Diagnosis and Management of Monoclonal Gammopathy and Smoldering Multiple Myeloma

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ABSTRACT

The presence of monoclonal proteins is common, with a prevalence in the United States around 5% that increases with age. Although most patients are asymptomatic, most cases are caused by a clonal plasma cell disorder. Monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM) are asymptomatic precursor conditions with variable risk of progression to multiple myeloma. In recent years, significant progress has been made to better understand the factors that lead to the development of symptoms and progression to myeloma. This review summarizes the current diagnosis treatment guidelines for MGUS and SMM and highlights recent advances that underscore a shifting paradigm in the evaluation and management of plasma cell precursor conditions.

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Monoclonal Gammopathy of Undetermined Significance

Background

Paul Ehrlich is credited with developing the concept of immune cells producing anti-infective weaponry, which he termed “side chains,” postulated to be receptors that could somehow be harnessed to fight infection.¹ Since that important hypothesis was made in Germany in 1897, several other key developments occurred in the ensuing 50 years allowing the identification and measurement of such proteins and the cells of origin, now known as antibodies and plasma cells, respectively. With the advent of serum protein electrophoresis, pioneered by Tiselius² and Longworth et al,³ investigators quickly noted the occurrence of monoclonal antibodies in the sera of both ill and healthy people, a phenomenon termed “essential hyperglobulinemia”⁴ and documented by others.⁵

However, researchers are indebted to the painstaking work of Robert Kyle, who coined the term *monoclonal gammopathy of undetermined significance* (MGUS) and established the framework that is still in use today.⁶ His seminal publication tracked the outcome of 241 patients found to have serum monoclonal proteins but no evidence of multiple myeloma (MM) and carefully documented their course with at least 5 years of follow-up. Kyle found that most patients would never develop a symptomatic disorder. This review addresses MGUS and the related entity smoldering multiple myeloma (SMM).

The International Myeloma Working Group (IMWG) defines MGUS as the presence of a monoclonal protein (M protein), detected by either serum or urine protein electrophoresis, or unexplained free light chain (FLC) excess in the absence of a monoclonal IgH heavy chain, with serum monoclonal protein levels <3 g/dL and <10% clonal plasma cells on bone marrow biopsy.⁷ In addition, the definition of MGUS requires that the individual have no symptoms of clinical myeloma (hypercalcemia, renal

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dysfunction, anemia, and/or lytic bone disease [CRAB criteria]). MGUS incidence varies greatly based on ethnicity and age, with lower levels encountered in Asia, approximately 0.4% to 2%,^{8,9} compared with those in Northern Europe and North America, with one study reporting an MGUS incidence of 6.1% in the United States.¹⁰ MGUS incidence increases with age¹¹; it is found in 3% to 4% of the population aged 50 to 60 years compared with approximately 10% among octogenarians. Landgren et al¹² found that in one portion of the NHANES study, which examined individuals aged 10 to 50 years, patients developed MGUS at a higher level but also at an earlier age compared with White and Mexican American individuals. Obesity has also been associated with an increased risk of MGUS¹³ and progression to MM.¹⁴

The search for a genetic cause of MGUS led to the discovery of hyperphosphorylated paratarg-7, a protein that may serve as an autoantigen driving chronic antigen stimulation and has been found in both familial and sporadic MGUS. The inheritance of paratarg-7 has been associated with a nearly 8-fold increased risk of developing MGUS¹⁵ and seems to be detected more frequently in African Americans than in Whites with MGUS.¹⁶ Other loci that may be important in the development of MGUS and MM have been found in genome-wide association studies, including 3p22.1 (rs1052501), 6p21.33 (rs2285803), 7p15.3 (rs4487645), and 17p11.2 (rs4273077).¹⁷ Certain environmental exposures have also been associated with the development of MGUS, including Agent Orange,¹⁸ pesticides,¹⁹ and most recently, participation in the 9/11 rescue operation.²⁰

Because most individuals found to have MGUS will never go on to develop a symptomatic plasma cell disorder, routine screening for MGUS is not recommended. However, previous studies have found an increased risk of MGUS in first-degree relatives of patients with MM or other blood disorders.^{21–24} This risk seems even greater in first-degree relatives of African American patients with MM. Two large studies are underway to determine whether screening of these individuals will ultimately reduce the MM burden through early detection of precursor states: the Iceland Screens, Treats or Prevents Multiple Myeloma study (<https://www.blodskimun.is>) and the PROMISE study (<https://www.promisestudy.org>). This effort is important because it is clear that MGUS nearly always precedes the development of MM.^{25,26}

Diagnosis and Evaluation

Diagnosis of MGUS requires the presence of a monoclonal protein, which is typically determined through serum protein electrophoresis or less often by urine protein electrophoresis and classified by immunofixation. MGUS is generally divided into 3 types: non-IgM MGUS (ie, IgG or IgA, or rarely IgD and IgE), IgM MGUS, and light-chain MGUS. Light-chain MGUS is defined as having an

Table 1. Diagnostic Criteria for Monoclonal Gammopathies

Diagnosis	Criteria (All Must be Met, Unless Otherwise Noted)
Non-IgM MGUS	1. <10% BMPC 2. Serum monoclonal protein (non-IgM) <3 g/dL 3. No SLiM-CRAB criteria ^a
IgM MGUS	1. <10% BMPC 2. Serum IgM monoclonal protein <3 g/dL 3. No symptoms attributable to underlying lymphoplasmaic disorder (anemia, hyperviscosity, adenopathy, organomegaly, or constitutional symptoms)
Light chain MGUS	1. Abnormal FLC ratio (<0.26 or >1.65) 2. Increased level of the appropriate involved light chain (increased κ FLC in patients with ratio >1.65 and increased λ FLC in patients with ratio <0.26) 3. No immunoglobulin heavy chain expression on immunofixation 4. Urinary monoclonal protein <500 mg/24 h 5. <10% BMPC 6. No SLiM-CRAB criteria ^a
MGRS	1. Presence of monoclonal immunoglobulin or light chain 2. Kidney biopsy showing renal impairment related to the monoclonal protein ^{28,27} 3. Diagnostic criteria for MM or other lymphoplasmaic disorder not met
MGCS ^b	1. Presence of monoclonal immunoglobulin or light chain 2. Symptoms or clinical manifestations attributable to the presence of monoclonal protein ³¹ 3. Diagnostic criteria for MM or other lymphoplasmaic disorder not met
SMM	No SLiM-CRAB criteria ^a plus at least 1 of the following: 1. BMPC $\geq$ 10% 2. Serum M-spike $\geq$ 3 g/dL (or urine paraprotein $\geq$ 500 mg/24 h in the absence of a serum M-spike)
MM	1. BMPC $\geq$ 10% ^c 2. Presence of any SLiM-CRAB criteria ^a

Abbreviations: BMPC, bone marrow plasma cells; FLC, free light chain; MGCS, monoclonal gammopathy of clinical significance; MGRS, monoclonal gammopathy of renal significance; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; SMM, smoldering multiple myeloma.

^aSerum calcium >1 mg/dL higher than the upper limit of normal or >11 mg/dL; creatinine clearance <40 mL/min or serum creatinine >2 mg/dL; hemoglobin >2 g/dL below the lower limit of normal, or a hemoglobin value <10 g/dL; $\geq$ 1 osteolytic lesion on skeletal radiography, CT, or PET/CT; BMPC $\geq$ 60%; FLC ratio (involved/uninvolved) $\geq$ 100; >1 focal lesion on MRI.

^bProposed.

^cIf a patient has clear evidence of myeloma-defining events with <10% BMPC, with no alternate explanation for these criteria, then it is reasonable to diagnose and treat as MM without meeting this criterion.

abnormal FLC ratio, elevation in the appropriate light chain, and the absence of an Ig heavy chain on immunofixation.²⁷ Diagnostic criteria of these MGUS subtypes and other plasma cell precursor conditions are detailed in Table 1.

Recently, another entity associated with monoclonal protein has emerged: the monoclonal gammopathy of renal significance (MGRS), defined as a clonal proliferation that leads to the production of a nephrotoxic monoclonal protein or fragment but does not otherwise meet the criteria of other recognized diagnoses.²⁸ Patients with MGRS tend to have more proteinuria than

those with typical MGUS and, by definition, some degree of renal impairment. The prevalence of this disorder is uncertain but may affect from 1.5% to 6% of patients with MGUS.²⁹ To meet the definition of MGRS, a renal biopsy must be performed and carefully analyzed by immunohistochemistry and electron microscopy. Subtypes of MGRS include renal lesions such as immunotactoid glomerulonephritis, proliferative glomerulonephritis with monoclonal immunoglobulin deposits, and monoclonal gammopathy-associated C3 glomerulopathy.³⁰ It is now recognized that in addition to these various renal manifestations, monoclonal proteins can, albeit rarely, present with a broad spectrum of clinical manifestations. Fermand et al³¹ proposed yet another clinical entity, monoclonal gammopathy of clinical significance (MGCS), which comprises a broad spectrum of symptomatic clinical syndromes related to an underlying M protein, frequently manifesting with neuropathy, vasculitis, or dermatologic changes.

Once patients are found to have a monoclonal protein, they must be evaluated with attention to any symptoms or other clinical elements that would potentially change management strategy. It can be challenging for clinicians to determine whether symptoms, which are often nonspecific, are related to the monoclonal protein or to other comorbidities; therefore, a careful and focused history and physical examination are required, with attention given to symptoms such as fatigue, pain, dyspnea, peripheral neuropathy, easy bruising, peripheral edema, nail or skin changes, and macroglossia. The presence of such symptoms may indicate that the patient has underlying MM, but can also be associated with conditions such as amyloid light-chain amyloidosis, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes), or MGCS. Patients with MGUS with unexplained osteopenia should also be carefully scrutinized to make sure that bone loss is not actually related to undiagnosed MM. In addition, patients with some forms of non-Hodgkin lymphoma (NHL) and chronic lymphocytic leukemia (CLL) can present with small monoclonal proteins, and therefore these disease entities should be considered in the differential diagnosis. On physical examination, it is important to look for features such as an enlarged tongue, periorbital bruising, lymphadenopathy, organomegaly, and right-sided heart failure. Other suggested diagnostic testing is found in Table 2. Asymptomatic patients with low-risk MGUS, defined as those with an IgG isotype, a serum M-spike <1.5 g/dL, a urine M-spike <200 mg/24 hours, and a normal FLC ratio, may be able to forgo a bone marrow biopsy and be observed, because results of the biopsy are unlikely to upstage them to either SMM or MM.³² In patients who do undergo a diagnostic bone marrow biopsy, those with >5% plasma cells have a greater risk of

progression to MM³³ than those with a lower number of clonal plasma cells. Cytogenetic and fluorescence in situ hybridization (FISH) studies performed on those plasma cells may reveal alterations in the IgH locus, such as t(11;14) and trisomies, but no specific mutation reliably predicts progression from MGUS to myeloma.³⁴ High-risk mutations such as a p53 deletion, t(4;14), and t(14;16) are less commonly encountered^{35–37} among patients with MGUS.

Customarily, skeletal surveys have been used to screen for bone lesions in patients with MGUS; however, plain radiographs consistently underperform compared with newer techniques such as low-dose whole-body CT or MRI.^{38–40} In patients with MGUS and higher levels of M protein, increased FLC, or bony symptoms or advanced osteoporosis, some form of advanced imaging is preferred to rule out MM.⁴¹ For individuals with IgM MGUS, some investigators have recommended omitting bone imaging and instead using CT to search for adenopathy and organomegaly.⁴² Several investigations have found an increased risk of osteoporotic fractures in patients with MGUS,^{43–45} suggesting the potential utility of periodic bone density testing in patients with MGUS, although it is currently not considered routine practice.

Follow-Up

Once MGUS is discovered, patients do warrant follow-up because of the risk of disease progression to MM and Waldenström macroglobulinemia, as well as other illnesses, including NHL and CLL. A recent retrospective study using SEER data found that patients with MGUS who did not receive at least one follow-up visit had significantly higher rates of kidney failure, hypercalcemia, and fracture.⁴⁶ In a study involving how to effectively triage patients with MGUS, Rajkumar et al⁴⁷ evaluated a number of clinical features and found that individuals with an abnormal FLC ratio, a non-IgG monoclonal protein, or an M protein level >1.5 g/dL were at highest risk of progression; if all 3 characteristics were represented, then the risk of MM progression was 58% after 20 years. For reasons that are unclear, IgM MGUS is associated with approximately twice the risk of annual progression (ie, 1% to 2% per year).⁴⁸ Therefore, patients with higher-risk MGUS (ie, presence of a higher M spike, abnormal FLC ratio, or non-IgG MGUS) should be followed serially, with a follow-up visit within 6 months of diagnosis. Because the risk of progression from MGUS to malignancy is greatest within the first year of diagnosis,⁴⁹ the follow-up period can then be extended to annual or semiannual if there has been no change in either M protein or FLC levels or other parameters (eg, appearance of anemia or renal insufficiency). Patients with low-risk MGUS can be followed less frequently, such as semiannually, after an initial follow-up

Table 2. Suggested Initial Evaluation for MGUS and SMM

	Asymptomatic	Unexplained Osteoporosis Present	Unexplained Peripheral Neuropathy	Unexplained Renal Insufficiency	Unexplained Right-Sided Heart Failure	IgM MGUS	SMM
CBC with differential	X	X	X	X	X	X	X
Creatinine, calcium, albumin, LDH	X	X	X	X	X	X	X
SPEP	X	X	X	X	X	X	X
Serum immunofixation	X	X	X	X	X	X	X
Serum quantitative immunoglobulins	X	X	X	X	X	X	X
FLCs and ratio	X	X	X	X	X	X	X
UPEP, 24-h urine protein, and immunofixation	X	X	X	X	X	X	X
Troponin, NT-proBNP	—	—	X	X	X	—	—
Anti-MAG antibodies	—	—	X	—	—	X	—
Electromyography	—	—	X ^a	—	—	—	—
Serum VEGF level	—	—	X ^b	—	—	—	—
Bone marrow biopsy and aspirate	X ^c	X	X	X	X	X	X
Cytogenetic and FISH ^d analysis	X	X	X	X	X	X	X
Congo Red staining of skin biopsy or affected organ ^e	—	—	X	X	X	—	—
Advanced skeletal imaging ^f	X ^c	X	X	X	X	—	X
Conventional CT scans	—	—	—	—	—	X	—
EKG and echocardiogram	—	—	—	—	X ^g	—	—

Abbreviations: EKG, electrocardiogram; FISH, fluorescence in situ hybridization; FLC, free light chain; LDH, lactate dehydrogenase; MAG, myelin-associated glycoprotein; MGUS, monoclonal gammopathy of undetermined significance; NT-proBNP, N-terminal pro-brain natriuretic peptide; SMM, smoldering multiple myeloma; SPEP, serum protein electrophoresis; UPEP, urine protein electrophoresis; VEGF, vascular endothelial growth factor.

^aTypically in consultation with neurology.

^bIf involved light chain is lambda, to evaluate for POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes).

^cMay be omitted if all criteria are met: IgG isotype, serum M-spike <1.5 g/dL, 24-hour urine paraprotein <200 mg, and normal FLC ratio.

^dIncludes del(13), del(17p), t(4;14), t(11;14), t(14;16), t(14;20), +1q, and del(1p).

^eIn addition to dedicated Congo Red staining for symptomatic patients, Congo Red staining of the bone marrow to screen for amyloidosis is reasonable if a first-time bone marrow biopsy is performed for any patient with a monoclonal protein.

^fWhole-body low-dose CT preferred. Whole-body MRI, MRI of spine and bony pelvis, and ¹⁸FDG-PET/CT are acceptable alternatives (listed in preferred order) if whole-body low-dose CT is not available. Bone survey is no longer an acceptable imaging modality unless no alternative exists.

^gCardiac MRI may be a more sensitive test that can be ordered depending on initial findings and suspicion of cardiac amyloidosis. Technetium pyrophosphate scanning can be used to look for non-amyloid light-chain cardiac amyloidosis.

shows stability, and often by a primary care provider rather than a specialist. Referral back to a hematologist/oncologist is warranted in the event of any significant changes, such as the appearance of anemia, renal insufficiency, or a significant increase in M protein level. Long-term follow-up of patients with MGUS has shown that they experience greater mortality from diseases such as CLL and NHL, but also from other solid tumors and cardiovascular disease, compared with matched control patients.⁵⁰ However, at this time, no additional health screenings are recommended.

To date, no data suggest that routine treatment of MGUS is beneficial, and it should not be attempted outside of a clinical trial. There are some exceptions to this rule. Patients with IgM MGUS-related peripheral neuropathy and anti-myelin-associated globulin antibodies may benefit from interventions that target the abnormal B-cell clone.⁵¹ Such treatment may prevent progression of peripheral neuropathy. In addition, patients with MGUS are increasingly thought to require therapy directed toward

elimination of the clone, causing the specific nephrotoxic immunoglobulins to protect renal function.

Smoldering Multiple Myeloma

Background

SMM is a clonal plasma cell disorder of intermediate risk existing on a continuum of malignant potential between MGUS and MM. After its initial description in 1980,⁵² the definition of SMM was subsequently defined by the IMWG as a clonal plasma cell disorder with ≥10% clonal bone marrow plasma cells (BMPCs) and/or a serum paraprotein level of ≥3 g/dL (or a urine paraprotein level of ≥500 mg/24 hours in the absence of a serum M-spike) with no CRAB criteria or pathologic features of amyloidosis.⁵³ In 2014, the IMWG updated the diagnostic criteria for MM to include patients with asymptomatic disease meeting ≥1 “SLiM” criteria (ie, ≥60% plasma cells, light chain ratio involved:uninvolved ≥100:1, and

MRI with >1 focal lesion) as having myeloma-defining events and recommended treatment initiation for these patients because of an unacceptably high risk of progression to symptomatic disease.⁷ This recommendation was based on data suggesting that the 2-year risk of progression to symptomatic myeloma is approximately 70% for patients with ≥ 2 focal skeletal lesions on MRI,^{54,55} 64% to 72% among those with a serum FLC ratio of ≥ 100 or ≤ 0.01 ,^{56,57} and 95% for those with $\geq 60\%$ BMPCs.^{56,58} Current diagnostic criteria for MGUS, SMM, and MM are displayed in Table 1. For decades, SMM has been managed essentially as high-risk MGUS, but new insights into disease biology and the development of highly effective and well-tolerated treatments for MM have generated substantial interest in determining whether there may be patients with SMM who would benefit from early intervention. Because the risk of progression to MM can be highly variable, it is important to identify which patients with SMM are at highest risk of progression to MM so that end-organ damage can be avoided.

Risk of Progression

Among all patients with SMM, the risk of progression to symptomatic myeloma is estimated at approximately 10% per year for the first 5 years after diagnosis.⁵⁹ However, there is significant heterogeneity regarding the risk of progression for individual patients; several models have been proposed to characterize this risk. A Spanish myeloma group published the first prediction model, which incorporated 2 risk factors: (1) the percentage of BMPCs with aberrant immunophenotype by flow cytometry, and (2) immunoparesis, or a reduction in the quantity of uninvolved (ie, non-paraprotein) immunoglobulins.⁶⁰ In 2008, a group from the Mayo Clinic published a separate model using clinical features, specifically the percentage of BMPCs ($\geq 10\%$), a serum M-spike (≥ 3 g/dL), and an abnormal serum FLC ratio (≤ 0.125 or ≥ 8) as risk factors for progression.⁶¹ This model became widely accepted because of its easy

application and reliability in discriminating outcomes. In 2018, the Mayo Clinic group updated its diagnostic criteria, now referred to as the “20/2/20” criteria, which redefined the cutoff values as BMPCs $\geq 20\%$, an M-spike of ≥ 2 g/dL, and an FLC ratio ≥ 20 .⁶² An area-under-the-curve analysis determined that the new criteria had a superior ability to accurately prognosticate the risk of progression to MM compared with the 2008 criteria. The IMWG subsequently validated this 20/2/20 model in a cohort of 2,004 patients, showing the ability of the model to discriminate prognosis among these 3 categories, with a 2-year risk of progression of 5%, 17%, and 47% among low-, intermediate-, and high-risk patients, respectively.⁶³ A summary of these models and their prognostic risk calculation is provided in Table 3.

One of the most striking features of these prognostic models is that even among patients in the low-risk subsets, the risk of progression to MM is the greatest within the first 2 years after diagnosis. However, among patients who have not progressed to MM by 5 years, the annual risk decreases substantially. This observation suggests that there are at least 2 different patterns of disease biology among diagnoses of SMM: one pattern represents “presymptomatic myeloma” that could benefit from early intervention to prevent end-organ damage, and the other represents “MGUS-like” disease that follows an indolent course.

Several other clinical and biological factors have been evaluated as prognostic markers for progression to MM. Multiple studies have shown that certain cytogenetic abnormalities, including t(4;14), del(17p), +1q, and hyperdiploidy, confer a higher risk of progression to symptomatic MM.^{64,65} These adverse cytogenetic abnormalities were an independent risk factor for progression in the Mayo Clinic 2018 cohort,⁶² but the number of patients who were evaluable was too small for inclusion in the model. Alterations in gene expression, such as myc activation,^{66,67} and high-risk gene expression profiling by GEP-70⁶⁸ have also been associated

Table 3. Risk Models in Smoldering Myeloma

Model	n	Risk Factors	Risk of Progression
PETHEMA study (Pérez-Persona et al, 2007 ⁶⁰)	93	1. $>95\%$ of BMPC with aberrant markers by flow cytometry 2. Immunoparesis, defined as reduction of ≥ 1 uninvolved heavy chains in the serum to $<LLN$	0 factors: 4% at 5 y 1 factor: 46% at 5 y 2 factors: 72% at 5 y
Mayo Clinic study (Dispenzieri et al, 2008 ⁶¹)	273	1. BMPC $\geq 10\%$ 2. Serum M-spike ≥ 3 g/dL 3. FLC ratio ≤ 0.125 or ≥ 8	1 factor: 12% at 2 y, 25% at 5 y, 50% at 10 y 2 factors: 27% at 2 y, 51% at 5 y, 65% at 10 y 3 factors: 52% at 2 y, 76% at 5 y, 84% at 10 y
Mayo Clinic study (Lakshman et al, 2018 ⁶²)	421	1. BMPC $\geq 20\%$ 2. Serum M-spike ≥ 2 g/dL 3. FLC ratio ≤ 0.05 or ≥ 20	0 factors: 9.7% at 2 y, 22.5% at 5 y, 52.7% at 10 y 1 factor: 26.3% at 2 y, 46.7% at 5 y, 65.3% at 10 y 2–3 factors: 47.4% at 2 y, 81.5% at 5 y, 96.5% at 10 y

Abbreviations: BMPC, bone marrow plasma cells; FLC, free light chain; LLN, lower limit of normal.

with progression to MM. Evolving paraprotein is a dynamic marker that has been shown to indicate a very high risk of progression to symptomatic myeloma in multiple studies.^{69–71} Rajkumar et al⁷² proposed a set of criteria for high-risk SMM, defined as $\geq 10\%$ BMPCs with any combination of proposed high-risk factors, including cytogenetics, gene expression profiling, and isotype. This definition has been used as broad inclusion criteria for clinical trial enrollment but has yet to be validated in an independent patient cohort and is not yet used broadly in clinical practice. It is likely that in the future, several of these factors will be incorporated into new risk models and management decisions for patients with SMM.

Management of SMM

The current standard of care for management of SMM, regardless of the risk of progression, is observation. However, this standard is now being challenged by exciting clinical trial data suggesting that early intervention can prevent, or at least delay, progression to symptomatic MM, particularly among patients at high risk. Two general strategies have been proposed and are being evaluated in multiple clinical trials: a prevention strategy using low-intensity therapy and a curative approach intended to eradicate the neoplastic clone with high-intensity treatment.

The preventive approach is supported by substantial preclinical data suggesting profound immune dysregulation as the disease progresses from MGUS to SMM to MM.^{73–77} Lenalidomide is an immunomodulatory drug that exerts its antimyeloma activity through multiple mechanisms, including the enhancement of T-cell- and natural killer cell-mediated cytotoxicity against myeloma cells,^{78–81} and is a backbone of MM therapy. The QUIREDEX trial⁸² randomized patients to observation versus time-limited low-intensity therapy using lenalidomide and dexamethasone (Rd), followed by maintenance lenalidomide. In this study, Rd was well tolerated and resulted in improved progression-free survival (PFS; median not reached vs 21 months; hazard ratio [HR], 0.18) and 3-year overall survival (OS; 94% vs 80%; HR, 0.31) compared with observation alone. However, this approach was not adopted into clinical practice, largely because the trial used an SMM definition not widely accepted in the United States and also did not require advanced imaging to rule out lytic lesions. As such, patients who were asymptomatic but actually had a myeloma-defining event were likely enrolled, accounting for the rapid progression to MM seen in the observation arm.

The phase III ECOG-E3A06 trial⁸³ randomized patients with intermediate- or high-risk SMM based on Mayo Clinic 2008 criteria⁶¹ to receive continuous

lenalidomide monotherapy (25 mg on days 1–21 of 28-day cycles) versus observation, and required advanced imaging during study enrollment to exclude patients with MM. In this study, despite a modest overall response rate of 50% with very few achieving a very good partial response or better, the lenalidomide group had a substantially superior PFS (91% vs 66% at 3 years; HR, 0.28; $P=.002$), with the most profound benefit seen among patients with high risk per the Mayo Clinic 2018 criteria (HR, 0.09).⁶² Grade 3/4 adverse events were observed in 41% of patients in the treatment arm, and although the trial was designed to use continuous therapy, more than half of the patients discontinued lenalidomide (median time on therapy was approximately 2 years), and 80% of the patients remaining on lenalidomide at 12 months required a dose reduction. The rate of secondary primary malignancies was 5.2% in the lenalidomide arm compared with 3.5% in the observation arm. Despite the added toxicity from lenalidomide, no change in health-related quality-of-life scores between the 2 arms was seen after 24 cycles. Although the data are too immature to show an impact on OS, this study overcame many of the limitations of the QUIREDEX study⁸² and provides a rationale for the use of lenalidomide as a treatment for high-risk SMM.

Daratumumab (Dara) is an anti-CD38 monoclonal antibody with multiple mechanisms^{84–87} that is well tolerated and widely used in the treatment of plasma cell disorders. The CENTAURUS study⁸⁸ evaluated single-agent Dara in several dosing strategies for the treatment of SMM. Dara resulted in an overall response rate of 37.5% to 56.1% and a 24-month PFS of 75.6% to 87.8%.⁸⁸ The AQUILA trial (ClinicalTrials.gov identifier: NCT03301220), which randomizes patients to subcutaneous Dara vs observation, and the phase III DETER-SMM trial (EAA173; NCT03937635), which randomizes patients to Dara/Rd versus Rd, are ongoing and will help further explore the optimal preventive approach to high-risk SMM. Additional phase II–III interventional studies are listed in supplemental eTable 1 (available with this article at JNCCN.org).

Contrary to the preventive strategy, a curative approach to SMM is backed by the rationale that long-term survival in MM is highly correlated with deep response to antimyeloma therapy, particularly measurable residual disease (minimal residual disease [MRD]) negativity.^{89–91} Proponents of this strategy have proposed that treatment using high-intensity therapy, such as triplet or quadruplet combination induction, with or without autologous stem cell transplantation (ASCT), may eradicate the precursor clone and result in a cure for a large subset of patients with SMM. In a phase II study of carfilzomib/lenalidomide/dexamethasone (KRd) and 2 years of lenalidomide

maintenance in patients with newly diagnosed high-risk SMM,⁹² all 18 patients achieved a very good partial response or better, and 10 of 18 continued to be MRD-negative by next-generation flow cytometry and had a 4-year PFS of 71% with a median follow-up of 43.3 months. The phase II GEM-CESAR study⁹³ enrolled 90 patients with high-risk SMM to receive induction using KRd for 6 cycles, followed by ASCT, 2 cycles of KRd consolidation, and 2 years of maintenance lenalidomide. In that study, 30-month PFS was 93%, and among patients who had finished consolidation, $\geq 70\%$ achieved a complete response, with 57% achieving MRD negativity by next-generation flow cytometry. Eleven patients discontinued treatment, including 2 deaths, but the overall frequency of grade 3–4 adverse effects was low. The ASCENT trial (NCT03289299) is evaluating treatment using Dara/KRd for 12 cycles, followed by maintenance Dara/lenalidomide. This multicenter phase II trial is still accruing and represents a nontransplant alternative with a curative approach.

Overall, recent data from both strategies (ie, limited low-intensity treatment vs aggressive, MM-like treatment) suggest that researchers and physicians are nearing a paradigm shift in the standard management of patients with SMM, particularly those who are at high risk of progression. Although there is some concern about treating a proportion of patients who may never experience progression to overt malignancy, it is likely that our ability to prognosticate progression will improve with the adoption of cytogenetics and/or molecular studies into risk stratification models. Furthermore, there are now multiple randomized phase III studies that show improved PFS with a lenalidomide-based preventive strategy, particularly among patients with high risk. Critics have expressed concern that lenalidomide has not clearly shown an OS benefit in SMM and that low-intensity therapy may select for a resistant and/or more aggressive clone in patients who experience progression to MM. Alternatively, a high-intensity approach may ultimately cure some patients, but with substantial toxicity compared with a prevention strategy. There are no randomized data to compare outcomes directly between these 2 treatment approaches. Response rates are much higher among the intensive-treatment regimens, with a high proportion achieving a deep response, including MRD negativity. However, because the frequency of progression events at 2 to 3 years is similar for both strategies, this tendency may indicate that in a precursor state, achievement of a deep response with MRD negativity may not be as important to long-term survival.⁹⁴ Supporting this hypothesis are data showing that stem-like memory cells are enriched in the bone marrow microenvironment of patients with MGUS but absent in those with MM,⁷⁷ suggesting that immunomodulatory

therapy may help achieve long-term disease control by reverting patients with “presymptomatic myeloma” to an “MGUS-like” state. Nonetheless, both strategies seem promising, and long-term follow-up of these highlighted trials will be required to determine if one strategy is superior to the other.

Summary and Recommendations

Before considering the optimal management strategy for treating SMM, the first priority must be to establish that the patient does in fact have SMM. In addition to measuring serum and urine paraprotein and evaluating for symptomatic myeloma, all patients with suspected SMM require a bone marrow biopsy, FLC measurement, and advanced imaging. We support the IMWG recommendation in favor of whole-body low-dose CT for all patients with suspected SMM, but acknowledge that this modality is unavailable in many areas; therefore, whole-body MRI, MRI of the spine and pelvis, and/or PET scan are reasonable alternatives.⁹⁵ Patients who have a myeloma-defining event ($\geq 60\%$ BMPCs, serum FLC ratio of ≥ 100 or ≤ 0.01 , and/or ≥ 2 focal bone lesions) should be considered as having symptomatic MM and should be treated as such. Cytogenetic evaluation of the bone marrow aspirate with a comprehensive myeloma FISH panel, including t(4;14), t(11;14), t(14;16), t(14;20), gain(1q), del(17p), and hyperdiploidy, should be performed on every patient, because this information may provide important prognostic information and potentially impact future treatment decisions. A comprehensive summary of recommendations for the workup of patients with SMM can be found in the NCCN Clinical Practice Guidelines in Oncology for Multiple Myeloma.⁹⁶

After confirming a diagnosis of SMM, the current standard of care is risk stratification and observation with monitoring for changes in the quantity of paraprotein or the development of CRAB criteria. We recommend surveillance every 3 to 6 months, with closer monitoring of patients who are at high risk, particularly with increasing parameters indicative of an evolving pattern. If a patient is estimated to have an approximately 50% risk of progression to MM in 2 years according to any of the models, then treatment with lenalidomide for 2 years can be considered, in light of results from the QUIREDEX⁸² and ECOG-E3A06⁸³ trials. However, note that although PFS data are encouraging, no OS data are currently available from the ECOG dataset. Furthermore, although the toxicity seen in that dataset was consistent with the known profile of lenalidomide, the high rate of attrition in the ECOG study shows that patients may be less willing to accept adverse effects when it is unknown whether an individual will ever progress to MM. Although a curative approach has theoretical appeal, until there are mature

randomized data supporting an intensive management strategy, such an approach cannot be supported outside of a clinical trial. Because of the rapidly developing nature of the treatment landscape in SMM, we recommend that whenever feasible, patients should be referred to a center with a myeloma specialist and always be considered for enrollment in a clinical trial, a partial list of which is provided in supplemental eTable 1.

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Diagnosis and Management of Monoclonal Gammopathy and Smoldering Multiple Myeloma

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eTable 1: Active Phase II/III Interventional Trials in Smoldering Multiple Myeloma

eTable 1. Active Phase II/III Interventional Trials in SMM

Trial	Phase	Key Inclusion Criteria	Intervention	n ^a	Results	Safety Profile (Grade ≥3 AE)
Currently enrolling trials						
DETER-SMM (EAA173) (ClinicalTrials.gov identifier: NCT03937635)	III	High-risk SMM [1 of following: FLCr, M-spike ≥ 3, t(4;14), del(17p), gain(1q)]	Dara/Rd vs Rd	288	N/A	N/A
NCT03839459	II	Any SMM	Denosumab	20	N/A	N/A
NCT03850522	II	High risk (Mayo 2018 ⁶²)	PD-L1 peptide vaccination	20	N/A	N/A
HO147 (NCT03673826)	II	High risk (Mayo 2008 ⁶¹ or PETHEMA ⁶⁰)	KRd vs Rd	120	N/A	N/A
ASCENT (NCT03289299)	II	High risk (Mayo 2018 ⁶² or high score)	Dara/KRd	83	N/A	N/A
NCI-2018-01614 (NCT03631043)	II	Intermediate- or high-risk SMM (PETHEMA ⁶⁰)	Personalized vaccine	30	N/A	N/A
DEFENCE (NCT03792763)	II	High risk (Mayo 2008 ⁶¹) plus only 1 SLiM criterion ^b	Denosumab	164	N/A	N/A
Completed enrollment						
ECOG-E3A06 ⁶³ (NCT01169337)	III	All SMM	Lenalidomide vs observation	182	PFS 91% vs 66% at 3 y (HR, 0.28 in favor of lenalidomide); ORR 50% vs 0%; VGPR 5.5%, PR 45.5%	Neutropenia (13.6%), infection (10.2%), rash (5.7%), dyspnea (5.7%), fatigue (6.8%), hypertension (9.1%), hypokalemia (3.4%)
CENTAURUS ⁶⁸ (NCT02316106)	II	Intermediate or high risk	Dara (intense vs intermediate vs short dosing schedule)	123	Arm 1 (intense): ORR 56.1%, CR ≥ 4.9%, VGPR 24.4%, PR 26.8% Arm 2 (intermediate): ORR 53.7%; CR ≥ 9.8%, VGPR 14.6%, PR 12% Arm 3 (short): ORR 37.5%; VGPR 17.5%, PR 20.0% PFS (arm 1 vs 2 vs 3, respectively): 87.8% vs 80.5% vs 75.6%	Overall grade 3 or 4 (arm 1, 2, 3, respectively): 43.9%, 26.8%, 15.0%
NCT01572480 ⁶²	II	High risk (per Mayo 2008, ⁶¹ PETHEMA ⁶⁰ , or Rajkumar)	KRd	12	With median follow-up of 15.9 mo, patients with SMM had 100% PFS and 100% ORR (100% CR, 87.5% MRD by MFC)	Lymphopenia (50%), thrombocytopenia (34%), rash (34%), leukopenia (17%), anemia (17%), neutropenia (17%), electrolyte abnormalities (17%), endocrine (17%), hepatobiliary (8%), musculoskeletal (8%), pulmonary (8%), vascular (8%), GU/renal (8%), infection (8%), cardiac (8%)
GEM-CESAR ⁷³ (NCT02415413)	II	High risk (per PETHEMA ⁶⁰) ^c	KRd + ASCT	90 (90)	Median follow-up, 32 mo: PFS 93%, OS 98%, after consolidation: CR ≥ 70%; MRD – 57%	Neutropenia (6%), thrombocytopenia (11%), infections (18%), skin rash (9%), hypertension (1%)
E-PRISM ⁶⁸ (NCT02279394)	II	High risk (per Rajkumar et al ⁷²)	Elotuzumab/Rd	51 (34)	CBR 97%; ORR 71% (9 VGPR, 15 PR) No progression to MM	Hypophosphatemia (23%), neutropenia (8%), infection (8%), anemia (3%), pulmonary embolism (3%), rash (3%), diarrhea (3%)

(continued on next page)

eTable 1. Active Phase II/III Interventional Trials in SMM (cont.)

Trial	Phase	Key Inclusion Criteria	Intervention	n ^a	Results	Safety Profile (Grade ≥3 AE)
Completed enrollment (cont.)						
NCT02916771 ⁹⁹	II	High risk (per Rajkumar et al ⁷²)	Ixazomib/Rd	63 (45)	ORR 91% (14 sCR, 9 VGPR, 18 PR, 4 MR); ORR 97% among patients completing induction phase No progression to MM	Grade 3: hypertension (6.3%), hypophosphatemia (4.2%), and rash (4.2%) Grade 4: thrombocytopenia (4.4%), neutropenia (4.4%), hyperglycemia (2.2%)
NCT02960555 ¹⁰⁰	II	High risk (per PETHEMA)	Isatuximab	61 (24)	CBR (≥MR) 79%; ORR 62.5%; MRD – [NGF 10 ⁻⁵], 1 (5%); VGPR, 4 (17%); PR, 10 (42%); MR 4 (18%); SD, 5 (21%); PFS 92%; OS 100%	Infusion reaction, 2 (8.3%); headache, 1 (4.2%); neutropenia, 1 (4.2%); infection, 1 (4.2%)
AQUILA (NCT03301220)	III	BMPC ≥10% plus 1 of M-spike ≥3, FLC >8, immunoparesis, or BMPC 50%–60%	Subcutaneous Dara vs observation	390	N/A	N/A
NCT03236428	II	MGUS or low-risk SMM	Dara	42	N/A	N/A

Abbreviations: AE, adverse events; ASCT, autologous stem cell transplantation; BMPC, bone marrow plasma cells; CBR, clinical benefit rate; CR, complete response; Dara, daratumumab; FLC, free light chain; FLCr, serum free light chain ratio of ≥8 or ≤0.125; GU, genitourinary; HR, hazard ratio; KRd, carfilzomib/lenalidomide/dexamethasone; MFC, multicolor flow cytometry; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; MR, minimal response; MRD, measurable residual disease; N/A, not available; NGF, next-generation flow; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; Rd, lenalidomide/dexamethasone; sCR, stringent complete response; SD, stable disease; SMM, smoldering multiple myeloma; VGPR, very good partial response.

^aNumber of patients enrolled (evaluable patients in parentheses).

^b≥60% BMPCs, a serum FLCr of ≥100 or ≤0.01, and/or ≥2 focal bone lesions.

^cIncludes SLiM (n=28; 32%).