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Fundamentals of Treating Smoldering Multiple Myeloma

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Abstract

Plasma cell disorders remain a rarity and management of these diseases remains a challenge for clinicians. The definition of plasma cell disorders was first characterized in 1980, although a greater understanding of the pathophysiology of the disease has been seen within the last decade. As diagnostic tests and treatment modalities have greatly improved, the International Myeloma Working Group (IMWG) updated the criteria for diagnosis of Multiple Myeloma in 2014. Because of the advancement in diagnostic studies and update in the IMWG criteria for MM, patients who were previously identified as smoldering multiple myeloma (SMM) are now considered to have multiple myeloma (MM) and are started on therapy. As emphasis on stratification for high-risk SMM surges, emerging data has supported inclusion of genomic analysis and biomarkers reflective of disease biology in the clinical management of plasma cell disorders as signatures associated with high-risk SMM may likely impact disease risk and clinical outcomes. Justification for new standard criteria and inclusion of genomic analysis were absolutely necessary as data showing early intervention in high-risk SMM patients can extend survival emerged. Such emerging data has raised the question of when exactly should treatment for plasma cell dyscrasias be initiated. Presently, observation for high-risk smoldering individuals remains the standard of care, although, outcomes continue to be evaluated and individuals with high risk smoldering can be recommended for clinical trials that challenge the current management of SMM. Newer clinical trials continue to emerge suggesting that alternatively, early treatment for individuals with SMM leads to improved outcomes. This review will provide fundamental information for clinicians in defining MGUS, SMM, and MM, discussing prognostic indicators and risk profiling, and evaluating outcomes for early treatment in SMM patients.

Keywords: Smoldering multiple myeloma; Fluorescent in situ hybridization

Introduction

Multiple Myeloma (MM) represents 1.6% of all new cancer cases in the United States. In 2015, there will be an estimated 26, 850 new cases of MM and approximately 11,240 people will die of the disease. Although a rare disease, MM is more common in men than women and among Blacks compared to Caucasians. The number of new cases of myeloma was 6.3 per 100,000 men and women per year based on 2008-2012 cases [1]. The incidence of MM has been reported to increase in most studies, but in recent years the incidence has stabilized. In Olmsted County, Minnesota, the rate was 4.6/100,000 in 1945-2001. Regression analysis of Olmsted County age- and sex-adjusted incidence rates during 3-year periods showed no statistically significant trend during the 56-year span [2]. The factor primarily responsible for the apparent increase in incidence and mortality rates among patients with MM in many studies is improved case ascertainment, especially among the elderly [3].

As rarity in plasma cell disorders persist, management of these diseases has been a challenge for clinicians [4]. The definition of plasma cell disorders was first characterized in 1980, although a greater understanding of the pathophysiology of the disease has been seen within the last decade. Robert Kyle first characterized smoldering multiple myeloma (SMM) in a landmark publication where records of Mayo Clinic patients with the diagnosis of multiple myeloma were reviewed before January 1, 1974 with follow up for at least five years or more. Six out of 334 cases fulfilled criteria for the diagnosis of MM but no end-organ damage (hypercalcemia, renal insufficiency, anemia, or skeletal lesions) was identified. Multiple myeloma did not develop in any of the six patients during the given period of follow up [5].

The definitions of smoldering multiple myeloma and MM were eventually formalized by the IMWG in 2003 [6]. Historically, the disease definition of MM was clinicopathological, needing overt clinical manifestations of serious end-organ damage before diagnosis could be made. In contrast, SMM patients were asymptomatic with no evidence of end-organ damage. This problem superimposed that patients could not get early therapy to prevent organ damage, which prevented any attempts at cancer treatment at an early stage when in its most susceptible microenvironment-dependent state [6]. The 2003 IMWG criteria were acceptable in an era of restricted treatment options with substantial toxic effects and studies did not show any apparent clinical benefit from early intervention. In 2014, The International Myeloma Working Group (IMWG) updated the criteria for diagnosis of Multiple Myeloma [7]. Advances in laboratory and imaging techniques called for an update on factors that were regarded as meeting the criteria for CRAB features. As diagnostic tests and treatment modalities have greatly improved, justification for a new standard criteria were absolutely necessary as data showing early intervention in high-risk asymptomatic or SMM patients can extend survival emerged [4,7]. Such emerging data has raised the

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Table 1: Criteria for plasma cell disorders [7].

Plasma Cell Disorder	Criteria	Progression Rate	Recommendations for Plan of Care
MGUS (Monoclonal gammopathy of undetermined significance)	-Monoclonal protein < 30g/L, -Clonal bone marrow plasma cells 5-10% -Absence of CRAB C7criteria- hypercalcemia, renal failure, anemia, bone lesions	0.5-1.5% per year	Follow up every 6 months with blood work including – CBC/CMP +Phos LDH Beta-2 Microglobulin Serum Protein Electrophoresis Serum Immunofixation Serum Free Light Chains IgG/IgA/IgM If WNL for 1 year, follow up annually PET-CT or MRI specific prn with symptoms of bone pain
SMM (Smoldering Multiple Myeloma)	-Monoclonal protein (IgG or IgA) >30g/L AND/ OR -Clonal bone marrow plasma cells 10 - 60% -Absence of CRAB criteria- hypercalcemia, renal failure, anemia, bone lesions	-10% per year for the 1st 5 years -3% per year for the next 5 years -1%-2% per year for the next 10 years	Follow up every 3 months with blood work including – CBC/CMP +Phos LDH Beta-2 Microglobulin Serum Protein Electrophoresis Serum Immunofixation Serum Free Light Chains IgG/IgA/IgM If WNL for 1 year, follow up annually PET-CT or MRI specific prn with symptoms of bone pain
MM (Multiple Myeloma)	Clonal bone marrow plasma cells ≥10% OR Biopsy-proven bony or extramedullary plasmacytoma AND -Any one or more of the following: Myeloma defining events: -Presence of any of the following referred from CRAB criteria- Hypercalcemia: serum calcium >0·25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2·75 mmol/L (>11 mg/dL) Renal insufficiency: creatinine clearance <40 mL per min or serum creatinine>177 μmol/L (>2 mg/dL) Anemia: hemoglobin value of >20 g/L below the lower limit of normal, or a hemoglobin value <100 g/L Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT Any one or more of the following biomarkers of malignancy: -Clonal bone marrow plasma cell percentage ≥60% -Involved: uninvolved serum free light chain ratio ≥100 >1 focal lesions on MRI studies	N/A	Treatment recommended

question of when exactly should treatment for plasma cell dyscrasias be initiated. This review will provide fundamental information for clinicians in defining plasma cell disorders of MGUS, SMM, and MM, extrapolating on prognostic indicators and risk profiling, and evaluating treatment initiation for SMM.

Defining plasma cell disorders MGUS, SMM, MM

Monoclonal gammopathy of undetermined significance (MGUS) is a condition in which a monoclonal protein (m protein) produced by plasma cells is found in blood, commonly detected by serum protein electrophoresis. MGUS is usually benign, although has been known to be associated with inflammatory or infectious disease states or, in some occasions, progression to myeloma. MGUS is present in approximately 3-4% of individuals over the age of 50 years [8]. The diagnosis of MGUS is confirmed once the absence of features that can be attributed to a malignant disease is ruled out including an m protein <30 g/L, clonal bone marrow plasma cells 5-10%, and absence of symptoms referred to in the CRAB criteria - absence of hypercalcemia, renal failure, anemia, and bone lesions [7] (Table 1).

Smoldering multiple myeloma (SMM) or asymptomatic multiple myeloma is a condition in which an increased level of m protein and/or an increased percentage of clonal bone marrow plasma cells are detected in the absence of myeloma defining events. The diagnosis of SMM is confirmed with an m protein >30 g/L and/or clonal bone marrow plasma cells 10-60%, and absence of symptoms in the CRAB criteria [7] (Table 1). The risk of progression to malignant disease is higher in smoldering multiple myeloma, approximating 10% per year [9].

Multiple Myeloma is a condition in which plasma cells are malignant and release a higher amount of m protein, which deposit into different parts of the body, usually affecting the kidneys and bones and ultimately causing end organ damage. MM is confirmed in the presence of an m protein or clonal bone marrow plasma cells >10%, and the presence of symptoms referred to in the CRAB criteria - hypercalcemia, renal failure, anemia, and bone lesions. As part of the

Table 2: SMM risk models for progression of disease.

Study	Risk Model Factors	Number of Risk Factors	Risk Category	5 year Risk to Progression
MAYO CLINIC [22]	-Monoclonalprotein < 30g/L -Clonal bone marrow plasma cells ≥10% -FLC Ratio <0.125 or >8	1 out of 3 2 out of 3 3 out of 3	Low Intermediate High	25% 51% 76%
SPANISHGROUP (PETHEMA) [23]	Immunoparesis Clonal bone marrow plasma cells ≥95%	0 out of 2 1 out of 2 2 out of 2	Low Intermediate High	4% 46% 72%
Other features	**References**	**n/Total n**	**Median Time To Progression**	
BMPC ≥60%	[25]	21/655	• Median TTP = 7 months (95% CI, 1.0-12.9)	
SERUM INVOLVED/UNINVOLVED FLC ≥100	[26]	Jul-96	• Median TTP = 8 months	
PROGRESSIVE LESIONS ON WHOLE-BODY MRI	[28]	31/63	• Median TTP from second MRI = 9 months (95% CI, 7-36)	
>1 FL ON WHOLE-BODY MRI	[29]	23/149	• Median PFS of >1 FL= 13 months	
EVOLVING TYPE OF SMM	[30]	22/53	• Median TTP of evolving type= 16 months	
GEP70RISK SCORE > −0.26	[17]	31/87	• 24-month TTP estimate= 51.2%	
APCS ≥95%	[23]	56/93	• Median TTP of ≥95% aPCs= 34 months	
T(4;14) OR DEL 17P OR +1Q21	[16]	88/248	Adverse prognosis • del(17p13) median TTP= 2.04 years • t(4,14) median TTP= 2.91 years • +1q21 median TTP= 3.86 years	
	[15]	44/351	Median TTP • t(4,14) was 28 months • Deletion 17p was 24 months	

updated 2014 IMWG diagnostic criteria, MM can also be confirmed by clonal bone marrow plasma cell percentage of >60% or serum free light chain ratio >100 or >1 focal lesion on MRI studies [7] (Table 1).

Clonal heterogeneity of plasma cell disorders

The spectrum of plasma cell disorders are characterized by multiple clones of neoplastic plasma cells harboring various molecular genetic aberrations that likely signify prognostic value and clinical course. Chromosome ploidy status and immunoglobulin heavy chain (IgH) rearrangements are two older conventional genetic classifications used to stratify patients into prognostic groups and can be evaluated by karyotyping, fluorescence in situ hybridization (FISH), and molecular profiling techniques. Hyperdiploidcytogenetics are often associated with better prognostic outcome. Individuals considered high-risk with poorer prognosis are found to be hypodiploid, t(4;14) (p16;q32) or t(14;16)(q32;q23) [10,11]. Genetic mutations can often co-exist together with higher prevalence. For instance, t(4;14) has also been associated with a high prevalence of chromosome 13 monosomy [12]. Interestingly, specific mutations, such as IgH gene rearrangements and chromosome aberrations may span the spectrum of plasma cell disorders from early MGUS to symptomatic MM, differing in frequency and occurrence rates as one transitions from early to late disease [13,14]. Although still speculative, it is generally understood that specific early mutations likely dominate early multiple myeloma pathogenesis, while secondary aberrations occur later and are involved in later disease states such as relapsed/refractory MM or plasma cell leukemia. With disease progression comes further proliferation of secondary chromosome aberrations or expansion of more aggressive clones. These secondary aberrations can involve MYC rearrangements, del(13q), del(17p), and deletion of 1p and/or amplification of 1q. Of these anomalies, del(17p) and t(4,14) has been associated with an increased risk of SMM transforming to symptomatic MM, conferring high risk and aggressive disease [15,16].

A prospective, observational clinical trial (n=331) by Dhodapker and colleagues, which analyzed data from MGUS and SMM patients reports that all major gene expression profile (GEP) molecular subtypes of MM are usually already present in the precursor stages [17]. Dhodapker, et al. suggests that the molecular heterogeneity of MM is established early in the course of the disease and absence of these factors in SMM patients predicted low risk of progression, similar to MGUS. In comparison with MGUS, the SMM cohort had a higher proportion of patients with GEP signatures of high risk. Thus, it is essential to recognize the mixed clonal heterogeneity of plasma cell disorders, specifically in SMM patients, which conceivably have a huge impact on clinical outcomes, especially if untreated or treated later on. For instance, in Korde and colleagues' clinical and correlative pilot study at the National Institutes of Health Clinical Center, patients with newly diagnosed MM (NDMM) or high-risk SMM were enrolled to assess the safety and efficacy of carfilzomib-lenalidomide-dexamethasone therapy [18]. The study was limited with small numbers, but deeper responses were observed in patients with high-risk SMM than in patients with NDMM. Although additional studies are needed to determine whether deeper responses in high-risk SMM translate into a clinical benefit beyond waiting to treat after symptom development and that cross trial comparisons should be viewed cautiously, observed conclusions are that high rates of deep response (CR and MRD- negativity) in patients with SMM are confirmed and expand on prior CRd results, including those from NDMM and patients with relapsed or refractory disease. Overall, therapeutic regulation of disease burden, clonal evolution, and tumor microenvironment in SMM still remains to be completely understood, but the data demonstrates that signatures associated with high-risk MM may likely impact disease risk and possibly clinical outcomes. Data ultimately supports inclusion of genomic analysis and biomarkers reflective of disease biology in the clinical management of plasma cell disorders [19].

Risks for progression of disease to multiple myeloma

Multiple Myeloma is almost always preceded by an asymptomatic

Table 3: Clinical trials for smoldering multiple myeloma.

Identifier	Phase	Title	Therapy	Status	Allotted Enrollment	Dates	
NCT00480363	3	QUIREDEX: Revlimid (Lenalidomide) and Dexamethasone (ReDex) Treatment Versus Observation in Patients With Smoldering Multiple Myeloma With High Risk of Progression (QUIREDEX)	Lenalidomide & Dexamethasone	Completed	n=120	Start Completion	May 2007 July 2013
NCT01572480	2	Carfilzomib, Lenalidomide, and Dexamethasone for Smoldering Multiple Myeloma	Carfilzomib, Lenalidomide, & Dexamethasone	Active Not Recruiting	n=18	Start Completion	March 2012 Sept 2018
NCT01965834	2	Phase II study to evaluate fenofibrate therapy in patients with smoldering or symptomatic multiple myeloma	Fenofibrate	Active Not Recruiting	n=30	Start Completion	March 2012 March 2017
NCT02316106	2	A study to evaluate three dose schedules of daratumumab in participants with smoldering multiple myeloma	Daratumumab	Recruiting	n=120	Start Completion	May 2015 Nov 2020
NCT02415413	2	Carfilzomib in treatment patients under 65 years with high-risk smoldering multiple myeloma	CRd induction, high dose melphalan with transplant, CRd consolidation and Rd maintenance.	Recruiting	n=90	Start Completion	May 2015 May 2020
NCT02279394	2	Trial of combination of elotuzumab & lenalidomide +/− dexamethasone in high-risk smoldering multiple myeloma	Elotuzumab	Recruiting	n=82	Start Completion	Dec 2014 Oct 2023
NCT01169337	3	Lenalidomide or observation in treating patients with asymptomatic high-risk smoldering multiple myeloma	Lenalidomide	Recruiting	n=224	Start Completion	Oct 2010 July 2026
NCT02492750	1/2	Lenalidomide and dexamethasone with or without anakinra in treating patients with early stage multiple myeloma	Lenalidomide, Dexamethasone, and Anakinra.	Recruiting	n=120	Start Completion	April 2016 July 2020
NCT02697383	1	Ixazomib (MLN9708) and Dexamethasone in High Risk Smoldering Multiple Myeloma: A Clinical and Correlative Pilot Study	Ixazomib and Dexamethasone	Recruiting	n=14	Start Completion	Feb 2016 Feb 2017

premalignant stage although the specific biological triggers from precursor disease to active disease are still unknown [20]. The risk to progression from MGUS or SMM to MM is affected by several factors including the type of monoclonal protein, the concentration of monoclonal protein or percentage of abnormal plasma cells within the bone marrow, involvement of light chains or the serum free light-chain ratio, proportion of phenotypically clonal plasma cells, and core cytogenetic abnormalities [21]. Depending on the sum and severity of these factors, an individual can be categorized for risk severity to progression by the terms low, intermediate and high risk. Studies on risk modeling by Mayo Clinic [22] and Programa Para El Estudio Y La Terapeutica De Las Hemopatias Malignas (PETHEMA) Spanish group criteria have further defined probability of transformation [23] (Table 2). Despite significant incongruity between the two risk models [24], both studies do take into consideration key factors that contribute to possible malignancy; thus, both models can be utilized as a predictive tool as each may represent various levels of prognostication including tumor biology or deliberation of disease burden [21]. Nevertheless, evaluation of both studies simultaneously has yet to be demonstrated in an all-inclusive multivariate analysis.

Moreover, Neben, et al. [16] and Rajkumar, et al. [15] analyzed chromosomal aberrations on time to progression (TTP) in patients with SMM, specifically 17pdel, t(4,14), and 1qgain. In Neban's, et al. study, the chromosomal abnormalities 1q21, 5p15/5q35, 9q34, 13q14.3, 15q22, 17p13, t(11;14)(q13;q32), and t(4;14)(p16.3;q32) were assessed in CD138-purified myeloma cells by interphase fluorescent in situ hybridization (FISH) alongside clinical parameters in a consecutive series of 248 patients with SMM. The high-risk aberrations in active myeloma (i.e., del(17p13), t(4;14), and +1q21) present in 6.1%, 8.9%, and 29.8% of patients significantly confer adverse prognosis in SMM with hazard ratios (HRs) of 2.90 (95% CI, 1.56 to 5.40), 2.28 (95% CI, 1.33 to 3.91), and 1.66 (95% CI, 1.08 to 2.54), respectively. Neben, et al. concluded that the high-risk chromosomal aberrations del(17p13), t(4;14), and +1q21 are adverse prognostic factors in SMM just as they are in active myeloma [16]. Rajkumar, et al. studied cytogenetic subtypes of patients with SMM (n=351) by FISH and found 154 patients (43.9%) had trisomies, 127 (36.2%) had immunoglobulin heavy chain (IgH) translocations, 14 (4%) both trisomies and IgH translocations, 53 (15.1%) with no abnormalities detected and 3 (0.9%) had monosomy 13/del(13q) in the absence of any other abnormality. Among 127 patients with IgH translocations, 57 were t(11;14), 36 t(4;14), 11 musculoaponeurotic fibrosarcoma (MAF) translocations, and 23 other or unknown IgH translocation partner. Time to progression to MM was significantly shorter in patients with the t(4;14) compared with patients with t(11;14), median 28 versus 55 months, respectively, P=0.025. The median TTP was 28 months with t(4;14) (high-risk), 34 months with trisomies alone (intermediate-risk), 55 months with t(11;14), MAF translocations, other/unknown IgH translocations, monosomy13/del(13q) without other abnormalities, and those with both trisomies and IgH translocations (standard-risk), and not reached in patients with no detectable abnormalities (low-risk), P=0.001. There was also a trend to shorter TTP with deletion 17p (median TTP, 24 months). Overall survival from diagnosis of SMM was significantly inferior

with t(4;14) compared with t(11;14), median 105 versus 147 months, respectively, P=0.036 [15].

Other studies have subsequently identified high risk factors in individuals with SMM (Table 2). Rajkumar and colleagues' study have identified that the median TTP to MM was significantly shorter among the patients with 60% or more bone marrow involvement, as compared with those having less than 60% involvement (P< 0.001) [25]. Progression to myeloma occurred within 2 years of the diagnosis in 95% of the patients with 60% or more bone marrow plasma cells, with a median time to progression of 7 months (95% CI, 1.0 to 12.9). Kastritis, et al. and Larsen, et al. have identified abnormal free FLC ratio as a risk factor for progression to symptomatic myeloma [26,27]. Kastritis, et al. found that TTP was 8 months and Larsen, et al. found that median TTP was 15 months (95% CI, 9-17) with a FLC (involved/uninvolved) ratio ≥100. Merz, et al. and Hillengass, et al. identified progressive lesions on whole-body MRI as a risk factor for progression [28,29]. Merz, et al. reports that focal lesions should be followed serially over time to determine progression potential [28]. Hillengass and colleague's performed a study (n=149) and reported that >1 focal lesions were the strongest adverse prognostic factors for progression (P< .001) therefore recommending use of a whole body MRI for risk stratification of patients with SMM [29]. Rosinol and colleague's study (n=53) recognizes a shorter TTP in patients with evolving SMM, characterized as a progressive increase in serum m protein, a previously recognized MGUS and a significant higher proportion of IgA type. The median TTP in the overall series was 3.2 years and the only feature associated with a shorter time to progression was the evolving versus non-evolving type (1.3 *vs.* 3.9 years respectively, P=0·007) [30]. As aforementioned, Dhodapkar and colleague's study reports that an increased risk score (>-0.26) (based on a validated 70-gene model, GEP-70) was an independent predictor of the risk of progression to MM [17]. Perez-Persona's, et al. study investigated markers for risk of progression in MGUS (n=407) and SMM (n=93) including proportion of bone marrow aberrant plasma cells (aPC) within the bone marrow plasma cells (BMPC) compartment (aPC/BMPC) as assessed by flow cytometry. Patients with a marked predominance of aPCs/BMPC (≥ 95%) at diagnosis displayed a significantly higher risk of progression both in MGUS and SMM (P< .001) [23].

Decision to treat smoldering myeloma

The original study by Kyle, et al. concluded that the overall risk of progression from smoldering multiple myeloma to malignant disease is 10% per year for the next 5 years, 3% per year for the next 5 years and 1%-2% per year for the next 10 years [9]. Cumulative risk of progression for all SMM patients was noted to be 73% at 15 years with median time to progression at 4.8 years [9] (Table 2). However, the risk of progression to myeloma for high risk SMM is even greater, approximating median TTP of 75% in 5 years [21]. Because of the advancement in diagnostic studies and update in the IMWG criteria for MM, patients who were previously identified as SMM are now considered to have MM and are started on therapy sooner than later [7]. Moreover, this raises the question of whether treatment should be adopted for what is considered high-risk SMM. Presently, observation for high-risk smoldering individuals remains the standard of care, although, outcomes continue to be evaluated and individuals with high risk smoldering can be recommended for clinical trials (Table 1). Between 1988 through 2001, clinical studies were inferior in showing significant benefit in treating patients with reason being lack of efficacy and even high toxicities in treatments such as Vincristine, Adriamycin, and dexamethasone (VAD) or melphalan and prednisone (MP) [31-33]. It was in 2001 that Rajkumar's and colleagues study (n=16) explored use of thalidomide and demonstrated a PR in 38% of SMM patients [34]. In 2003, Barlogie, et al. also explored the use of thalidomide and reported a 25% PR in SMM patients [35]. Between 2008 to 2013, various clinical trials emerged exploring other potential agents including bisphosphonates and anakinra. Musto, et al. compared zolendronic acid versus watchful waiting and found a decreased incidence of skeletal related events with those receiving the bisphosphonate (55.5% *vs.* 78.3%; P=0.041) [36]. Lust's, et al. study (n=47) found that 11% of SMM patients taking anakinra achieved a partial response [37]. As more clinical trials continue to emerge, it may possibly become clearer of whether there is truly some significant benefit in early treatment with SMM patients.

Today's emerging therapies

A recent clinical trial challenged the current management of SMM, suggesting that alternatively, early treatment for individuals with SMM does lead to improved outcomes. Mateos and Spanish Myeloma Group from Programa para el Tratamientode Hemopatias Malignas/Group Espanol de Mieloma (PETHEMA/GEM) colleagues conducted a randomized, open-label, phase 3 trial (QUIREDEX) study, randomly assigning patients (n=119) with high-risk smoldering myeloma to treatment or observation [38] (Table 3). Patients in the treatment group received an induction regimen (lenalidomide at a dose of 25 mg per day on days 1 to 21, plus dexamethasone at a dose of 20mg per day on days 1 to 4 and days 12 to 15, at 4-week intervals for nine cycles). This was followed by a maintenance regimen of lenalidomide, 10 mg per day on days 1 to 21 of each 28-day cycle for 2 years. Mateos, et al. concluded that treating high-risk SMM patients with lenalidomide and dexamethasone improves time to disease progression (not reached *vs.* 21 months; hazard ratio [HR], 0.18; P< 0.001) and 3-year overall survival (94% *vs.* 80%; HR, 0.31; P=0.03) compared with watchful waiting. Consequently, it is suggested that early treatment for patients with high-risk smoldering myeloma delays progression to active disease and increases overall survival [38].

A smaller phase II NCI study (n=45), patients either SMM or NDMM received 8, 28-day cycles of Carfilzomib-lenalidomide-dexamethasone (CRd) [18] (Table 3). Carfilzomib was administered intravenously over 30 minutes on days 1, 2, 8, 9, 15, and 16 (starting dose, 20 mg/m^2 on days 1 and 2 of cycle 1; target dose, 36 mg/m^2 thereafter). Lenalidomide 25mg was administered orally on days 2 through 21 of cycle 1 and on days 1 through 21 of cycles 2 through 8. Dexamethasone was administered intravenously or orally on days 1, 2, 8, 9, 15, 16, 22, and 23 (20 mg for cycles 1-4 and 10 mg for cycles 5-8; dexamethasone was not administered on day 1 of cycle 1). Transplant-eligible patients underwent stem cell collection after 4 cycles of CRd treatment and continued with treatment. Over the study period, all 12 SMM patients achieved at least a CR. The median time to CR or sCR was 6 (2-20) cycles for all patients. As previously mentioned, deeper responses were observed in patients with high-risk SMM as in patients with NDMM (at least nCR rate of 100% *vs.* 62%, respectively). CRd therapy demonstrates efficacy in high-risk

SMM with all subjects achieving at least a very good partial response. Among the 28 patients with NDMM and the 12 with SMM achieving at least a nCR, MRD negativity was found in 28 of 28 (100% [95% CI, 88%-100%]), 11 of 12 (92% [95% CI, 62%-100%]) (multiparametric flow cytometry), 14 of 21 (67% [95% CI, 43%-85%]), and 9 of 12 (75% [95% CI, 43%-94%]) (next-generation sequencing), respectively. Korde's, et al. study provides further evidence to support future large-scale trials of tolerable regimens, including autologous stem transplant (NCT02415413), capable of achieving high rates of sustainable MRD-negative responses for SMM patients.

Alternative emerging studies continue to make way in investigating whether established MM treatments are beneficial for SMM patients (Table 3). There are four phase 2 studies currently recruiting patients, including a) evaluation of fenofibrate in patients with SMM (NCT01965834), b) evaluation of three dose schedules of daratumumab (a CD-38 antibody) in participants with SMM (NCT02316106), c) KRd induction, high dose melphalan with transplant, KRd consolidation, and lenalidomide plus dexamethasone consolidation a (NCT02415413), and d) a trial combination of elotuzumab (a monoclonal antibody targeting lymphocytic activation molecule F7) and lenalidomide with or without dexamethasone in high risk SMM patients (NCT02279394) [11]. There is a phase 3 study sponsored by the NCI with either lenalidomide or watchful observation for patients with SMM (NC01169337), and a phase 1/2 study for SMM patients with lenalidomide and dexamethasone with or without anakinra (NCT02492750) [11]. There is also a phase 1 single arm study sponsored by Memorial Sloan Kettering Cancer Center with Ixazomib (an oral proteasome inhibitor) and low dose dexamethasone for patients with high-risk SMM to assess best overall response rate, defined as a partial response or better (NCT02697383).

In addition to the monoclonal antibody trials mentioned above for SMM patients, other evolving and promising therapeutic methods for early treatment in SMM are immunotherapies. Bae and colleagues performed an *ex vivo* study evaluating HLA-A2-specific peptides (heteroclitic XBP1 US, heteroclitic XBP1 SP, native CD138, and native CS1, for their ability to elicit multipeptide-specific cytotoxic T lymphocytes (MP-CTLs) using T cells from SMM patients [32]. From a clinical perspective, this type of immunotherapy could be utilized as a vaccine to prevent progression of disease in SMM patients to symptomatic MM, and may be more effective in earlier disease states before severe immune dysregulation has a taken place. Results demonstrate that MP-CTLs generated from SMM patients' T cells show successful anti-MM responses and increased total $CD3^+CD8^+$ T cells (>80%) and cellular activation ($CD69^+$) within the memory SMM MP-CTL ($CD45RO^+/CD3^+CD8^+$) subset after repeated multipeptide stimulation, suggesting that multipeptide combination has the potential to induce effective and durable memory MP-CTL in SMM patients [39]. Another promising conceptualization of an immunotherapy study involves the *ex vivo* generation of activated T cells specific to a particular antigen known as chimeric antigen receptor cells (CARs) [40]. Currently, CAR T-cell therapy has yet to be investigated in SMM patients.

Conclusion

Clinicians are progressively gaining a better understanding of plasma cell dyscrasia pathophysiology and are grasping the significance of genomic analysis inclusion for risk stratification of high-risk SMM patients. Consequently, clinicians are momentously impacting disease management and outcomes for SMM patients. As data showing early intervention in high-risk SMM patients can extend survival emerges, observation may become obsolete and clinicians may become more inclined to start treatment sooner than later. Whilst newer approaches to MM treatment continue to emerge, in time, the question will be whether those therapies will be beneficial for patients with SMM. Further evaluation is absolutely necessary and it is important to analyze whether the course of action taken will provide patients quality of life with minimal drug toxicity and have a meaningful impact to survival benefit.

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