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REVIEW ARTICLE

Multiple myeloma gammopathies

Changing paradigms in diagnosis and treatment of monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM)

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Abstract

Multiple myeloma (MM) is a highly heterogenous disease that exists along a continuous disease spectrum starting with premalignant conditions monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM) that inevitably precede MM. Over the past two decades, significant progress has been made in the genetic characterization and risk stratification of precursor plasma cell disorders. Indeed, the clinical introduction of highly effective and well-tolerated drugs begs the question: would earlier therapeutic intervention with novel therapies in MGUS and SMM patients alter natural history, providing a potential curative option? In this review, we discuss the epidemiology of MGUS and SMM and current models for risk stratification that predict MGUS and SMM progression to MM. We further discuss genetic heterogeneity and clonal evolution in MM and the interplay between tumor cells and the bone marrow (BM) microenvironment. Finally, we provide an overview of the current recommendations for the management of MGUS and SMM and discuss the open controversies in the field in light of promising results from early intervention clinical trials.

Introduction

Multiple myeloma (MM) is a plasma cell neoplasm that arises from the malignant transformation of antigen-stimulated, post-germinal center, and terminally differentiated long-lived plasma cells in the bone marrow (BM) [1]. Almost all cases of MM arise from an asymptomatic, premalignant condition known as monoclonal gammopathy of undetermined significance (MGUS) [2]. MGUS is defined by a serum non-IgM-type monoclonal protein of <3 g/dL (typically non-IgM-type), <10% clonal BM plasma cells, and the absence of end-organ damage (Fig. 1) [3]. MGUS may progress to another asymptomatic, but more advanced premalignant stage known as smoldering multiple myeloma (SMM) [4]. SMM is defined by a serum monoclonal protein (typically IgG or IgA) of ≥3 g/dL or urinary monoclonal protein ≥500 mg per 24 h, and/or 10–60% clonal BM plasma cells (Fig. 1) [3]. A diagnosis of active MM requires the presence of one of one of more myeloma-defining events which include (1) end-organ damage (i.e. CRAB features: hyperCalcemia, Renal failure, Anemia, lytic Bone lesions), (2) ≥60% clonal plasma cells in BM, involved-to-uninvolved serum free light-chain (FLC) ratio ≥100, and (3) >1 focal lesion on MRI. In addition to myeloma-defining events there must be associated clonal BM plasma cells >10% and/or biopsy proven bony or extramedullary plasmacytoma (Fig. 1) [3].

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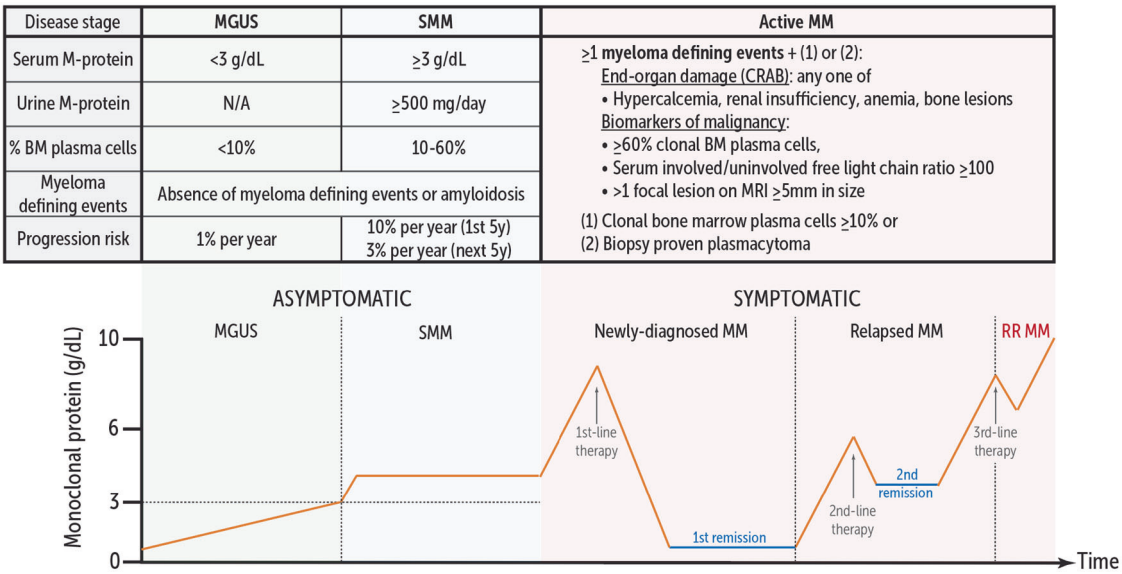

Fig. 1 Clinical model of disease progression in MM: the IMWG diagnostic criteria. MM arises from an asymptomatic precursor disease MGUS which is characterized clinically by low tumor burden (M-protein <3 g/dL, %BMPC < 10%) and a risk of progression to symptomatic MM of about 1% per year. As tumor burden increases beyond a threshold (M-protein ≥3 g/dL, %BMPC 10–60%), the disease progresses to SMM, another asymptomatic disease state prognostically distinct from MGUS based on its risk of progression of about 10% per year for the first 5 years, 3% per year for the next 5 years, and 1% per year thereafter. Symptomatic MM is diagnosed when the patient develops ≥1 myeloma-defining events and BMPC ≥ 10% or biopsy proven plasmacytoma. MM is incurable as patients progressively acquire resistance to therapy progressing through different line of treatment and eventually die.

Epidemiology of MM and precursor diseases

MGUS

The overall prevalence of MGUS has been estimated at 2.4% [5]. The median age of MGUS diagnosis is 70 years and <2% of patients with MGUS are <40 years old signifying that MGUS is predominantly a disease of the elderly [6, 7]. The age-adjusted prevalence of MGUS is highest in the black population (0.99%), followed by Mexican Americans (0.55%), and lowest in whites (0.21%) [6]. Aside from age and race, other risk factors for the development of MGUS include hereditary factors (increased risk of MGUS in first-degree relatives of patients with MGUS) [8], male sex (twofolds higher risk) [9], immunocompromised state (e.g., HIV patients, posttransplant immunosuppression) [10], occupational exposure to toxins such as asbestos, fertilizers and pesticides, aromatic hydrocarbons, mineral oils, petroleum, and paint [11], as well as cigarette smoking [6]. Interestingly, while neither diabetes nor obesity were found to be associated with the development of MGUS, two independent studies reported that metformin therapy among diabetes patients protected against MGUS transformation to MM [12, 13]. It is possible that metformin's anti-MM effect might have more to do with its ability to induce autophagy through the inhibition of STAT3 and BCL-2 rather than its antihyperglycemic activity [14].

Monoclonal gammopathy of clinical significance (MGCS) and monoclonal gammopathy of renal significance (MGRS)

The concept of MGCS was recently accepted by consensus to describe a group of monoclonal gammopathies that do not meet the diagnostic criteria for symptomatic MM but can be differentiated from MGUS/SMM due to specific clinical manifestations and paraprotein-related organ damage [15]. These manifestations result from the (1) deposition of monoclonal light and/or heavy chain immunoglobulin (MIg) (e.g., AL amyloidosis, type I cryoglobulinemia, MIg deposition disease, acquired Fanconi syndrome), (2) autoantibody activity of MIg (e.g., type II mixed cryoglobulinemia, cold agglutinin disease, C1 inhibitor deficiency angioedema, IgM-associated peripheral neuropathy), (3) activation of the alternative complement pathway (e.g., C3 glomerulonephritis, complement-mediated thrombotic microangiopathy), (4) secretion of cytokines (e.g., POEMS syndrome), (5) selective adsorption of proteins (e.g., von Willebrand factor, factor X) by clonal plasma cells of amyloid fibrils, and/or (6) other unknown mechanisms (e.g., Schnitzer syndrome, scleroderma, and TEMPI syndrome) [15]. Unlike asymptomatic MGUS, patients with MGCS have evidence of organ damage and early recognition and diagnosis is paramount, as prompt treatment is generally indicated to preserve organ function [15].

Separately, the International Kidney and Monoclonal Gammopathy Research Group (IKMG) introduced the concept of MGRS in 2012 (and refined it in 2017) to describe monoclonal gammopathies that produce nephrotoxic MIg that do not meet defined hematologic criteria for treatment of a specific malignancy [16]. MGRS includes monoclonal gammopathies (MGUS, SMM, Waldenstrom's macroglobulinemia, monoclonal B cell lymphocytosis, low-grade CLL, and low-grade B cell non-Hodgkin lymphoma (NHL)) that are associated with a spectrum of kidney lesions including organized or non-organized deposition of monoclonal light and/or heavy chain immunoglobulin [17–20]. An important exception is light-chain cast nephropathy that is the only form of renal damage considered as a myeloma-defining event by the IMWG and prompting a diagnosis of active MM [21].

SMM

SMM was first defined by Kyle and Greipp in 1980 to describe a group of six patients who despite fulfilling the laboratory criteria for MM, did not have evidence of end-organ damage [22]. On the other end of the spectrum, SMM is differentiated from MGUS by a much higher risk of progression to MM [23]. A consensus definition for SMM was developed by the International Myeloma Working Group (IMWG) in 2003; 23 years after SMM was first described [24]. This delay was largely due to the paucity of therapies that were both effective and well-tolerated in MM, resulting in the recommendation of watchful waiting approach until symptomatic disease developed in patients with SMM [25]. The 2003 IMWG criteria defined SMM as either the presence of serum M-protein ≥3 g/dL or ≥10% monoclonal plasma cells within the BM in the absence of end-organ (CRAB criteria) damage [26]. In 2010 the IMWG refined the criteria for the diagnosis of SMM/MM [3]. Specifically, the category of ultra-high risk SMM (defined by serum free light-chain (sFLC) ratio ≥100, ≥60% BM plasma cells, or ≥2 focal BM lesions in the skeleton based on MRI) was recognized to identify patients who carry a risk of progression at 2 years of ≥80% and for whom cytoreductive treatment may be warranted to avoid impending organ damage [3]. Based on the revised IMWG criteria of 2014, ultra-high risk SMM are currently considered to have active MM and treatment is recommended.

The actual prevalence of SMM is not well-defined due to the difficulty in acquiring epidemiological data stemming from lack of population-based disease registries, paucity of epidemiologic studies resulting from the lack of International Classification of Diseases (ICD) codes differentiating SMM from active MM, as well as recent changes to the diagnostic criteria of SMM. However, studies show that ~8–20% of patients carrying a diagnosis of MM actually have SMM [27–29]. Based on these studies, the incidence of SMM can be estimated at 0.4–0.9 cases per 100,000 persons [27–29]. Using the National Cancer Database (NCDB) and defining SMM as patients with ICD-O-9732 (plasma cell myeloma) who were either placed on active surveillance or did not receive any therapy in the first 3 months following diagnosis, Vuyyala et al. estimated that SMM made up 17.1% of patients with MM identified between 2010 and 2014 [30]. The same study reported that the black population had an earlier age of diagnosis of SMM (median age of diagnosis 66 years in blacks compared to 70 years in whites) [30]. The rate of progression from SMM to MM was also found to be higher in the black population compared to whites and also higher in younger SMM patients compared to older patients [30].

MM

MM accounts for 1% of all cancers and 10% of all hematologic malignancies, making it the second most common blood cancer behind non-Hodgkin lymphoma (NHL). Epidemiological studies estimate the worldwide 5-year prevalence of MM at ~230,000 patients [31]. The age-standardized incidence rate of MM in the United States is ~6.9 per 100,000 persons (SEER), or about 30,000 new diagnoses each year [3, 32]. Predominantly a disease of the elderly, the median age of patients at diagnosis of MM is 66–70 years, with 37% of patients under 65 years and 0.02–0.3% under 30 years [33, 34]. Similar to its precursor states (MGUS and SMM), there is marked racial disparity in the incidence and age of onset of MM, which suggests that racial heterogeneity is present early in myeloma tumorigenesis and carries through disease progression [6, 35]. Specifically, African-Americans are twice as likely to have MM compared to their white counterparts and this disparity is even greater in the under 40-year-old age group (more than threefold excess risk) [24]. The median age of diagnosis of MM is 4 years younger for blacks (66 years) compared with whites (70 years) [24]. The risk of progression to MM from MGUS, however, is the same between blacks and whites [36]. The increased incidence and younger age of diagnosis of MM in blacks therefore likely reflects the higher prevalence of MGUS [5, 37, 38].

Models of progression from MGUS and SMM to MM

Clinical model of progression

The clinical model of MGUS progression to SMM, based around the IMWG diagnostic criteria, is largely determined by arbitrary cutoffs for serum M-protein concentration of

Table 1 Primary cytogenetic abnormalities. The table below summarizes the cytogenetic abnormalities that occur early in the disease course that underlie transformation of a normal post-germinal center plasma cell into a premalignant plasma cell clone.

Abnormality	Gene(s)/chromosomes affected	Frequency (%)		Implications in SMM		Ref.
		In MGUS	In MM	Progression risk	Median TTP	
Hyperdiploidy: Trisomy(ies) without IgH abnormality	Trisomy of odd-numbered chromosomes (but not chromosomes 1, 13, 21)	50[a]	55[a]	Intermediate	3 years	[94, 95]
IgH-translocations						
• t(11;14)	*CCND1*	12[a]	19[a]	Standard	5 years	
• t(4;14)	*FGFR-3* and *MMSET*	9[a]	13[a]	High	2 years	
• t(14;16)	*C-MAF*	3[a]	4[a]	Standard	5 years	
• t(14;20)	*MAFB*	3[a]	1[a]	Standard	5 years	
• t(6;14)	*CCND3*	0[a]	1[a]	Standard	5 years	
IgH translocations with trisomy(ies)			15[b]	Standard	5 years	
Isolated monosomy 14			4.5[b]	Standard	5 years	
Other cytogenetic abnormalities in absence of (1) IgH translocations, (2) trisomy(ies), or (3) monosomy 14			5.5[b]			
Normal	NA		3[b]	Low	7–10 years	

[a]Data obtained from van Nieuwenhuijzen et al. [94].

[b]Data obtained from Rajan and Rajkumar [95].

3.0 g/dL, urine M-protein concentration of 500 mg/day, and BM plasmacytosis of 10% (Fig. 1) [3]. SMM is therefore currently defined based on arbitrary thresholds of clonal burden instead of reflecting specific genetic/biological characteristics [39]. In spite of this, studies have shown that a majority of patients with asymptomatic myeloma who met these cutoffs (classified as SMM) had greater risks of progressing to MM in the short term when compared to patients who did not (classified as MGUS) [39]. Specifically, about 30% of patients meeting the criteria for SMM progress in the first 2 years, 20% in the ensuing 3 years, and a further 20% in the following 5 years vs. a fixed risk of ~1% per year in MGUS [4, 7, 40, 41]. However, for the remaining 30% of patients with SMM who do not progress after 10 years, the progression risk decreases to about 1% per year (similar to MGUS). In essence, this tells us that a "malignant switch" of clonal plasma cells has most likely occurred in the 70% of SMM that progressed and the time to progression (TTP) reflects the accumulation of disease burden beyond a tipping point. However, this also tells us that the remaining 30% of patients that fulfill the criteria for SMM based on clonal burden have the same risk of progression as MGUS and are, in every practical sense, in fact MGUS (i.e., a clonal proliferation of "benign" plasma cells) [39]. This highlights the limitations of a clinical model of progression and points out the importance of pursuing a molecular model of progression where MGUS, SMM, and MM are defined by distinct molecular characteristics instead of arbitrary clinical criteria reflecting tumor burden.

Molecular model of progression

Several challenges exist when studying the genetic changes underlying progression of asymptomatic to symptomatic MM. First is the paucity of paired samples at diagnosis and progression. Next, unlike other hematological malignancies such as acute myeloid leukemia (AML) that are usually characterized by low genome complexity, MM and to a lesser extent MGUS and SMM have highly complex and heterogenous genomic landscapes [42–46]. As a result, targeted and/or exome-based approaches, which are able to characterize mutations and have worked well for studying AML, are inadequate to fully identify whole-genome duplication events and key structural variations (e.g., translocations, copy number abnormalities (CNAs)), that occur as a result of chromothripsis, chromoplexy, and templated insertions, which are major drivers of MM progression [43, 46]. For example, cytogenetic studies show that trisomies and/or 14q32 IGH chromosomal translocations are the main myeloma initiating events (observed in almost 100% of precursor MM cells) that underlie the transformation of normal plasma cells to MGUS (Table 1), while CNAs and/or IGH translocations represent secondary cytogenetic abnormalities that contribute to progression from MGUS/SMM to MM (Table 2) [47]. Conversely,

Table 2 Secondary cytogenetic abnormalities. The table below summarizes the cytogenetic abnormalities that occur later in the disease course that underlie malignant transformation and progression of premalignant MGUS/SMM to MM.

Abnormality	Gene(s) affected	Frequency (%)		Ref.
		In MGUS	In MM	
Gains				[94, 96]
• 1q	*CKS1B* and *ANP32E*	25[a]	50[a]	
• 12p	*LTBR*			
• 17q	*NIK*			
Deletions				
• 1p	*CDKN2C, FAF1, and FAM46C*	6[a]	40[a]	
• 6q			33[b]	
• 8p			25[b]	
• 11q	*BIRC2* and *BIRC3*	7[a]	7[a]	
• 13	*RB1* and *DIS3*	30[a]	70[a]	
• 14q	*TRAF3*		38[b]	
• 16q	*CYLD* and *WWOX*		35[b]	
• 17p	*TP53*	1[a]	12[a]	
Translocations				
• t(8;14)	*MYC*	3–4[a]	20[a]	
• t(4;14)	*FGFR-3* and *MMSET*			
• t(14;16)	*C-MAF*			
• t(14;20)	*MAFB*			
• Other non-IGH@ translocations				
Oncogenic pathways				
• MAPK activation	*NRAS*	36[a]	33[a]	
	KRAS	<1[a]	33[a]	
	BRAF	27[a]	19[a]	
• MYC dysregulation	*MYC*	<1[a]	67[a]	
• Constitutive NFKB activation	*TRAF6, CYLD*	<1[a]	20[a]	

[a]Data obtained from van Nieuwenhuijzen et al. [94].

[b]Data obtained from Morgan et al. [96].

attempts at characterizing the landscape of secondary mutations in MM show a lower prevalence of these mutations in MGUS/SMM compared with MM [45, 46, 48–50]. This suggest that these mutations are likely to contribute to MGUS/SMM progression to MM.

More recently, the use of whole-genome sequencing (which enables detection of structural variants and complex genomic aberrations) to characterize 67 MM genomes serially collected from 30 patients showed that chromothripsis and cycles of templated insertions were mostly clonal and conserved during evolution, suggesting that they play a key role in the early stages of myelomagenesis [51]. On the other hand, events such as chromoplexy, whole-genome duplication, and focal deletions on oncogenes were picked up later in the disease stage, suggesting that these are potentially involved with relapse and drug resistance [51]. The whole-genome analysis of ten-paired samples from non-high-risk SMM cases that progressed to MM revealed two different models of progression based on gene mutations, translocations, CNAs, and mutational signatures [52]. The first model, termed "static progression", is one in which the same subclonal architecture in smoldering disease was retained as patients progressed to MM. In this model, the SMM clone is genomically indistinguishable (and essentially is) MM, suggesting that TTP, which was found to be generally less than a year, solely reflects the time taken for sufficient accumulation of tumor burden to cause symptomatic disease [52]. The other model, coined "spontaneous evolution", is one in which SMM progression to MM requires the stochastic acquisition of new mutations [52]. Consistent with this, patients in the spontaneous evolution group had a longer TTP [52].

Limitations of genomics research: the role of the BM microenvironment in MM pathogenesis

One limitation of the current state of genomics research in myeloma is that the majority of studies focus only on MM cells, which unfortunately does not provide sufficient insight into the complex role the BM microenvironment plays in MM. Similar to long-lived plasma cells which are the physiological counterparts of MM cells, MM relies on the BM microenvironment for survival [43]. The cancer-naive niche is suboptimal for MM growth and studies show that BM stromal cells (BMSCs) derived from patients with MM are able to promote the proliferation of myeloma stem cells to a greater extent when compared to healthy donor BMSCs. Indeed, studies in solid cancers show that cancer cells are able to induce phenotypic changes in the microenvironment to prepare premetastatic niches conducive for metastatic spread, highlighting the reciprocal relationship between cancer and the microenvironment [53, 54]. Overall, the BM microenvironment exerts a selective pressure that promotes the expansion of subclones with selective advantage and facilitate their progression to symptomatic disease whilst simultaneously limiting the expansion of subclones that are unable to adapt to the microenvironment [55–57]. In addition, the ability to avoid immune destruction is necessary for the accumulation of tumor burden [58]. In the context of MM, the immunosuppressive BM microenvironment plays a key role in determining whether an

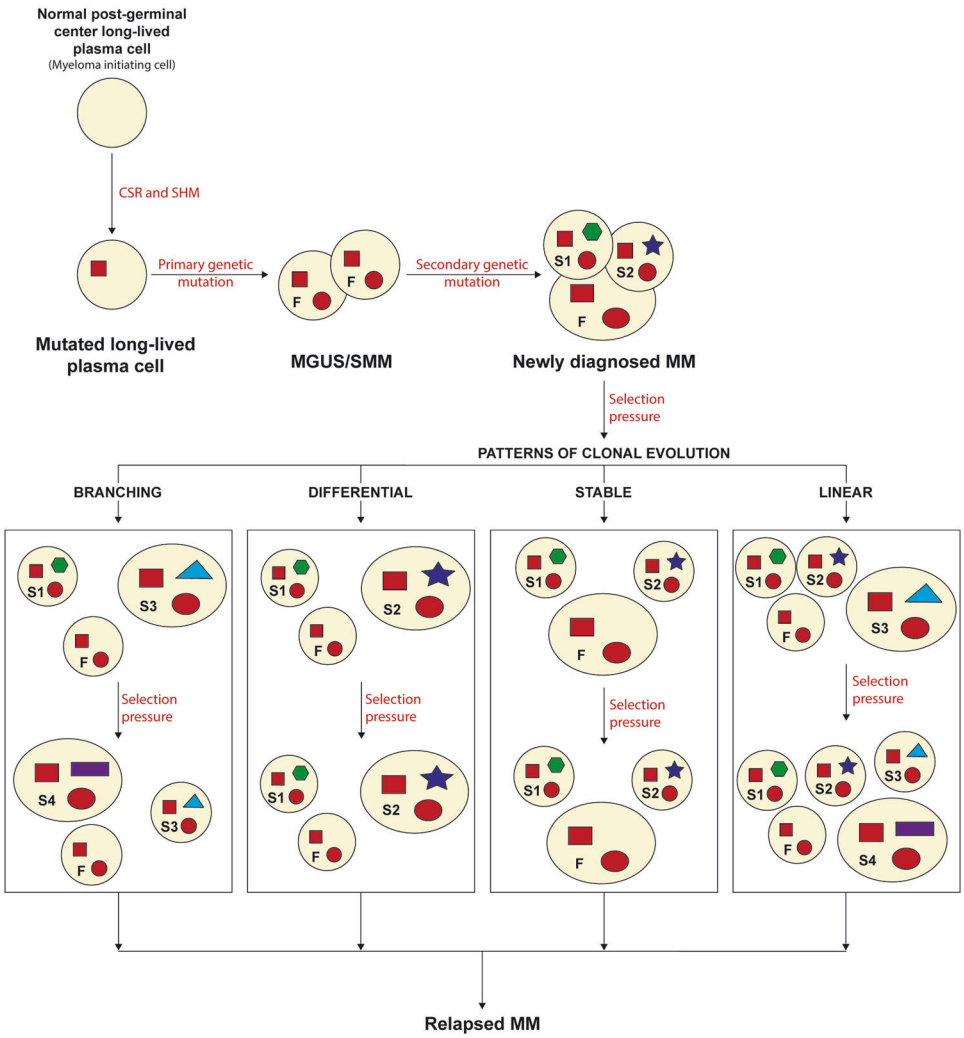

Fig. 2 Clonal model of disease progression in MM. The myeloma founder clone (F) arises due to an initial genetic event (red square and circle) (i.e., class switch recombination, somatic hypermutation, and primary cytogenetic abnormalities). In the BM, the founder clone (F) acquires further mutations (green hexagon and blue star) to evolve to MM. Selective pressure within the BM microenvironment results in clonal evolution which may follow branching, differential, stable, or linear patterns. The founder clone (F) and 4 subclones (S1–S4) are representative of MM clonal heterogeneity. All subclones share some mutations (red circle and square) with the founder clone.

individual with MGUS/SMM remains stable at the precursor disease state or progresses to MM [59, 60]. A cross-sectional study demonstrated that a higher percentage of MGUS patients with immunosuppression (defined as ≥1 suppressed uninvolved immunoglobulins) progressed to MM when compared to those without immunosuppression (58% vs. 20%). In addition, 54% of patients with light-chain MGUS who progressed had immunosuppression, whereas only 12% of those without progression were immunosuppressed [60]. A more in-depth discussion on the role of the BM milieu in MM progression can be found in a recent review by Ho et al. [57].

Clonal model of progression

At the cellular level, MM begins with the immortalization of a post-germinal long-lived plasma cell that subsequently homes to the BM [43, 61, 62]. As the disease progresses, four different patterns of clonal evolution have been observed: (1) branching, (2), differential, (3) stable, and (4) linear (Fig. 2) [49]. In the branching and linear models, further "driver mutations" are acquired which lead to genomic heterogeneity and changes in subclonal dominance; a reflection of the ability of myeloma to dynamically adapt to different microenvironments (Fig. 2) [63–67]. Distinguishing between branching and linear evolution may have therapeutic implications. Specifically, in linear models, targeting a genetic lesion would be effective in killing off all cells derived from that point. In branching evolution models, therapeutic success hinges on targeting early clonal lesions instead of late subclonal events. On the other hand, stable evolution is analogous to the "static progression" model of SMM progression discussed earlier. Other models such as neutral evolution, in which natural selection and clonal competition are not key determinants of molecular changes, have not been conclusively shown in a significant number of myeloma cases to date [43]. Nonetheless, once a cell with clonal selective advantage emerges, Pawlyn and Morgan propose that, at earlier disease stages, clonal selective sweep occurs as the BM niches are either available

or amenable to displacement [43]. However, as the disease advances and the BM niche becomes saturated and unable to be competitively replaced, the subclones that are already in situ can restrict the dominance of newly emerging higher-risk subclones. At this stage, Pawlyn and Morgan propose that regional specific evolution occurs resulting in the formation of localized ecosystems (e.g., focal lesions), giving rise to intraclonal diversity[43].

Models of risk stratification in myeloma

Risk stratification models to predict MGUS progression

MGUS progresses to MM at an average rate of about 1% per year [7, 40, 41]. However, depending on a number of known risk factors (e.g., familial history, male sex, black population, advanced age, and tumor burden), and most probably also a host of as-yet-unknown factors, some individuals progress at a much faster rate [68]. A number of risk stratification models aimed at predicting MGUS progression have been proposed, three of which are summarized in Table 3. The Mayo Clinic published a study in 2005 looking at 1148 patients with MGUS and found that these patients could be stratified into 4 different risk groups (low, low-intermediate, high-intermediate, and high) based on the number of risk factors they had out of the following "Mayo 3 criteria": (1) M-protein >1.5 g/dL, (2) non-IgG isotype (IgA or IgM), and (3) free light-chain (FLC) ratio <0.26 or >1.65 [69]. Low-risk MGUS was associated with 0 risk factors and a 5% absolute risk of progression at 20 years; low-intermediate-risk MGUS was associated with 1 risk factor and a 21% absolute risk of progression at 20 years; high intermediate-risk MGUS was associated with 2 risk factors and a 37% absolute risk of progression at 20 years; and high-risk MGUS was associated with 3 risk factors and a 58% absolute risk of progression at 20 years [69]. A Spanish study published in 2007 identified (1) DNA aneuploidy and (2) ≥95% of abnormal plasma cells within the BM plasma cell compartment (aPC/BMPC) as independent variables that could predict risk of progression in 407 patients with MGUS [70]. Specifically, patients with 0 risk factors had a 4% risk of progression at 5 years; those with 1 risk factor had a 46% risk of progression at 5 years, and patients with 2 risk factors had a 72% risk of progression at 5 years [70]. The same group published a separate study in 2010 exploring the prognostic value of (1) evolving MGUS (defined as ≥10% increase in M-protein by third year as confirmed by two consecutive measurements separated by ≥1 month) and (2) ≥95% aPC/BMPC in 311 patients with MGUS [71]. Patients with 0 risk factors had a 2% cumulative probability of progression (CPP) at 7 years; those

Table 3 Risk stratification models to predict MGUS progression to MM or related disorders. The table below outlines the various risk stratification models used in MGUS.

No of risk factors	2005 Mayo clinic study [69] ($n = 1148$)		2014 Swedish study [72] ($n = 728$)		2010 Spanish study [71] ($n = 311$)		2007 Spanish study [70] ($n = 407$)	
	Risk factors	Risk of progression at 20 years	Risk factors	Risk of progression at 10 years[b]	Risk factors	Risk of progression at 7 years	Risk factors	Risk of progression at 5 years
0	1. Serum M-protein ≥1.5 g/dL 2. Non-IgG subtype 3. Abnormal FLC ratio	5% 21% 37% 58%	1. Serum M-protein ≥1.5 g/dL 2. Non-IgG subtype 3. Abnormal FLC ratio 4. Immunoparesis[a]	4% 6% 12% 23%	1. Aberrant phenotype in ≥95% of BMPCs 2. Evolving MGUS[c]	2% 16% 72%	1. Aberrant phenotype in ≥95% of BMPCs 2. DNA aneuploidy	4% 46% 72%
1								
2								
3								
4				40%				

[a]Reduction below the normal limit in the levels of ≥1 uninvolved immunoglobulins.

[b]Data extracted from Fig. 2 of Turesson et al. [72].

[c]≥10% increase in M-protein by third year as confirmed by two consecutive measurements separated by ≥1 month.

with 1 risk factor had a 16% CPP at 7 years; and patients with 2 risk factors had a 72% CPP at 7 years [71]. Finally, a 2014 Swedish study of 728 patients with MGUS found that a combination of 4 clinical parameters: Mayo 3 criteria ((1) M-protein >1.5 g/dL, (2) non-IgG isotype (IgA or IgM), and (3) free light-chain (FLC) ratio <0.26 or >1.65) and (4) immunoparesis (reduction below the normal limit in the levels of ≥1 uninvolved immunoglobulins) could predict risk of progression [72]. Patients with 0 risk factors had a ~4% CPP at 10 years; those with 1 risk factor had a ~6% CPP at 10 years; those with 2 risk factors had a ~12% CPP at 10 years; those with 3 risk factors had a ~23% CPP at 10 years; and patients with 4 risk factors had a ~40% CPP at 10 years [72]. Unfortunately, there are no studies providing head-to-head comparisons between the different risk stratification models for MGUS and we therefore do not have any data on the concordance between these models.

Risk stratification models to predict SMM progression

As discussed previously, the risk of progression of SMM to MM is, in general, estimated at about 10% per year for the first 5 years, 3% per year for the next 5 years, and 1% thereafter [4]. However, similar to MGUS, these estimates can grossly over- or underestimate an individual patient's risk depending on his/her intrinsic risk factors. The two main risk stratification models in SMM (i.e., the Mayo Clinic Criteria and the Spanish model) were recently updated to incorporate the revised 2014 IMWG diagnostic criteria and both now adopt a 2/20/20 criteria (serum M-protein >2 g/dL, BMPC > 20%, FLC ratio >20, with or without high-risk cytogenetics) (Table 4) [73, 74]. Prior to the update, the original 2008 Mayo Clinic Criteria (which used different cutoffs for serum M-protein, BMPC%, and FLC ratio) and the Spanish PETHEMA model (which was based on multiparametric flow cytometric evaluation of aberrant BMPC and immunoparesis) [23, 70] showed considerable heterogeneity and significant discordance (28.6% concordance) in overall patient risk classification in a head-to-head comparison [75]. Nonetheless, based on the updated 2018 Mayo Clinic Criteria (Table 4), low-risk SMM is associated with 0 risk factors and has a 6 and 16% risk of progression at 2 and 5 years; intermediate-risk SMM is associated with 1 risk factor and has a 32 and 59% risk of progression at 2 and 5 years; and high-risk SMM is associated with ≥2 risk factors and has a 69 and 100% risk of progression at 2 and 5 years [74]. In comparison, the updated Spanish model reported that patients with low-risk SMM (0 risk factors) had a 5% risk of progression at 2 years; those with intermediate-risk SMM (1 risk factor) had a 17% risk of progression at 2 years; and patients with high-

Table 4 Risk stratification models to predict progression of SMM to MM or related disorders. The table below outlines two of the most widely adopted risk stratification models used in SMM, the Spanish PETHEMA model and Mayo Clinic criteria.

Updated Spanish study (with cytogenetics) [73] ($n = 952$)			Updated Spanish study (without cytogenetics) [73] ($n = 1151$)			2018 updated Mayo Clinic Criteria [74] ($n = 417$)			
Risk factors	No of risk factors (risk group)	Risk of progression at 2 years	Risk factors	No of risk factors (risk group)	Risk of progression at 2 years	Risk factors	No of risk factors (risk group)	Risk of progression at 2 years	at 5 years
1. Serum M-protein >2 g/dL 2. Serum FLC >20 3. BMPCs >20% 4. High-risk cytogenetics [t(4;14), t(14;16), 1q gain, or del 13q]	0 (low)	8%	1. Serum M-protein >2 g/dL 2. Serum FLC >20 3. BMPCs >20%	0 (low)	5%	1. Serum FLC >20 2. BMPCs >20% 3. High-risk cytogenetics [del17p, t(4;14), or hyperdiploidy]	0 (low)	6%	16%
	1 (low-intermediate)	21%		1 (intermediate)	17%		1 (intermediate)	32%	59%
	2 (intermediate)	37%		≥2 (high)	46%		2 (high)	69%	100%
	≥3 (high)	59%							

risk SMM (≥2 risk factors) had a 46% risk of progression at 2 years [73].

Risk stratification models to predict survival in MM

The purpose of risk stratification in MM is to prognosticate and assist with therapeutic decision-making. The first widely used clinical staging system reflecting tumor burden in MM based on the degree of anemia, hypercalcemia, monoclonal protein level, and bony involvement was introduced in 1975 by Durie and Salmon [76]. Eventually, the clinical introduction of novel therapies in the early 2000s resulted in the loss of the Durie Salmon staging system's prognostic accuracy. The International Staging System (ISS), which uses only β_2-microglobulin (β_2M) and serum albumin as prognostic markers, was then introduced in 2005. Unlike the Durie Salmon system, the ISS keeps its prognostic value even with the routine use of proteasome inhibitors and immunomodulatory drugs (IMiDs) [77]. However, neither systems considered the underlying molecular heterogeneity of MM. This led the IMWG to revise the ISS in 2015 to include lactate dehydrogenase (LDH) levels and high-risk cytogenetics (Table 5), which became the aptly named revised ISS (R-ISS) [78]. Separately, the Mayo clinic also introduced the mSMART (Mayo Stratification for Myeloma and Risk-adapted Therapy) risk stratification model which utilizes cytogenetics, plasma cell labeling index, and gene expression profiling as prognostic factors [79].

Overview of current recommendations for the management of MGUS and SMM

MGUS and SMM are commonly diagnosed incidentally by laboratory testing of asymptomatic individuals who present for other conditions. The vast majority of MGUS or SMM patients do not progress further and remain in the state of stable disease (SD) for years [80]. Currently, there is no recommended treatment for MGUS or SMM and "watch and wait" strategy is recommended with optional use of bisphosphonate for SMM patients [80]. The rationale for this is based largely on unsuccessful results from prior studies investigating melphalan-prednisone, thalidomide, or bisphosphonates that showed either no differences or inferior outcomes with early treatment approaches [81, 82].

However, with recent therapeutic developments especially in the field of cancer immunotherapy offering promise of highly specific, minimally toxic, and durable responses, there might be added value in initiating treatment earlier in the course of disease (i.e., MGUS/SMM) when tumor burden and clonal heterogeneity is low and especially prior to the development of a cancer tolerant BM niche characteristic of progressive, refractory disease. Indeed, the rapid advancement in drug development has led to the discovery of safer agents with fewer off-target effects which has brought back to the fore once again the question as to whether MGUS and SMM patients should be treated to reduce disease morbidity and mortality by preventing progression to symptomatic MM and possibly with curative intent. In line with this, clinicians have since started exploring the treatment of MGUS and SMM within the context of clinical trials, especially in individuals with high risk of progression.

Table 5 Revised ISS. The table below outlines the R-ISS criteria for prognostication and risk stratification of newly diagnosed MM patients.

R-ISS [78]		
Stage	Criteria	5-year OS
I	All of the following criteria must be met: • Serum β2-MG <3.5 mg/L • Serum albumin ≥3.5 g/dL • No high-risk cytogenetics • Normal serum LDH	82%
II	Not stage I or III	62%
III	Both of the following criteria must be met: 1. Serum β2-MG >5.5 mg/L and 2a. High-risk cytogenetics or 2b. Elevated serum LDH *High-cytogenetics: t(4;14), t(14;16), del(17p)	40%

A look at what's on the horizon

Clinical trials for treatment of SMM

Lenalidomide-based therapy

The Spanish Myeloma Group was the first to conduct a large-scale phase III clinical trial on early treatment in asymptomatic disease. In this trial, patients with asymptomatic high-risk SMM were treated with dexamethasone and lenalidomide or received no treatment until disease progression [83]. High-risk SMM was defined by having (1) ≥10% BM plasma cell and (2) a monoclonal component (serum IgG ≥3 g/dL, serum IgA ≥2 g/dL, or urinary Bence Jones protein >1 g per 24 h) or only one of the two criteria plus ≥95% phenotypically abnormal BM plasma cells with reductions of one or more uninvolved immunoglobulins of ≥25%. High-risk SMM patients were treated with induction therapy of dexamethasone and lenalidomide (9 cycles), followed by maintenance therapy with lenalidomide for 2 years or until disease progression. Median TTP was not reached in the treatment group and was 21 months in the control group that did not receive any therapy. Symptomatic

disease developed in 76% (47/62) of patients in the observation group, compared to only 23% (13/57) in the treatment group. During the induction phase of treatment, 79% (45/57) achieved a PR or better, including 7% with a stringent CR (sCR), 7% with a CR, and 11% with a very good PR (VGPR). Patients on maintenance therapy had a mean follow-up time of 26 months (range 4–40). Twenty-four patients developed biologic progression of disease during this time, and low-dose dexamethasone was added to the maintenance therapy of 18 of these patients. Of the patients on maintenance therapy, 3 had a PR, 11 patients had SD, and symptomatic myeloma developed in 4 patients. The ORR in the treatment group was 90%. Patients in the treatment group also had better long-term survival. In the treatment group, 3-year and 5-year survival was 98% and 94%, respectively, compared to 80 and 78% in the control group. Toxicity of the lenalidomide and dexamethasone treatment was moderate. Grade 1 and 2 infections were the most common non-hematological adverse effect, and 5-year cumulative risk of a second primary tumor was not significantly different between the treatment and control groups. The recently presented 10-year follow-up data showed that dexamethasone and lenalidomide use in SMM had a sustained survival benefit in prolonging OS (median OS not reached in treatment arm vs. 7.8 years in the control arm) as well as delaying progression to symptomatic MM. At median follow-up of 10.8 years, progression to MM occurred in 49% of patients in the treatment arm vs. 90% of patients in the control arm and the median TTP was 9.0 vs. 2.1 years in the treatment vs. control arm [84]. Importantly, in patients who progressed to active MM, the early use of dexamethasone and lenalidomide in SMM was not associated with resistance to standard of care therapy at the time of progression. Instead patients who received dexamethasone and lenalidomide prior to progression had better, albeit statistically insignificant, median OS compared to patients who did not (6.4 vs. 4.7 years in the treatment vs. control arm) [84].

Overall, this phase III study demonstrated that early intervention in high-risk SMM with lenalidomide and dexamethasone significantly delayed progression to symptomatic disease and provided an overall survival benefit for the patients. Despite the promising results of the Spanish trial however, there are a few caveats to consider. Firstly, the median age in the control group (69 years old) was higher than the treatment group (63 years old). Secondly, patients who developed biologic progression of disease during the maintenance were treated off-protocol with lenalidomide and dexamethasone which made it difficult to interpret the efficacy of the individual agents to treat early stage, asymptomatic SMM. Lastly, this study was conducted prior to the use of modern imaging techniques that are currently used in the diagnosis of MM, which raised concerns that some of the patients enrolled in the study had very early stage MM instead of SMM.

To address the concerns of the Spanish trial, a recent open-label, phase III clinical trial (E3A06) was conducted to assess the efficacy of single-agent oral lenalidomide for SMM [85]. Fifty percent of patients receiving lenalidomide therapy had a PR or better (44/88; 40 PR, 4 VGPR) and median time to response was 5 months. There were no responses seen in the control group (no treatment). PFS was significantly higher in the lenalidomide group (HR 0.28, $p = 0.002$). 1-, 2-, and 3-year PFS in the treatment group was 98%, 93%, and 91%, vs. 89%, 76%, and 66% in the control group, respectively. Cumulative incidence of progression after 3 years in the lenalidomide group was 7.6% compared to 31.6% in the control group. There were also fewer deaths in the lenalidomide group (2 patients) compared to the control group (4 patients), but this was not statistically significant (HR for death 0.46, 95% CI 0.08–2.53). Subgroup analysis was conducted based on risk group (high, intermediate, and low) as determined by the 2008 and 2018 Mayo Clinic criteria (Table 4). In all subgroups, PFS in the lenalidomide group was favorable to the control group, but this difference was most pronounced in high-risk SMM patients as determined by the 2018 Mayo Clinic Criteria. This trial included a phase II run-in period to assess the safety of oral lenalidomide therapy. During the phase II run-in, 45% (20/44) of patients experienced a grade 3 or 4 adverse event. One death due to pulmonary embolism was reported in this study which was considered to be related to lenalidomide therapy. During the phase III trial, similar rates of adverse events were seen in the lenalidomide group. Overall, this study demonstrated that lenalidomide treatment in patients with SMM significantly delays progression to symptomatic MM compared to the current "watch-and-wait" strategy and provides justification for early medical intervention in patients with SMM.

A smaller phase II pilot study evaluated the use of carfilzomib with lenalidomide and dexamethasone (CRd) [86]. The CRd regiment has been studied in the treatment of relapsed MM. Here, CRd was used in patients with newly diagnosed MM as well as high-risk SMM as defined by the 2008 Mayo Clinic Criteria. For the purposes of this paper we will focus on the results from the SMM cohort. After 2 cycles of CRd, all 12 patients with high-risk SMM achieved at least a PR, with 6/12 (50%) patients achieving a VGPR. 11 of the 12 patients completed 8 cycles of CRd, after which all 11 patients achieved at least a VGPR with 6/11 (55%) stringent CRs, 2/11 (18%) CRs, and 3/11 (27%) near CRs. The median time to CR or stringent CR was 6 cycles (range 6–20). Of the patients who achieved a best overall response of near CR, 11/12 (92%) of patients were minimal residual disease (MRD) negative as determined by multiparametric flow cytometry. This last finding is especially

important as MRD negativity is associated with improved survival [87]. Furthermore, CRd was reasonably well tolerated with the most common adverse effect being lymphopenia and gastrointestinal disorders. One patient discontinued treatment after 6 cycles due to grade 3 congestive heart failure which was likely related to carfilzomib therapy. Although these results are promising, larger studies are needed to establish the clinical benefit of CRd in SMM. A current phase II trial is being conducted to evaluate the benefit of CRd compared to lenalidomide and dexamethasone alone in high-risk SMM (NCT03673826).

Cancer vaccines for SMM

The cancer vaccine field has traditionally been plagued by high developmental costs and risks with high probability of failures such as the high-profile setbacks experienced by Sanofi with TroVax for metastatic renal cell carcinoma and Takeda's Cell Genesys prostate cancer program [88]. However, recent advances in target selection, vaccine technology, and immunomodulation have led to renewed interest and progress in the development of therapeutic cancer vaccines for hematological malignancies [89]. PVX-410 is a novel cancer vaccine being developed for patients with SMM [90]. PVX-410 is an HLA-A2-restricted vaccine is composed of 4, synthetic, peptide antigens thought to stimulate cytotoxic T lymphocytes to initiate an anti-MM immune response in patients. A small phase I/IIa study was set up to investigate the safety and efficacy of PVX-410 with or without lenalidomide in HLA-A2 positive patients with moderate-risk, or high-risk SMM. 19 of 20 (95%) evaluable patients developed an immune response to PVX-410, and the addition of lenalidomide increased the magnitude of the immune response. Furthermore, patients receiving combination treatment had a significantly higher proportion of effector memory cells compared to PVX-410 alone. Given the short duration of the trial, the clinical effect of the treatment was modest. All patients who received PVX-410 alone achieved SD as their best clinical response. In patients who received combination therapy, 1 achieved a PR, 4 achieved MR, and 4 had SD. The PVX-410 was generally well tolerated and generally included injection site pain and discomfort that were grade 1 or 2 in severity. Overall this trial demonstrated the immunogenicity of the PVX-410 vaccine in patients with SMM. Longer studies are needed to elucidate the clinical effect of PVX-410 in slowing the progression of SMM to symptomatic disease.

Another cancer vaccine currently being investigated in SMM is the PD-L1 peptide vaccine (NCT03850522). PD-L1 is an immunological checkpoint module thought to be involved in the progression from SMM to symptomatic MM. It is hypothesized that targeting this immunological pathway will delay or potentially prevent the progression to symptomatic disease.

Other trials for SMM

There are currently numerous ongoing trials investigating different agents in the treatment of SMM to delay or prevent progression to symptomatic MM. The tyrosine kinase inhibitor Ibrutinib is currently being investigated as a therapeutic strategy for patients with high-risk SMM (NCT02943473). Ibrutinib inhibits Bruton tyrosine kinase which is involved in the downstream proliferation and activation of B cells and may play in role in preventing progression of SMM. A pilot study of single-agent Pembrolizumab, an anti-PD-1 checkpoint inhibitor, in SMM reported an ORR of 8% (1 patient with sCR, 11 SD, and 1 progressive disease) at 27-month follow-up [91]. Isatuximab and Daratumumab are anti-CD38 monoclonal antibodies that are FDA approved for the treatment of MM and are currently being investigated for their potential role in slowing disease progression in patients with SMM (NCT02960555, NCT03236428, and NCT02316106). Specifically, a phase 2 trial (CENTAURUS) randomized patients with intermediate- or high-risk SMM to Daratumumab monotherapy on three different dosing schedules (intense, intermediate, and short dosing) [92]. At median follow-up of 25.9 months, the study reported a CR rate of 4.9%, 9.8%, and 0% and progressive disease/death rate of 0.059, 0.107, and 0.15 for intense, intermediate, and short dosing, respectively [92]. The median PFS was ≥24 months in all arms and the 24-moth PFS rates were 89.9%, 82%, and 95% for intense, intermediate, and short dosing, respectively [92].

Treating SMM to delay progression or to cure?

Initially, the focus of early treatment of precursor disease has been to delay progression to MM, avoid MM-related complications, and minimize treatment-related side effects. To this end, low-intensity treatments with high efficacy and minimal side effects have been studied in clinical trials looking at delaying progression to MM as discussed in the previous sections. Recently however, highly effective chemotherapy regimens incorporating autologous stem cell transplant (ASCT) have resulted in a high rate of MRD negative responses in newly diagnosed MM, highlighting that disease eradication and deep responses are feasible. In light of these data, recent efforts have been made to pursue aggressive treatment in high-risk SMM patients using PI and IMiD-based combination therapies ± ASCT with an intent to cure. This is the case for the GEM-CESAR study which enrolled 90 high-risk SMM patients (defined as BMPCs ≥10% and serum M-protein ≥3d/dL, or 95% of aberrant PCs within the total

PCs BM compartment) and treated them with 6 induction cycles of carfilzomib, lenalidomide, and dexamethasone (KRd) ($n = 90$; ≥CR: 42%); followed by intensification with melphalan and ASCT (HDT-ASCT) ($n = 83$; ≥CR: 64%), consolidation with 2 cycles of KRd ($n = 83$; ≥CR: 72%), and maintenance with lenalidomide and dexamethasone for up to 2 years (NCT02415413) [93]. Importantly, MRD negativity was observed in 31%, 56%, and 63% of patients after induction, HDT-ASCT, and consolidation, respectively [93]. After 1 year of maintenance therapy ($n = 40$), 85% of patients were ≥CR, 10% VGPR, 5% PR, and the MRD-negative rate was 68% [93]. The OS rate was 98% (at 28 months follow-up) and the PFS rate was 93% (at 30 months follow-up) [93]. One limitation of the GEM-CESAR study, however, is the lack of a comparator arm. Nonetheless, the PFS rate at 30 months in the GEM-CESAR study (treating to cure) was similar to the 2- and 3-year PFS rate (93% and 91%, respectively) in the E3A06 study (treating to delay progression) previously discussed. Although these early results suggest that the two approaches are comparable at least in the short-term, one concern with the use of low-intensity treatments to delay progression is the potential for clonal selection especially in high-risk patients. Longer follow-up including analysis of duration of response to second line treatment in patients evolving to MM will be key in determining whether low-intensity approaches will select for highly virulent clones, resulting in overall poorer outcome in patients progressing to MM, and whether more active therapy will be necessary to prevent clonal selection. Nonetheless, we believe these data provides the rationale to offer low-intensity treatment aimed at delaying progression in selected SMM, particularly elderly patients or patients with comorbidities, in whom deferring progression for several years can be functionally considered a cure, can preserve quality of life and can practically mitigate the risk of MM-related complications such as renal failure and bone disease. For younger patients with longer life expectancy, longer follow-up with PFS and OS data will be critical to aid in decision-making regarding disease eradicating approaches in SMM.

Clinical trials for treatment of MGUS

Thus far we have focussed on potential treatments for patients with SMM. However, since both SMM and MM are always proceeded by MGUS, there is an argument to be made to treat this disease at the earliest possible stage. There are trials investigating different therapeutic strategies in patients with MGUS to prevent progression to symptomatic disease. A phase II trial using Daratumumab is being investigated in patients with high-risk MGUS (NCT03236428). Another early phase I study is investigating a novel dendritic cell-based cancer vaccine against DKK1 in various plasma cell dyscrasias, including MGUS (NCT03591614). Another interesting phase I trial is assessing the role of rifaximin, an antibiotic, in patients with monoclonal gammopathies to determine the effects on plasma cells and monoclonal immunoglobulins (NCT03820817). Given the clinical course of MM and the immunological dysregulation in MM, initiating treatments prior to the development of immunosuppression with the goal of preventing progression of MGUS may bring us closer to a cure for MM and warrant additional investigation. Similar to SMM, longer follow-up is needed to assess the impact of early treatment on MGUS natural history and clonal selection.

Conclusion

Despite significant therapeutic advances over the last decade, MM remains incurable. Improvements in our understanding of the biology and pathogenesis of MM has led to a paradigm shift in the management of MM and its precursor states: MGUS and SMM. The once widely held belief that MM should only be treated at the symptomatic stage has been challenged by the introduction of novel therapies that are both safe and effective. Indeed, clinical trials have shown that early treatment of high-risk asymptomatic disease with novel agents significantly delays progression to symptomatic disease and improves progression free survival outcomes in patients. However, one of the biggest challenges is identifying individuals with asymptomatic myeloma who are at highest risk of progression and may therefore derive the largest benefit from early treatment approaches. While the creation (and continued refinement) of risk stratification models (i.e., Mayo Clinic model and Spanish model) have been very helpful, there are still significant limitations in these models especially in the context of modern therapies. For example, studies have shown that the survival of patients with high-risk cytogenetic MM (del17p, t(4;14), or t(14;20)) can be similar to standard-risk patients if intensified treatment with a combination of proteasome inhibitors and immunomodulatory drugs and ASCT is pursued [79]. There is therefore an urgent need to improve our understanding of the molecular basis of disease progression and risk stratification models in asymptomatic disease in parallel with our efforts to optimize early treatment for asymptomatic disease.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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