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REVIEW ARTICLE

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# Monoclonal gammopathies of undetermined significance and smoldering myeloma

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**Abstract**

Monoclonal gammopathy of undetermined significance (MGUS) is a clonal plasma cell disorder implicated as a precursor of multiple myeloma (MM), while smoldering multiple myeloma (SMM) is a malignant plasma cell disorder without evidence of a myeloma-defining event(s) (MDE). This is a review article of both disorders outlining their current definition and management according to the current standard of care. We focus on the pathogenesis of MM and the role of MGUS and SMM in the development of active MM. MGUS is a benign disorder and, subsequently, is followed by observation. In contrast, for SMM, although the current standard of care is "watch and wait", this paper will explore the circumstances in which treatment should be considered to prevent MDE.



**Keywords:**
monoclonal gammopathy of undetermined significance, multiple myeloma, smoldering multiple myeloma

## Introduction

Monoclonal gammopathies are a group of disorders with altered immunological homeostasis and the presence of abnormal monoclonal protein in the blood and/or urine. These proteins may have no immediate or long-term clinical significance or can be associated with clinical relevance such as monoclonal gammopathy of renal significance (MGRS), paraneoplastic syndromes (e.g., neuropathy) or evolution into malignant clonal diseases (MM, AL amyloidosis, Waldenström's macroglobulinemia, chronic lymphocytic leukemia, and non-Hodgkin's lymphoma). The condition of benign monoclonal gammopathy was first described in 1978 by Dr Kyle in 241 asymptomatic patients with evidence of monoclonal protein in the serum, yet no evidence of MM, AL amyloidosis, or Waldenström's macroglobulinemia at the time of diagnosis [1, 2]. Ultimately, the term was changed to monoclonal gammopathy of undetermined significance (MGUS) [3]. Smoldering multiple myeloma (SMM), a disorder first coined in 1980, described six patients with 10% or more plasma in the bone marrow (BM) and no evidence of end-organ dysfunction at diagnosis; however, with a potential of malignant transformation to MM, it was defined as asymptomatic multiple myeloma (AMM) [4]. SMM includes a broad spectrum of patients from low to a high risk of development of end-organ damage defining MM [5].
The definitions of multiple myeloma (MM), SMM, and MGUS, with detailed diagnostic criteria are presented in table I [6].

## Multiple myeloma

MM is usually a progressive plasma cells (PCs) malignancy leading to end-stage organ disease with significant morbidity and subsequent mortality. It is diagnosed based on the International Myeloma Working Group (IMWG) criteria updated in 2014 [7], including the presence of clonal BM PCs ≥10% confirmed via trephine biopsy or biopsy-proven solitary bony or extramedullary plasmacytoma and at least one myeloma-defining event(s) (MDE). Prior to 2014, the end-organ destruction was classified under the acronym CRAB. However, in the newest criteria it has evolved into MDEs, updated to SLiM CRAB acronym, which identifies the following MM symptoms:

**C** (calcium) – 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);
**R** (renal insufficiency) – creatinine clearance <40 mL/min or serum creatinine >177 mmol/L (>2 mg/dL);
**A** (anemia) – hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin value <100 g/L;
**B** (bone lesions) – at least osteolytic lesions on skeletal radiography, computed tomography (CT), or fusion 18F-fluorodeoxyglucose positron-emission tomography (18F-FDGPET/CT);

as well as the following biomarkers of malignancy:

**S** (sixty) – clonal BM PC percentage (60%) with clonality established by showing kappa/lambda light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence;
**Li** (light chains) – involved to uninvolved serum-free light chain ratio > 100 (measured in the serum Freelite assay);
**M** (magnetic resonance) – more than one focal lesion on magnetic resonance imaging studies, each of them at least 5 mm in size.

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***Table I. Criteria for diagnosis of MGUS, smoldering MM, and MM***

| MGUS | Smoldering MM | Multiple myeloma |
|---|---|---|
| Serum M protein <3g/dL assessed in electrophoresis and immunofixation | Serum monoclonal protein (IgG/IgA)≥3g/dL or urinary monoclonal protein ≥500 mg per 24 h | M protein present (IIMM, LCMM) or absent (NSMM) – not required for the diagnosis |
| Clonal bone marrow plasma cells <10% in the trephine biopsy | Clonal bone marrow plasma cells 10%–60% in the trephine biopsy | Clonal bone marrow plasma cells ≥10% in the trephine biopsy |
| Absence of end-organ damage (no CRAB features) and amyloidosis | Absence of myeloma-defining events or amyloidosis | Myeloma-defining events |

The diagnostic criteria were updated to identify the group of patients who would have been previously diagnosed with SMM, but who have biomarkers that almost always predetermined the development of CRAB features. This would prolong the inevitable diagnosis of MM and significantly delay the implementation of treatment.

MM is the second most common blood malignancy following lymphoma with an estimated 32,110 new diagnoses and 12,960 deaths in 2019 in the United States, which was roughly 1.8% of all new cancer cases in the United States [8]. Most commonly, the median age of MM at diagnoses is 69–70 years; only 2% of patients are <40 years and 38% >70 years [9, 10].

The prognosis has vitally improved in recent years; the overall survival (OS) was only 1 year prior to the introduction of alkylating agents in the 1950s to a median of 5.5 years in the 2000s [11]. This improvement in survival is due to the introduction of target therapy (proteasome inhibitors, immunomodulatory agents, and monoclonal antibodies) and the incorporation of high-dose chemotherapy with autologous stem cell transplants [12, 13].

Despite the growing improvements in treatment and survival, MM remains an incurable disease; therefore, increasing survival, improving quality of life, and researching its evolution are the relevant goals of ongoing research [14].

### *Pathogenesis and role of premalignant conditions in the development of MM*

MM is a disease characterized by uncontrolled growth and proliferation of malignant PCs. The pathogenesis remains poorly understood. Numerous risk factors have been implicated; however, a specific cause/effect has yet to be elucidated. An epidemiologic study carried out by Alexander et al. [15] confirmed that incidence rates increase with age, particularly after age 50, and are higher in men, particularly African American men. Although relatively low, there is an increased propensity for the development of MM and other B-cell malignancies in families. Although a variety of autoimmune diseases have been implicated as increasing the risk of development of MM, only pernicious anemia and ankylosing spondylitis have been associated with an increased risk [16]. Many environmental factors, such as ionizing radiation, exposure to benzenes, and petroleum as well as smoke and other industrial and agricultural toxins, were hypothesized to contribute to the pathogenesis [16, 17]. The US government recognizes three potential risk groups: troops exposed to Agent Orange during the Vietnam War period, extensively exposed workers after 9/11, and troops who served at Camp Lejeune, North Carolina. As mentioned, MGUS is a precursor of MM. In a study conducted by Landgren et al. [17], they found that almost all MM cases studied had a preceding incidence of MGUS [17, 18, 19]. Similar findings have been described in studies carried out by the Mayo Clinic in the group of United States veterans, thus highlighting the pivotal role of MGUS in the pathogenesis of MM [18, 19]. There is increasing data to support the concept of intraclonal heterogeneity and the existence of simultaneous multiple clones of tumor cells at the time of diagnosis [20–25]. This was demonstrated for MM by Morgan et al. [24] and Keats et al. [26], describing clonal evolution from MGUS to MM and plasma cell leukemia (PCL). As this theory is likely to be a part of the natural progression of MM, it also serves to emphasize a potential target for treatment or the need to initiate treatment in the early stages of this heterogeneity, for instance, MGUS [13, 22, 24, 25–28].

Although MM is thought to evolve in this sequence, its propagation is a result of a multitude of factors: inherited genetic variation, myeloma cell gene mutations, deletions, and amplifications which occur throughout the natural history of the disease [29, 30, 31]. Another crucial factor in the translation of PCs to MM is the impact of the BM microenvironment. This had an implication in the clinical trials focused on altering the microenvironment, with some potential treatment targets revealed [21, 32, 33]. It is now largely acknowledged that the progression of myeloma is as a result of immune dysregulation and loss of immune system surveillance. For instance, the BM microenvironment in MM has been shown to create a protected area for tumor cells through the secretion of growth factors and cytokines and via upregulation of inhibitory receptor/ligand pairs such as programmed death receptor-1/programmed death ligand (PD-1/PD-L1). Furthermore, increased numbers of circulating myeloid-derived suppressor cells and the inhibition of effective antigen presentation by dendritic cells, coupled with the loss of regulatory T cells and TH17 cells from the T-cell reserve, are all components believed to contribute to propagation of MM cells, their proliferation, and disease progression [34–38].

## Monoclonal gammopathy of undetermined significance

MGUS is a premalignant PC disorder. The more prevalent type, non-IgM MGUS, generally originates from mature PCs that have had switch recombination and may lead to MM [31, 39]. The specific diagnostic criteria for MGUS defined by the IMWG are presented in table I [40].

*Table II. Risk stratification for progression of monoclonal gammopathy of undetermined significance to multiple myeloma*

| Risk group | No. of patients | Relative risk | Absolute risk of progression at 20 years (%) | Absoluter risk of progression at 20 years accounting for death as a competing risk (%) |
|---|---|---|---|---|
| Low-risk (serum M protein <1.5 g/dL, IgG subtype, normal FLC ratio (0.26–1.65) | 449 | 1 | 5 | 2 |
| Low-intermediate-risk (any one factor abnormal) | 420 | 5.4 | 21 | 10 |
| High-intermediate -risk (any two factors abnormal) | 226 | 10.1 | 37 | 18 |
| High-risk (all three factors abnormal) | 53 | 20.8 | 58 | 27 |

*Adapted from Monoclonal gammopathy of undetermined significance and smoldering (asymptomatic) multiple myeloma: IMWG consensus perspective risk factors for progression and guidelines for monitoring and management [40]*

### *Prevalence*

Population-based studies have demonstrated that the production of MGUS can begin as young as 30 years of age; however, accurate percentages are not available. MGUS was found in approximately 3% of people aged ≥50 years and roughly 5% of people ≥70 years [41–45]. The prevalence of MM is twofold higher in the African American populations, which is due to a higher incidence of MGUS, thought to be due to the initial pathogenesis beginning at an earlier age [44].

### *Progression of MGUS to MM*

The risk of progression to MM has been demonstrated by Kyle et al. to increase cumulatively by 1.5% per year [40, 41, 46]. The risk of progression can be estimated based on defined risk factors; the most definitive of these are the concentration of M protein > 1.5 g/dl, immunoglobulin isotype (non-IgG), and abnormal serum-free light chain (sFLC) ratio [40, 47]. Focusing on non-IgM MGUS patients, the projected risk at 20 years is 30% if they possess two risk factors, 20% for those with only one risk factor, and 7% for those who possess no risk factors (Tab. II) [39].

The immunoglobulin isotype is also a key indicator of risk. Patients with IgM or IgA monoclonal proteins are at higher risk of progression in contrast to those with IgG monoclonal protein. The risk of progression among patients with IgM MGUS is nearly 11 times that of a normal, comparable population [48]. Similarly, the percentage of BM PCs is of significance in risk assessment. In a study by Cesana et al. [49], they observed that MGUS patients with greater than 5% BM PCs were at greater risk of malignant transformation. Further studies by this group demonstrated that the evolution of the disease was just 6.8% when the BM PCs were less than 10% while it was significantly greater at 37% in patients with BM PCs at 10%–30% [50]. The IMWG concluded that patients with ≥10% PCs are considered to have SMM or MM [40]. Additionally, serum-free light chain ratios have prognostic value in MGUS. Rajkumar et al. [51] reported that 382/1,148 patients with aberrant FLC ratios at diagnosis demonstrated a higher risk of progression to myeloma compared to those with normal serum-free light chain ratios. Recent studies by Landgren et al. [52] further highlight these prognostic factors in the acceleration of MGUS to MM. They found that changes in the immune marker values varied over time. They studied 685 MGUS patients of which 187 progressed from MGUS to MM and some from light chain MGUS to light chain MM. By analyzing the M spike concentration and serum FLC for each patient sample, they found that they were both increased and correlated with a higher risk of MM. The high-risk score was evident in the serum for up to 5 years before the diagnosis of the MM, thus highlighting the biomarkers that can predict MGUS progression and the potential for the treatment of high-risk MGUS before disease in and, further, the importance of constant follow-up in MGUS patients [52, 53].

### *Management of MGUS*

Traditionally, the management of MGUS has been a “watch and wait” strategy. MGUS patients are monitored, as recommended above, for progression to MM; the frequency of the recommended serial evaluations is described below.

### *MGUS with low risk of progression*

If the serum monoclonal protein is <15 g/L, IgG type, and the FLC ratio is normal, the risk of eventual progression to myeloma or related malignancy is low. In these patients, complete blood count, creatinine, and calcium values are usually indicative of MGUS and should be evaluated regularly. A BM examination or radiography is not routine; however, if a patient presents with renal insufficiency, hypercalcemia, bone lesions, or unexplained anemia, a BM aspiration would be required. These patients should have their serum protein electrophoresis in 6 months, and if this is not indicative, they can be followed up every 2–3 years [40, 41, 54].

### *MGUS with intermediate and high risk of progression*

If an MGUS patient has a serum monoclonal protein >15 g/L, IgA or IgM protein type, or an abnormal FLC ratio, a BM aspirate and biopsy should be done to rule out an MM or another PC malignancy. BM needs to be evaluated by both conventional cytogenetics and fluorescence in situ hybridization (FISH) [40, 41, 54].

### *Implications of MGUS and roles for potential treatments*

Whereas the standard of care for MGUS is observation, recent clinical trials support the concept that early treatment initiation may improve survival and decrease the risk of an MDE [55].

Melton et al. [56] described the prevalence of osteoporosis and fractures among MGUS patients. They were greater than in the

general population of age-matched controls. Further research demonstrated the increased incidence of fractures, in particular of the hip and vertebral column, in addition to greater osteoporosis and hypercalcemia [57, 58]. This highlights a potential proactive role of bisphosphonates or rank-ligand inhibitors as well as calcium/vitamin D supplementation in MGUS patients, as has been routinely incorporated into the management of osteoporosis [59].

Although there is no specific treatment for MGUS, it has been shown to reduce life expectancy even when a malignant transformation is not present. MGUS patients have decreased survival from a diagnosis of 8.1 years in comparison to 12.4 years for matched controls [39, 60, 61]. Additionally, MGUS patients have been shown to have numerous complications and associated comorbidities, including MGRS, bone fractures, peripheral neuropathy, cardiovascular diseases, and immunodeficiency [57].

Patients with impaired immune system are two to three times more likely to develop bacterial and viral infections [58]. In several studies on survival in MGUS, infections have shown to have a standard mortality ratio (SMR) of between 1.5 and 2, and with pneumonia, sepsis, pyelonephritis, and tuberculosis as the most common causes of death [62, 63]. This is likely to be due to impairment of both innate and adaptive immunity and, in particular, a reduction in the number of NK cells, CD $19^{+}$ cells, as well as the blood immunoglobulin level [64]. This would seem to highlight the importance of encouraging MGUS patients to have herpes zoster vaccinations following the Centers for Disease Control and Prevention guidelines for routine vaccinations.

Similar to MM, which is often associated with renal involvement, MGUS has also been implicated in renal disease. The term MGRS was first coined by the International Kidney and Monoclonal Gammopathy Research Group in 2012. It is a heterogeneous spectrum of renal diseases that culminate as a result of the aggregation of deposited monoclonal immunoglobulin in the kidney [65]. Generally, patients are found to have unidentified deterioration of renal function and proteinuria, which may result in renal failure [60]. These disorders occur as a result of clonal B-cell proliferation with monoclonal antibody production and associated with potential capability of complement deregulation [47, 61]. Treatment is indicated in these disorders to prevent from further deposition of monoclonal immunoglobulins in the tubules and glomeruli, leading to irreversible damage and complications of end-stage renal failure. Therapy should be modeled after the treatment paradigms for MM targeting the clonal PCs producing the immunoglobulins with the goal of improving/maintaining renal function [60].

### *Recommendations*

Currently, a population study is being carried out in Iceland called iStopMM (**I**celand **S**creens **T**reats or **P**revents **M**ultiple **M**yeloma). This study aims to assess the blood of 140,000 adults aged > 40 in Iceland to assess the first signs of MM. Simultaneously, the study is looking into particular areas in Iceland where MM cases are known to be higher, to try to identify risks associated with the development of the disease. The results of this study will no doubt implicate precursors of myeloma such as MGUS and potentially identify a greater rationale for treatment [66]. In light of the issues mentioned above and the risk of malignant transformation associated with high-risk MGUS, clinical trials utilizing anti-myeloma therapeutic approaches are actively enrolling patients to prevent MDE to improve the future quality of life for these patients. One such example is a Phase II clinical trial utilizing the anti-CD38 monoclonal antibody daratumumab in patients with high-risk MGUS and low-risk SMM. Another study is assessing the anti-inflammatory properties of celecoxib in MGUS and SMM patients in preventing the development of MM [2]. A search of the clinicltrials.gov database shows that there are 10 active trials of therapeutic intervention in MGUS with an additional 11 recently completed. The results of these studies, among others, may be pivotal in redefining MGUS and its management in the not so distant future.

## Smoldering multiple myeloma

### *Definition*

SMM is synonymous with asymptomatic MM (AMM). It is characterized by at least 10% clonal PCs and/or at least 3 g/dL of monoclonal protein level. These patients are without any evidence of end-organ destruction (no CRAB end-organ damage: hypercalcemia, renal insufficiency, anemia, lytic bone disease). The specific diagnostic criteria for SMM, defined by the IMWG are presented in table I [40].

### *Prevalence*

The median age of incidence is similar to that of MM from 69 to 70 years of age [41, 67, 68]. The incidence of SMM is estimated to be between 10% and 15% of MM patients. Extrapolating from a population study by Ravindran et al., it is believed to have an occurrence rate of 0.9 per 100,000, which corresponds to approximately 4,400 new cases of SMM in the United States in 2019 [8, 69, 70].

### *Progression and risk factors*

The risk of progression to symptomatic disease or MM differs from that of MGUS; Kyle et al. projected the risk of 10% per year for the first 5 years following diagnosis, decreasing to 3% for the next 5 years and finally 1% in the years following to the 10th year [67, 68]. Given these figures the probability of advancement to symptomatic disease was 51% at 5 years, 66% at 10 years, and 73% at 15 years [40, 71]. The prognostic factors associated with the greatest risk of evolution of SMM to MM are dependent on BM plasmacytosis and the serum monoclonal protein level at diagnosis [71].

In 2014, the IMWG redefined the criteria for MM diagnosis. They included new laboratory and imaging markers. This allowed for the identification of high-risk SMM patients who were most at risk of progression and, more importantly, in need of treatment to prevent end-organ damage (80% at 2 years likelihood of an MDE). The markers that were included in the new criteria were BM PC infiltration of 60% or greater, an sFLC ratio of ≥100 (or <0.01), or at least one focal lesion on cross-sectional imaging of the whole body by magnetic resonance imaging (MRI) – now termed in acronym SLiM (BM percentage – 60, light chain ratio, MRI) criteria. These criteria

highlight biological as well as radiographic findings associated with an increased risk of development of an MDE. The new definition included patients with high-risk SMM into the treated group, since earlier these patients were followed only by observation [7, 72].

### *How to identify high-risk SMM in the remaining patients*

There are several models on how to predict the risk of progression in SMM; the most widely accepted models from the Mayo Clinic and PETHEMA are presented in table III [73].

#### *The Mayo Clinic model*

This model uses serum M protein, BM plasmacytosis, and the sFLC ratio. Their study, which was carried out on 273 SMM patients, found that an sFLC ratio of >8, a serum M protein level of ≥3 g/dL, or BM PCs of ≥10% lead to a 76% risk of progression in 5 years. Likewise, the progression risk for patients with two risk factors or "intermediate risk" was 51% and 25% if only one risk factor was possessed [74].

#### *The PETHEMA model*

This model quantifies aberrant BM PCs by use of flow cytometry. Using flow cytometry, the group was able to distinguish the number of neoplastic cells and normal PCs using surface markers. They found that 95% or greater aberrant BM PCs correlated to a higher risk of progression in SMM patients. In addition, there was immunoparesis, which is defined by a decrease below the lower limit of normal in one or two of non-involved immunoglobulins. This model predicts that patients with both aberrant PCs and immunoparesis have a risk of progression of 72% within 5 years, patients with one risk factor have an intermediate risk of 46% of progression in the same time, and finally, none of these factors would have a 4% chance of progression [75, 76].

#### *Genetic models*

Neben et al. [77] analyzed chromosomal alterations by FISH. This group found that previously proven high-risk aberrations for MM had implications in SMM, del(17p13), and t(4;14) and +1q21 leads to poor prognosis, time to progression (TTP), and requirement of treatment in SMM. The highest risk was associated with del(17p13) [77, 78]. Another study using human genome analysis in multiple arrays using the GEP-70 score (a genomic assay for prediction of event-free and OS in asymptomatic, newly diagnosed, and relapsed MM) in addition to the proliferation index may accurately reflect the malignant potential of the tumor cells. These findings, which correlate high-risk MM with high risk of progression in progenitor diseases, highlight how understanding the biology of high-risk MM may be the key to disease prevention [79, 80].

#### *Radiographic models*

Newer imaging techniques such as MRI and PET/CT can detect the myeloma-defining phenomenon significantly earlier than plain radiographs. While CT and plain radiographs can detect lytic bone lesions in the bone, MRI can assess the BM, therefore demonstrating certain growth patterns and may identify disease in its early stage [31]. In a large study using MRI for diagnosis of MM, focal lesions were noted in 74% of patients using MRI versus 56% of patients with skeletal surveys [33, 73]. Furthermore, Hillengass et al. [81] reported in a study of 544 SMM patients that MRI found that at least 30% of patients had BM manifestations of myeloma similar to that seen in MM. In SMM patients, the presence of bone lesions on MRI has shown to significantly increase their TTP [82]. A study by Wang et al. [82] found that TTP could be as little 1.5 years in patients with abnormal MRI in comparison to 5 years when the MRI was normal. Hillengass et al. [83] also identified that 28% of SMM patients had focal lesions not detected with routine radiographs; even a single lesion was predictive for disease progression.

Like MRI, FDG-PET/CT is important, as FDG-PET uptake can show focal FDG avid disease while CT demonstrates bone damage. This imaging may play a potential role in evaluating the treatment response in patients [84, 85]. Although PET/CT has low sensitivity for early precursors of the disease, a positive result in SMM is an important marker. Conversely, a negative PET/CT in MGUS has a high specificity and, thus, could be used for assessment of the prognostic risk in the future.

***Table III. Smoldering multiple myeloma risk models***

| Model | Main variants | Risk factors |
|---|---|---|
| Mayo | Serum M protein, BM Plasmacytosis, sFLC ratio | M protein level>3 g/dL, plasmacytosis>10%, sFLC ratio < 8 |
| PETHEMA | Multiparametric flow cytometry, serum immunoglobulins | >95% aberrant plasma cells and immunoparesis |

#### *20 February 2020 model*

In addition to the different models presented above, a new criteria for identification of a high-risk SMM subgroup have been proposed. Lakshman et al. [5] described a higher risk of progression in 400 SMM patients with BM PC%>20%, M-protein>2 g/dL, and FLC ratio > 20 to be predictive for risk of progression: the risk of an MDE was 46% at 2 years. Further supporting this model, a Phase III study was completed by the Eastern Cooperative Oncology Group (ECOG; E306) in 182 SMM patients. Patients were randomized to lenalidomide and observation groups [86]. The primary endpoint was progression-free survival (PFS). They reported that at 35 months there was a 72% reduction in the risk of progression to symptomatic disease in the lenalidomide group. When comparing the two groups, they found that PFS at 1, 2, and 3 years in the treatment arm was 98%, 93%, and 91% in the lenalidomide arm, in comparison to 89%, 75%, and 66% in the observation arm. They concluded that patients with high-risk SMM using the 20 February 20 model were candidates for early treatment with lenalidomide [87]. Despite this, there were several faults noted with this study. Biran et al. [88] noted that only 56 of the patients were high-risk defined by the Mayo 2018 criteria and, subsequently, out of these 56 high-risk patients, 31 were randomized to the observation arm. Furthermore, these patients

were only followed for a median of 35 months. Moreover, nearly half of the patients (47.2%) had aberrant findings on MRI when enrolled, which may suggest that these patients had symptomatic MM at the time of randomization. The studies' primary endpoint of PFS is not an accurate marker in a disease with no current cure available. Therefore, it would be more factual to state that time-to-myeloma is delayed rather than prolonged survival. Finally, the question of why would one treat a myeloma patient with single-agent lenalidomide, when essentially all studies show that triplets, or even quadruplets, are superior to doublets in frontline myeloma therapy [88]. As noted previously, and by the authors of this article, clonal evolution is a pivotal process in the development of MM, thus a single-agent treatment is unlikely to target clonal heterogeneity.

### Management

All patients suspected of SMM should have the following diagnostic and baseline screening tests:

- Complete blood count;
- Chemistry profile with measurement of calcium, creatinine, albumin, beta-2 microglobulin, and LDH;
- Quantitative immunoglobulins, serum protein electrophoresis, serum immunofixation electrophoresis, and sFLC assay;
- 24-h urine collection for total urine protein, urine protein electrophoresis, and urine immunofixation electrophoresis;
- A baseline BM biopsy for cytogenetics, FISH can be done, however, it is not routinely preformed in SMM;
- A skeletal survey, including low-dose whole-body CT, PET-CT, or MRI of the whole-body or spine [7].

The IMWG recommends all the tests mentioned above, initially and at follow-up 2–3 months after the diagnosis. While an MRI is not mandatory, a BM biopsy and skeletal survey are recommended. Paraprotein parameters should be repeated every 4–6 months for at least 1 year and, if they remain stable, intervals can be increased to every 6–12 months [40, 72]. Depending on the results and risk stratification using the recommended models, the follow-up plan can be estimated in a way similar to that presented in table IV [40, 71]. Regular monitoring is mandatory as recent studies have shown how serum immune markers for precursors of MM can change over time [29, 52].

### Treatment

Historically, similar to MGUS, the treatment for SMM was observation. Older studies on SMM treatments have failed to show an OS or quality-of-life benefit. This was mainly due to ineffective available therapies and toxicities of these therapies (mainly alkylating agents). More modern therapies are targeted with a number of potential combinations which are substantially better tolerated.

### Early trials

Three small studies compared early therapy with melphalan plus prednisone versus observation or melphalan plus prednisone treatment at the time of progression. These studies failed to show any increase in OS [89, 90].

*Table IV. Management of smoldering multiple myeloma [40]*

| Plasma cell disorder | Management |
|---|---|
| Low risk | Annual follow-up |
| Intermediate risk | Monitor every 6 months |
| High risk | Consider clinical trial/monitor every 2–3 months |
| Early myeloma/"Ultra high-risk SMM" | Treat as you would treat symptomatic MM |

Similarly, other trials with thalidomide and bisphosphonates failed to show improvement in OS and had numerous adverse events associated in particular with neuropathy [91], while thalidomide alone in SMM also proved disappointing [92].

Witzig et al. [93] presented a Phase III study of thalidomide plus zoledronic acid versus zoledronic acid alone in patients with SMM. They demonstrated that the risk of progression to active MM could be decreased using this combination of drugs; however, the study limitations were small sample size and high toxicity of the study drugs.

### Modern approaches in SMM

The Spanish (PETHEMA) myeloma group tested lenalidomide plus dexamethasone for high-risk SMM (see definitions above). A total of 119 patients were randomized to the treatment or observation. In the treatment group the TTP was not met, while the median TTP in the observation arm was 21 months. Similarly, the 3-year OS in the treatment arm was higher, at 94% versus 80%. In all, 79% of treated patients in the induction phase and 90% in the maintenance phase achieved a partial response. Therefore, this treatment in early high-risk SMM decreased TTP and improved OS in this study [94]. Although this study demonstrated increased PFS and OS, the study had limitations as it is difficult to assess the efficacy of a combination treatment and the lack of accurate imaging in this study makes it difficult to confirm whether these patients had no myeloma-defining criteria. Furthermore, the median follow-up was 6 years, which was not a significant time to assess PFS [87].

Lonial et al. [86] compared lenalidomide versus observation in 182 patients. In the treatment arm, response to therapy was observed in 50% of patients, in comparison to no response in the observation arm. There was a significant improvement in PFS in the treatment arm in comparison to the observation arm (hazard ratio, 0.28; 95% CI = 0.12–0.62; $p$ = 0.002). Thus, they concluded that lenalidomide treatment delayed progression to an MDE in SMM patients. As discussed previously, there were several drawbacks to this study design.

Korde et al. [94] reported treatment with carfilzomib, lenalidomide, and dexamethasone (KRd) with lenalidomide maintenance in patients with high-risk SMM and newly diagnosed MM. All patients with SMM achieved at least a very good partial response during the study period. Concerning the most common of any-grade adverse events, 12 patients with high-risk SMM lymphopenia (12 [100%]) and gastrointestinal disorders (11 [92%]) were reported. A Phase III study is actively enrolling patients further to test this treatment on SMM patients [95].

*Table V. Diagnostic and therapeutic management in MGUS, SMM, MM*

| Disease | MGUS | SMM | MM |
|---|---|---|---|
| **Management** | • Baseline screening<br>• Follow-up every 2–3 years | • Baseline screening<br>• Follow-up initially 2–3 months, then 4–6 months for the first year, if stable every 6–12 months | • Baseline screening<br>• Staging as in IMWG recommendations |
| **Treatment** | • Watch and wait | • Watch and Wait | • Systemic therapy (chemotherapy) followed by autologous hematopoietic stem cell transplantation (auto-HSCT) in transplant-eligible patients<br>• Preferred multidrug therapy – triplets, including in the frontline the following regimens: bortezomib/lenalidomide/dexamethasone or cortezomib/cyclophosphamide/dexamethasone, although several others are used depending on the patient status |

In a trial designed to potentially cure early stages of myeloma, GEM-CESAR (NCT02415413) is a Phase II single-arm clinical trial using a KRd backbone for induction followed by high-dose therapy and autologous stem cell transplant and maintenance, essentially treating high-risk SMM as symptomatic myeloma. The primary endpoint of the study was minimal residual disease negativity rate evaluated by next-generation flow post-induction and post-transplant. At a median of 30 months, 93% of the patients are alive and free from progression. Following consolidation, the overall response rate was 100% and the complete response rate was 76%. The minimal residual disease (MRD) negativity rate following consolidation was 63%. Although this is a very intense treatment sequence, with a substantially higher response rate than lenalidomide as a single agent in the ECOG E306 study, the 3-year PFS was similar to that reported in the E306 study. As a result, we must consider whether such an intense regimen is necessary [97].

The treatment of this disease in the absence of symptoms is a difficult decision. The main role of therapy in SMM is to improve OS and not impact the quality of life; therefore, the future of the therapeutic intervention in SMM may be the use of novel therapies that work directly on the immune system regulation and surveillance and maintain control of the malignant cells or treatments, which ultimately cure this disease at its earliest stage [72, 98].

The diagnostic and therapeutic management of MGUS, SMM, and MM is summarized in table V.

## Future approaches to MGUS and SMM

In the future, better-defined biomarkers will be evaluated in clinical trials to select those patients who are at the highest risk for developing MDE. For example, Ghobrial et al. [99] found immune system dysregulation in particular natural killer cells and loss of cytotoxic T cells is a major contributor to the progression of MGUS and SMM. Furthermore, the use of chimeric antigen receptor T cells in MM has been shown to be an interesting target for treatment and several other targets are being tested [100]. At present, all SMM patients must undergo rigorous evaluation at initial workup to exclude subclinical symptomatic disease and provide risk stratification patients with low and intermediate risk. SMM should be closely monitored and potentially included in clinical studies. At present, patients with high-risk SMM should not be treated outside of a clinical trial until we more precisely identify those patients who are most likely to develop MDE.

### *Authors' contributions*

All authors contributed to the writing of the paper based on the current literature review.

### *Conflict of interests*

None.

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### *Ethics*

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform Requirements for manuscripts submitted to Biomedical journals.

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