Monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM): novel biological insights and development of early treatment strategies

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Monoclonal gammopathy of unknown significance (MGUS) and smoldering multiple myeloma (SMM) are asymptomatic plasma cell dyscrasias, with a propensity to progress to symptomatic MM. In recent years there have been improvements in risk stratification models (involving molecular markers) of both disorders, which have led to better understanding of the biology and probability of progression of MGUS and SMM. In the context of numerous molecular events and heterogeneous risk of progression, developing individualized risk profiles for patients with MGUS and SMM represents an ongoing challenge that has to be addressed by prospective clinical monitoring and extensive correlative science. In this review we discuss the current standard of care of patients with MGUS and SMM, the use of risk models, including flow cytometry and free-light chain analyses, for predicting risk of progression. Emerging evidence from molecular studies on MGUS and SMM, involving cytogenetics, gene-expression profiling, and microRNA as well as molecular imaging is described. Finally, future directions for improving individualized management of MGUS and SMM patients, as well as the potential for developing early treatment strategies designed to delay and prevent development of MM are discussed. (*Blood*. 2011; 117(21):5573-5581)

Introduction

Multiple myeloma is a malignant neoplasm of plasma cells in the bone marrow associated with an overproduction of monoclonal (M)–protein often causing characteristic osteolytic lesions, anemia, renal failure, and hypercalcemia.[1] In contrast, monoclonal gammopathy of unknown significance (MGUS) is an asymptomatic plasma cell dyscrasia that is present in more than 3% of the general white population older than age 50 and has an average multiple myeloma progression risk of 1% per year.[2] Smoldering multiple myeloma (SMM) is another asymptomatic plasma cell disorder but carries a higher risk of progression to frank multiple myeloma (10% per year the first 5 years) compared with MGUS.[3] Indeed, both MGUS and SMM represent the quintessential model for studying multiple myeloma precursor disease, and to develop early intervention strategies.

The etiology of MGUS remains unclear and it is a current topic of investigation. Race seems to play a role given the observation that prevalence of MGUS is 2- to 3-fold higher in African-Americans and blacks from Africa compared with whites.[4,5] Other identified risk factors for MGUS include older age, male sex, exposure to pesticides, and family history of MGUS or MM.[2,6,7] Thus, previous studies support a role for both genetic and environmental factors in the development of multiple myeloma and its precursor states.[8]

Two independent studies have demonstrated that most cases of multiple myeloma are preceded by MGUS. In the Prostate, Colorectal, Lung and Ovarian Cancer Screening Trial, annual serum samples were collected from 77 469 healthy donors prospectively. Among 71 patients who during a 10-year follow-up time developed multiple myeloma, serum samples consistently demonstrated MGUS in the years before the malignant diagnosis.[9] Another study, based on the Department of Defense Serum Repository, showed a very similar finding.[10]

Current clinical practice relies on careful surveillance as the cornerstone for management of multiple myeloma precursor disease. Indeed, definitions of MGUS and SMM have evolved, and characterization of clinical subtypes and risk stratification models have led to better understanding of disease biology and probability of progression. Despite this, a number of inherent diagnostic challenges continue to plague physicians while managing their patients. Molecular tools used to better identify MGUS and SMM signature profiles provide answers to long-sought questions and dilemmas. Indeed, more research effort is needed in this area. Gaining molecular insight into multiple myeloma precursor disease may have a dramatic impact on clinical management in the future. As expected, several clinical investigations have already begun to study treatment options in these precursor states.

Distinct clinical subtypes of MGUS and SMM

Benign monoclonal protein was first described by Waldenström in 1960 after abnormal narrow hypergammaglobulinemia bands were noted in the serum of healthy individuals on serum protein electrophoresis (SPEP).[11] Kyle coined the term "monoclonal gammopathy of undetermined significance" in 1978 after observing that asymptomatic patients with monoclonal protein have a higher risk of developing multiple myeloma, Waldenström macroglobulinemia, light-chain amyloidosis, or related disorders.[12] Since then, definitions of MGUS have undergone several reiterations.

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Over the past few years, 3 distinct clinical subtypes (non-IgM MGUS, IgM MGUS, and light-chain MGUS) have emerged from MGUS as a disease entity (Table 1).[13] Each subtype seems to follow its own biologic dictums while displaying individualistic clinical tendencies. A number of studies have allowed researchers to investigate the natural history of each MGUS subtype on an individual categorical basis.[14-16] It remains to be seen whether clinical heterogeneity can ultimately be attributed to simply identifying the original cell of clonal insult or rather the result of a set of complex molecular events that may account for the different clinical subtypes.

The most well-characterized MGUS subtype is non-IgM MGUS and seems to be related to a clonal population of phenotypic aberrant plasma cells (Table 1). The M-protein isotypes from non-IgM MGUS patients can be further classified into IgG (69%), IgA (11%), and biclonal (3%).[2] In addition, IgD and IgE comprise a very small portion of all non-IgM MGUS cases.[2] Malignant transformation of non-IgM MGUS approximates 1% per year and typically develops into multiple myeloma rather than lymphoproliferative disorders.[14]

Based on data from the Mayo Clinic, 17% of all MGUS is of the IgM variety and usually tends to result from aberrant lymphocyte or lymphoplasmacytoid proliferation (Table 1).[2] As such, IgM MGUS has a predilection for developing Waldenström macroglobulinemia or other lymphomas while rarely progressing to IgM MM.[15] Typical surface immunophenotype of cells express IgM^+, $CD5^{+/-}$, $CD10^-$, $CD19^+$, $CD20^+$, and $CD23^+$.

Light-chain MGUS, similar to the non-IgM subtype, seems to be related to clonal aberrant plasma cells (Table 1). Light-chain MGUS is characterized by absent heavy-chain (ie, M-protein) production but presence of a skewed free light-chain (FLC) ratio because of an increase in the involved light chain.[16] Light-chain multiple myeloma accounts for 20% of all newly diagnosed multiple myeloma cases.[17] The following review highlights precursor disease originating from clonal plasma cells.

In 2003, the International Myeloma Working Group (IMWG) developed consensus definitions of the known monoclonal gammopathies.[17] MGUS was defined as the presence of serum M-protein < 3 g/dL with fewer than 10% monoclonal plasma cells in the bone marrow; smoldering myeloma was defined as either serum M-protein ≥ 3 g/L or $\geq 10\%$ monoclonal plasma cells in the bone marrow. In contrast to these laboratory-based definitions, a diagnosis of multiple myeloma is based on the clinical assessment of myeloma-related end-organ impairment in the presence of an M-protein and/or monoclonal plasma cells. In the 2003 IMWG criteria, end-organ damage was defined using both the classic "CRAB" criteria of hypercalcemia (serum calcium > 11.5 mg/dL), renal failure (defined by creatinine > 1.95 with no other etiology), anemia (hemoglobin < 10 g/dL), or skeletal lesions (lytic lesions by skeletal survey, osteoporosis with pathologic fractures, or cord compression), and additional criteria including recurrent bacterial infections (> 2 in 12 months), amyloidosis, or symptomatic hyperviscosity.[17]

In the updated 2010 IMWG diagnostic criteria, plasma cell MGUS is defined as having serum M-protein < 3 g/dL, clonal plasma cell population in bone marrow $< 10\%$, and absence of end-organ damage (CRAB criteria of multiple myeloma).[18] The CRAB criteria have been slightly revised in the 2010 version and they include hypercalcemia with calcium level > 11.5 mg/dL, renal insufficiency with serum creatinine > 2.0 mg/dL or estimated creatinine clearance < 40 mL/min, normochromic normocytic anemia with a hemoglobin value < 10 g/dL (or a hemoglobin value < 2 g/dL below the lower limit of normal), and bone lesions (lytic lesions, severe osteopenia, or pathologic fractures).[18]

Reflective of a higher disease burden state, SMM is distinguished from MGUS by higher cutoff values while maintaining lack of end-organ damage. IMWG diagnostic criteria from 2010 establishes SMM as having serum M-protein > 3 g/dL, and/or clonal plasma cell population in bone marrow $> 10\%$, and lack of end-organ damage (CRAB criteria).[18] Based on retrospective data from the Mayo Clinic, risk of progression from SMM to multiple myeloma is 10% per year for the first 5 years, 3% per year for the next 5 years, and 1% for the subsequent 10 years (Table 1).[3] The equivalent of SMM found in IgM and light-chain monoclonal gammopathies is smoldering Waldenström macroglobulinemia and idiopathic Bence Jones proteinuria, respectively (Table 1).[13]

Predicting progression with current clinical risk models

As stated, we currently lack reliable biologic markers that allow us to predict which multiple myeloma precursor patients will progress, and which will not. Based on available clinical markers, 2 major schools of thought, from the Mayo Clinic and the Spanish study group, have surfaced regarding establishing predictive risk models from MGUS/SMM to multiple myeloma (Table 2). The Mayo Clinic model emphasizes clonal plasma cell burden with monoclonal protein values and skewed free light-chain ratios.[19,20] The Spanish study group uses multiparametric flow cytometry techniques to identify aberrant plasma cell populations.[20]

The Mayo Clinic risk stratification model for MGUS identifies 3 major risk factors for progression: non-IgG isotype, serum M-protein concentration > 1.5 g/dL, and a skewed FLC-ratio (normal reference: 0.26-1.65).[19] At 20 years of follow-up, absolute risk of progression for MGUS patients with 0, 1, 2, and 3 risk factors is 5%, 21%, 37%, and 58%, respectively (Table 2).[19] For SMM, risk factors for progression include bone marrow plasma cells $> 10\%$, serum M-protein concentration > 3 g/dL, and a skewed FLC-ratio (normal reference: 0.125-8.0). Cumulative risk of progression at 10 years for SMM patients with 1, 2, and 3 risk factors is 50%, 65%, and 84%, respectively (Table 2).[20]

In contrast, the Spanish study group has established multiparametric flow cytometry as a tool to identify aberrant plasma cell populations.[21] Normal bone marrow plasma cells demonstrate CD138 and bright CD38 marker expression. Aberrant plasma cell (aPC) populations express dim CD38, $CD56^+$, lack of $CD19^-$, and/or absence of $CD45^-$.[21] In 407 MGUS patients and 93 SMM patients, Perez-Persona and colleagues established that an aPC/normal bone marrow plasma cell (BMPC) ratio $> 95\%$ is associated with higher risk of progression ($P < .001$).[21] According to the Spanish study group, MGUS risk factors for progression are aPC/BMPC $> 95\%$ and DNA aneuploidy. Progression free survival at 5 years for MGUS patients with 0, 1, and 2 risk factors is 2%, 10%, and 46% ($P < .001$), respectively (Table 2).[21] SMM risk factors for progression include aPC/BMPC $> 95\%$ and immunoparesis (decreased uninvolved gammaglobulin levels).[21] At 5 years, progression free survival for SMM patients with 0, 1, and 2 risk factors is 4%, 46%, and 72%, respectively (Table 2).[21]

Current clinical management strategies

In 2011, the cornerstone of managing multiple myeloma precursor disease involves a prudent "watch and wait" strategy. Outside of clinical trials, there are no current standardized treatment options

Table 1. Disease definitions for the monoclonal gammopathies: MGUS and related disorders

Type of monoclonal gammopathy	Premalignancy with a low risk of progression (1%-2% per year)	Premalignancy with a high risk of progression (10% per year)	Malignancy
IgG and IgA (non-IgM) monoclonal gammopathies*	**Non-IgM MGUS** All 3 criteria must be met: • Serum monoclonal protein < 3 g/dL • Clonal bone marrow plasma cells $< 10\%$, and • Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) that can be attributed to the plasma cell proliferative disorder	**Smoldering multiple myeloma** Both criteria must be met: • Serum monoclonal protein (IgG or IgA) ≥ 3 g/dL and/or clonal bone marrow plasma cells $\geq 10\%$, and • Absence of end-organ damage such as lytic bone lesions, anemia, hypercalcemia, or renal failure that can be attributed to a plasma cell proliferative disorder	**Multiple myeloma** All 3 criteria must be met except as noted: • Clonal bone marrow plasma cells $\geq 10\%$ • Presence of serum and/or urinary monoclonal protein (except in patients with true nonsecretory multiple myeloma), and • Evidence of end-organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically ○ Hypercalcemia: serum calcium > 11.5 mg/dL or ○ Renal insufficiency: serum creatinine > 2 mg/dL or estimated creatinine clearance < 40 mL/min ○ Anemia: normochromic, normocytic with a hemoglobin value of > 2 g/dL below the lower limit of normal or a hemoglobin value < 10 g/dL ○ Bone lesions: lytic lesions or severe osteopenia attributed to a plasma cell proliferative disorder or pathologic fractures
IgM monoclonal gammopathies	**IgM MGUS†** All 3 criteria must be met: • Serum monoclonal protein < 3 g/dL • Clonal bone marrow lymphoplasmacytic cells $< 10\%$, and • Absence of end-organ damage such as anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly that can be attributed to the underlying lymphoproliferative disorder	**Smoldering Waldenström macroglobulinemia** Both criteria must be met: • Serum IgM monoclonal protein ≥ 3 g/dL and/or bone marrow lymphoplasmacytic infiltration $\geq 10\%$, and • No evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly that can be attributed to the underlying lymphoproliferative disorder	**Waldenström macroglobulinemia** All criteria must be met: • IgM monoclonal gammopathy (regardless of the size of the M-protein), and • $\geq 10\%$ bone marrow lymphoplasmacytic infiltration (usually intertrabecular) by small lymphocytes that exhibit plasmacytoid or plasma cell differentiation and a typical immunophenotype (eg, surface IgM^+, $CD5^{+/-}$, $CD10^-$, $CD19^+$, $CD20^+$, $CD23^-$) that satisfactorily excludes other lymphoproliferative disorders including chronic lymphocytic leukemia and mantle cell lymphoma • Evidence of anemia, constitutional symptoms, hyperviscosity, lymphadenopathy, or hepatosplenomegaly that can be attributed to the underlying lymphoproliferative disorder. **IgM myeloma** All criteria must be met: • Symptomatic monoclonal plasma cell proliferative disorder characterized by a serum IgM monoclonal protein regardless of size • Presence of 10% plasma cells on bone marrow biopsy • Presence of lytic bone lesions related to the underlying plasma cell disorder and/or translocation t(11;14) on fluorescence in situ hybridization.
Light-chain monoclonal gammopathies	**Light-chain MGUS** All criteria must be met: • Abnormal FLC ratio (< 0.26 or > 1.65) • Increased level of the appropriate involved light-chain (increased kappa FLC in patients with ratio > 1.65 and increased lambda FLC in patients with ratio < 0.26) • No immunoglobulin heavy-chain expression on immunofixation • Clonal bone marrow plasma cells $< 10\%$, and • Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) that can be attributed to the plasma cell proliferative disorder	**Idiopathic Bence Jones proteinuria** All criteria must be met: • Urinary monoclonal protein on urine protein electrophoresis ≥ 500 mg/24 h and/or clonal bone marrow plasma cells $\geq 10\%$ • No immunoglobulin heavy-chain expression on immunofixation • Absence of end-organ damage such as hypercalcemia, renal insufficiency, anemia, and bone lesions (CRAB) that can be attributed to the plasma cell proliferative disorder	**Light-chain multiple myeloma†** • Same as multiple myeloma except no evidence of immunoglobulin heavy-chain expression

MGUS indicates monoclonal gammopathy of undetermined significance; and FLC, free light chain.

*Occasionally patients with IgD and IgE monoclonal gammopathies have been described and will be considered to be part of this category as well.

†Note that conventionally IgM MGUS is considered a subtype of MGUS, and similarly light-chain multiple myeloma is considered as a subtype of multiple myeloma. Unless specifically distinguished, when the terms MGUS and multiple myeloma are used in general, they include IgM MGUS and light-chain multiple myeloma, respectively. (Reprinted with permission.[13])

Table 2. Risk stratification schemes for MGUS and SMM

Risk stratification scheme	No. of risk factors	No. of patients (%)	20-year progression, %	RR
Mayo Clinic for MGUS patients[55]	0	449 (38)	5	1
Risk factors: M-protein > 1.5 g/dL, non-IgG MGUS, FLC ratio < 0.26 or > 1.65	1	420 (37)	21	5.4
	2	226 (20)	37	10.1
	3	53 (5)	58	20.8
	Total	1148 (100)	20	N/A
			5-year progression, %	
Spanish study group for MGUS patients[21]	0	127 (46)	2	1
Risk factors: ≥ 95% aPC, DNA aneuploidy	1	133 (48)	10	5
	2	16 (6)	46	23
	Total	276* (100)	8.5	N/A
Mayo Clinic for SMM patients[20]	1	76 (28)	25	1
Risk factors†: marrow plasma cells ≥ 10%, M-protein ≥ 3 g/dL, FLC ratio < 0.125 or > 8	2	115 (42)	51	2.0
	3	82 (30)	76	3.0
	Total	273 (100)	51	N/A
Spanish study group for SMM patients[21]	0	28 (31)	4	1
Risk factors: ≥ 95% aPC, immunoparesis	1	22 (25)	46	11.5
	2	39 (44)	72	18
	Total	89‡ (100)	46	N/A

MGUS indicates monoclonal gammopathy of undetermined significance; SMM, smoldering multiple myeloma; RR, relative risk; FLC, free light chain; N/A, not applicable; and aPC, aberrant plasma cell.

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

†Patients must have at least one of the first 2 risk factors to meet criteria for SMM.

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

for MGUS or SMM. Aggressive disease monitoring is based on whether patients fit into MGUS or SMM precursor disease and the above-outlined risk factors in the Mayo Clinic model and Spanish study group model (Table 2).[18]

For the first time, the 2010 IMWG guidelines suggest risk-stratifying all patients with MGUS and SMM and differentially monitoring patients on the basis of their risk category.[18] Importantly, the recommendations state that patients with low-risk MGUS (~ 50% of all MGUS cases) by the Mayo Clinic criteria (IgG M-protein < 1.5 g/dL with normal FLC ratio) in the absence of concerning symptoms such as anemia or poor renal function, no further initial evaluation is needed. Subsequently, low-risk MGUS patients should be followed with SPEP, CBC, calcium, and creatinine at 6 months and, if stable, every 2-3 years.[18] As an alternative strategy, the 2010 IMWG suggests that check-up of low-risk MGUS be performed only when symptoms for multiple myeloma arise, thus abrogating the need for scheduled long-term follow-up in stable patients.[18,22]

In contrast to low-risk MGUS, the 2010 IMWG guidelines state that MGUS patients with any risk factor (ie, intermediate- or high-risk MGUS; see Table 2) should be evaluated using baseline bone marrow examination with cytogenetics and fluorescence in situ hybridization (FISH) studies, in addition to bone imaging studies such as skeletal surveys.[18] Intermediate- and high-risk MGUS patients should be followed with an SPEP every 6 months for the first year, followed by annual SPEP and routine laboratory tests.[18]

For SMM patients, given their increased risk of progression, the 2010 IMWG guidelines state that an SPEP and physician visit should be repeated every 2-3 months for first year, followed by every 4-6 months for 1 year, with eventual 6- to 12-month evaluations if clinically stable thereafter.[18] In SMM, beyond mandatory baseline bone marrow examination and skeletal survey, the guidelines recommend an MRI of the spine and pelvis because it can detect occult lesions and, if present, predict for a more rapid progression to multiple myeloma.[18,23]

It is critical to recognize that in a disease such as multiple myeloma, where defining criteria rely on the presence or absence of end-organ damage, diagnosis is only as good as the tools and technology able to detect end-organ damage. Whereas researchers strive to improve on the available diagnostic armamentarium, clinical acumen on the part of the physician should be emphasized while playing a central role in disease monitoring. For instance, in SMM or high-risk MGUS patients highly suspicious to harbor bone disease, imaging evaluation may be better served by obtaining MRI or PET-CT rather than traditional skeletal surveys.

Last, MGUS or SMM patients with unexplained anemia or renal disease should be evaluated for other underlying causes as well as with complete bone marrow examination including cytogenetics and FISH studies.

Genetic aberrations and other molecular markers

General understanding of tumor microenvironment interactions and genetic aberrations leading to multiple myeloma has prompted researchers to better characterize molecular and pathogenetic events surrounding multiple myeloma precursor disease. Somewhat surprising is the notion that there are striking similarities detected between myeloma precursor disease states and frank symptomatic multiple myeloma. Such molecular insights raise the question that scratching the surface of high-risk precursor disease may reveal more in common biologically with multiple myeloma than previously realized.

In brief, cytogenetic aberrations in multiple myeloma can be divided into 2 general entities with partially overlapping features, hyperdiploid (approximately 50%) and nonhyperdiploid (approximately 40%).[24-28] The hyperdiploid group includes recurrent trisomies with 48-74 chromosomes.[29] The nonhyperdiploid group (< 48 or > 74 chromosomes) is often associated with translocations involving immunoglobulin heavy-chain (IgH) locus at 14q32

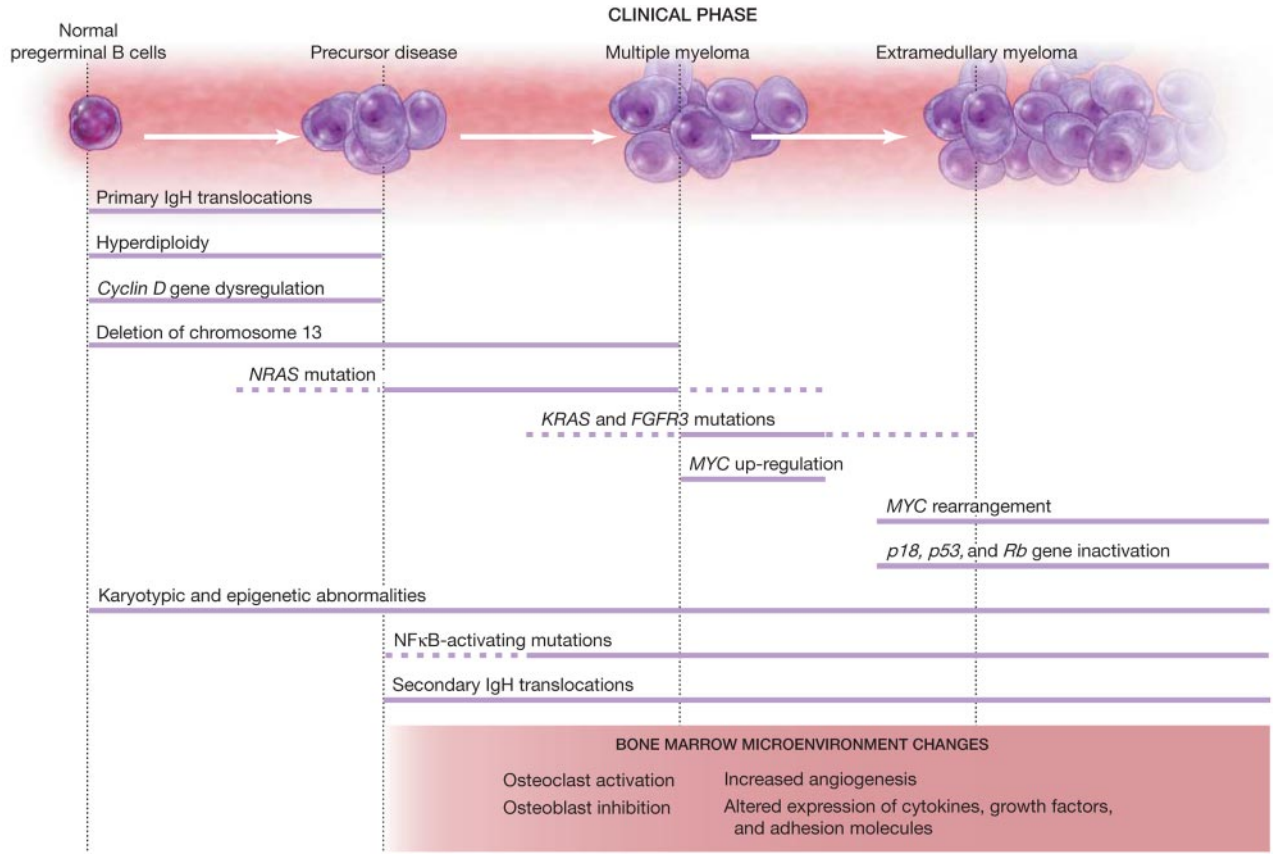

Figure 1. Biological events related to progression to multiple myeloma. The biologic transition from normal plasma cells to multiple myeloma precursor disease (monoclonal gammopathy of undetermined significance [MGUS] and smoldering myeloma) to multiple myeloma consists of many overlapping oncogenic events. These events do not all occur in each affected individual, for example, hyperdiploidy is present in approximately 50% of precursor and multiple myeloma tumors. In this illustration, solid lines approximate the period during which the oncogenic event is likely to occur; dashed lines indicate less certainty in the timing. Once an oncogenic event occurs, it almost always persists. The 2 major types of early events include IgH translocations [most commonly: t(4;14), t(14;16), t(6;14), t(11;14), and t(14;20)] and hyperdiploidy, although most tumor cells have only one of these two events. Either of these can coexist with deletion of chromosome 13, although this abnormality most commonly (> 80% to 90% of patients) occurs with the t(4;14), t(14;16), and t(14;20) IgH translocations.[38,39] A unifying early event in most, perhaps all, precursor and multiple myeloma tumors is the dysregulation of a *cyclin D* gene. Secondary translocations, sometimes involving an Ig locus, can occur at any stage of myelomagenesis. Activating mutations of *NRAS* and *KRAS* are each present in about 15% of multiple myeloma tumors; *NRAS* mutations are present in MGUS tumors and *KRAS* mutations are absent from MGUS tumors. Constitutive activation of the nuclear factor κB (NFκB) pathway is mediated by mutations in some tumors during progression.[38] Other events, such as *Rb* gene inactivation or deletion of *p53* or *p18* genes, are mostly seen at the level of advanced intramedullary or extramedullary multiple myeloma.[38,65] Through the stage of intramedullary multiple myeloma, the tumor cells are strongly dependent on the bone marrow microenvironment.[66] The reciprocal interaction of the bone marrow microenvironment and the tumor cells results in changes in the bone marrow microenvironment, which are responsible for the lytic lesions that are characteristic of multiple myeloma. Extramedullary tumor cells have developed features that make them independent of the bone marrow microenvironment. (Reprinted with permission.[37])

and includes hypodiploid, near tetraploid, and pseudodiploid tumors.[29] In a study using FISH, Chiecchio et al found that 72/189 (42%) MGUS, 70/127 (63%) SMM, and 223/338 (57%) multiple myeloma cases were hyperdiploid.[30] IgH rearrangements were found to have similar prevalence rates among 78/189 (41%) MGUS, 44/125 (35%) SMM, and 183/398 (46%) multiple myeloma.[30] Although chromosome 13 deletion prevalence is higher among multiple myeloma patients (50%) compared with MGUS patients (25%), studies suggest a higher frequency among patients with t(4,14) and t(4,16) rearrangements.[27,30] In 2003, an international workshop assembled to review cytogenetic studies evaluated whether MGUS and SMM cases have detectable anomalies that are often found in multiple myeloma.[31] Indeed, *p53* deletions and *p18* deletions and mutations have been associated with aggressive, extramedullary multiple myeloma.[29] Point mutations, such as *N-RAS*, *K-RAS*, *MYC* up-regulation, and gain or loss of chromosome 1q or 1p, also seem to correlate with disease progression from myeloma precursor disease of MGUS and SMM.[32-36] Based on the current literature, Figure 1 summarizes major biologic events related to progression from precursor disease to multiple myeloma.[37-40]

Newer molecular techniques, such as gene-expression profiling (GEP), have been employed to identify molecular signatures associated with progression from precursor disease to multiple myeloma. For example, Zhan et al investigated 52 genes in plasma cells derived from healthy controls, MGUS, SMM, and multiple myeloma patients.[35] In their study, the authors reported that hierarchical clustering identified 4 groups from GEP analysis.[36] However, these GEP groups have not yet been validated in an independent cohort of precursor patients and correlated to clinical outcome. Importantly, one has to keep in mind that GEP analyses of MGUS have inherent problems. The percentage of plasma cells is low (by definition < 10%), so that there is significant contamination with other kinds of cells despite selection of $CD138^+$ cells on magnetic beads. Also, in MGUS patients—unlike in multiple myeloma patients—monoclonal plasma cells are likely to be significantly contaminated with normal plasma cells (because of the relatively low percentage of monoclonal plasma cells in MGUS). Until we have better processing methods and better assays, one has to be very cautious when interpreting GEP analyses of plasma cells selected by CD138 expression from MGUS patients.

MicroRNA (miRNA) profiling has also yielded interesting results while further characterizing MGUS and SMM compared with multiple myeloma patients. miRNAs are noncoding single-stranded RNA molecules known to influence various tumor behavior by regulating gene expression.[41] Compared with healthy controls, MGUS and multiple myeloma patients seem to up-regulate miR-21, miR-106b, miR-181a, and miR-181b; which are miRNAs involved in B- and T-cell lymphocyte differentiation as well as oncogene regulation.[42] Based on our current knowledge, notable differences reveal up-regulation of miR-32 and miR-17∼92 cluster among multiple myeloma patients not found in MGUS patients.[42] Future studies are needed to further elucidate the role of miRNAs in multiple myeloma precursor disease and in relation to progression to frank symptomatic multiple myeloma.

Molecular imaging

As stated earlier, definitions of multiple myeloma precursor disease is based on lack of end-organ damage, including bone lytic lesions. The skeletal survey, the gold standard imaging modality to detect osteolytic lesions,[43] is a series of plain films that include the chest, skull, humeri, femora, pelvis, and anteroposterior and lateral images of the whole spine. However, the skeletal survey is insensitive for detection of osteolytic lesions as it requires at least 30% cortical bone destruction.[44] Common drawbacks of this technique are that lesions are often subject to misinterpretation, timely nature of obtaining all the necessary images, and an inability to detect intra- and extramedullary disease.

Whereas familiar techniques such as CT, FDG PET-CT, and MRI are becoming more readily accepted in detecting multiple myeloma disease in the mainstream, novel imaging may also find a future role in clinical investigations. For instance, 18-F is sensitive bone tracer that is useful for detecting both osteolytic and osteoblastic lesions in the skeleton.[45] As such, 18-F PET-CT may be a more sensitive technique in appreciating osteolysis in early precursor disease states, such as high-risk SMM, and remains to be investigated in clinical trials.

Past research endeavors suggest that an "angiogenic switch" occurs as precursor myeloma disease progresses into MM.[46] Dynamic contrast MRI (DCE-MRI) is a noninvasive imaging technique used to evaluate microcirculatory parameters, reflecting angiogenesis in tumor environments. In a study comparing 22 healthy controls, 60 MGUS patients, 65 SMM patients, and 75 symptomatic newly diagnosed multiple myeloma patients, DCE-MRI was able to detect a gradual increase in microcirculation, respectively.[47] In one patient, a pathologic DCE-MRI pattern was able to herald progression 6 months before actual multiple myeloma diagnosis.[47]

Treatment studies focusing on smoldering multiple myeloma

With the knowledge gained from molecular insights and diagnostics, such as GEP profiling and DCE-MRI, it is conceivable that a future paradigm shift may prompt treatment of multiple myeloma precursor disease.[37] Currently, standard of care dictates that MGUS and SMM patients should not receive therapy outside clinical trials. Potential for therapeutic toxicity must be weighed against benefits achieved by treating a precursor state. When comparing risk of progression and disease biology between MGUS and SMM, high-risk SMM patients are an identifiable group that may seem to have the most beneficial gain from early treatment, if any.

One of the first clinical trials assessing early treatment versus treatment on progression in asymptomatic patients used alkylator-based therapy with melphalan and prednisone, and demonstrated no difference in response rates or overall survival (Table 3).[48] Novel agents, such as immunomodulatory drugs, are more attractive candidates for therapeutics in early precursor disease because of toxicity and efficacy profiles. Also, there have been other therapeutic strategies focusing on bone marrow microenvironment changes, such as bone remodeling. In a single-arm study treating 76 SMM patients with pamidronate and thalidomide, Barlogie et al showed that obtaining a PR may be paradoxically associated with shorter time to salvage therapy (Table 3).[49] Another study comparing zoledronic acid versus surveillance demonstrated reduced skeletal events in the treatment arm (55.5% vs 78.3%; $P = .04$ zoledronic vs control, respectively) but no difference in median time to progression (Table 3).[50] An ongoing PETHEMA phase 3 trial is currently investigating treatment with lenalidomide/dexamethasone versus surveillance in high-risk SMM patients. Interim analysis indicates that at 19 months of follow-up, about 50% of patients in the surveillance arm progressed to multiple myeloma whereas no treated patients progressed.[51] However, using this strategy, it is unknown whether treating SMM patients improves overall survival or quality of life, as such data are not yet available. Furthermore, another investigation has been launched by ECOG/SWOG in North America to compare lenalidomide alone versus clinical surveillance in SMM patients. In addition, at the National Cancer Institute in Bethesda, we have recently opened an SMM trial that features administration of IPH2101; a monoclonal anti–killer IgG–like receptor (KIR) antibody that blocks inhibitory KIR receptors on NK cells, thereby augmenting NK cell–mediated killing of myeloma cells.

At this time, no drugs have been approved for SMM. Although it requires the launching of larger studies and with longer follow-up, it seems reasonable to argue that future approvals of drugs for SMM should based on overall survival advantages, and that progression-free survival is not adequate. Indeed, overall survival is defined as a clinically relevant end point to be used for new drug approvals for multiple myeloma in the appropriate trial design settings.[52] In our opinion, this topic is particularly important given current concerns about potential excess risks of second malignancies after extended dosing with certain myeloma drugs in the setting of newly diagnosed multiple myeloma.[53]

Summary and future directions

MGUS and SMM are asymptomatic plasma cell disorders with a propensity to transform to frank multiple myeloma. Currently, in clinical practice, these patients are followed clinically without treatment until progression. Heterogeneity and ambiguity continue to present a clinical challenge in MM precursor disease. In recent years there have been improvements in risk stratification models that have led to better understanding of disease biology and probability of progression. However, additional studies and endeavors are needed. The eventual hope is that such extensive correlative work may identify those patients who may benefit from early treatment and to allow development of intervention strategies based on rational science, and thereby change the landscape of current clinical management for multiple myeloma precursor disease.[37]

Table 3. Selected clinical studies of strategies to prevent progression of SMM, MGUS, and early-stage multiple myeloma

Reference	Study design	Intervention	No. of patients	Outcome/comment
Hjorth 1993[48]	Randomized controlled trial	Initial vs deferred MP therapy	50 SMM and IMM (25/25)	Similar response rate, response duration, and survival
Rajkumar 2001[56]	Single-arm pilot study	Thalidomide	16 SMM and IMM	MR or better in 11/16; microvessel density did not predict response
Musto 2008[50]	Open-label, randomized controlled trial	Zoledronate	163 SMM (81/82)	Zoledronate for 1 y decreased risk of skeletal-related disease, but TTP was similar ($P = .83$)
Barlogie 2008[49]	Single-arm phase 2 trial	Thalidomide/pamidronate	76 SMM	Median TTP 7 y; PR identifies subset requiring earlier salvage therapy for symptomatic disease
Lust 2009[57]	Single-arm phase 2 trial	Anakinra (IL-1 receptor antagonist)	47 SMM and IMM (25 received anakinra and DEX)	Median PFS was 37.5 mo MR (n = 3), PR (n = 5); 8 patients stable on drug for 4 y
Golombick 2009[58]	Single-blind, randomized, crossover 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[59]	Double-blind, randomized controlled trial	Celoxicib vs placebo	36 MGUS and SMM	Aim: to test whether celoxicib reduces the M-protein concentration
Mateos 2007-ongoing[60]	Open-label randomized controlled trial	Lenalidomide + DEX vs observation	120 "high-risk" SMM	Aim: to evaluate whether lenalidomide + DEX extends TTP
Ballester 2009-ongoing[61]	Unblinded, nonrandomized trial	Omega-3 fatty acids	48 MGUS, SMM, or CLL*	Aim: to assess whether omega-3 fatty acids reduce activated NF-κB levels in peripheral blood lymphocytes
Zonder 2009-ongoing[62]	Single-arm pilot study	Green tea extract	17 MGUS or SMM*	Aim: to test whether green tea extract reduces the M-protein concentration
Lonial 2010-ongoing[63]	Open-label randomized controlled trial	Lenalidomide vs observation	370 "high-risk" SMM*	Aim: to evaluate whether lenalidomide extends TTP
Landgren 2010-ongoing[64]	Single-arm phase 2 trial	Anti-KIR monoclonal antibody	21 SMM	Aim: to evaluate whether anti-KIR reduces the M-protein concentration > 50% from baseline

Adapted from Waxman et al.[54]

SMM indicates smoldering multiple myeloma; MGUS, monoclonal gammopathy of undetermined significance; MP, melphalan/prednisone; IMM indolent multiple myeloma (asymptomatic but with evidence of end-organ damage); MR, minor response (25%-50% decrease in M-protein); TTP, time to progression; DEX, dexamethasone; PFS, progression-free survival; and PR, partial response (≥ 50% decrease in M-protein).

*Estimated enrollment

With recent trials underscoring the value of ongoing treatment trials for SMM patients, one can envision several scenarios resulting from treatment of SMM.[54] Aimed at preventing progression, SMM could be treated as a chronic disease, with relatively low-toxic therapy used to control the malignant clone. Alternately, highly active therapy could be used with the goal of cure, although this may prove challenging in the context of current treatment options. However, to responsibly perform any such trial, well-designed correlative studies should be performed to assess for the theoretical possibility of unexpected long-term adverse events or select for more aggressive disease.[54]

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