolving pattern = 2 points - serum M-protein ≥ 3 g/dL = 1 point - immunoparesis = 1 point	0 points 1 point 2 points 3 points	2.4% 31% 52% 80%