Future Directions in the Evaluation and Treatment of Precursor Plasma Cell Disorders

Salomon Manier, MD, Karma Z. Salem, MD, David Liu, MD, and Irene M. Ghobrial, MD

Overview

Multiple myeloma (MM) is an incurable disease that progresses from a premalignant stage termed monoclonal gammopathy of undetermined significance (MGUS) and an intermediate stage of smoldering multiple myeloma (SMM). Recent major advances in therapy with more effective and less toxic treatments have brought reconsideration of early therapeutic intervention in management of SMM, with the goal of reducing progression of the disease before the occurrence of end-organ damage to MM and improving survival. Key to this effort is accurate identification of patients at high risk of progression who would truly benefit from early intervention. In this review, we discuss the current definitions, risk factors, risk stratification, prognosis, and management of MGUS and SMM, as well as new emerging therapeutic options under active investigation.

Multiple myeloma evolves through a spectrum of disease from a premalignant stage of MGUS to an intermediate stage of SMM and finally presents with symptoms and signs of end-organ damage that lead to the diagnosis of MM. Recent studies have indicated that almost all cases of MM are preceded by the precursor state of MGUS or SMM. Over the years, the diagnosis of MM required evidence of end-organ damage attributable to the neoplastic clone of plasma cells, the so-called CRAB criteria identified by hypercalcemia, renal failure, anemia, and osteolytic bone lesions. This definition was intended to be conservative to avoid unnecessary and toxic administration of chemotherapy to patients with asymptomatic disease. However, with major advances in therapy, and identification of potential biomarkers that can distinguish MM from premalignant stages, it became necessary to revise the disease definition of MM.

In 2014, the International Myeloma Working Group (IMWG) updated the diagnostic criteria for MM to add three markers that can identify additional patients not yet meeting CRAB criteria who should nevertheless be treated. These were termed myeloma-defining events (MDEs) and constituted the presence of clonal bone marrow (BM) plasma cells greater than or equal to 60%, serum free light chain (FLC) ratio greater than or equal to 10, provided the involved FLC level is higher than or equal to 100 mg/L, or more than one focal lesion on MRI or CT and PET-CT.

Importantly, the revised definition excluded patients previously considered to have SMM with ultra-high risk of progression (80% within 2 years) who are now classified as MM based on the updated diagnostic criteria. However, it should be noted that the revised diagnostic criteria for MM upstages only a small proportion of patients with SMM. Thus, SMM as an entity continue to be relevant and important. Therefore, there is a need to better define the clinical and molecular characteristics of patients with MGUS and SMM that predict progression to MM. Here, we review the diagnostic criteria and risks of progression for MGUS and SMM and delineate potential therapeutic options that can be used for patients with high-risk SMM.

Definition, Incidence, and Risk of Progression of MGUS

MGUS is a premalignant precursor of MM. It is defined by a serum M-protein concentration lower than 3 g/dL and/or an abnormal FLC ratio (< 0.26 or > 1.65), less than 10% clonal plasma cells in the BM, and absence of MDEs or evidence of Waldenstrom macroglobulinemia or amyloidosis (Table 1). When first clinically recognized, MGUS has likely been present in an undetected state for a median duration of more than 10 years.

MGUS is present in over 3% to 4% of the population older than age 50 and increases with age to 8.9% in people older than age 85. Therefore, one of the most important risk factors for MGUS is age. In addition to an accumulation of cases, the age-related increase in prevalence of MGUS is related to a true increase in incidence with age.
Apart from age, there are several factors that are associated with a higher risk of developing MGUS, including African American race and a familial history of myeloma. Other factors such as the presence of autoimmune disorders are less well delineated. Persons of African and African American descent have a threefold increased prevalence even after adjusting for socioeconomic and other risk factors, suggesting a genetic predisposition among this population. An increased prevalence of MGUS in Africans relative to Caucasians has also been reported in Ghana. Two studies have shown that the risk of MM and MGUS is increased threefold in relatives of individuals with MGUS. In addition, an increased risk of developing non-Hodgkin lymphoma and chronic lymphoid leukemia was also observed in this group. Collectively, these data are consistent with an inherited twofold to fourfold genetic susceptibility to MM. The genetic basis of inherited MM susceptibility is incompletely understood. However, recent genome-wide association studies (GWAS) identified seven loci contributing to inherited genetic susceptibility to MM. These seven loci were also associated with an increased risk of developing MGUS. Another GWAS study in the Nordic region identified a novel MM risk locus at ELL2. There are three subtypes of MGUS: non–immunoglobulin M (IgM) MGUS, IgM MGUS, and light-chain MGUS. Non-IgM MGUS carries a risk of progression to MM or solitary plasmacytoma, whereas IgM MGUS is associated with a risk of progression to Waldenström macroglobulinemia. Light-chain MGUS is a newly discovered entity that is associated with a risk of progression to the light-chain type of MM. All forms of MGUS can progress to Ig light-chain amyloidosis. MGUS is associated with a lifelong risk of transformation to MM or a related malignancy at a rate of 1% per year. In some patients, however, the risk may be as high as 58% in 20 years. The size and subtype of the M protein at diagnosis of MGUS and an abnormal serum FLC ratio are well-established prognostic factors for progression. As such, MGUS can be risk stratified using three simple variables: the serum FLC ratio, the size of the M protein, and the type of M protein (Table 2). Patients with serum M protein < 1.5 g/dL, IgG class, and normal FLC ratio are considered low-risk MGUS and have only a 2% lifetime risk of progression. In general, patients with MGUS must be reassessed in 6 months, and if stable yearly thereafter. A number of lifestyle and environmental risk factors have been proposed to increase the risk of progression from MGUS to MM, including obesity, immune dysfunction, and agricultural, chemical, and radiation exposure. Of these, obesity is probably the most consistently reported association. Studies are ongoing to determine the mechanism of progression of MGUS and to explore preventive strategies.

In addition to the risk of progression, MGUS can also be associated with several other clinical problems including sensorimotor peripheral neuropathy (MGUS neuropathy), membranoproliferative glomerulonephritis, lichen myxedematosus (papular mucinosis, scleromyxedema), pyoderma gangrenosum, or necrobiotic xanthogranuloma.

### TABLE 1. IMWG Diagnostic Criteria for MGUS, SMM, and MDEs

<table>
<thead>
<tr>
<th>IMWG Criteria, 2014 Version</th>
<th><strong>MGUS</strong></th>
<th><strong>SMM</strong></th>
<th><strong>MDEs</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum M protein</td>
<td>&lt; 3 g/dL or abnormal FLC ratio</td>
<td>&gt; 3 g/dL</td>
<td>Evidence of end-organ damage (CRAB criteria):</td>
</tr>
<tr>
<td>Involved/uninvolved serum FLC ratio</td>
<td>(&lt; 0.26 or &gt; 1.65) with increased level of appropriate involved light chain</td>
<td>AND/OR urinary monoclonal protein &gt; 500 mg per 24 hours</td>
<td>Hypocalcemia: serum Ca &lt; 0.25 mmol/L (&lt; 1 mg/dL) above upper limit of normal</td>
</tr>
<tr>
<td>Clonal BM plasma cells</td>
<td>&lt; 10%</td>
<td>AND/OR clonal BM plasma cells &gt; 10% or &lt; 60%</td>
<td>Renal insufficiency: serum creatinine &gt; 173 μmol/L (&gt; 2 mg/dL)</td>
</tr>
<tr>
<td>Absence of MDEs or amyloidosis</td>
<td></td>
<td>AND/OR bone marrow</td>
<td>Anemia: hemoglobin value of &gt; 2 g/dL below the lower limit of normal or a hemoglobin value &lt; 10 g/dL</td>
</tr>
<tr>
<td>Bone lesions: one or more lytic lesion(s) on skeletal radiography, CT, or PET-CT</td>
<td></td>
<td></td>
<td>Bone lesions: one or more lytic lesion(s) on skeletal radiography, CT, or PET-CT</td>
</tr>
<tr>
<td>Clonal BM plasma cell percentage</td>
<td>&gt; 60%</td>
<td></td>
<td>Clonal BM plasma cell percentage ≥ 60%</td>
</tr>
<tr>
<td>Involved/uninvolved serum FLC ratio</td>
<td>&gt; 100</td>
<td></td>
<td>Involved/uninvolved serum FLC ratio ≥ 100</td>
</tr>
<tr>
<td>More than one focal lesions on MRI</td>
<td></td>
<td></td>
<td>More than one focal lesions on MRI</td>
</tr>
</tbody>
</table>

Abbreviations: IMWG, International Myeloma Working Group; MGUS, monoclonal gammopathy of undetermined significance; SMM, smoldering multiple myeloma; MM, multiple myeloma; MDEs, myeloma-defining events; FLC, serum free light chain; BM, bone marrow.

**KEY POINTS**

- Multiple myeloma is always preceded by precursor conditions including MGUS and smoldering myeloma.
- The rate of progression of MGUS is at 1% per year, but the rate of progression of SMM is 10% per year, with a high rate of progression of 50% at 2 years for those with high-risk features.
- Patients with high-risk SMM should be offered clinical trials to prevent progression or carefully observed to avoid end-organ damage.
- Patients with MGUS and SMM have different risk stratifications and rates of progression.
- Some patients may benefit from early therapeutic interventions, specifically in high-risk SMM.
and Greipp in 1980 and was followed by many other descriptions terming it indolent MM, or Durie Salmon stage I. In 2003, the IMWG defined SMM as having a serum M-protein level higher than or equal to 3 g/L and/or greater than or equal to 10% monoclonal plasma cells in the BM (Table 3). Although the incidence and prevalence of SMM in the population is not well defined, it has been estimated to represent approximately 8% to 20% of patients within the MM spectrum.

The update to the disease definition of MM automatically resulted in revised diagnostic criteria for SMM as it excludes patients with ultra-high–risk SMM who are now considered as having overt MM (Table 1). Despite that, it remains a major clinical dilemma with an overall risk of progression of 10% per year for the first 5 years, 3% per year for the next 5 years, and 1% per year for the last 10 years. This suggests that the current definition of SMM is highly biologically and clinically heterogeneous.

### TABLE 2. Risk of Progression of Monoclonal Gammopathy of Undetermined Significance to Myeloma or Related Disorders

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Relative Risk of Progression</th>
<th>Cumulative Absolute Risk of Progression at 20 Years (%)</th>
<th>Cumulative Absolute Risk of Progression at 20 Years Accounting for Death as a Competing Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk: Serum M Protein &lt; 1.5 g/dL, IgG Subtype, Normal Free Light Chain Ratio (0.26–1.65)</td>
<td>1</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Low-Intermediate Risk: Any One Factor Abnormal</td>
<td>5.4</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td>High-Intermediate Risk: Any Two Factors Abnormal</td>
<td>10.1</td>
<td>37</td>
<td>18</td>
</tr>
<tr>
<td>High Risk: All Three Factors Abnormal</td>
<td>20.8</td>
<td>58</td>
<td>27</td>
</tr>
</tbody>
</table>

Adapted from Rajkumar et al with permission from the publisher.
*Estimates in this column represent the risk of progression assuming that patients do not die of other causes during this period.
**Estimates in this column represent the risk of progression calculated by using a model that accounts for the fact that patients can die of unrelated causes during this time.

### TABLE 3. Risk Stratification of Patients with Smoldering Myeloma Based on Mayo Clinic and Spanish Criteria

<table>
<thead>
<tr>
<th>Model</th>
<th>Risk Factors</th>
<th>No. of Risk Factors</th>
<th>5-Year Progression (%)</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayo Clinic Model</td>
<td>M protein ≥ 3 g/dL</td>
<td>1</td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>≥ 10% BM plasma cells</td>
<td>2</td>
<td>51</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>FLC ratio &lt; 0.125 or &gt; 8</td>
<td>3</td>
<td>76</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>51</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Spanish (PETHEMA) Model</td>
<td>≥ 95% aPC</td>
<td>0</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Immunoparesis</td>
<td>1</td>
<td>46</td>
<td>11.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2</td>
<td>72</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>46</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

Proposed New Criteria for High-Risk SMM

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Relative Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immuno-paresis with reduction of two uninvolved Ig isotypes</td>
<td></td>
</tr>
<tr>
<td>Serum involved/uninvolved FLC ratio ≥ 8 (but &lt; 100)</td>
<td></td>
</tr>
<tr>
<td>Progressive increase in M-protein level (evolving type of SMM)</td>
<td></td>
</tr>
<tr>
<td>BM clonal plasma cells 50% to 60%</td>
<td></td>
</tr>
<tr>
<td>aPC immunophenotype (≥ 95% of BM plasma cells are clonal) and reduction of one or more uninvolved Ig isotypes</td>
<td></td>
</tr>
<tr>
<td>t(4;14) or del 17p or 1q gain</td>
<td></td>
</tr>
<tr>
<td>Increased circulating plasma cells</td>
<td></td>
</tr>
<tr>
<td>MRI with diffuse abnormalities or one focal lesion</td>
<td></td>
</tr>
<tr>
<td>PET-CT with focal lesion with increased uptake without underlying osteolytic bone destruction</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BM, bone marrow; FLC, serum free light chain; NA, not applicable; aPC, abnormal plasma cells; IgA, immunoglobulin A; SMM, smoldering multiple myeloma.
clinical entity where a subset of patients have a very indolent course of disease that mimics an MGUS-like state, whereas others have a more aggressive course of disease that has been described as “early myeloma” or “CRAB-negative myeloma.” Unfortunately, there are currently no molecular factors to differentiate these two clinically and biologically distinct groups of patients. For this reason, additional studies are required to identify markers of progression within these patients.

There are three subtypes of SMM: IgA, IgG, and light chain. The median time to progression (TTP) for IgA and IgG SMM is 27 and 75 months, respectively. Light-chain SMM has a cumulative probability of progression to active MM or light-chain amyloidosis of 27.8% at 5 years, 44.6% at 10 years, and 56.5% at 15 years. The current factors associated with risk of progression are mainly based on the level of tumor burden in these patients assessed by the degree of tumor involvement in the BM and the quantification of monoclonal protein in the peripheral blood.

The two most widely used risk stratification methods are the Mayo Clinic and the PETHEMA Spanish group classifications. The Mayo Clinic criteria are primarily based on the levels of serum protein markers (serum protein electrophoresis and FLC assay) and the percentage of plasma cells in the BM. The risk stratification of the PETHEMA Study Group, on the other hand, focused on the use of multiparameter flow cytometry of the BM to quantify the ratio of abnormal, neoplastic plasma cells to normal plasma cells and reduction of uninvolved Igs. Interestingly, a head-to-head comparison between the PETHEMA and the Mayo Clinic risk models showed notable discordance reflected in many patients being classified as high risk in one model and low risk in the other model. Other risk factors that have been examined include the role of IgA (vs. IgG) isotype, the presence of proteinuria, circulating plasma cells, a high proliferative rate of BM plasma cells, and abnormal MRI findings.

SMM can also be subclassified based on underlying cytogenetic abnormalities. Patients with t(4;14), 1q gain, and/or del17p are considered high-risk SMM (median TTP of approximately 24 months). Patients with hyperdiploidy are considered intermediate-risk (median TTP of approximately 34 months). Other cytogenetic abnormalities including t(11;14) are considered standard risk (median TTP, 54 months). Patients with SMM who have no evidence of cytogenetic abnormalities on fluorescence in situ hybridization (FISH) studies are considered low risk (median TTP, 101 months).

An international workshop assembled to review cytogenetic studies to evaluate whether MGUS and SMM cases have the same detectable anomalies that are often found in MM. Point mutations in NRAS and KRAS, MYC upregulation, and gain or loss of chromosome 1q or 1p seem to correlate with disease progression from MGUS and SMM. A progressive increase in the incidence of copy number abnormalities from MGUS to SMM and to MM has also been recently observed. Although MM has more copy number abnormalities than its precursor states, MGUS is as genetically aberrant as MM and does not appear to be associated with a particular chromosomal imbalance but rather with an expansion of altered clones that are already present in MGUS.

A study of transcriptional profiling using gene expression profiling has identified signatures that can identify patients with MGUS versus SMM versus MM. However, this study has major limitations given that the percentage of plasma cells present in MGUS cases is low and the samples are inherently contaminated with normal nontransformed plasma cells.

Based on all these factors, a new classification for high-risk SMM has been proposed by Rajkumar et al to identify patients at high risk of progression to MM (25% per year) as defined by the criteria listed in Table 3. Although these biomarkers were defined before the revisions to the diagnostic criteria, because the proportion of patients with SMM affected and upstaged as a result of the new criteria are small, the effect on the estimates for progression would likely be minimal. Identification of high-risk SMM is of particular importance because these patients are at considerable risk of end-organ damage and are candidates for clinical trials and/or intervention. In contrast, patients with SMM without high-risk factors likely have a risk of progression of 5% per year or less.

MANAGEMENT OF MGUS AND SMM

Patients with MGUS are not offered therapeutic options to date and close observation is indicated in these patients. A recent study demonstrated that prior knowledge of MGUS and close monitoring had significantly better overall survival (median survival, 2.8 years) than patients with MM without prior knowledge of MGUS (median survival, 2.1 years). In fact, low M-protein concentration (< 0.5 g/dL) at MGUS diagnosis was associated with poorer MM survival, presumably because those patients were not closely followed for disease progression.

All patients suspected to have SMM need an MRI of the spine and pelvis (or ideally whole-body MRI) or whole-body CT or PET-CT. BM examination with FISH studies and multiparametric flow cytometry are also required. The standard of care for SMM remains observation with reevaluations of the patients every 3–4 months. In low-risk patients, follow-up can be reduced to once every 6 months after the first 5 years. Imaging studies must be repeated if changes in clinical features or M protein occur. For patients at high risk, follow-up should continue indefinitely, and should include periodic imaging studies to rule out asymptomatic progression. Patients with SMM can be initiated on therapy without waiting for CRAB features to appear if follow-up testing shows the development of other MDE or early detection of MM bone disease on the basis of advanced imaging studies. Patients with a baseline MRI showing diffuse infiltration, solitary focal lesion, or equivocal lesions, need follow-up examinations in 3–6 months to rule out progression.
Investigators attempted to assess whether early therapeutic intervention can lead to substantial improvement in survival and response. There are two major goals in early therapeutic intervention: the first is prevention of progression, and the second is definitive therapy to achieve complete remission with the hope that all subclones will be eradicated at this early disease state and cure can be achieved.

The major barrier to early intervention has been defining the group of patients who would truly benefit from this early treatment as they would have otherwise progressed to symptomatic disease. Indeed, if SMM is a heterogeneous mix of patients with early myeloma and MGUS-like myeloma, then identification of those with early MM will allow for intervention only in those patients who truly warrant therapy.

**Bisphophonates**

Bisphophonates have shown promise in reducing the risk of skeletal-related events (SREs) in SMM, but have not been shown to delay progression to MM or prolong survival. In a randomized trial of pamidronate (once monthly for 12 months) versus observation, the incidence of SRE was 39% versus 73%, respectively (p = .009). In another trial of zoledronic acid (monthly for 12 months) versus observation, the incidence of SRE was 56% versus 78%, respectively (p = .041). The reduction in SREs is an important endpoint, and based on these two trials, consideration must be given to bisphosphonates. We recommend once-yearly bisphosphonate in patients at low risk, and once every 3-4 months in select patients with high-risk SMM.

**Lenalidomide**

The most critical study of therapy in SMM that has reignited interest in therapeutic intervention in this patient population came from the PETHEMA group using lenalidomide and dexamethasone compared with observation. Mateos et al reported on 119 patients with high-risk SMM who received either observation or lenalidomide and dexamethasone in an open-label randomized trial. Patients treated with lenalidomide and dexamethasone had a superior 3-year survival without progression to symptomatic disease (progression-free survival; 77% vs. 30%; p < .001) and a superior 3-year overall survival (94% vs. 80%; p = .03) from the time of registration. However, this study was criticized by many groups because of how asymptomatic biochemical progression was handled in both arms, the short overall survival of the abstention group and the use of salvage therapy in the abstention group. Because of these concerns, additional studies are needed before implementing therapeutic interventions as a standard of care in patients with high-risk SMM.

**Investigational Therapies**

More intensive treatment approaches similar to MM are also being investigated in high-risk SMM. These include triplet therapy with carfilzomib, lenalidomide, and dexamethasone, as well as combining combination therapy, autologous stem cell transplantation, and maintenance. Immune-based approaches using elotuzumab or daratumumab or vaccine therapies are also being investigated in patients with high-risk SMM.

On the basis of available data, we recommend that patients with high-risk SMM be offered clinical trials testing early intervention or observed closely. However, given the high risk of progression, select patients with high-risk SMM with multiple risk factors or evidence of biologic progression (rising M-protein level) can be considered for MM therapy.

There are no specific factors to make this determination, and clinical judgment is needed.

**FUTURE DIRECTIONS**

Further research is needed to identify factors involved in progression of MGUS and SMM to MM. We must identify additional reliable biomarkers of malignancy. Finally, we need a portfolio of clinical trials designed to determine whether early intervention can improve survival or provide a path to prevent or cure MM. The question remains whether these efforts will lead to a cure in myeloma or potentially to an early screening and intervention modality that will completely eradicate the progression to symptomatic disease, making myeloma a preventable disease. Only well-designed clinical trials will be able to determine which interventions are most effective, what populations should be targeted, and when interventions should take place.

---

**References**


