Smoldering Multiple Myeloma: Pathophysiologic Insights, Novel Diagnostics, Clinical Risk Models, and Treatment Strategies

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Abstract: Smoldering multiple myeloma (SMM) is a plasma cell disorder first described in 1980 when 6 patients were observed to meet the diagnostic criteria of multiple myeloma, defined as bone marrow plasmacytosis of 10% or greater or M protein level of 3 g/dL or greater, but did not have end-organ damage. Subsequent studies showed that the cumulative risk of SMM progression to symptomatic myeloma in 15 years was 73%. Since this time, advances have been made in understanding the biology of progression; namely, the contribution of branching evolution and microenvironment models to clonal heterogeneity. In parallel to this, clinical risk models using standard platforms of serum, bone marrow, and fluorescence in situ hybridization markers along with newer technologies of flow cytometry, gene expression profiling, and magnetic resonance imaging have been developed for prognostic stratification. Treatment has extended to the early myeloma category owing to more sensitive diagnostic approaches. The development of novel treatments will have to take into consideration our current knowledge of biological transformation. While it may be attractive to initiate early treatment in light of recent studies for high-risk SMM patients, clinical trial evidence of efficacy vs toxicity is still in its infancy. In our opinion, high-risk SMM patients should be strongly encouraged to enroll in treatment clinical trials, but treatment with unapproved agents or indications is not supported outside of trials.

Introduction

Owing to its complexity, the underlying pathobiology in the initiation and progression of multiple myeloma (MM) and its precursor diseases has not been completely elucidated. Therefore, this paper aims to give further insight into these underlying mechanisms by

first presenting different potential models of myeloma progression; then by describing clinical risk models, the evolution of sensitive diagnostic platforms in the age of evolving novel therapies, and the role of "early" intervention; and finally by proposing prognostic categories, with particular emphasis on diagnostic and treatment strategies for smoldering MM (SMM).

Asymptomatic MM or SMM, which was first described in 1980, exists in the center of the myeloma spectrum between monoclonal gammopathy of undetermined significance (MGUS) and symptomatic MM.[1] Specifically, Kyle and colleagues reviewed 334 MM patient records in a period of 5 years and discovered that 6 of these patients had fulfilled the laboratory criteria for MM—either by serum M protein level or excess bone marrow plasma cells—yet never developed end-organ disease (no anemia, hypercalcemia, or lytic bone lesions) and remained asymptomatic despite not receiving treatment. It was 23 years later, in 2003, that the first consensus statement by the International Myeloma Working Group (IMWG) was published, describing and defining SMM as consisting of a serum M protein level of 30 g/L or greater and/or bone marrow clonal plasma cells of 10% or greater with no end-organ damage or symptoms (defined by hypercalcemia, renal insufficiency, anemia, bone lesions, or other manifestations, including hyperviscosity, amyloidosis, or recurrent bacterial infections, defined as >2 episodes in 12 months).[2]

Subsequent to this report, investigators determined that most often MM was preceded by SMM that was preceded by MGUS, and that the risk of progression from SMM was greater than that from MGUS. In a retrospective review of 276 SMM cases, 59% of patients eventually developed MM or amyloidosis. The overall risk of progression was determined to be 10% per year for the first 5 years, 3% per year in the next 5 years, and 1% per year afterward; the cumulative probability of progression was 73% after 15 years.[3] The 2 most important predictors of progression were determined to be the level of serum M protein and the proportion of bone marrow involvement. The definition of SMM remained the same in the 2010 IMWG consensus guidelines, with only slight modification of the calcium, renal insufficiency, anemia, or bone lesions (CRAB) criteria.[4]

With the advent of new genetic and molecular technologies, important insights have been gained into the underlying pathobiology of progression through the myeloma spectrum from the normal plasma cell compartment to MM. Despite the field's advances in identifying and describing these early and late molecular and cellular events, a unique and unifying mechanism—whether genetic, epigenetic, or stromal—to explain cohesively the underlying pathophysiologic pathways of malignant progression has not been identified. There likely is no single mechanism behind all cases of MM.

Normal Plasma Cell Biology

Plasma cells originate from the B-cell lineage, and develop after lineage commitment of hematopoietic progenitor cells in the bone marrow. In the bone marrow, the primary immunoglobulin (Ig)–producing landscape is created when the V, D, and J heavy chain (IgH) gene segments are rearranged.[5] Pro-B cells mature into pre-B cells after rearrangement of the IgH gene segments and expression of the pre–B-cell receptor, which is the first checkpoint in the maturation process and leads to clonal expansion and rearrangement of the immunoglobulin light chain (IgL) segments.[6,7] If the Ig κ locus is not successfully rearranged, the λ locus is rearranged.[5] Successful arrangement of this B-cell receptor with expression of surface IgM allows passage through the second checkpoint, and those that pass negative selection exit from the bone marrow to secondary lymphoid tissues. Before full B-cell maturity, cells undergo a second round of negative selection while developing in the spleen. Most B cells subsequently circulate through the spleen, lymph nodes, and bone marrow.

After B cells encounter cognate antigen, they continue to develop further by affinity maturation. Germinal centers are developed when follicular B cells encounter antigen and stimulation from T cells. B cells next undergo critical class switch recombination and somatic hypermutation to produce antibodies of different IgH isotypes.[6] Plasma cells (PC), which have high-affinity B-cell receptors, class switch recombination, and switched immunoglobulin isotypes, leave the germinal centers.[7] The double strand breaks that occur during these rearrangements can lead to oncogenic translocations, which are one of the main characteristics of MM. Therefore, given that many of the normal endogenous DNA events occur early in the maturation of the B-cell lineage, it is not surprising that MM shares similar genetic aberrations with other B-cell malignancies. The most unifying aberration due to a variety of different genetic mechanisms is the dysregulation of cyclin D, critical to cell cycle progression and nearly always aberrantly expressed in the plasma cell diseases.[8]

Categorization by Standard Laboratory Technologies

Based on older standard techniques of cytogenetics and fluorescence in situ hybridization (FISH), 2 categories and associated risk have been described. The molecular heterogeneity of myeloma can be observed at the cytogenetic chromosomal level, where myeloma cells may exhibit either hyperdiploidy or nonhyperdiploidy.

These categories were first described in the setting of symptomatic myeloma. However, preliminary evidence is arising that these cytogenetic and FISH characteristics might also have a role in SMM risk determination, which we describe later. Hyperdiploid chromosomal gains are observed in approximately half of MM cases by interphase FISH and, given that they are just as frequently observed in MGUS, some may consider it an early initiation event. However, this alone is not sufficient to immortalize plasma cells.[6,9] The hyperdiploid phenotype involves mostly trisomies of the odd numbered chromosomes[10,11] except for chromosomes 1 and 13, and is associated with improved clinical outcomes.[12]

To better understand the role of hyperdiploidy, global gene expression profiling (GEP) was performed to describe the molecular pathways and signatures associated with this subtype.[13] It was determined that overexpression of biosynthesis genes secondary to increased gene copy number was the hallmark association with hyperdiploidy, and that 4 biological clusters exist. The pathways activated as part of the clusters included: (1) overexpression of various cancer testis antigen and mitosis/proliferation-related genes; (2) overexpression of the hepatocyte growth factor (HGF) and interleukin 6 (IL-6) genes, leading to activation of the Ras/mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K)/Akt pathways; (3) overexpression of genes involved in nuclear factor κB (NF-κB) signaling and involved in NF-κB–induced anti-apoptosis; and (4) underexpression of HGF and the above genes.[13]

In the hyperdiploid subtype, chromosomal copy number alterations, via a gene dosage effect, may increase the expression of some genes. However, the large number of genes found and affected on a given chromosome makes it challenging to identify the specific, pathologically involved gene loci.[14] Studies have suggested that chromosomal copy number aberrations are functionally associated with changes in gene expression of specific pathways. Samur and colleagues developed a gene-wise dosage effect score to determine the concordance between gene copy number and gene expression changes. The authors found that 16% of the genes found on the typical trisomy chromosomes were upregulated, and at the individual gene level determined that some genes were sensitive and others resistant to copy number changes. The authors concluded that dosage effect is widespread and variable across the genome.[14]

The nonhyperdiploid subtype is characterized by monosomy 13, hypodiploidy, and pseudodiploid and near-tetraploid variants, and is strongly (73%-85% of cases) associated with translocations of the IgH chain located on chromosome 14 and monosomies of chromosomes 13, 14, 16, and 22.[12,15-17] In a study of 109 patients, the authors determined that 16 of the 18 patients with hypodiploidy and 9 of 10 patients with tetraploidy had IgH translocations.[18] Less commonly (15% of cases), hyperdiploidy can coexist with these 14q32 translocations.[17,19] There are 5 main IgH translocations that consist of a variety of different fusion partners, each conferring a different prognostic risk. However, in general, nonhyperdiploid MM leads to more aggressive disease and is more often associated with detrimental prognostic markers (chromosome 17 [p53] abnormalities, chromosome 1q amplification, and 1p deletion).

These primary translocations are believed by some to be early and perhaps initiation events in the evolution of MM. However, with the use of more sensitive technologies, subclonal populations have been described that do not contain the clonal IgH translocation.[6] The most common MM translocation, t(11;14) involving cyclin D1, is observed in MGUS in addition to MM. This is followed by t(4;14) in 15% of cases, which involves fibroblast growth factor receptor 3 (FGFR3), an oncogenic tyrosine kinase, and multiple myeloma SET domain (MMSET), a histone methyltransferase for histone H3 lysine 36 dimethylation (H3K36me2). When overexpressed, MMSET becomes hypermethylated, leading to a more open chromatin state and global epigenetic and gene expression changes.[20,21] Loss of MMSET expression alters adhesion properties, suppresses growth, and induces apoptosis in MM cells.

The reciprocal upregulation of MMSET and its downstream genes alters pathways involved in the p53 network, cell cycle regulation, and integrin signaling, and therefore is a critical epigenetic regulator.[8] Moreover, in a study of 178 newly diagnosed MM patients, of the 18% with the t(4;14) translocation, 32% lacked expression of FGFR3, despite expression of the MMSET chimeric transcript, and displayed a complete loss of one FGFR3 copy on interphase FISH. This suggests that in some cases of this IgH translocation, MMSET possibly has more of a role in pathogenesis.[22]

The (14;16) translocation leads to the upregulation of the transcription factor c-Maf and downstream expression of cyclin D2, adhesion molecules, and bone marrow interaction factors.[21] The other major translocations are t(14;20), affecting MAFB, and t(6;14), which causes dysregulation of cyclin D3.[15] These translocations occur in the nonfunctional IgH allele consistent with MM cells producing mature immunoglobulin from the functional allele. It is important to note that because these aberrations have been described not only in symptomatic MM but also in the precursor states, they are not likely to be the defining events between precursor disease and symptomatic MM. For example, FISH analysis was performed on 127 SMM patients and showed that the prevalence of IgH translocations or hyperdiploidy were similar to symptomatic MM.[9]

Subclonal Evolution, Heterogeneity, and Models of Progression

Based on current literature, 3 conceptual main models of biological progression have been proposed. Below we discuss these models of linear progression, branching evolution, and the microenvironment effector.[6,10,23,24]

Model 1: Linear Progression

A classical and perhaps simplistic approach to clonal evolution and malignant progression of the PC is the concept of linear evolution. Once the initiation "hits" are incurred and cells are immortalized, more and more molecular and genetic aberrations accumulate, pushing clinical disease forward. This concept of transformation involves multiple steps and mechanistically different types of aberrations. As these abnormal PCs accumulate lesions such as somatic mutations, copy number and epigenetic variation, and post-treatment immune modulation, the genetic landscape is modified and temporally becomes further heterogeneous.[6,25] Because of this complexity and vast number of identified "carrier" mutations, definitive (epi)genetic and molecular driver alterations that lead to this type of malignant progression cannot, for the most part, be identified.[10] Disease on the clinical spectrum moves further down to aggressive forms manifested by the clinical CRAB criteria.

Model 2: Complex Progression and Branching Evolution

As discussed above, there is vast heterogeneity between MM subtypes, and there is new evidence confirmed through single nucleotide polymorphisms (SNPs) and other analyses that clonal evolution occurs in a nonlinear or branching fashion.[24] In this model, the premalignant PC undergoes a series of divisions and accumulations of genetic lesions, some pathologic, in a Darwinian fashion, to create a repertoire of possible subclones, some evolutionarily enriched to survive. One possibility is that molecular heterogeneity is preserved via a cancer stem cell (CSC), which might aid in explaining the existence of genetically distinct clones giving rise to phenotypically different clonal expansions during clinical progression. The CSC hypothesis states that a few CSCs are responsible for the propagation of the bulk of a tumor and can remain undetected and dormant, and often resist treatment.[26-28] Previous work has suggested that MM CSCs might be CD138 and CD19 negative; might be CD20, CD27, and CD34 positive; or might consist of clonotypic memory B cells. However, given discrepant findings likely due to heterogeneity, a specific phenotype for MM CSCs and their definitive role in myeloma have not been established.[28-30] Alternatively, the relatively drug-resistant and dormant cells, through activation of internal and external pathways, might be mature myeloma cells.

Tumor heterogeneity likely arises as a result of the random Darwinian searches for phenotypic adaptation to the microenvironment. However, in this model, this diversity exists prior to clinical transformation to symptomatic myeloma.[31] Given the genetic complexity of MM clones, it is unlikely that a linear series of clonal expansions grows to dominate the neoplasm bulk.[32] More likely, there are a multitude of preexisting subclones containing various genetic alterations. By adapting to the microenvironment, and competing with one another through clonal interference, these subclones create a dynamic neoplastic process. It is the particular genetic subclone with the advantage that maintains, propagates, and predominates over the tumor bulk in later advanced, metastatic, and chemorefractory disease.[31] For example, in a case of childhood acute lymphoblastic leukemia, Anderson and colleagues described the initiating event as the *ETV6-RUNX1* gene fusion and the downstream driver copy number alterations. They detected 8 genetic abnormalities in single cells, creating specific subclonal genetic signatures, which displayed complex and nonlinear (branching) evolutionary histories, leading to a dynamic clonal architecture that changed temporally owing to the microenvironment and macroenvironment.[33] In fact, Walker and colleagues, using whole-genome sequencing, showed that intraclonal heterogeneity exists in all stages of PC disorders. In 4 high-risk SMM patients who ultimately developed symptomatic disease, the genetic changes existed prior to progression.[34] Interestingly, another study of 123 high-risk SMM patients (defined by the presence of ≥10% bone marrow PCs and IgG M protein level of ≥3 g/dL, Bence-Jones proteinuria >1 g/24 h, or ≥95% aPCs and immunoparesis) showed that although chromosomal abnormalities detected by FISH and SNP arrays at diagnosis were not associated with risk of progression, the overexpression of 4 *SNORD* genes was.[35]

Model 3: Microenvironmental Factors

In a third model of progression, the microenvironment plays an important role in the transformation from precursor to symptomatic disease. For example, normal PCs are integrally dependent on their stromal neighboring cells for survival, and studies have suggested that the stroma is very dynamic and required for malignant transformation, progression, and therapeutic resistance.[6,36] Malignant progression relies on the dynamic manipulation of the normal, intricate interactions of cellular inhabitants within the niche, which are constantly adapting for the malignant clone, in a stromal-dependent manner, to proliferate and metastasize.[37] The sharing of growth signals and factors secreted by stromal cells aid malignant heterogeneity by switching proliferative phenotypes to motile phenotypes. Liu and colleagues, using an evolutionary game theoreti-

Table 1. Current Diagnostic Criteria for Plasma Cell Disorders

Plasma Cell Disorder	Serum M Protein	Monoclonal Light Chain Restricted Plasma Cells	End-Organ (Symptomatic) Damage CRAB Criteria
MGUS	<3 g/dL	<10%	Absent
Smoldering MM	≥3 g/dL	≥10%	Absent
Multiple myeloma	Any amount must be present except in nonsecretory MM	Usually ≥10% but not a requirement	Any of the following: Calcium >10 mg/dL Serum creatinine >2 mg/dL or CrCl <40 mL/min Hemoglobin <10 g/dL Lytic lesions, severe osteopenia, or pathologic fracture

Based on the International Myeloma Working Group Stockholm 2013 expert discussions, updated consensus criteria will be published soon. Recent studies suggest that additional features such as bone marrow plasmacytosis of at least 60%,[58] an abnormal serum free light chain ratio of at least 100 (involved/uninvolved),[57] and/or focal bone marrow lesions detected by functional imaging (including positron emission tomography/computed tomography and/or magnetic resonance imaging)[50,52] in asymptomatic individuals may warrant a clinical diagnosis of multiple myeloma.

CrCl, creatinine clearance; CRAB, calcium, renal insufficiency, anemia, or bone lesions; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma.

This table is adapted from Landgren O. *Hematology (Am Soc Hematol Educ Program)*. 2013;2013(1):478-487[24] and includes information from Kyle RA et al. *Leukemia*. 2010;24(6):1121-1127[4] and Mikhael JR et al. *Mayo Clin Proc*. 2013;88(4):360-376.[19]

cal model, investigated the emergence of malignant clones based on differential inherent properties of the neoplasm and stroma through interaction.[38] By investigating the temporal evolution of the neoplastic population, the investigators showed the role of cooperation in forming a malignant tumor and the resulting dominance of one subclonal phenotype in the context of complete elimination of another phenotype.

In addition, recent work has suggested that the host micro-environmental stromal cells and CSCs interact with each other through intercellular communication either to keep CSCs dormant or, alternatively, to activate them, resulting in cell proliferation and metastasis.[31] There is recent evidence that in neoplasms, mesenchymal stem cells play a crucial role in the bone marrow compartment in the intercellular interaction with CSCs, and ultimately influence their migration out of the bone marrow. Furthermore, it has been shown in breast cancer that mesenchymal stem cells can support the cancer's growth, invasiveness, and metastatic potential.[26]

Clinical Risk Models for Progression

Attempts to understand the biology involved in transition from MGUS and SMM to symptomatic MM are ultimately important in determining the optimal time for intervention and identifying the cases where intervention will lead to improved outcomes. Table 1 defines the 3 main PC disorders—MGUS, SMM, and MM—per the 2010 IMWG diagnostic criteria.[4,24] Clinically, patients are described as having one of these PC disease states. It has become evident, however, that not all cases within a given disease definition carry the same risk and 5 independent models with varying validation have been developed as discussed below (Table 2).

The PETHEMA Model: Flow Cytometry

The PETHEMA (Programa para el Estudio de la Terapeutica en Hemopatia Maligna) group devised a model in 2007 to determine risk for SMM progression. This group focused on the quantification of aberrant bone marrow plasma cells (aPC) using multiparametric flow cytometry to distinguish the ratio of neoplastic to normal PCs by surface markers. CD138-positive cells that had absence of CD19 and/or CD45, decreased expression of CD38, and overexpression of CD56 were used for identification of aPCs. In 93 SMM patients, the group identified that a 95% or greater predominance of aPCs in the bone marrow PC compartment was associated with a significantly higher risk of progression in SMM.[39] SMM patients with 95% or greater aPCs and immunoparesis (defined by a reduction below the lower limit of normal in 1 or 2 of the uninvolved immunoglobulins) were identified as independent risk factors in SMM patients. Patients with both 95% or greater aPCs and immunoparesis (high risk), 1 of these risk factors (intermediate risk), or none of these risk factors (low risk) had a 5-year risk of progression to MM of 72%, 46%, and 4%, respectively. In another study, flow cytometry was used to predict risk of progression for 311 MGUS and 61 SMM patients with either evolving or nonevolving subtypes of disease.[40] Interestingly, immunophenotypic analysis more clearly identified and predicted risk than the classification of evolving vs nonevolving MGUS or SMM (defined as having an increase of at least 10% of the PC compartment in the first year or third year, respectively confirmed by 2 consecutive measurements separated by at least 1 month).

The Mayo Clinic Model: Standard Markers

The other widely accepted risk model was developed in 2008 by the Mayo Clinic group, which reported on 273

Table 2. SMM Clinical Risk Models of Progression

Model	Platform	High-Risk Determinants
Mayo[41]	Serum M protein; BM plasmacytosis; sFLC ratio	M protein level ≥3 g/dL & plasmacytosis ≥10% & sFLC ratio >8 (involved/uninvolved)
PETHEMA[39]	Multiparametric flow cytometry; serum immunoglobulins	≥95% aberrant plasma cells & immunoparesis
Heidelberg[43]	Interphase FISH	Presence of del(17p13), t(4;14), or +1q21
Arkansas[46]	GEP70 gene expression profiling	Gene-signature risk score ≥0.26
Imaging[50]	MRI or PET/CT	Greater than 1 focal lesion or FDG-PET avidity

BM, bone marrow; FDG-PET, ^{18}F-fluorodeoxyglucose–positron emission tomography; FISH; fluorescence in situ hybridization; PET/CT, positron emission tomography/computed tomography; PETHEMA, Programa para el Estudio de la Terapeutica en Hemopatia Maligna; MRI, magnetic resonance imaging; sFLC, serum free light chain; SMM, smoldering multiple myeloma.

evaluable patients with SMM. A serum free light chain (sFLC) ratio of 0.125 or lower or of 8 or greater, bone marrow PCs of 10% or greater, and a serum M protein level of 3 g/dL or greater (high risk) conferred a 5-year progression risk to MM of 76%.[41] The 5-year risk for those with 2 risk factors (intermediate risk) or 1 risk factor (low risk) was 51% and 25%, respectively. However, despite the benefit of having these 2 models in predicting risk of progression and devising clinical trials to determine the appropriate time and method of clinical intervention, they have been shown not to correlate perfectly with one another. In a prospective natural history study of 77 SMM patients who were risk stratified based on both the Mayo and the PETHEMA models, the concordance of the overall patient risk classification was 28.6%; the discordance extended to classifying patients as low- vs high-risk, low- vs non–low-risk, and high vs non–high-risk.[42]

The Heidelberg Model: FISH

In addition to the models described above, 3 other models have been proposed in the risk prognostication of SMM. As discussed, precursor disease and MM share many common alterations. To determine the contribution to risk of SMM progression, Nebel and colleagues evaluated the presence of 1q21, 5p15/5q35, 9q34, 13q14.3, 15q22, 17p13, t(11;14)(q13;q32), and t(4;14)(p16.3;q32) by interphase FISH on 248 SMM CD138-purified patient samples.[43] The investigators determined that the MM high-risk alterations consisting of del(17p13), t(4;14), and +1q21 were also associated with poor prognosis, time to progression, and requirement of treatment in SMM and were present in 6.1%, 8.9%, and 29.8% of patients, respectively. Somewhat unexpectedly, hyperdiploidy—found in almost half the patients—was associated with poor risk. Risk was most pronounced with del(17p13) (56% vs 30%; hazard ratio, 2.90; P<.001). These high-risk cytogenetics, in addition to 95% or more of the plasma cells being malignant and the Mayo model, were found, in multivariate analysis, to be independent predictors of outcome. The stage (by the International Staging System) and immunoparesis were not associated with risk. In a report by the Mayo Group, 351 SMM patient samples underwent cytoplasmic immunoglobulin FISH analysis to determine the underlying cytogenetic subtype.[44] Of the 127 samples with IgH translocations, 57 consisted of t(11;14) and 36 consisted of t(4;14). Most importantly, the authors also found that patients with t(11;14) compared with t(4;14) had improved time to progression to symptomatic MM, with a median of 55 vs 28 months, respectively (P=.025), and overall survival, with a median of 147 months vs 105 months, respectively (P=.036).

The Arkansas Model: Gene Expression Profiling

In a fourth model, the Arkansas Group—using the GeneChip human genome U133 Plus 2.0 genome expression microarray from Affymetrix—published research in 2007 showing that, compared with normal PCs, PC dyscrasias had 52 genes involved in key cancer pathways, which were differentially expressed.[45] Furthermore, unsupervised hierarchical clustering of 351 patients with MM, 44 with MGUS, and 12 with SMM identified 4 major signatures. MM patients with an MGUS-like signature were associated with improved survival. In a recent (2014) report, a prospective observational study (SWOG S0120) of 331 MGUS and SMM patients was conducted to evaluate the performance of the GEP70 70-gene signature.[46] An increased GEP risk score was found to be an independent predictor of the risk of progression to symptomatic MM. The high-risk category of SMM patients based on elevated sFLC, M spike, and GEP70 risk score (defined as ≥0.26, and GEP-proliferation index ≥2.73) was found to have a 67% 2-year risk of progression to symptomatic MM requiring therapy. This study showed that all the major defined molecular subtypes of MM exist in the precursor stages, contributing to the notion that MM heterogeneity likely exists in the precursor states. In addition, as GEP signatures for MM are refined and technical limitations overcome—such as processing and selection of CD138

aberrant PCs—validated expression signatures associated with risk of progression from precursor diseases to MM are also likely to be introduced in the clinic as a more sensitive approach to predicting progression.

Imaging Models: Based on MRI and PET/CT

Paralleling these advances in laboratory medicine, radiographic techniques that are more sensitive than the classical skeletal survey are now used to determine bone and bone marrow involvement; these techniques play a part in overall prognostication of the SMM patient. Patients without "symptomatic" CRAB-defined disease might have occult bone lesions identified by whole-body magnetic resonance imaging (MRI) or positron emission tomography/computed tomography (PET/CT), therefore significantly increasing their risk of progression. One of the largest trials addressing the use of MRI involved 611 patients being treated for MM. Focal lesions were detected in 74% of patients with MRI, compared with 56% of patients using skeletal surveys.[47] In patients otherwise diagnosed as having SMM, occult bone lesions on MRI have been shown to be a significant risk factor for progression, and a spinal MRI can be especially important during the initial workup of SMM.[48] SMM usually has normal appearance of the bone marrow, but when focal lesions are present, the risk of rapid progression is high.[49] Not unexpectedly, different patterns of infiltration seen in myeloma patients by MRI (variegated, focal, multifocal, diffuse, and diffuse plus focal) have been associated with stage of disease. In the prospective observational SWOG trial (S0120), spinal MRI imaging of 156 SMM patients revealed at least 1 focal lesion in 25 patients and was associated with an almost 3-fold increased risk of progressing to symptomatic myeloma.[46]

In another study of 149 SMM patients who underwent MRI, focal lesions were present in 28% of patients. Having more than 1 lesion was the strongest adverse prognostic factor, with a 3-fold increased risk on multivariate analysis. Diffuse bone marrow infiltration was the second strongest factor associated with progression to symptomatic MM, and was associated with a 2.4-fold increase in risk.[50] In a follow-up study, 63 SMM patients underwent serial whole body MRIs to determine the utility of MRI in predicting progression. Of the 31 patients (49%) who had evidence of progression on MRI, 25 developed symptomatic MM.

Despite the presence of focal lesions, patients with a stable MRI had no higher risk of progression to clinical myeloma.[51] FDG-PET/CT imaging may play a potential role in analyzing response to myeloma treatment, especially after transplant.[52] It has the advantage of defining metabolically active bone lesions compared with other modalities. However, its utility in the initial work up of SMM might be more limited given SMM's relatively low proliferation rate and subsequent PET/CT's low sensitivity in detecting early myeloma lesions.[49] However, a positive PET/CT in an SMM patient is highly significant. In MGUS, a negative PET/CT has been found to have a very high specificity, and may be 1 future indication for its use.[53]

Evolution of Earlier Therapy

For the most part, earlier clinical trials that evaluated initiating treatment prior to development of symptomatic disease had failed to show a clinical benefit, likely owing to older MM regimens and design of trials.[24] However, with the advent of novel, more efficacious, and less toxic drugs, time to treatment initiation is in the process of being redefined, especially for high-risk SMM.

Recently, a randomized phase 3 trial that enrolled 119 high-risk SMM patients evaluated treatment with the novel regimen of induction lenalidomide plus dexamethasone for nine 4-week cycles followed by 2 years of maintenance low-dose lenalidomide; patients in the control group were observed.[54] The primary endpoint of progression and median time to symptomatic MM was met (not reached vs 21 months; hazard ratio, 0.18 [95% CI, 0.09-0.32; $P<.001$]) after a median follow-up of 40 months. Furthermore, patients in the treatment arm had a higher 3-year survival rate than those in the observation arm, and a partial response or better was attained in 90% of patients during the maintenance phase. Although this trial met its objective, a number of confounding factors limit extrapolation of these results to the general population or using this regimen outside of clinical trials. Specifically, the inclusion criteria (flow cytometry) used for defining high-risk SMM is not universally available; early myeloma factors such as sFLC ratio and bone marrow tumor load were not elucidated and baseline MRI was not done to determine occult lesions; and use of dexamethasone was allowed in the treatment group at laboratory progression but the observation group was only treated after CRAB criteria were met, creating a time-to-event bias.

In a single-arm pilot study, 12 high-risk (defined by Mayo clinic or PETHEMA models) SMM patients underwent induction therapy with carfilzomib, lenalidomide, and dexamethasone for eight 4-week cycles followed by 2 years of low-dose lenalidomide maintenance.[55] Among patients who completed 4 cycles of therapy, 100% achieved a very good partial response or better, and of the patients who achieved a complete response or stringent complete response (58%), the median time was 5 cycles. There are several other ongoing trials incorporating more mechanistically novel and aggressive treatment regimens, the results of which will shed further insight into treating SMM. However, prior to formal recommendations on treating

SMM, more refined consensus and trial inclusion criteria for high-risk SMM will need to be devised and aggressiveness of treatment regimen will need to be determined.

Alternatively, depending on the specific risk type of SMM, more or less aggressive therapies may be needed either at the asymptomatic or symptomatic active phase of the disease. For example, patients with lower-risk SMM may not require aggressive regimens and might be able to avoid the toxicity of such regimens. Along these lines, bisphosphonate treatment has been evaluated in SMM with the hypothesis that a relatively less toxic drug might be able to limit progression by blocking development of lytic lesions and altering the bone marrow microenvironment. A prospective, multicenter, open-label trial compared the use of 4 mg monthly zoledronic acid IV vs observation in 163 randomly assigned asymptomatic myeloma patients for 1 year.[56] Although there was no difference between the arms in time to progression to symptomatic myeloma, the rate of skeletal-related events at progression was significantly lower in the zoledronic acid–treated group (55.5% vs 78.3%; *P*=.041). However, active treatment was associated with more adverse events, including 1 case of osteonecrosis of the jaw.

Although many of the newer myeloma chemotherapeutic regimens are tolerated well, patients can incur long-term morbidity from treatment. Some rare complications observed with the use of MM regimens include cardiac dysfunction, venous thromboembolism, neuropathy, and secondary cancers. Ongoing and future SMM trials will change the benefit-risk assessments when deciding on treating SMM. This will largely be because of an improved understanding of various SMM molecular and clinical subtypes and determination of both prognostic and predictive markers to guide treatment. Second, treatments for MM will become more efficacious and less toxic. Currently, many studies on SMM use time to MM progression as the endpoint. However, given the relatively limited data on SMM, robust clinical trial endpoints need to be determined and surrogates for overall survival and clinical benefit established, including the use of minimal residual disease status as a marker of deep responses. Especially, with the treatment of asymptomatic myeloma, important secondary endpoints including quality of life and other patient-reported outcomes will need to be incorporated. Finally, in calculating the benefit to risk of treatment, the overall financial burden of delivering expensive novel therapies for long periods will need to be addressed.

Redefining Multiple Myeloma

As studies are conducted and completed, giving us more information on the benefit of treating high-risk SMM, certain cases of SMM that do not meet the diagnostic criteria for myeloma based on CRAB criteria should be biologically considered "early myeloma" or stage 0 MM and be treated. These determinants include focal bone marrow lesions on MRI or PET/CT, as discussed above, the sFLC ratio, and bone marrow PC percent involvement. In a retrospective analysis of 586 SMM patients, of the 90 patients with an sFLC ratio of 100 or greater (involved/uninvolved), 98% progressed to MM with a median time to progression of 15 months. In contrast, the group with an sFLC of less than 100 had an sFLC of less than 55 months.[57] Bone marrow infiltration was retrospectively evaluated in a cohort of 655 SMM patients; 21 patients at diagnosis had at least 60% bone marrow PCs.[58] The median time to progression to symptomatic myeloma was significantly shorter in this group compared with those with less than 60% bone marrow PC involvement. Within 2 years of diagnosis of these 21 patients, 95% progressed to symptomatic myeloma with a median time of 7 months, compared with 20% in patients with less than 60% bone marrow PC involvement. Based on expert discussions at the IMWG meeting in Stockholm in June 2013, it is anticipated that updated consensus criteria will be defined in the near future to include otherwise asymptomatic patients who have the above early myeloma markers.

Table 3. Management Strategies for SMM

Plasma Cell Disorder	Management
Low-/intermediate-risk SMM	Monitor as per IMWG guidelines[4] or consider clinical trial
High-risk SMM	Consider enrollment in interventional clinical trial
Early myeloma	Treat as indicated for symptomatic MM

IMWG, International Myeloma Working Group; MM, multiple myeloma; SMM, smoldering multiple myeloma.

Practical Treatment Considerations

All SMM patients at diagnosis should receive an initial workup to exclude active disease, according to the IMWG 2010 recommendations, including risk stratification for prognostication (Table 3).[4] First, patients diagnosed with SMM should not be treated outside of clinical trials. Patients with a low or intermediate risk of progression should be monitored per the IMWG guidelines or enrolled in clinical trials. Management of high-risk SMM is evolving as further insight into the disease is gained. However, we cannot make universal recommendations on treatment until further trials are completed, more evidence is collected, and caveats are understood. Therefore, for high-risk SMM patients, in concurrence with current

guidelines, we strongly urge enrollment in interventional clinical trials to address the current gaps in our knowledge.

In standard clinical practice, during the first year, SMM patients should be initially monitored very closely with surveillance myeloma laboratory testing every 2 to 3 months, given the high risk of progression early in the diagnosis. Subsequent intervals should be stretched to 4 to 6 months. Once SMM patients at diagnosis have been ruled out as having symptomatic myeloma, MRI can be considered to exclude occult bone involvement, which—as discussed above—is a strong marker of progression.

The National Comprehensive Cancer Network (NCCN) guidelines also approach SMM in this fashion.[59] Specifically, observation every 3 to 6 months or enrollment in a clinical trial is recommended, with surveillance by standard laboratories, quantitative immunoglobulins, serum and urine protein electrophoresis, and skeletal survey annually, along with bone marrow biopsy, sFLC ratio, MRI, PET/CT, or flow cytometry as clinically indicated until development of symptomatic disease. Finally, SMM patients who have been identified as having early myeloma (defined by bone marrow involvement, sFLC ratio, or MRI/PET findings) should be approached as having Stage 0 MM and treated with standard symptomatic MM regimens as discussed above, which the NCCN guidelines recognize as changing criteria for MM in the near future.

A New Era for Smoldering Myeloma

Much insight into the pathophysiology of SMM has been gained since its initial description in 1980 based on 6 patient cases, but the field still has knowledge gaps to fill. For novel effective myeloma treatments to be devised, key questions regarding the biological models of myeloma will need to be understood, especially in regard to the importance of clonal heterogeneity in the context of branching evolution and the role of the microenvironment. Clinical models of progression suggest that there are low-, intermediate-, and high-risk categories involved in transformation of SMM to symptomatic disease. However, as discussed, these models are small and almost always based on retrospective data. Future prospective models are urgently needed. Emerging data derived from clinical studies targeting high-risk SMM patients suggest that early treatment improves progression-free and overall survival. However, these studies have been small and have trial design limitations in the background of non-negligible toxicity. Larger studies with longer follow-up and better monitoring of minimal residual disease are needed to advance the field. In our opinion, further evidence is required before treatment of SMM outside of clinical trials is ready for prime time.

Disclosures

The authors have no relevant conflicts of interest to disclose.

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