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

Adam J. Waxman,[1,2] Michael Kuehl,[3] Arun Balakumaran,[4] Brendan Weiss,[1,5] Ola Landgren[1]

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 ≥ 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.

Clinical Lymphoma, Myeloma & Leukemia, Vol. 10, No. 4, 248-257, 2010; DOI: 10.3816/CLML.2010.n.053
Keywords: Disease classification, Free light chain, M-protein, MGUS, Precursor disease

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

[1]Medical Oncology Branch, National Cancer Institute, Bethesda, MD
[2]Clinical Research Training Program, NIH Clinical Center, Bethesda, MD
[3]The Genetics Branch, National Cancer Institute, Bethesda, MD
[4]National Institute of Dental and Craniofacial Research, Bethesda, MD
[5]Hematology-Oncology Service, Department of Medicine, Walter Reed Army Medical Center, Washington, DC

Submitted: Nov 10, 2009; Revised: Dec 31, 2009; Accepted: Jan 5, 2010

Address for correspondence: Ola Landgren, MD, PhD, National Cancer Institute, National Institutes of Health, Center for Cancer Research, Medical Oncology Branch, 9000 Rockville Pike, Bldg 10/Rm 13N240, Bethesda, MD
Fax: 1-301-402-0172; e-mail: landgreo@mail.nih.gov

Table 1 International Myeloma Working Group Diagnostic Criteria for Monoclonal Gammopathy of Undetermined Significance, Smoldering (Asymptomatic) Myeloma, and Multiple Myeloma[19]

Disorder	Monoclonal Gammopathy of Undetermined Significance	Smoldering (Asymptomatic) Myeloma	Multiple Myeloma
M-protein	< 3 g/dL	≥ 3 g/dL	Any
	AND	***OR***	
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.

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 case-series 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 ≥ 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 end-organ 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