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How I approach smoldering multiple myeloma

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The current standard of care in smoldering multiple myeloma (SMM) is close surveillance, outside of clinical trials. Efforts are being made to understand the pathobiologic process that leads to the progression of SMM to active MM. This review provides a critical description of available data, including risk factors and risk models of progression, as well as clinical trials investigating interventions for this patient population. We describe 2 cases in which patients were seen before the concept of a myeloma-defining event was established. Today, based on the International Myeloma Working Group criteria, both patients would have been identified as experiencing myeloma-defining events, and therapy would have been initiated. These cases show that occasionally, patients can undergo observation only, even when they exceed criteria for high-risk SMM.

Introduction

Smoldering multiple myeloma (SMM) is an asymptomatic clonal proliferation of plasma cells that can progress to MM. It was first described in 1980,[1,2] and since then, efforts have been made to identify laboratory and imaging markers for impending MM. The first identified markers of progression risk included light chain proteinuria and plasma cell proliferative index (labeling).[3] SMM is defined by the presence of either serum monoclonal protein ≥3 g/dL (or ≥500 mg per 24-hour urine) or ≥10% clonal bone marrow plasma cells (BMPCs) without evidence of a myeloma-defining event.[4]

SMM is a heterogeneous entity[5] comprising 3 patient populations: in the first, disease biology resembles that of monoclonal gammopathy of undetermined significance (MGUS); in the second, disease is slowly progressing to MM; and in the last, disease is myeloma in evolution and will develop into overt disease in <2 years. There is an urgent need for better risk stratification for all 3 groups. The risk of progression to MM decreases over time; overall risk of progression is 10% per year for the first 5 years (50% in 5 years), 3% per year for the next 5 years (65% in 10 years), and 1% per year for thereafter (similar to the risk of progression from MGUS).[5] An estimated 25% of patients with SMM never progress to symptomatic disease.

Patients with high-risk SMM (HR-SMM) are described as having disease in which the risk of delaying therapy exceeds any benefits of continued observation. Can this group be reliably identified? There are several risk models of progression to active MM,[6-8] but there is a significant degree of discordance between these risk models,[9,10] and there is currently no uniformly accepted definition of HR-SMM. HR-SMM is not a disease. It represents a statistical estimate of time to symptom development. Consensus suggests that an 80% likelihood of symptomatic myeloma within 24 months of diagnosis is sufficient to warrant intervention in an otherwise asymptomatic individual.[4]

The search for early interventions in SMM arises from the significant rate of early mortality in MM, which was previously found to be >10%,[11] and the risk of irreversible kidney damage, spinal cord compression, debilitating fractures, and chronic pain related to bone disease. The ideal strategy would involve not treating too early, to avoid the toxicity of therapy, and not treating too late, to avoid irreversible complications, balancing toxicity with need for treatment in asymptomatic patients. Finding this sweet spot is challenging.

Currently, many patients with MM achieve deep and durable responses.[12-23] Curative therapy in MM is not available. The term functional cure has been proposed when patients survive long enough to die as a result of other causes, but the pathway to this end point is not defined and is measured only in retrospect.[24] Some HR-SMM trials aim for clonal eradication,[25,26] whereas others are designed to evaluate whether therapy in the era of novel agents can safely delay progression to MM and identify optimal combinations and schedules.[27-30] One of these trials showed an overall survival (OS) benefit for therapy vs observation.[28]

There is consensus on not treating patients with low- or standard-risk SMM, because the time to develop active myeloma may be many years. The current standard of care for patients with SMM is active monitoring until progression to MM, and this is reflected by the fact that no drugs are US Food and Drug Administration/European Medicines Agency approved for treatment of SMM. In 2014, the International Myeloma Working Group changed its criteria for diagnosis of MM.[4] This was the first time that therapy was recommended for asymptomatic patients at very high risk of

symptomatic progression (80% progression in 2 years). These guidelines, outlining so-called myeloma-defining events, recommend therapy for patients with ≥1 of 3 markers of progression: ≥60% BMPCs, serum free light chain (sFLC) ratio ≥100 (this seems to be significant only if urine monoclonal protein is >200 mg/d),[31] and >1 focal lesion on magnetic resonance imaging (MRI) scan. These criteria are based on retrospective studies[32-35] that identified these parameters at presentation as leading to high risk of progression. Therefore, the concept of treating a patient with SMM who has been monitored for several years whose sFLC ratio rises to 100 is not addressed by these criteria. The new criteria upstage ∼15% of SMMs to active myeloma.[36] High sFLC ratio was not found to predict short time to progression (TTP) in a Danish population-based cohort study.[37]

Understanding the genetic factors that drive progression of SMM to active MM can help identify those patients who may benefit from early intervention.[35] In HR-SMM, most of the genetic changes necessary to give rise to MM are already present.[38-42] However, the exact mechanism by which progression to MM occurs remains unclear.[43] A validated model showed that specific genomic aberrations (alterations in the mitogen-activated protein kinase pathway, MYC, or the DNA repair pathway) can help risk stratify patients with SMM.[44] Another likely explanation is a change in interaction with the BM microenvironment,[45-47] causing loss of immune regulation.[48-50] Table 1 summarizes the current controversies in SMM therapy.

Risk-stratification models for SMM progression

A wide variety of parameters predicting progression have been evaluated based on retrospective cohorts, including size of the M protein,[49,50] type of heavy chain involved,[51-53] involved sFLC ratio[54] and difference between involved and uninvolved FLCs, immunoparesis,[54] percentage of clonal plasma cells in the BM,[53,54] urinary light chain excretion,[51,53,54] circulating plasma cells,[55] and fluorescence in situ hybridization (FISH) abnormalities.[38,56,57] An important criterion of progression in evolving SMM was defined as a constant increase in the serum M protein in each of the first 2 consecutive monitoring visits 3 months apart.[58]

The need for tools that can accurately predict disease course led to the development of several risk-stratification models. Table 2 summarizes some of the risk models. The PETHEMA risk model is based on 2 criteria: ≥95% aberrant BMPCs by multiparameter flow cytometry and immunoparesis[6] (Table 2). Multiparameter flow cytometry to identify immunophenotypically aberrant plasma cells is not widely used, which limits widespread introduction of this risk model. The 2008 Mayo Clinic model separates SMM into 3 risk categories based on 3 criteria: serum M protein ≥3 g/dL, clonal BMPCs ≥10%, and sFLC ratio >8 or <0.125[7] (Table 2). The 2018 Mayo Clinic model separates SMM into risk categories based on 3 criteria: M protein >20 g/L, clonal BMPCs >20%, and sFLC ratio >20[8] (Table 2). The International Myeloma Working Group risk model[59] validates the 2018 Mayo Clinic criteria (Table 2), includes the same 3 parameters, and adds cytogenetic abnormalities. However, cytogenetic data were available in only 35% of the cohort. Like the other models described, this is not a dynamic model and bases a decision to treat an individual patient on results at a single time point. In 1 study, reproducibility of the FLC ratio demonstrated a 25% difference in 16 (43%) of 37 patients and a 50% difference in 13 (35%) of 37 patients.[60] Moreover, today's ratio of 25 may be 18 next week. There is a notable discrepancy in BMPC percentages using different methods of observation,[61] and an estimate of 20% BMPCs may be <20% in another laboratory. Are these the criteria to use in deciding to administer continuous therapy to an asymptomatic patient based on a single office visit?

Table 1. Topics of debate in SMM therapy

Topic
What is the ideal time to start therapy?
Which patient populations should be treated?
Which therapies would best benefit patients with SMM? Cure vs control?
How long should patients with SMM be treated?
What are the most appropriate end points in clinical trials for SMM?

In the QuiRedex[28] and Eastern Cooperative Oncology Group (ECOG) trials,[27] the 2 randomized phase 3 trials that showed benefit with treating HR-SMM, used different criteria for high-risk disease. A study showed a concordance of only 29% between the populations defined as high risk in different studies.[9] Among 38 patients classified as having HR-SMM by the PETHEMA model, only 4 were high risk by the Mayo 2018 model. The assumption is that patients classified as high risk by these models have a 75% risk of progressing to symptomatic MM at 5 years, and 50% will progress in the first 2 years. Therefore, by definition, patients with SMM who have not progressed at 5-year follow-up cannot be considered high risk. Two clinical trials of SMM therapy used a cutoff of 5 years of monitoring for patient enrollment.[27,28] Enrolling patients previously under observation for multiple years before randomization skews the population under study toward non–high-risk cohorts.

Several studies have emphasized the importance of biomarkers evolving during monitoring.[62-64] The first[62] used 3 criteria: evolving change in monoclonal protein level (≥10% increase within the first 6 months of diagnosis and ≥25% increase in serum M protein or immunoglobulin within the first 12 months), decrease in hemoglobin level (≥0.5-g/dL decrease within 12 months of diagnosis), and BMPCs ≥20%.[62] The 2-year progression risk was 82% in individuals who demonstrated both evolving monoclonal protein and evolving hemoglobin and 91% in those with all 3 risk factors. The median TTP was 12, 5, 2, and 1 years among patients with 0 to 3 risk factors, respectively. The prognostic significance of evolving change in hemoglobin as defined in this study was not confirmed in a study conducted by the Levine Cancer Center group.[65] In that study, the model incorporated evolving change in serum M protein, BMPCs ≥20%, and sFLC ratio ≥8. The presence of 0 to 1 of these risk factors identified a population at lower risk of progression. The 2-year progression rate for patients with 3 risk factors was 25%, so this study could not identify a subpopulation for whom therapeutic intervention would be justified.

Table 2. Risk models of progression from SMM to active MM

Model	Risk factors	Risk groups	Outcomes
PETHEMA	1. ≥95% aberrant BMPCs by flow cytometry (defined as $CD38^+$ cells with absence or underexpression of CD19 and/or CD45 or overexpression of CD56) 2. Immunoparesis (reduction of ≥1 uninvolved heavy chain)	0, low risk 1, intermediate 2, high risk	PFS at 5 y: Low risk, 4% Intermediate risk, 46% High risk, 72%
Mayo 2008	1. BMPCs ≥10% 2. M spike ≥3 g/dL 3. sFLC ratio ≤0.125 or ≥8	0/1, low risk 2, intermediate risk 3, high risk	PFS at 5 y: Low risk, 25% Intermediate risk, 51% High risk, 76%
Mayo 2018	1. BMPCs >20% 2. M spike >2 g/dL 3. sFLC ratio <0.05 or >20	0, low risk 1, intermediate risk 2/3, high risk	Median TTP: Low risk, 110 mo Intermediate risk, 68 mo High risk, 29 mo
IMWG 2020	1. sFLC ratio: 0-10, 0 points 10-25, 2 points 25-40, 3 points >40, 5 points 2. M spike (g/dL): 0-1.5, 0 points 1.5-3, 3 points >3, 4 points 3. Percentage of BMPCs 0-15, 0 points 15-20, 2 points 20-30, 3 points 30-40, 5 points >40, 6 points 4. FISH abnormalities* No, 0 points Yes, 2 points	0-4 points, low risk 5-8 points, low/intermediate risk 9-12 points, intermediate risk >12 points, high risk	Risk of progression at 2 y: Low risk, 3.8% Low/intermediate risk, 51.1% Intermediate risk, 26.2% High risk, 72.5%

PETHEMA, Programa Español de Tratamientos en Hematología.

*FISH abnormalities include t(4;14), t(14;16), 1q gain, and del 13q/monosomy 13.

Another study that used a dynamic model[63] identified immunoparesis, rising M protein level (64% increase), falling hemoglobin (1.57-g/dL decrease), and increasing difference in sFLC (169% increase) in the first year after SMM diagnosis as predictors for progression. Patients with ≥60% BMPCs and those with sFLC ≥100 (myeloma-defining events) had only a 41% and 44% risk of progression at 2 years, respectively. The fourth dynamic study[64] showed that rising serum M protein was associated with a 3-year progression rate of 71% and median time to clinical progression of 1.1 years.

Dynamic risk models that account for changes in markers during observation should be validated in a larger cohort. The concept of deciding to initiate therapy based on a snapshot of activity is not optimal for the individual patient. We think it is better to record multiple snapshots over time to create a movie of disease biology. We monitor patients with SMM closely for changes in hemoglobin, creatinine, M protein, and involved sFLC and do not commit to therapy based on laboratory results at a single time point, outside of clinical trials. Moreover, this is a useful way to get to know the patient and his or her beliefs and build trust with the patient and family. A retrospective study showed that monitoring alone cannot prevent complications.[66] However, this study was conducted before the widespread use of the sFLC assay or advanced imaging. Moreover, there was no prespecified monitoring interval.

To summarize, outside of trials, we do not use any of the models presented here, because we will not treat a patient based on any of them. We closely monitor patients and assess disease biology on a case-by-case basis, attempting to provide an individualized approach.

Therapeutic interventions in SMM

The concept of treating MM before it becomes symptomatic was first proposed in a prospective study of 50 patients with asymptomatic myeloma using melphalan and prednisone therapy at diagnosis vs at progression. This intervention did not delay progression to MM and did not improve OS.[67]

Two philosophic approaches to HR-SMM therapy are being evaluated: control (low-intensity therapy aiming to delay time to end organ damage) vs eradication (intensive therapy aiming to eradicate the malignant clone and potentially cure the disease). The only clinical trial that has shown an OS benefit with intervention in SMM is the QuiRedex study.[28] This was a phase 3 multicenter trial that randomly assigned 119 patients to lenalidomide and dexamethasone (Rd) vs observation. In long-term follow-up at 6 years, the median TTP was not reached vs 23 months (hazard ratio, 0.24), and the median OS was not reached in the treatment arm vs 117.6 months in the observation arm (hazard ratio, 0.43).[68] Even though this study demonstrated OS and PFS

benefits, it had limitations. The study recruited patients before the widespread use of advanced imaging (eg, positron emission tomography [PET]–computed tomography [CT] or MRI), now considered required before deciding a patient with SMM should undergo observation. In the trial, patients underwent a radiographic skeletal survey. Therefore, it is likely that patients with myeloma bone disease, by current definitions, were included in the study. This is hinted at by the high progression rate in the observation arm (21% at 10 months). Progression was defined only by the development of the formal CRAB (calcium elevation, renal dysfunction, anemia, and bone disease) criteria, and it did not include progression criteria based on a small but steady decrease in hemoglobin or increase in creatinine or calcium level, M protein velocity, or light chain change.[69] Moreover, the study did not include mandatory interval skeletal imaging, so patients with asymptomatic new bone lesions would not have started therapy in the observation arm until the bone lesions became painful. Therefore, outcomes in the observation arm may have been worse because of failure to carefully monitor or respond to changes during observation. Delaying intervention in the face of a rapidly rising monoclonal component does not always reflect today's clinical practice and could have had an impact on outcomes. The main importance of this study is that it was the first proof-of-concept study supporting further investigation of therapy with novel agents in high-risk SMM.

The phase 2 randomized CENTAURUS study evaluated daratumumab monotherapy administered according to 3 different schedules[30] (Table 3). The primary end points were CR rate and percentage of patients who progressed or died divided by total duration of PFS in patient-years. The coprimary endpoint of CR >15% was not met. Progression in this study included criteria of biochemical progression.[70] The median follow-up was only 25.8 months. Five, 7, and 10 patients progressed in the intensive, intermediate, and short arms, respectively. It is interesting to note that in 20 of the 22 patients who progressed, the progression event was SLiM (≥60% clonal plasma cells, light chain ratio ≥100, and MRI > 1 focal lesion) based, and only 2 patients progressed with lytic lesions. None of the carefully monitored patients progressed with renal failure, fracture, or symptomatic hypercalcemia. Unfortunately, this study did not have an observation arm, so even though median PFS was not reached, it may reflect a study population that was not high risk (22 progressions among 123 patients enrolled). Isatuximab monotherapy, administered for a fixed duration of 30 cycles, was evaluated in a phase 2 study that included 24 patients.[71] The ORR was 63% (VGPR or better in 22%), and the treatment was well tolerated.

Another important phase 3 trial was ECOG E3A06. This trial evaluated single-agent lenalidomide administered until progression vs observation in 182 patients with intermediate- or high-risk SMM.[27] Originally, the study included patients diagnosed in the year before enrollment, but because of low accrual, after 2013, patients were enrolled if they were diagnosed in the 5 years before enrollment. Both the ECOG E3A06 and CENTAURUS studies allowed enrollment if patients were diagnosed up to 5 years before registration. However, a patient not progressing for that long before trial entry in our opinion is not high risk.

Advanced imaging in the ECOG E3A06 study was used at baseline (MRI); 47% of patients had abnormal MRI findings, raising the question of whether some of the patients had active MM, because PET-CT was not a study requirement. The primary end point was PFS, and the definition of progression included biochemical progression. The ORR was 50%, and PFS was significantly longer in the lenalidomide group. However, in the observation arm, at 24 months only 24% of patients had progressed, much less than the anticipated 50%, suggesting this was not truly a high-risk population. By the 2018 Mayo Clinic criteria, 58 patients enrolled were low risk, and by the 2008 Mayo Clinic criteria, 49 patients were low risk. The study randomly assigned only 29 high-risk patients (based on the 2008 Mayo Clinic criteria), with 14 high-risk patients randomly assigned to the treatment arm. No statistic for PFS was applied, possibly because the numbers were underpowered for reporting purposes. Missing data on FISH genetics in 102 of 182 patients did not enable inferences about FISH as a risk factor for progression. This study included a QOL assessment, with a nonsignificant difference in mean change score at 24 cycles. Overall, the low rate of progression and the adverse event rate make it difficult to recommend this as standard practice.

The ASCENT and GEM-CESAR trials investigated a curative approach to high-risk SMM, using MRD negativity as a surrogate end point for OS. The ASCENT trial used 6 cycles of daratumumab added to carfilzomib plus Rd (KRd) induction followed by 6 additional cycles of consolidation with daratumumab plusKRd and 1-year maintenance with daratumumab and lenalidomide.[26] No treatment-related deaths were observed. The phase 2 GEM-CESAR trial evaluated induction with KRd followed by autologous stem cell transplantation (ASCT), KRd consolidation, and maintenance for 2 years.[25] At 30-month follow-up, the ORR was 100% (CR or better, 76%), with an MRD negativity rate of 63%. The 3-year PFS rate was 93%, similar to that in the ECOG E3A06 trial using single-agent lenalidomide.

A phase 2 single-center study reported outcomes of 54 patients treated with 8 cycles of KRd followed by 24 cycles of lenalidomide maintenance.[29] At baseline, advanced imaging was performed (MRI spine and PET-CT). It also included criteria not previously included in SMM clinical trials: high-risk FISH abnormalities, progressive increase in M protein level, increased peripheral blood circulating plasma cells, and MRI with diffuse abnormalities or 1 focal lesion, PET-CT with a focal lesion, or increased uptake without underlying osteolytic bone destruction. The primary end point of this study was the MRD-negative CR rate, which was achieved in 70% of patients. Only 2 patients developed MM (both had lytic bone lesions off therapy), and 6 patients met the biochemical progression criteria. This was the first SMM study excluding patients with active myeloma using both CT and MRI as screening tools. This study included a significant number of minorities (33%). There was no control group. Table 3 summarizes the recent phase 2 and 3 clinical trials in SMM. Of note, the table represents cross-trial comparisons with heterogeneous populations enrolled, and direct comparisons should not be made.

To summarize, the data presented define which treatment modality would best serve patients with SMM. Trials that use lenalidomide,[27] Rd,[28] or single-agent daratumumab[30] are potentially undertreating active MM, because doublets are inferior to triplets, and ASCT remains an integral part of therapy for transplantation-eligible patients with MM. However, patients whose disease has MGUS-like biology should not be treated,

Table 3. Phase 2 and 3 clinical trials in SMM

	Phase	High-risk definition	Intervention	Control arm	No of patients	Results	Safety
QuiRedex	3	BMPCs ≥10% and monoclonal component (defined as IgG level ≥3 g/dL, IgA level ≥2 g/dL, or urinary Bence Jones protein level >1 g per 24 h) or only 1 of 2 criteria described above plus at least 95% phenotypically aberrant plasma cells in BMPC compartment, with immunoparesis	Rd: 9 cycles followed by lenalidomide maintenance for 2 y	Observation	119	At 6 y, TTP was not reached vs 23 mo, and median OS was not reached vs 117.6 mo	5% VTE, 6% grade 3 infection; 1 patient died as a result of therapy toxicity
CENTERIUS	2	BMPCs ≥10% to <60% and at least 1 of the following: serum M protein ≥3 g/dL (IgA ≥2 g/dL), urine M protein >500 mg per 24 h, abnormal FLC ratio (<0.126 or >8), or serum M protein <3 g/dL but ≥1 g/dL	Daratumumab monotherapy in 3 different regimens: intense (weekly in cycle 1, every other week in cycle 2-3, every 4 wk in cycle 4-7, and every 8 wk in cycles 8-20), intermediate (every week in cycle 1 and every 8 wk in cycles 2-20), or short (only 1 cycle of weekly daratumumab)	No	123	Coprimary end point of CR >15% was not met; ORR was 56%, 53.7%, and 37.5% in intensive, intermediate, and short arms, respectively	5.7% stopped therapy because of PD and 5% because of AEs (pneumonia, thrombocytopenia, unstable angina, hypomania, balance disorder, and breast disorder); 2 patients died; in terms of safety, grade 3 or 4 AEs were reported in 44%, 27%, and 15% of patients in intensive, intermediate, and short arms, respectively
ECOG E3A06	3	≥10% BMPCs and sFLC ratio <0.26 or >1.65	Single-agent lenalidomide (25 mg per day on days 1-21 every 28-d cycle) until progression	Observation	182	ORR was 50% and PFS was significantly longer in lenalidomide group (HR, 0.28; 95% CI 0.12-0.62; $P = .002$)	Grade 3 or 4 nonhematologic toxicity occurred in 25 patients (28%) in intervention arm, and 40% discontinued therapy because of AEs; 3-y cumulative incidence of invasive second primary malignancies was 5.2% in treatment arm vs 3.5% in observation arm
GEM-CESAR	2	Presence of both ≥10% BMPCs and M protein ≥3 g/dL, or if only 1 criterion was present, patients must have >95% aberrant plasma cells by immunophenotyping and immunoparesis	Induction with KRd followed by ASCT, KRd consolidation, and maintenance for 2 y	No	90	At 30-mo follow-up, ORR was 100% (≥CR 76%), and MRD negativity (measured by NGF with LOD 10-6) of 63%	

AE, adverse event; CI, confidence interval; HR, hazard ratio; IgA, immunoglobulin A; LOD, limit of detection; ORR, overall response rate; PD, progressive disease; QOL, quality of life; VTE, venous thromboembolism.

Table 3. (continued)

	Phase	High-risk definition	Intervention	Control arm	No of patients	Results	Safety
ASCENT	2	High-risk was defined as presence of any 2 of the following: serum M spike >2 g/dL or involved to uninvolved FLC ratio >20 or BMPC percentage >20%) or IMWG score ≥9 using risk scoring system using FLC ratio, serum M spike, marrow plasma cell percentage, and presence of high-risk FISH	6 cycles of daratumumab plus KRd induction followed by additional 6 additional cycles of consolidation with daratumumab KRd and 1-y maintenance with daratumumab and lenalidomide	No	46	Pending (end point is sCR)	No treatment-related deaths were observed; grade ≥3 AEs were seen in 52% of patients
Kazandjian 2021	2	Serum M protein ≥3 g/dL, IgA isotype, immunoparesis, sFLC ratio ≥8, clonal BMPCs 50%-60%, abnormal BMPC immunophenotype by flow; it also included criteria not previously included in SMM clinical trials: high-risk FISH abnormalities [t(4;14) or del(17p) or 1q gain], progressive increase in M protein level (evolving type of smoldering myeloma; increase in serum M protein by ≥25% on 2 successive evaluations within 6 mo), increased circulating plasma cells, and MRI with diffuse abnormalities or 1 focal lesion, PET/CT with focal lesion, increased uptake without underlying osteolytic bone destruction	KRd followed by 24 cycles of lenalidomide maintenance	No	54	Median rate of MRD-negative CR was 70% with median duration of 5.5 y; ORR was 100% and median duration of response was not reached with 96-mo duration of response of 77.4%	Nonhematologic grade 3 AEs were reported in 39% of cohort and included all-grade VTE in 11 patients (20%) and grade 3 VTE in 6 patients (11%); only 1 patient had grade 3 hypertension, 1 had grade 3 heart failure after 6 cycles and discontinued therapy, and 1 had grade 3 atrial fibrillation
Manasanch 2019	2	Not reported in ASH abstract	Isatuximab monotherapy	No	24	ORR 63% (≥VGPR in 22%)	5 grade 3 AEs that resolved to baseline; QOL was improved by end of cycle 6
Nadeem 2021	2	Defined criteria proposed by Rajkumar et al[4]	Ixazomib plus Rd for 9 cycles followed by ixazomib and lenalidomide for 15 cycles for total of 24-mo period	No	61	ORR in participants who completed at least 2 cycles of treatment was 90.9% (CR, 21.8%; VGPR, 18.2%; PR, 50.9%)	No patients discontinued treatment because of toxicity; most common grade ≥3 toxicities were neutropenia (20%), hypophosphatemia (13%), leukopenia (11%), rash (9%), lymphocytopenia (5%), and thrombocytopenia (5%)

AE, adverse event; CI, confidence interval; HR, hazard ratio; IgA, immunoglobulin A; LOD, limit of detection; ORR, overall response rate; PD, progressive disease; QOL, quality of life; VTE, venous thromboembolism.

Table 4. Baseline assessment and monitoring for patients with SMM

Test	At baseline	How often do we repeat it
CBC	Yes	3-6 mo
Vitamin B12, TSH, folic acid, iron, transferrin, and ferritin	Yes	When hemoglobin decreases
Creatinine	Yes	3-6 mo
Calcium	Yes	3-6 mo
Alkaline phosphatase	Yes	12 mo
24-h urinary protein	Yes	12 mo
NT-proBNP and troponin	Yes	12 mo
SPEP and IEP	Yes	3-6 mo
sFLC	Yes	3-6 mo
Skeletal imaging	PET-CT (if unavailable, we recommend TBLDCT and MRI of spine and pelvis)	TBLDCT every 6-12 mo if monoclonal protein is rising
BM biopsy and aspirate and FISH	Yes	When progression is suspected

CBC, complete blood count; IEP, immunofixation; NT-proBNP, N-terminal probrain natriuretic peptide; SPEP, serum protein electrophoresis; TBLDCT, total-body low-dose CT scan; TSH, thyroid-stimulating hormone.

even with so-called innocent therapies. One might argue that current therapies for MM are less toxic than previous therapies; therefore, early treatment is reasonable when weighing the risks vs benefits. Patients treated with bortezomib may face a lifelong burden of neuropathy,[72-74] and patients treated with lenalidomide often experience fatigue, diarrhea, and venous or arterial thrombosis,[75-78] with a doubling of the risk of second primary malignancies[79] after ASCT. The cardiac toxicity of carfilzomib may be life threatening,[80,81] and the increased risk of infection, including fatal infection, with all types of therapies[82-84] is well recognized. The financial toxicity[85] and emotional stress involved in receiving therapy are also important considerations in the decision to treat asymptomatic patients.

Clinical trial end points

What are appropriate clinical trial end points in a disease like SMM? A study evaluated the characteristics of 32 clinical trials for SMM.[86] Only 1 trial reported OS. The surrogate end points used in most trials were depth of response and PFS. Waiting for an OS advantage can take a long time, but there are additional end points that are clinically relevant: QOL, irreversible rise in creatinine, and symptomatic bone disease. PFS may only represent lead-time bias in asymptomatic patients.[87,88]

Another important concept in SMM studies is PFS2,[89] defined as the time from randomization to progression during next-line treatment or death resulting from any cause. It shows the influence of therapy for SMM on the efficacy of subsequent therapies. Patients in the cited clinical trials seemed to respond well to induction. However, none of these studies reported PFS2, which is an important end point, because it is crucial to refute the concept that treating early may cause resistant clones to emerge at progression. We believe that the most important end points in clinical trials evaluating early intervention in HR-SMM are OS, MRD negativity, PFS2, fractures, renal impairment, and QOL.

Patient cases

Case 1 A 68-year-old man presented with proteinuria of 370 mg per day in 2010. λ FLC was 274 mg/dL, with no symptoms of myeloma or amyloidosis. Immunofixation showed a possible band in the β region. BM showed 5% λ light chain–restricted plasma cells, with no high-risk genetic abnormalities. The fat pad was Congo red negative. Over 10 years, light chains trended upward and fluctuated over a wide range (274-772 mg/dL), with a February 2022 value of 886 mg/dL. Repeat BM contained 5% plasma cells. The κ/λ ratio was always <0.01. Urinary protein ranged between 170 and 817 mg per 24 hours. The patient developed no signs of renal failure or hypercalcemia, and hemoglobin was stable between 12 and 13 g/dL. CT skeletal survey

Table 5. Ongoing phase 2 and 3 clinical trials in SMM

	Phase	Intervention	Primary outcome
DETER-SMM (NCT03937635)	3	Daratumumab plus Rd vs Rd	OS, functional assessment score
ITHACA (NCT04270409)	3	Isatuximab plus Rd vs Rd	Safety, Cmax of isatuximab, PFS
AQUILA (NCT03301220)	3	SQ daratumumab vs active monitoring	PFS
HO147SMM (NCT03673826)	2	KRd vs Rd	PFS
NCT04776395	2	Iberdomide and dexamethasone vs iberdomide montherapy	ORR
PRISM (NCT04775550)	2	Daratumumab plus bortezomib and Rd	MRD negativity at 2 y
E-PRISM (NCT02279394)	2	Elotuzumab plus Rd	PFS at 2 y

SQ, subcutaneous.

was performed twice yearly and remained normal. This patient continues to be monitored.

Case 2 In 2012, a 62-year-old woman was found to have hemoglobin of 11 g/dL. Serum IgA was 1800 mg/dL, and immunofixation showed an IgA λ monoclonal protein with an M spike of 1.7 g/dL and λ free light chain of 94 mg/dL. BM showed 11% plasma cells, with FISH showing 1q gain and 13q deletion. CT skeletal survey was negative. By December 2018, IgA had risen to 3800 mg/dL and λ free light chain to 161 mg/dL, with κ/λ ratio <0.01, serum M spike of 2.7 g/dL, and hemoglobin of 11.3 g/dL. BM biopsy showed 40% clonal plasma cells, and PET-CT showed diffuse mild fluorodeoxyglucose uptake in the axial skeleton. After 9 years of monitoring (April 2021), hemoglobin declined over a period of 3 months, from 11 to 9.4 mg/dL. Therapy was recommended, and she declined. After 2 months, her hemoglobin was 6.4 g/dL, creatinine had risen from normal to 2 mg/dL, sFLC λ was 388 mg/dL, and IgA was 4010 mg/dL, and the patient initiated induction chemotherapy. After 2 months of therapy, hemoglobin had risen to 9 g/dL and creatinine had normalized, and the patient achieved VGPR. Twenty-one days after ASCT, her IgA was 48 mg/dL.

Both patients had a high risk of progression at the time of diagnosis (FLC ratio >100), and we chose not to treat these patients, even though many experts would have advocated starting therapy many years earlier. The first patient had very high FLCs that gradually increased over follow-up. His urinary protein levels were not very high, which is supportive of a lower risk of progression.[31] We are monitoring him closely (every 2-3 months) for changes in hemoglobin and renal function, and repeat imaging is performed every 6 to 12 months. This strategy has provided him 11 years without therapy. The second patient had progressive anemia, and her monoclonal protein was rising, which was reversible with therapy. We believe that the movie is superior to the snapshot, and outside of a trial, monitoring the patient for several months before a therapy decision is made is appropriate. Table 4 shows the baseline assessment we perform and how we monitor patients with SMM. Advanced imaging (PET-CT and MRI of spine and pelvis) is an essential part of baseline assessment. It is important to emphasize that during follow-up, we also evaluate for signs and symptoms of amyloidosis, because SMM may also progress to amyloid light chain amyloidosis, even without a rise in sFLCs.

Future perspectives

The future holds great promise in terms of risk stratification and treatment of SMM. Dynamic models based on genetic markers repeatedly assessed during monitoring[90] will help predict the risk of progression to MM and help ensure that patients selected for trials are truly at high risk of progression.

Multiple clinical trials have addressed various therapies for SMM. Table 5 summarizes the ongoing phase 2 and 3 clinical trials in SMM. The DETER-SMM trial (registered at www.clinicaltrials.gov as #NCT03937635) is randomly assigning patients to daratumumab plus Rd vs Rd, and the ITHACA trial (NCT04270409) is enrolling patients for treatment with isatuximab plus Rd vs Rd. These are the 2 phase 3 randomized controlled trials offering treatment in both study arms. The AQUILA trial (NCT03301220) is randomly assigning 390 patients to daratumumab vs observation. The phase 2 E-PRISM trial (NCT02279394) is evaluating elotuzumab, lenalidomide, and dexamethasone, and preliminary results show an ORR of 71% and no progression to MM. Another phase 2 trial is evaluating the all-oral combination of ixazomib, lenalidomide, and dexamethasone (NCT02916771), and the ORR is 91%.[91] Stimulation of the immune system might have a role in preventing progression to MM. A phase 1/2b study assessed the use of PVX-410 multipeptide vaccine with or without lenalidomide in 22 patients with SMM. This intervention was safe and produced a sustained increase in $CD8^+$ memory T cells.[92] These phase 2 studies must be followed by phase 3 studies, because in SMM, a therapeutic decision based on studies that do not have a comparator arm is problematic.

The next possible step would be to tailor therapy based on genetic data, for example, to evaluate the efficacy of targeted therapy with venetoclax in preventing progression in patients wtih HR-SMM with t(11;14). To cure MM with early intervention, the role of early immunotherapy must be assessed.

Conclusions

The current standard of care in SMM is close surveillance, outside of clinical trials, irrespective of risk status. Participation in clinical trials is highly encouraged. Two large randomized clinical trials have demonstrated benefit with early intervention in HR-SMM, but the definition of high risk is different among clinical trials, and the discordance between those definitions is high. We believe that the data published so far do not justify lowering the treatment threshold. Therefore, before recommending therapy in this heterogeneous patient population, more data must be published to uniformly select patients who might benefit from intervention, and models should include dynamic parameters. We believe it is reasonable, outside of a study, to monitor a patient closely before committing to treatment. Research identifying more accurate genomic markers that would enable us to assign individual risk more precisely is ongoing.

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Authorship

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Footnote

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