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Smoldering (Asymptomatic) Multiple Myeloma: Revisiting the Clinical Dilemma and Looking Into the Future

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Abstract

Recent studies show that multiple myeloma (MM) is consistently preceded by an asymptomatic precursor state. Smoldering MM (SMM) is a MM precursor defined by an M-protein concentration ≥ 3 g/dL and/or $\geq 10\%$ bone marrow plasma cells, in the absence of end-organ damage. Compared with individuals diagnosed with monoclonal gammopathy of undetermined significance (MGUS), patients with SMM have a much higher annual risk of developing MM. However, based on clinical observations, the natural history of SMM varies greatly, from stable MGUS-like disease to highly progressive disease. Using conventional clinical markers, SMM patients can be stratified into 3 risk groups. Importantly, because of considerable molecular heterogeneity, we currently lack reliable markers to predict prognosis for individual SMM patients. Furthermore, until recently, potent drugs with reasonable toxicity profiles have not been available for the development of early MM treatment strategies. Consequently, current clinical guidelines emphasize the application of close clinical monitoring followed by treatment when the patient develops symptomatic MM. This review focuses on novel biomarkers, molecular profiles, and microenvironmental interactions of interest in myelomagenesis. We also discuss how the integration of novel biologic markers and clinical monitoring of SMM could facilitate the development of early treatment strategies for high-risk SMM patients in the future.

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Introduction

Multiple myeloma (MM) is a hematologic neoplasm characterized by the proliferation and accumulation of malignant plasma cells in the bone marrow and overproduction of monoclonal proteins. Approximately 20,000 new cases are diagnosed annually in the United States.^{1,2} In contrast, monoclonal gammopathy of undetermined significance (MGUS) is an asymptomatic plasma cell dyscrasia with a 1% average annual risk of progression to MM afflicting approximately 3.2% of white patients over 50 years of age.^{3–5} Smoldering multiple myeloma (SMM) is another asymptomatic precursor to MM with a much higher annual risk of progression. Roughly 3000 cases are diagnosed annually in the United States, though estimates of prevalence are not reliable as a result of previous inconsistent diagnostic criteria and underdiagnosis from its asymptomatic nature.⁶ Based on retrospective data from the Mayo Clinic, SMM has a 10% average annual risk of progression to MM for the first 5 years after diagnosis, decreasing to 3% annually for the following 5 years, and becoming the same 1% annual rate of progression as MGUS thereafter.⁷ Treatment of MM has been reserved for symptomatic disease. At this time, MM treatment includes autologous stem cell transplantation, immunomodulatory drugs (thalidomide and lenalidomide), and bortezomib. Although these therapeutic strategies have facilitated improved survival, cure remains elusive, and the therapeutic index of most of these strategies makes them inappropriate for use in asymptomatic disease.^{8–10} As such, current guidelines recommend close interval follow-up and monitoring for progression to symptomatic MM.⁷

Importantly, 2 recent studies have answered the fundamental question of whether all cases of MM are preceded by a precursor state. The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial is a prospective study of 77,469 healthy volunteers with annually collected serum samples. Samples collected before diagnosis from the 71 individuals who developed MM demonstrated that MM was consistently preceded by MGUS in all cases.¹¹ Another recent study utilizing the Department of Defense Serum Repository to evaluate 30 MM cases with available prediagnostic serum samples found that all cases of non-immunoglobulin (Ig)D MM with serum available within 4 years of diagnosis showed evidence of previous MGUS.¹² These independent observations establish an essential role for precursor disease in the pathogenesis of MM. In the context of improved molecular prognostic indicators and a growing treatment armamentarium of less toxic agents, these findings suggest that there may be a treatment time window before the development of clinically apparent myeloma.

Diagnostic Criteria

Kyle and Greipp were the first to describe SMM as a distinct entity in 1980 as an “illness that met the criteria of MM but has not had a progressive course,” a corollary to smoldering leukemia.¹³ In this caseseries of 6 patients, all 6 patients had 10% bone marrow plasma cells and 3 g/dL of monoclonal (M) protein without progression to MM for at least 5 years.¹³ Following this initial description, several other studies of SMM were completed using criteria comprising patients with mild anemia, requiring M-protein < 4.5 g/dL, marrow plasma cells > 15%, ignoring percent marrow plasma cells entirely, and requiring Bence-Jones proteinuria.^{14–16} Many studies included separate definitions of SMM and indolent

multiple myeloma (IMM), with IMM being described as either “mildly symptomatic” MM or a form of MM in which minimal end-organ damage was clinically evident without symptoms. For instance, patients with lytic bone lesions noted on imaging who had not yet suffered a pathologic fracture were classified as having IMM in some studies.^{14,17} Often, both SMM and IMM were combined into the entity of asymptomatic MM, though in other cases SMM and asymptomatic MM were considered equivalent.^{14,15,18} As a result of these varying definitions, comparing data on SMM collected before 2003 is problematic.

In 2003, the International Myeloma Working Group (IMWG) released a consensus on the specific diagnostic criteria for the known monoclonal gammopathies.¹⁹ Definitive clinical criteria were developed to differentiate between MGUS, SMM, and MM and other plasma cell disorders (Table 1). Specifically, SMM was defined as either M-protein ≥ 3 g/dL or marrow plasma cells $\geq 10\%$ in the absence of end-organ damage. In contrast, MGUS was defined as the presence of an M-protein of < 3 g/dL and $< 10\%$ bone marrow plasma cells, no detectable end-organ damage, and the exclusion of all other plasma cell disorders. Of note, the IMWG did not include any numerical cutoffs for a diagnosis of symptomatic MM, only requiring the presence of endorgan damage in the setting of an M-protein and clonal plasma cells. The IMWG defined end-organ damage as either the classic “CRAB” symptoms of hypercalcemia (serum calcium ≥ 1 mg/dL above the upper limit of normal), renal failure (creatinine > 1.95 mg/dL), anemia (hemoglobin < 10 g/dL), or bone lesions (lytic lesions or osteoporosis with compression fractures). Less classic myeloma-related organ impairment includes recurrent bacterial infections (> 2 in 12 months), symptomatic hyperviscosity, and amyloidosis.¹⁹ It is important to note that the IMWG did not include a definition of IMM and the term eventually fell out of use; those patients meet IMWG criteria for MM. Currently, asymptomatic MM is synonymous with SMM. However, excess bone resorption measured by quantitative bone biopsy and biomarkers of bone turnover suggests that bone disease not detectable by skeletal survey is present even in MGUS.^{20,21} This finding may explain the 1.4 relative risk of fracture (2.7 for axial fractures) seen in patients with MGUS independent of malignant transformation.^{22,23} Thus it is important to consider that clinical criteria for end-organ damage are highly dependent on the sensitivity of the methods used to detect the damage. The definition of end-organ damage might change in the coming years as imaging technology and molecular markers improve.

Pathogenesis

Although MGUS and SMM can be differentiated based on clinical diagnostic parameters,¹⁹ there are no definitive molecular or immunophenotypic markers to differentiate the plasma cells of MGUS, SMM, or MM.²⁴ In fact, based on clinical features, it has been proposed that SMM may not be a distinct biologic entity.²⁵ Rather, the diagnosis of SMM includes patients who fit at least 3 distinct clinical pictures: (1) abnormally active but stable MGUS; (2) slowly increasing M-protein or percent marrow plasma cells without detectable end-organ damage; and (3) highly progressive disease with end-organ damage that is not yet detectable (Figure 1).

Progression to MM is related to both intrinsic changes of plasma cells and the extrinsic influence of bone marrow stromal cells, angiogenesis, and immunologic factors. Plasma

cells in premalignant states preceding MM are notable for genomic complexity believed to be mediated at least partly through antigenic stimulation.⁶ The current understanding, supported by studies of gene expression in myeloma cell lines,^{26,27} is that MGUS, SMM, and MM cells produce an abnormally broad superfamily of immunoreceptors signaled by both paracrine factors like interleukin (IL)-6 produced by the bone marrow stroma and exogenous pathogen-associated molecular patterns.^{6,28} This results in sustained clonal proliferation. Other studies have suggested that IL-1 β , with high expression in MM and some SMM and low expression in MGUS and other SMM, may amplify this proliferation by increasing IL-6.^{29–31}

Other techniques have been used to probe complex interactions in the bone marrow. Flow cytometry has been used to determine ratios of normal and immunophenotypically abnormal plasma cells (aPCs). Characteristic changes in aPCs include absent CD19, lack of CD45, decreased CD38, and/or overexpression of CD56.³² Ratios of normal plasma cells to aPCs have been shown to differentiate MGUS from MM ($P < .0005$).³³ Nearly all cases of MM have 95% aPCs, compared with 60% (56/93) of cases of SMM and 18% (73/407) of MGUS cases.³⁴ A much smaller study using gene expression profiling of bone marrow endothelial cells found 9 genes encoding extracellular matrix proteins differentially expressed in patients with MGUS versus MM.³⁵ Several studies have shown differences in both the cellular and secreted components of the microenvironment in patients with MGUS and MM,³⁶ but a study of the microenvironmental changes in SMM is lacking. Such studies could potentially elucidate the role of the microenvironment in the progression from SMM to MM. However, focusing on the cells of the microenvironment is challenging because they require careful sorting of the numerous cell types that reside in the marrow. Adding to this complexity, it is likely that alterations in the microenvironment may allow for both enhanced growth of malignant plasma cells and expansion of the overall plasma cell niche. Signaling from aPCs likely promotes changes in the microenvironment. Future studies are needed to explore these issues.

Also, there have been studies designed to explore the hypothesis that conversion from asymptomatic to symptomatic disease may be related to an “angiogenic switch” resulting from an alteration in the milieu of proangiogenic and antiangiogenic cytokines allowing for malignant proliferation.^{37–39} Although these studies of the microenvironment have discriminated among groups of patients based on their diagnoses, they have yet to provide a unifying explanation of how these clinical entities differ from one another.

The microenvironment could, in part, mediate epigenetic differences in the plasma cells of patients with MGUS, SMM, and MM; this has been explored. MicroRNAs (miRNAs) are short, noncoding RNA sequences that modulate many biologic processes by paring with target mRNAs and regulating their expression.⁴⁰ Indeed, miRNAs may act as oncogenes or tumor suppressors, contributing to myelomagenesis.⁴¹ A recent study using miRNA microarrays compared the miRNA signatures in patients with MM, MGUS, and healthy controls, finding significant differences among the 3 groups. Specifically, upregulation of several miRNAs were present in both MGUS and MM samples, while miR-19a/b, which regulates the IL-6R/STAT3 pathway was overexpressed only in MM samples.⁴² Further studies of miRNA profiles in patients with SMM may be illustrative of its biologic character.

Hypermethylation of tumor suppressor genes can lead to their inactivation.⁴³ Methylation-specific polymerase chain reaction (MS-PCR) has been used to analyze methylation of several tumor suppressor genes such as *p15*, *p16*, *p27*, *ARF*, *SOCS-1*, *RASSF1A*, and *TP73*. Though rates of methylation of at least 1 of these genes are comparable in MGUS and MM, methylation of multiple genes is more common in MM.⁴⁴ However, this may be misleading. A study of patients with MGUS, SMM, and MM found that *p16* was hypermethylated in 24%, 28%, and 34%, respectively, with no significant differences in *p16* transcription by gene expression profiling or overall survival (OS).⁴⁵ Other studies have found *p16* methylation in 80%–90% of extramedullary MM and plasma cell leukemias.⁴⁶ These findings suggest that methylation of *p16* may be a late finding in aggressive disease and a marker for overall genetic damage rather than a necessary biologic change in the progression to active disease.

Monoclonal gammopathy of undetermined significance, SMM, and MM are not homogenous entities. Rather, there are 2 partially overlapping characteristic cytogenetic entities: the hyperdiploid state (approximately 50%) and primary IgH translocations (approximately 40%), of which there are at least 5 characteristic translocations at the heavy chain locus at 14q32.⁶ These variations can coexist with a deletion of chromosome 13, which is associated with t(4,14) and t(14,16) and their poor prognosis in MM.⁴⁷ Figure 2 shows these characteristic chromosomal changes that alter the regulation of oncogenes such as cyclin D, *MAF*, *MMSET*, and *FGFR3*.²⁴ However, 2 studies using fluorescence in situ hybridization (FISH) on clonal plasma cell populations from the bone marrow of 209 patients with MGUS and 49 with SMM were unable to find any significant cytogenetic differences between MGUS and SMM.^{48,49} In 2003, an international workshop reviewed various studies to determine that some cytogenetic anomaly is present in virtually all cases of MGUS and SMM; oftentimes these changes cannot differentiate MM from its precursors, though some events, such as p53 deletions and mutations or homozygous deletions of p18, are far more prevalent in highly aggressive, refractory, or extramedullary MM.^{24,50}

Point mutation analysis has been valuable, as it has led to the identification of NRAS and KRAS mutations with much higher frequencies in patients with MM as compared with MGUS, though they are overrepresented in tumors expressing cyclin D1. This indicates that the second, transformational event (Figure 2) may vary depending on the initial oncogenic event.^{51,52} Alternately, a case report of 5 annual FISH studies and genomic microarrays performed on a 30-year-old patient who progressed to MM after 4.5 years of having SMM observed a deletion of chromosomal band 1p23 and MYC oncogene translocation correlating with the transition from SMM to MM.⁵³ Although other studies have correlated a gain of chromosomal band 1q to MM,^{54,55} this prospective finding may open an avenue for future research in this area. MYC translocation is more common in advanced MM than newly diagnosed MM and is rare or absent in MGUS or SMM; MYC RNA expression is higher in MM than MGUS/SMM and very low in normal plasma cells.^{56,57} Thus, there may be an early increase in MYC expression as a result of epigenetic factors followed by a further increase because of chromosomal rearrangements. However, it is possible that this patient⁵³ could have had an uncommonly rapid transition from SMM to aggressive MM. Because of the heterogeneity of plasma cell neoplasia, prospectively collected; paired samples from the same patient can provide insights that are unattainable from studies

comparing populations of patients in different disease states at a single point in time. Although techniques such as gene expression profiling and MS-PCR can detect finer differences in gene expression, cytogenetic approaches will continue to be important to the future of evaluation of patients with SMM as the requisite technology is more readily available in clinical laboratories.

Overall, the pathogenesis of MGUS, SMM, and MM are poorly understood at this time, largely because of the striking heterogeneity of their molecular profiles. Clinically, SMM is a heterogeneous disorder consisting of disease with stable, MGUS-like features, an abrupt course to MM, and an intermediate, slowly progressive course (Figure 1). From a molecular perspective, gene expression profiling has revealed at least 7 subtypes of MM,⁵⁸ but a prospective study to correlate gene expression profiling and other biomarkers to clinical course in MGUS and SMM has not yet been performed. Although translational studies have made great strides toward generating new molecular descriptions of these disease entities and their transitions (Figure 2), they are still largely overlapping (Figure 1) and sampling bias may exist in small translational studies, necessitating validation with large prospective studies to develop molecular predictors for which patients will endure which clinical course.

Prognostic Factors

Recently, the application of flow cytometry-based immunophenotyping of plasma cells has contributed significantly to the risk stratification of patients with MGUS and SMM (Tables 2 and 3).^{34,59,60} Established factors related to progression to and from MGUS and SMM are listed in Figure 2.^{61–67} The risk of progression of MGUS is roughly 1% annually, though this risk is substantially higher for patients with an M-protein ≥ 1.5 g/dL, abnormal serum free lightchain (FLC) ratio, non-IgG MGUS, and $\geq 95\%$ aPCs by flow cytometry.^{34,67} Early clinical experience with SMM revealed that mild symptoms, Bence-Jones proteinuria, and abnormal peripheral blood labeling index correlated with a shorter time to progression (TTP).^{14–16}

Of importance, each of these studies noted significant heterogeneity in the clinical course of patients with SMM. In the first and largest systematic study focusing on SMM, retrospective data from 276 patients with SMM seen at the Mayo Clinic between 1970 and 1995 were collected. In this study, the heterogeneity of SMM was formalized through a subgroup analysis of patients stratified into 3 groups: $\geq 10\%$ bone marrow plasma cells and ≥ 3 g/dL of M-protein (group 1), $\geq 10\%$ bone marrow plasma cells and ≥ 3 g/dL of M-protein (group 2), or $\geq 10\%$ bone marrow plasma cells and ≥ 3 g/dL of M-protein (group 3). Patients in group 1 had a cumulative 15-year risk of progression of 87% with a median TTP of 2 years, patients in group 2 had 70% progression at 15 years with a median TTP of 8 years, and patients in group 3 had a cumulative risk of progression of 39% at 15 years with a median TTP of 19 years. Additionally, immunoparesis, a reduction in uninvolved immunoglobulins, was found to be an independent risk factor. Last, it was found that patients with an IgA heavy chain on average progressed faster than those with an IgG heavy chain.⁷ Analysis of serum samples from 273 of the 276 patients from the above study with an FLC assay later found an increase in the risk of progression to MM when the FLC ratio deviated outside the reference range of 0.125–8 defined in the study. This factor was used to refine the previous

risk stratification scheme, with the highest risk group 3 times more likely to progress at 5 years than the lowest risk group (Table 3).⁵⁹

Immunophenotyping with multiparameter flow cytometry is an attractive technique for determining prognosis in MGUS and SMM by identifying high levels of neoplastic plasma cells compared with normal ones, which is likely in patients whose disease has more malignant potential. Pérez-Persona and colleagues immunophenotyped bone marrow aspirates of 93 patients with SMM.³⁴ They found that in patients for whom these markers indicated 95% aPCs, the relative risk of progression at 5 years was 8.5 in patients with MGUS and 5.4 in patients with SMM, though the absolute risk of progression in SMM was much higher. Also importantly, this study found that reduction in at least 1 uninvolved immunoglobulin was an independent risk factor for progression of SMM (relative risk of 2.5). A risk stratification scheme generated from these data shows that the risk of progression for patients with neither, 1, or both risk factors at 5 years was 4%, 46%, and 72%, respectively, ($P < .001$; Table 3). A recent study by the same group found that 95% aPCs could differentiate risk within the subgroups of evolving SMM or MGUS, defined by a $> 10\%$ increase in M-protein 1 and 3 years from diagnosis, respectively. However, evolving SMM subtype was not found to be significant in a multivariate analysis of progression-free survival.^{68,69} Integrating other markers into such a risk stratification scheme will be key in determining which patients will ultimately progress.

An effort has been made to determine if degree of angiogenesis has prognostic value. Though a study of bone marrow biopsy samples from 400 patients with MGUS, SMM, or MM found a significant difference in median microvascular density and percentage of high-grade angiogenesis between MGUS/SMM and MM, there was no significant difference between MGUS and SMM.³⁸ Despite finding a significant population-level relationship, the heterogeneity within individual groups precluded the use of these characteristics to make prognostic decisions for individual patients. Dynamic contrast-enhanced magnetic resonance imaging (MRI), which examines wash-in and wash-out kinetics of MRI contrast in the bone marrow, has recently shown promising results for noninvasively differentiating the marrow microcirculation patterns of MGUS, SMM, and MM.^{39,70} Correlating these angiogenic findings with other biomarkers may show promise for further risk stratification of these patients.

Furthermore, proteasomes are nonlysosomal protein degradation units that degrade short half-life proteins involved in cellular functions including antigen signaling. They are overexpressed in MM.^{71–73} A study of circulating proteasome levels in patients with MGUS ($n = 20$), SMM ($n = 40$), and newly diagnosed MM ($n = 101$) found significantly elevated levels of circulating proteasomes in patients with MM relative to MGUS or SMM ($P < .001$) and in patients with MGUS or SMM relative to controls ($P < .001$).⁷³ There was no significant difference in circulating proteasome levels between patients with MGUS and SMM. A prospective study comparing changes in circulating proteasome levels and other biomarkers with clinical progression may have the potential to risk-stratify patients with SMM.

Clinical Management

Historically, the consensus opinion has been that patients with SMM should not be treated unless progression to MM occurs, though these patients should receive close follow-up with repeat laboratory testing at 2–3 months during the first year and every 4–6 months thereafter because of the high initial risk of progression.^{7,19} Among the first 2 studies examining treatment of SMM was a 1988 retrospective study of 23 patients with SMM and 10 patients with lytic lesions but no symptoms. These patients were treated with 1 of 2 chemotherapy regimens, but the study failed to show a statistically significant difference in the endpoints of remission or survival.¹⁴ As this study was limited in its size and design, a randomized controlled trial of initial (at diagnosis) versus delayed (at symptoms) treatment with melphalan/prednisone for 50 patients with SMM or IMM was performed, finding no difference in response rate, response duration, or survival.⁷⁴ Thus, it was deemed inappropriate to recommend patients to undergo a difficult chemotherapy regimen with no evidence of a clinical benefit.

However, both of these studies were performed when the best available treatment for MM was melphalan/prednisone, a regimen with a poor therapeutic index for treatment of an asymptomatic condition. The development of novel agents with improved efficacy and less toxicity have renewed interest in the treatment of SMM. Thalidomide is a noncytotoxic drug used to treat refractory MM that has been shown to have anti-inflammatory, antiangiogenic, and immunomodulatory properties.^{75,76} In 2001, a trial of thalidomide as treatment for SMM in 16 patients was performed. Partial response (PR) was achieved in 38% of the patients.¹⁸ These data may be confounded by the inclusion of patients with IMM who would now be classified as having MM. In 2008, a nonrandomized phase II trial including 76 patients with SMM treated with thalidomide and pamidronate did not show a clear overall benefit to treatment. Paradoxically, patients who initially displayed at least a PR to thalidomide had a shorter median time to treatment (< 2 years) than patients who showed no improvement (not reached in 8 years).⁷⁷ This may be a result of a greater initial response in patients with more proliferative tumors or selection of aggressive clones because of treatment. Hence, responsiveness to thalidomide may be an independent risk factor for progression. This study was further complicated by poor tolerance to thalidomide, as a result of peripheral neuropathy and dizziness resulting in discontinuation in greater than half of patients.⁷⁷

These dose-limiting toxicities have prompted the use of less toxic drugs that share mechanistic features with thalidomide.⁷⁶ Lenalidomide, is a second-generation immunomodulatory drug that has proven efficacy with dexamethasone in both relapsed/refractory and newly diagnosed MM.^{76,78–82} Although the side effect profile was improved relative to thalidomide, bone marrow suppression and venous thromboembolism remained as significant adverse events.^{79,83} The first phase III clinical trial using novel drugs (lenalidomide/dexamethasone vs. surveillance) in SMM is currently ongoing in Europe.⁸⁴ Preliminary results were presented at the 2009 American Society of Hematology annual meeting. In the surveillance arm, 50% of patients with high-risk SMM progressed to active MM in 19 months. However, in 45 patients who began and continued active treatment with

lenalidomide/dexamethasone, no disease progression was observed after a median follow-up of 16 months.⁸⁵

Small trials have studied other interventions with benign sideeffect profiles aimed at limiting the progression of SMM or MGUS, including anakinra, a targeted IL-1 receptor antagonist⁸⁶; curcumin, a traditional Indian spice with preclinical antimyeloma activity^{87–90}; and bisphosphonates, believed to block the initial formation of lytic lesions and alter the marrow microenvironment.^{91,92} As of yet, none of these studies have had sufficient power or study design to significantly alter clinical practice. Some data are further limited by use of nonstandard endpoints and response criteria.⁹³ Despite these limitations, these trials are indispensable in their ability to open avenues for further research. Selected published and ongoing clinical trials studying treatment of SMM are listed and described in Table 4.^{14,18,74,77,77,84,86,87,91,94–96} General strategies aimed at preventing progression of plasma cell dyscrasias are shown in Figure 2.

Conclusion

How do clinicians gain access to patients with SMM? Routine screening for MM precursor diseases is not indicated. Rather, patients with MGUS or SMM are identified because of incidental findings as part of the workup of several common symptoms and laboratory abnormalities. These are the patients who must be counseled regarding the variable risk of progression to MM. However, it is not currently possible to predict for the individual patient whether the underlying disease will progress to MM.⁹⁷ The high rate of progression of SMM into symptomatic disease makes the idea of an early treatment strategy appealing to clinicians, though as of yet no particular treatment regimen has demonstrated a clear benefit for these patients in terms of OS. Several promising clinical trials are already in progress (Table 4). Clinical trials of novel agents currently used to treat relapsed or refractory MM may be applied to SMM in the future. Pomalidomide, a third-generation immunomodulatory drug, has been found to be efficacious in patients with relapsed MM with less bone marrow suppression than lenalidomide.⁹⁸ Bortezomib, an inhibitor of the 26S proteasomal subunit, has been used successfully to treat both newly diagnosed and relapsed MM, though peripheral neuropathy and bone marrow suppression remain a clinical challenge.^{99,100} Carfilzomib, a second-generation proteasome inhibitor, has shown promise in 2 phase I trials and 1 phase II trial for the treatment of MM with potentially fewer side effects than bortezomib,¹⁰¹ though the frequent, intravenous administration of these drugs is not optimal for treatment of SMM. These newer drugs with more favorable side effect profiles may have the potential to be used in the treatment of SMM without the often treatment-terminating adverse effects of thalidomide. Also, several other small molecules and monoclonal antibodies have shown promise in preclinical and early clinical studies.¹⁰² The time may be right for the commencement of clinical trials of these novel agents in the treatment SMM, though such studies should be careful to analyze key endpoints such as TTP and OS as past experience has indicated that partial and complete responses may not be illustrative of benefit.

As we know from the vast number of potential genetic events implicated in MGUS, SMM, and MM, neither cases nor cells are homogenous. Ergo, there are at least 3 scenarios that

must be carefully considered in any clinical trial aimed at treating SMM (Figure 3). Early treatment has the potential to cure SMM even though MM is almost always incurable. Although this is an attractive goal, it would likely require more potent drugs, which in turn require better characterization of high-risk SMM cases. Second, early treatment could lead to the generation of a chronic, asymptomatic disease state requiring ongoing maintenance therapy. This may be likely given the trend toward using immunomodulatory and targeted agents. Alternately, a delay in progression to MM would be a success, though one must also weigh the possibility that such agents may cause unexpected long-term adverse events. For instance, the increased risk of acute leukemias and myelodysplastic syndromes in patients treated with melphalan was not initially noted. Last, theoretically one might speculate that early treatment could lead to a paradoxical decrease in survival or TTP because of selection of aggressive clones that are more capable of competing in the treatment-altered microenvironment.¹⁰³ Because we do not know if this scenario is likely to occur, if future trials indicate that MM developing after early treatment is more aggressive, this question should be addressed. Because none of these scenarios has been proven true, it is very important to conduct well-designed correlative studies in clinical trials aimed to treat SMM patients.

As SMM is quite clinically heterogeneous, it will be important to consider how to manage patients who fall into the clinical subgroups pictured in Figure 1. The stable MGUS-like patients most likely should not be treated as they have a low risk of progression. The patients with highly progressive, presymptomatic disease will likely be treated in the future as their disease will be active shortly. Whether to treat patients with slowly increasing M-protein or bone marrow plasma cells will require more information. To make better treatment decisions based on these clinical courses, we need to develop biomarkers to predict the course of patients with SMM. New biologic markers, which may include genomic and epigenomic information, serum protein studies, and/or imaging studies, may be able to identify these patients and refine their prognoses. These must first be validated in prospective trials. Improved knowledge regarding the molecular events linked to progression to and from SMM may redefine these clinical parameters into more objective biologic ones with superior correlation to prognosis and potential utility of treatment.

Though current evidence does not support the treatment of SMM outside of clinical studies, it does in our opinion support the development of early treatment trials that integrate molecular monitoring as described above. At the National Cancer Institute of the National Institutes of Health in Bethesda, we are developing natural history and treatment studies focusing on patients with MM precursor diseases (MGUS and SMM). Our goals are to provide molecularly based predictions of transformation from MGUS/SMM to MM and to counsel patients with regard to future clinical follow-up. We also offer novel treatments for patients with MM precursor diseases, aiming to delay progression and potentially offer cure.

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Figure 1. The Clinical Dilemma of Classifying Smoldering Myeloma

A. Proposed model of clinical entities comprising SMM and how they fit into the spectrum of plasma cell disorders. **B-E.** The shifting position of SMM in the context of MGUS and MM from the perspectives of epidemiology (**B**), symptomology (**C**), results of routine studies (**D**), and molecular profiles (**E**). Currently there are no specific pathologic features to reliably differentiate these three conditions.

Abbreviations: MGUS = monoclonal gammopathy of undetermined significance; MM = multiple myeloma; SMM = smoldering multiple myeloma

Figure 2. Etiology, Clinically Available Risk Factors, and Proposed Management Strategies for Prediction and Prevention of Transitions Between Clinically Defined Plasma Cell Disease States

Though precise mechanisms and timing of these transitions are poorly understood, they are believed to occur as a result of gradual, cumulative genetic and epigenetic insults. Many potential oncogenic events overlap throughout this pathogenic process. Current guidelines do not endorse any active management strategies, but proposed strategies are presented.

Abbreviations: aPC = abnormal plasma cell; Ig = immunoglobulin; IL = interleukin; MGUS = monoclonal gammopathy of undetermined significance; MM = multiple myeloma; NF-κB = nuclear factor-κB; SMM = smoldering multiple myeloma

Figure 3. Three Possible Scenarios Resulting From Treatment of Smoldering Myeloma

Progression of untreated high-risk SMM to clinically apparent myeloma is shown on the left. SMM patients with 2 or 3 risk factors (Table 3) have a median TTP of 5 years and 2 years, respectively. Scenarios 1–3 illustrate possible scenarios resulting from early treatment of SMM. Scenario 1 (center left) represents a complete cure of MM, which has not yet been reliably achieved by any current treatment modalities. This would likely require more intense treatment, necessitating improved risk stratification of patients. Ultimately, targeted therapies may be able to achieve cure. Scenario 2 (center right) represents the generation of a chronic, asymptomatic disease state requiring ongoing maintenance therapy. This is a likely outcome of using immunomodulatory and targeted agents available in the near future. Scenario 3 (right) illustrates the theoretical possibility of the selection of a particularly aggressive resistant clone. Although time to progression is extended in this scenario, overall survival may not be improved, as symptomatic disease might progress unchecked if available treatments become less effective following early treatment. Future studies are needed to fully explore these possibilities. Taken together, we do not know which, if any, of these scenarios are true. Therefore, clinical trials aimed at developing treatments for SMM should incorporate well designed correlative studies to examine the biology of treatment response. Abbreviations: SMM = smoldering multiple myeloma; TTP = time to progression

Table 1

International Myeloma Working Group Diagnostic Criteria for Monoclonal Gammopathy of Undetermined Significance, Smoldering (Asymptomatic) Myeloma, and Multiple Myeloma¹⁹

Disorder	Monoclonal Gammopathy of Undetermined Significance	Smoldering (Asymptomatic) Myeloma	Multiple Myeloma
M-protein	< 3 g/dL AND	3 g/dL OR	Any
Bone Marrow Plasma Cells	< 10%	10%	Any
Myeloma-Related Organ or Tissue Impairment ^a	Absent	Absent	Present
Comment	Requires exclusion of all other B-cell lymphoproliferative disorders	Indolent multiple myeloma Disease with end-organ damage but minimal symptoms	
		“CRAB” criteria: hypercalcemia, renal failure, anemia, lytic bone lesions	

^a Less common features of myeloma-related tissue impairment include recurrent bacterial infections (> 2 in 12 months), hyperviscosity, and amyloidosis. Adapted from International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. *Br J Haematol* 2003; 121:749–57

Table 2

Selected Risk Stratification Schemes for MGUS

A. Risk Factors: M-protein > 1.5 g/dL, Non-IgG MGUS, FLC Ratio < 0.26 or > 1.65⁶⁰

Number of Risk Factors	Number of Patients (%)	20-Year Progression	Relative Risk
0	449 (38)	5%	1
1	420 (37)	21%	5.4
2	226 (20)	37%	10.1
3	53 (5)	58%	20.8
Total	1148 (100)	20%	NA

B. Risk Factors: > 95% aPC, DNA aneuploidy³⁴

Number of Risk Factors	Number of Patients (%)	5-Year Progression	Relative Risk
0	127 (46)	2%	1
1	133 (48)	10%	5
2	16 (6)	46%	23
Total	276 (100) ^a	8.5%	NA

^a A total of 407 patients with MGUS were studied; 276 patients had available aneuploidy data.

Abbreviations: aPC = abnormal plasma cell; FLC = free light chain; Ig = immunoglobulin; MGUS = monoclonal gammopathy of undetermined significance; NA = not applicable

Table 3

Selected Risk Stratification Schemes for Smoldering Multiple Myeloma

A. Risk Factors^a: Marrow Plasma Cells > 10%, M-protein ≥ 3 g/dL, FLC Ratio < 0.125 or > 8⁵⁹

Number of Risk Factors	Number of Patients (%)	5-Year Progression	Relative Risk
1	76 (28)	25%	1
2	115 (42)	51%	2.0
3	82 (30)	76%	3.0
Total	273 (100)	51%	NA

B. Risk Factors: > 95% aPC, Immunoparesis³⁴

Number of Risk Factors	Number of Patients (%)	5-Year Progression	Relative Risk
0	28 (31)	4%	1
1	22 (25)	46%	11.5
2	39 (44)	72%	18
Total	89 (100) ^b	46%	NA

^aPatients must have at least 1 of the first 2 risk factors to meet criteria for SMM.

^b A total of 93 patients with SMM were initially studied; 89 had available immunoparesis data.

Abbreviations: aPC = abnormal plasma cell; FLC = free light chain; NA = not applicable; SMM = smoldering multiple myeloma

Table 4

Selected Clinical Studies of Strategies to Prevent Progression of SMM, MGUS, and Early-Stage MM

Study	Study Design	Intervention	Number of Patients	Outcome/Comment
Alexanian et al (1988) ¹⁴	Retrospective cohort study	VAD or MP	23 SMM, 10 IMM	Because the treatment of MM remains palliative, chemotherapy should be held until symptoms appear
Hjorth et al (1993) ⁷⁴	Randomized controlled trial	Initial vs. deferred MP therapy	50 SMM and IMM (25/25)	Similar response rate, response duration, and survival
Rajkumar et al (2001) ¹⁸	Single-arm pilot study	Thalidomide	16 SMM and IMM	MR or better in 11/16; microvessel density did not predict response
Musto et al (2008) ⁹¹	Open-label, randomized, controlled trial	Zoledronate	163 SMM (81/82)	Zoledronate for 1 year decreased risk of skeletal-related disease, but TTP was similar ($P = .83$)
Barlogie et al (2008) ⁷⁷	Single-arm phase II trial	Thalidomide/pamidronate	76 SMM	Median TTP, 7 years; PR identifies subset requiring earlier salvage therapy for symptomatic disease
Lust et al (2009) ⁸⁶	Single-arm phase II trial	Anakinra (IL-1 receptor antagonist)	47 SMM and IMM (25 received anakinra and DEX)	Median PFS was 37.5 months; MR (n = 3); PR (n = 5); 8 patients stable on drug for 4 years
Golombick et al (2009) ⁸⁷	Single-blind, randomized, cross-over pilot study	Curcumin vs. placebo	26 MGUS	5 of 10 patients with M-protein > 2 g/dL had decreased M-protein (12%–30% reduction)
Kalaycio (2004-Ongoing) ⁹⁴	Double-blind, randomized controlled trial	Celecoxib vs. placebo	36 MGUS and SMM	Aim: to test if celecoxib reduces the M-protein concentration
QUIREDEX Mateos et al (2007-Ongoing) ⁸⁴	Open-label, randomized, controlled trial	Lenalidomide + DEX vs. observation	120 ^a "high-risk" SMM	Aim: to evaluate if lenalidomide + DEX extend TTP
Ballester (2009-Ongoing) ⁹⁵	Unblinded, nonrandomized trial	Ω-3 fatty acids	48 ^a MGUS, SMM, or CLL	Aim: to assess if Ω-3 fatty acids reduce activated NF-κB levels in peripheral blood lymphocytes
Zonder et al (2009-Ongoing) ⁹⁶	Single-arm pilot study	Green tea extract	17 ^a MGUS or SMM	Aim: to test if green tea extract reduces the M-protein concentration

^a Estimated enrollment.

Abbreviations: CLL = chronic lymphocytic leukemia; CR = complete response (no detectable M-protein); DEX = dexamethasone; IL = interleukin; IMM = indolent multiple myeloma (asymptomatic but with evidence of end-organ damage); MGUS = monoclonal gammopathy of undetermined significance; MM = multiple myeloma; MP = melphalan/prednisone; MR = minor response (25%–50% decrease in M-protein); NF-κB = nuclear factor-κB; PFS = progression-free survival; PR = partial response (50% decrease in M-protein); SMM = smoldering multiple myeloma; TTP = time to progression; VAD = vincristine/doxorubicin/dexamethasone