The Road to Treating Smoldering Multiple Myeloma

Neha Korde,[1,2] Sham Mailankody,[1] Ola Landgren[1,2]

Abstract

The management of smoldering multiple myeloma (SMM) has been a challenge to clinicians, ever since the condition was first characterized in 1980. While the risk of progression to symptomatic myeloma is greater for SMM (10% per year) compared to MGUS (1% per year), several SMM patients remain asymptomatic for years without evidence of disease progression. Early clinical trials focusing on early treatment of SMM have been equivocal with no clear benefit. However, the last decade has seen a greater understanding of the pathogenesis of plasma cell disorders, including SMM, and development of better therapeutics. A recent randomized trial has provided evidence of clinical benefit with early treatment of high-risk SMM. In this review, we summarize issues related to the early treatment of SMM including risk stratification and possible outcomes with therapy initiation. In the context of reviewing recent clinical trial data supporting early treatment, we define challenges faced by clinicians and provide future directions to the road to treating SMM.

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Introduction

Smoldering multiple myeloma (SMM) is an asymptomatic precursor plasma cell disorder defined as either having a monoclonal protein (M-protein) $\geq$ 3 g/dL and/or having $\geq$ 10% plasma cells in the bone marrow.[1] Multiple myeloma (MM) is a symptomatic malignancy characterized by clonal plasma cells causing CRAB (hypercalcemia, renal insufficiency, anemia, and bone lytic lesions or fractures) end-organ damage. Almost all cases of MM are preceded by asymptomatic precursor disease states.[2,3] The term, SMM, was coined and characterized by Kyle and colleagues and noted to carry an average risk of progressing to malignancy of 10% per year.[4,5] In comparison, monoclonal gammopathy of unknown significance (MGUS) is an asymptomatic plasma cell condition defined as having M-protein $<$ 3 g/dL and $<$ 10% bone marrow plasma cells. The risk of MGUS transforming to symptomatic malignancy is 1% per year.[6] Traditional clinical practice depended on careful surveillance for all asymptomatic precursor disease states, including for MGUS and SMM patients.

Risk models have further delineated SMM subcategories with "high-risk" approximately carrying a 75% progression risk at 5 years.[7,8] Recent expert reviews have attempted to take this one step further by introducing the term, "ultra–high-risk SMM,"[9,10] and defining a group of SMM patients with $\geq$ 70% probability of progressing to symptomatic disease in 2 years. Although most agree on a need to identify asymptomatic SMM patients that behave biologically similar to MM because of the propensity toward symptomatic progression, a lack of consensus exists on defining high-risk SMM patients and implementing correct cost-effective tools and biomarkers required for the task. The most crucial argument for identifying these patients is that early intervention might improve clinical outcome in the correct setting. Until recently, studies had failed to show benefit of intervention for all asymptomatic SMM patients across the board.

Mateos and Spanish Myeloma Group from Programa para el Tratamiento de Hemopatías Malignas/Grupo Espanol de Mieloma (PETHEMA/GEM) colleagues published landmark results of the Lenalidomide and Dexamethasone Treatment Versus Observation (QUIREDEX) study, demonstrating that treating high-risk SMM patients (n = 119) with lenalidomide/dexamethasone (Len/Dex) improves time to symptomatic disease progression (not reached vs. 21 months; hazard ratio [HR], 0.18; $P < .001$) and 3-year overall survival (94% vs. 80%; HR, 0.31; $P = .03$) compared with observation.[11] These findings directly challenge current standards of approaching all SMM and MGUS patients with the same "watchful waiting" dogma by demonstrating that early intervention

[1]Multiple Myeloma Section, Lymphoid Malignancy Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD
[2]Myeloma Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

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Address for correspondence: Neha Korde, MD, Myeloma Service, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, NY, NY 10065
E-mail contact: neha.korde@gmail.com

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Table 1 Issues Related to Treating High-Risk SMM

Lack of Consensus Regarding High-Risk and Ultra–High-Risk Definitions
Feasibility of Biomarkers and Assays Required to Define Risk Categories
Cost-Effectiveness of Treatment
Quality of Life During Treatment
Biological Impact on Longitudinal Disease Course With Early Treatment
Standardizing Diagnostic Workup to Distinguish Symptomatic Disease

in high-risk SMM individuals leads to improved outcomes. Two important features were incorporated into the study design compared with predecessors: (1) a well-tolerated, highly efficacious combination of drugs was chosen in the intervention arm; and (2) a high-risk SMM population was targeted instead of all SMM patients. Although the QUIREDEX trial answers a number of long-awaited questions and investigators must be applauded for a bold contribution to the research, a few issues remain before these practices are instituted into everyday clinical practice (Table 1). In our opinion, high-risk and ultra–high-risk SMM patients should still be referred to clinical trials with biological end points (clonal evolution, minimal residual disease [MRD]) and clinical end points (time to progression, time to second line of treatment, cost-efficacy, screening populations, quality of life).

Early Treatment Trials in SMM

Past clinical studies have failed to show major benefits in treating asymptomatic SMM patients (Table 2).[11-20] A large part of these failures could be attributed to lack of efficacy and high toxicities. The first study to investigate initial versus deferred use of melphalan and prednisone in 50 asymptomatic MM patients failed to show benefit.[13] Based on these results and other studies[12,14] initiation of therapy in asymptomatic patients was not revisited until the emergence of thalidomide years later. In the first SMM thalidomide study (n = 16), 6 of 16 SMM and indolent MM patients (38%) demonstrated a partial response (PR).[15] A few years later, Barlogie and colleagues reported a 25% PR rate in SMM patients (n = 76) receiving thalidomide (200 mg/d) and monthly pamidronate. Surprisingly, patients achieving a PR had a shorter time to salvage therapy after progression. Moreover, investigators reported a 50% thalidomide discontinuation rate because of poor tolerability of the drug.[18] A few studies have investigated the potential role of bisphosphonates and clinical benefit in SMM. A larger study conducted by Musto and colleagues[17] compared zolendronic acid versus observation (n = 163) and found decreased incidence of skeletal-related events in the bisphosphonate arm (55.5% vs.78.3%; P = .041). No difference was observed in progression rates between the 2 arms or median time to progression.[17] In addition, a myriad of smaller trials have investigated or currently exploring the potential use of agents (green tea extract,[21] curcumin,[22] and anakinra[19]) with more benign side effect profiles and an aim to treat an essentially asymptomatic SMM population. Along with small sample sizes and heterogeneic end points, earlier SMM treatment trials usually had confounding weaknesses of treating all SMM patients while being unable to target those truly biologically similar to MM.

High-Risk SMM Definitions

It is essential to recognize that SMM is comprised of a mixed population of patients that ultimately vary in clinical outcome if left untreated. Approximately half of all SMM patients remain asymptomatic without clinical disease after 5 years. Two prevailing risk models help determine risk stratification for SMM patients (Table 3).[7,8,23,24] As mentioned earlier, high-risk SMM patients in both models are noted to have a 5-year progression rate of 72% to 76% with a median time to progression of < 2 years.[7,8] Eligible

Table 2 Selected Clinical Trials in SMM

Year	Regimen (Number of Patients)	Study/Study Design	Outcome
1988	VAD or MP (n = 33)	Alexanian et al[12] Retrospective series	Treat when symptoms develop
1993	MP upfront versus deferred (n = 50)	Hjorth et al[13] Randomized	No differences in response rates or survival
2000	MP upfront versus deferred (n = 145)	Riccardi et al[14] Randomized	No differences in response rates or survival
2001	Thalidomide (n = 16)	Rajkumar et al[15] Single arm	PR or better in 6 of 16 (37.5%)
2003	Thalidomide (n = 28)	Weber et al[16] Single arm	Response rates 36%
2008	Zolendronic acid versus control (n = 163)	Musto et al[17] Randomized	SREs in zoledronic versus control was 56% versus 78% (P = .041); no difference in median TTP
2008	Thalidomide/pamidronate (n = 76)	Barlogie et al[18] Single arm	Median TTP 7 years; PR requiring earlier salvage therapy; 50% discontinuation rate
2009	Anakinra (n = 47)	Lust et al[19] Single arm	PR in 5 of 47 (11%); median PFS 37.5 months
2011	Pamidronate versus observation (n = 177)	D'Arena et al[20] Randomized	No difference in progression rate and overall survival. SREs in pamidronate versus control was 39% versus 73% (P = .009)
2013	Len/Dex versus observation (n = 119)	Mateos et al[11] Randomized	3-Year OS Len/Dex versus observation was 94% versus 80% (HR, 0.31; P = .03); median TTP Len/Dex versus observation was NR versus 21 months (HR, 0.18; P < .001)

Abbreviations: HR = hazard ratio; Len/Dex = lenalidomide, dexamethasone; MP = melphalan, prednisone; NR = not reached; OS = overall survival; PFS = progression-free survival; SRE = skeletal related event; TTP = time to progression; VAD = vincristine, doxorubicin, and dexamethasone.