Blood and Lymphatic Cancer: Targets and Therapy

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REVIEW

Smoldering multiple myeloma: prevalence and current evidence guiding treatment decisions

This article was published in the following Dove Press journal:
Blood and Lymphatic Cancer: Targets and Therapy

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Abstract: Smoldering multiple myeloma (SMM) is an asymptomatic plasma cell proliferative disorder associated with risk of progression to symptomatic multiple myeloma (MM) or amyloidosis. In comparison to monoclonal gammopathy of undetermined significance (MGUS), SMM has a much higher risk of progression to MM. Thanks to advances in our understanding of the risk factors, the subset of patients with ultra-high risk of progression to MM (80%–90% at 2 years) has been identified. The revision of the diagnostic criteria resulted in changes in the management of this cohort of patients. In contrast to the management guidelines for MGUS patients, SMM patients need to be studied more intensively in order to identify biomarkers necessary for accurate risk stratification. In this review, we focus on the risk of progression from SMM to MM, as well as the influence of early treatment on overall survival, time to progression and quality of life.

Keywords: smoldering multiple myeloma, risk factor, biomarker, genomic aberrations, glycan analysis

Introduction

Smoldering multiple myeloma (SMM) was first defined by Kyle and Greipp in 1980.[1] They described a series of 6 patients who fulfilled the diagnostic criteria for multiple myeloma (MM) but had a different clinical outcome. Since then, the understanding of prevalence, diagnosis, risk of progression, and possible treatment has greatly increased. The occurrence of MM is preceded by an indolent expansion of clonal plasma cells (CPCs), known as monoclonal gammopathy of undetermined significance (MGUS) that progresses to SMM prior to malignancy. This disease continuum between MGUS, SMM, and MM provides a unique platform for investigating the genomic hierarchy, as well as the clonal heterogeneity and clonal evolution of these disease stages. Furthermore, proteomics analysis has provided valuable insight into the role of the tumor microenvironment in the regulation of cell survival, proliferation, differentiation, and metastasis. Genomic and proteomic analyses can potentially help us distinguish between a benign MM state, such as MGUS, from an asymptomatic malignancy such as SMM.

Diagnosis

In 2014, the International Myeloma Working Group (IMWG) updated the diagnostic criteria for MGUS, SMM and MM.[2] The distinction between the different disease stages is based on biological parameters and focuses on the presence of clinical symptoms (Table 1). MGUS is defined by a serum M-protein level of <3 g/dL, a bone marrow plasma cell (BMPC) infiltration of <10%, and the absence of clinical complications.

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Dovepress
http://dx.doi.org/10.2147/BLCTT.S136447

SMM is defined by serum M-protein (IgG or IgA) levels of ≥3 g/dL and/or clonal BMPCs of 10%–60% in the absence of myeloma defining events (MDEs) or amyloidosis. The updated IMWG diagnostic criteria for MM (Table 2) include presence of M protein in blood or urine, a BMPC infiltration of >10%, or biopsy-proven bony or extramedullary plasmacytoma as well as MDEs. MDE would include CRAB (calcium [elevated], renal failure, anemia, bone lesions) signs such as hypercalcemia, radiological bone lesions, anemia, and renal failure or any one or more of the following biomarkers of malignancy: a clonal BMPC percentage of >60%, involved/uninvolved serum free light chain (SFLC) ratio of >100 or >1, and focal lesions (FLs) detected by magnetic resonance imaging (MRI) studies.

Prevalence

The lack of population-based disease registries as well as changes in the diagnostic criteria over the last decade have made epidemiological data on the prevalence of plasma cell (PC) disorders (including SMM) difficult to acquire. However, the American National Cancer Data Base (NCDB) study provided some insight into the incidence of SMM, estimating it at 0.9 cases per 100,000 persons,[3] similar to that reported by a European study, where 0.4 cases per 100,000 persons were stated.[4] The median patient age at diagnosis in the NCDB was 67 years.

Pathogenesis and natural course of disease

The pathology of disease progression from benign MGUS to malignancy is characterized by a sequence of genetic aberrations. Such genetic aberrations begin with germline mutations that predispose to the disease are followed by early and likely malignancy-initiation mutations, while further acquisition of genomic aberrations ultimately leads to disease progression and resistance to treatment.

Primary events are usually divided into hyperdiploid-like trisomy of chromosomes 3, 5, 7, 9, 11, 15, 19, 21[6] and nonhyperploid-like translocations in the genes encoding Ig heavy chains (IgH).[7] The presence of specific chromosome abnormalities such as del(17p), t(4:14),1q gains,[8] and

Table 1 Revised International Myeloma Working Group diagnostic criteria for MGUS, SMM and MM

Criteria	Disease stage		
	MGUS	**SMM**	**MM**
Serum M-protein	<3 g/dL	Serum monoclonal protein - IgG or IgA ≥3 g/dL or Bence-Jones protein ≥500 mg/24 hours	
Bone marrow infiltration	<10%	Clonal BMPCs 10%–60%	>10% or biopsy-proven plasmacytoma when CRAB symptoms present or clonal BMPC percentage ≥60%
Presence of myeloma defining events or amyloidosis	None	None	**CRAB symptoms:** 1. 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) 2. renal insufficiency: serum creatinine >177 mmol/L (2 mg/dL) or creatinine clearance <40 mL/min; 3. anemia: hemoglobin value of >2 g/dL below the lower normal limit or a hemoglobin value <10 g/dL; 4. bone lesions: one or more osteolytic lesions revealed by skeletal survey, CT or PET-CT.

Note: Data from Rajkumar et al.[2]
Abbreviations: BMPC, bone marrow plasma cell; CRAB, calcium (elevated), renal failure, anemia, bone lesions; CT, computed tomography; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; PET-CT, positron emission tomography-computed tomography; SMM, smoldering multiple myeloma.

Table 2 Clinical evaluation of newly diagnosed SMM

Initial evaluation	History of present illness and past medical history Physical examination
FBC, bone marrow aspirate and biopsy	Percentage of bone marrow infiltration by clonal plasma cells, flow cytometry, conventional cytogenetics, and fluorescence in situ hybridization analysis
Biochemical studies	Creatinine, calcium; ß2-microglobulin, LDH, albumin
Protein studies	Total serum protein, serum protein electrophoresis, 24-h urine sample protein electrophoresis, serum and urine immunofixation, SFLCs, SFLCR
Radiological studies	Skeletal survey (CT) or PET-CT; MRI of thoracic and lumbar spine and pelvis or WB-MRI

Note: Data from Rajkumar et al.[2,5]
Abbreviations: FBC, full blood count; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; PET-CT, positron emission tomography-computed tomography; SFLC, serum free light chain; SFLCR, serum free light chain ratio; SMM, smoldering multiple myeloma; WB-MRI, whole-body magnetic resonance imaging.

hyperdiploidy, such as t(4;14), t(6;14), t(11;14), t(14;16) and t(14;20),[9] have been found to correlate with increased risk of disease progression from MGUS to SMM. Large, whole-exome sequencing and gene expression profiling studies have provided new insights into the clonal heterogeneity and evolution of the disease. In particular, a 70-gene expression profiling (GEP-70) signature[10] as well as a 4-gene signature (GEP-4)[11] are strong predictors of risk of progression from SMM to MM. Moreover, these gene expression signatures suggest that dysregulation of mitotic checkpoints contribute to the disease's genomic instability.[12] The top four genes in descending order of predictive power were *RRM2* (2p25-p24), beta subunit of ribonucleotide reductase (*RNR*), *DTL* (1q32) also called retinoic acid-regulated nuclear matrix-associated protein – *RAMP, TMEM48* (1p32.3) and *ASPM* (1q31). *RRM2* overexpression is associated with cellular invasiveness, metastasis and tumor angiogenesis by activation of the ERK1/2 signaling pathway in cancer. *DTL* has been implicated in oncogenesis of solid tumors via its role in apoptosis and cell cycle control. *ASPM* was shown previously to be a marker of poor prognosis in MM. The progression to clinical MM can also be linked to secondary driver events like activation of c-myc,[13,14] or other somatic mutations affecting MAPK, NFκB and DNA-repair pathways.[15,16]

Sequential whole-genome sequencing studies of SMM patients who progressed to MM demonstrated little difference in the median number of nonsynonymous single nucleotide variations (SNVs) present at both stages.[17] In these studies, progression to clinical MM in most patients did not involve new/recurrent somatic mutations, although there was some subclonal selection with progression. Moreover, differences in site-specific synonymous SNVs and copy number variations were observed to contribute to disease progression.[18]

Protein analysis, specifically looking at serum proteins found to have differences in abundance levels associated with disease phenotype, in this case SMM and MM patients, can provide clinicians with a suite of biomarkers that will aid the management of those patients who are of high risk into progressing to MM. While extensive work has been conducted on the use of proteomic methods to find potential biomarkers in MM patients, little evidence exists in the literature of the use of proteomics for the delineation of the different MM disease states. Mittermayr et al[19] recently profiled the glycomes of polyclonal IgG in different disease subgroups across the spectrum of PC disorders (MGUS, SMM, newly diagnosed MM, remission, relapse) and compared them to healthy controls. These authors showed a low total abundance of agalactosylated neutral glycans in the newly diagnosed and SMM, which suggested a potential association with inflammatory changes. Furthermore, they showed that the relapse myeloma group had the lowest abundance of total terminal galactose, while that of smoldering myeloma was highest. Such glycotraits could act as markers of disease progression.

The challenge of current genetic testing is to identify a subset of SMM patients that are of high risk into progressing to MM. With increased knowledge of the molecular pathways and genetic mutations occurring during SMM to MM progression, genetic testing has the potential to identify these high-risk patients and ultimately direct a tailored, patient-specific management strategy.

Risk assessment

Most of the patients diagnosed with SMM will eventually progress to symptomatic MM and will require treatment. The time-to-progression (TTP) to MM varies significantly among patients as SMM is a heterogeneous disorder (Tables 3 and 4). The overall risk of progression was found to be higher in the early years after diagnosis: 10% per year for the first 5 years, 3% per year during the following 5 years, and only 1% per year after 10 years. However, the cumulative probability of progression to active MM or amyloidosis (AL) was 51% at 5 years, 66% at 10 years, and 73% at 15 years.[20] Similar results were found in a prospective study published by Neben et al,[9] where a median time of progression at 5.6 years was reported with a cumulative progression rate of 46% over 5 years.

Tumor burden assessment

Bone marrow infiltration

Tumor burden can be assessed by the percentage of bone marrow infiltration by PCs or size of serum M-protein and presents a significant risk factor of progression. Kyle et al[21] showed that the percentage of bone marrow involvement correlates with the median TTP.[21] Further studies demonstrated that the risk of progression rises dramatically when the BMPCs level is ≥60% and the estimated risk of disease progression at 2 years is 90%.[22–24] This high-risk factor has been incorporated into the new IMWG MM diagnosis guidelines.[2]

SFLC ratio

SFLC ratio was evaluated as a marker for progression in SMM. Larsen et al[25] found that a serum involved/

Table 3 SMM risk factors associated with progression to clinical MM[#]

Risk factor	Assessment criteria	References
Tumor burden	>10% clonal plasma cell bone marrow infiltration	2,20
	≥3 g/dL of serum M-protein	2
	Serum free light chain ratio between 0.125 and 8	26
	Bence Jones proteinuria positive from 24-h urine sample	31
	Peripheral blood circulating PCs >5× 10^6/L	35
	Peripheral blood circulating PCs ≥150 by flow cytometry	36
Serum free light chain ratio	≥100	25
Immunoparesis and immunophenotyping	Immunoparesis (>25% decrease in one or both uninvolved immunoglobulins relative to the lowest normal value	32,27
	>95% of aberrant PCs by flow cytometry within the PC bone marrow compartment	43
Genetic abnormalities	t(4;14)	7,9
	del17p	
	+1q24	
	Hyperploidy	
	Gene expression profiling risk score >–0.26	10
Radiological assessment	Newly detected FLs or increase in diameter of existing FL and a novel or progressive diffuse infiltration on WB-MRI	37,38,39
	Positive PET-CT with no underlying osteolytic lesion	44

Notes: Risk factors as defined by Rajkumar et al.[5]
Abbreviations: FL, focal lesion; MM, multiple myeloma; PC, plasma cell; PET-CT, positron emission tomography-computed tomography; SMM, smoldering multiple myeloma; WB-MRI, whole-body magnetic resonance imaging.

Table 4 Clinical trials investigating the SMM risk factors for progression to clinical MM

Risk factor	Patients n	Patients with the risk factor n (%)	TTP	References
BMPCs ≥60%	655	21 (3.2)	2-year: 95%	22
	96	8 (89)	Median 15 months	23
	135	6 (4.4)	2-year: 100%	24
SFLC ratio >100	586	90 (15)	2-year: 79%	25
	96	7 (7)	Median 13 months	23
	321	23 (7)	2-year: 30%	27
Evolving pattern of serum paraprotein	53	22 (41)	Median 1.3 years	28
Immunophenotype	93	14 (15)	Median 51 months	32
Circulating clonal plasma cells	91	14 (15)	2-year: 71%	35
	100	9 (9)	2-year: 78% Median 9 months	36
Genetic abnormalities				
t(4;14)	351	36 (10)	Median 28 months	7
del(17p)	351	6 (2)	Median 24 months	7
t(4;14)	248	22 (9)	Median 5.7 years	9
del(17p)	248	15 (6)	Median 5.6 years	9
+1q21	248	73 (30)	Median 3.8 years	9
GEP-70	126	31 (29)	2-year: 49.7%	10
GEP-4	104	14 (13)	2-year: 81.8%	11
>1 focal lesion on MRI	149	23 (15)	Median 13 months	37
	67	9 (13)	2-year: 69%	39
Positive PET-CT with no underlying osteolytic lesion	120	19 (16%)	2-year: 48%	41

Abbreviations: BMPC, bone marrow plasma cell; MRI, magnetic resonance imaging; MM, multiple myeloma; PET-CT, positron emission tomography-computed tomography; SFLC, serum free light chain; SMM, smoldering multiple myeloma; TTP, time-to-progression.

uninvolved FLC ratio of at least 100 is associated with a risk of progression to symptomatic disease of 72% at 2 years.[25] A ratio of involved to uninvolved SFLC of ≥100 has been recently added to MDE and was included by the IMWG in recent guidelines.[2] In addition, a kappa/lambda SFLC ratio of <0.125 and >8 was found to be associated with an increase in the risk of progression to MM.[26] However, the Danish Myeloma Group[27] found no significant threshold for the SFLC ratio in their analysis of an SMM patient cohort.

Evolving pattern of serum paraprotein

The evolution of disease parameters, such as serum paraprotein or urine paraprotein, following the initial diagnosis is important in estimating the risk of progression. This concept was introduced more than a decade ago[28] and enables distinction between evolving and stable SMM.[29] The evolving type can be defined by: 1) if the concentration of M-protein is >3 g/dL at baseline and an increase in M-protein of at least 10% within the first 6 months; or 2) if the concentration of M-protein is <3 g/dL at baseline and a progressive increase in M-protein in each consecutive annual measurement over a 3-year period diagnosis is reported.[30]

Bence Jones proteinuria

The presence of Bence Jones proteinuria at diagnosis of SMM is associated with a risk of progression to malignancy. A study[31] of 147 SMM patients showed that individuals with M-protein and Bence Jones proteinuria have a significantly higher risk of progression to active disease (22 vs. 83 months, $P<0.001$). Furthermore, when the Bence Jones proteinuria exceeded 500 mg in 24-h urine samples, the risk was even higher, with a median TTP of 7 months.[31]

Immunophenotype

New generation multiparameter flow cytometry (MFC) has been used to determine SMM prognosis, by distinguishing and quantitating aberrant and normal PCs infiltrating the bone marrow. Pérez-Persona et al[32] showed that 60% of the SMM patients included in their study had an aberrant immunophenotype. The risk of progression to malignancy was significantly higher than those with lower percentage of malignant PCs.[32]

Circulating plasma cells (CPCs)

CPCs were detected at newly diagnosed MM and SMM.[33] Since there was only a weak correlation between tumor mass and CPCs, it was suggested that the appearance of CPCs may be a reflection of tumor biology.[34] The presence of $>5\times10^6$/L CPCs, estimated by slide-based immunofluorescence, is a risk factor associated with a shorter TTP.[35] In addition, the occurrence of at least 150 CPCs in 150,000 cellular events measured by means of 6-color flow cytometry was also shown to be associated with shorter TTP within 2–3 years in 78% of the analyzed patients.[36]

Immunoparesis

Immunoparesis is defined as the reduction in the levels of uninvolved immunoglobulins and presents an independent risk factor. Its prevalence correlates with tumor burden.[20,32] However, its value as a risk factor for progression remains controversial and varies between the studies.[9,23] Sørrig et al[27] recently reported that immunoparesis and M-protein levels of >30 g/L can significantly affect TTP to MM.[27]

Genetic changes

Certain cytogenetic abnormalities have major prognostic significance in symptomatic MM. One of the studies performed by the Mayo Clinic team[7] evaluated the prognostic value of cytogenetics in a cohort of 351 SMM patients. The TTP of patients with a 17p deletion was 24 months. Patients with a t(4;14) translocation had a median TTP of 28 months. Patients with trisomies progressed to malignancy after 34 months, while patients with other anomalies like t(11;14), MAF translocations, other IgH translocations, monosomy13/del(13q) after 55 months. Furthermore, the presence of cytogenetic abnormalities determined the overall survival (OS). After diagnosis of SMM, OS for patients with t(4;14) translocations was 105 months and 147 months for patients with t(11;14) aberrations. Based on these results, the authors described four SMM patient groups based on their risk of progression: 1) high-risk patients, harboring t(4;14) and/or del(17p); 2) intermediate-risk patients carrying trisomies; 3) standard-risk patients with t(11;14), t(14;16), or t(14;20), and trisomies/IgH translocation combination; and 4) low-risk patients where no cytogenetic abnormalities are detected.[7]

The Heidelberg group also demonstrated the significance of t(4;14), gain of 1q21 chromosome and hyperdiploidy as independent risk factors for progression to malignancy of SMM patients.[9] A different approach was explored by the SWOG S0120 study.[10] These authors analyzed the gene expression profiles of 105 SMM patients. The presence of a 70-gene expression profiling signature (which partly correlates with chromosome 1 abnormalities and identifies

high-risk SMM patients was found to be a strong predictor of risk of progression,[10] this was also true for a 4-gene signature.[11] Furthermore, the combination of elevated SFLC, M-spike, and GEP70 in a subset of high-risk patients leads to an even higher progression risk (67% at 2 years). More importantly, the absence of these factors in SMM patients predicted low progression risk.

Radiological assessment

The modern imaging techniques like MRI and positron emission tomography–computed tomography (PET-CT) are part of the workup of patients assessed for MM and SMM; furthermore, they can also predict progression risk in SMM. Hillengass et al[37] have demonstrated that 28% of patients with SMM had one or more FLs on whole-body MRI (WB-MRI).[36] The presence of more than 1 FL (15% of the study population) was associated with a higher risk of progression to symptomatic disease, with an estimated 2-year progression of 65%–70%. Various research groups have independently shown that the presence of new FLs or an increase in diameter of the existing FLs, as well as novel or progressive diffuse infiltration seen by means of MRI, are associated with high risk of progression to MM.[37–39]

PET-CT is considered a valuable tool for patients requiring PC disorder workup. Furthermore, is may be an alternative imaging modality for SMM assessment if WB-MRI is not available.[40] Zamagni et al[41] reported that positive PET-CT results with no underlying osteolytic lesions have been reported in 10% of patients. Positive PET-CT results were also associated with high risk of progression to symptomatic disease (48% at 2 years compared with 32% for PET-CT-negative; $P<0.007$).[41] Similar percentage of progression (56% at 2 years for PET-CT positive and 28% for PET-CT negative; $P<0.001$) was also identified by the Mayo Clinic Group[42] within a subgroup of 132 SMM patients. The rate of progression was even higher among patients where PET-CT was performed within 3 months of their diagnosis of SMM (74% in PET-CT positive vs. 27% in PET-CT negative).

Prediction of progression to MM

The most important step following the diagnosis of SMM is an insightful analysis of the risk of disease progression. Several models have been proposed, but unfortunately the components incorporated in these analyses are not consistent, thus making the assessment of the risk of progression to malignancy difficult (Table 5).

The most familiar prospectively validated models are the Mayo Clinic and the Spanish Myeloma Group models.[20,26,32] The Mayo Clinic model uses 3 risk factors including: 1) a monoclonal protein of >3 g/dL; 2) an abnormal SFLC ratio (<8 or >0.125); and 3) the extent of BMPC involvement (>10%). Each of these factors independently correlated with an increased risk of progression. The probability of progression at 5 years was 25%, 51%, and 76%, depending on whether the patients had 1, 2, or 3 risk factors, with a median TTP of 10, 5.1 and 1.9 years, respectively.

The Spanish Myeloma Group model is based on two risk factors: 1) predominance of clonal cells in the BMPC compartment using MFC; and 2) the presence of immunoparesis (defined as a decrease by >25% of the level of 1 of the 2 other uninvolved immunoglobulins). Depending on whether patients had none, one, or both risk factors, progression rates at 5 years were 4%, 46%, and 72%, respectively.[32]

Both studies suggested that the progression probability of patients with low-risk profile was 1% per year. Furthermore, both models were analyzed using a one-on-one comparison of 77 selected SMM patients. This study revealed a rather low concordance rate of 29% in overall patient risk classification.[45] However, it was suggested to use both models complementarily rather than alternatively, as well as adding new biomarkers to assess the risk of progression more accurately.

Other upcoming risk models incorporate novel clinical and biological disease attributes, such as the gene expression score or SFLC ratio. Two of the recent studies: the SWOG S0120 and the University of Pennsylvania models used criteria that also included genetic factors and thus defined a high-risk group that had more than 80% progression at 2 years.[11,46] Greater understanding of the disease development as well as more accurate identification of high-risk SMM patients will be crucial for success of future interventions.

Treatment approaches (literature review)

Early intervention studies evaluated the benefit of early versus delayed treatment with oral melphalan and prednisone for SMM patients. No benefit in terms of response rate, progression-free survival, or OS[50,51] was shown. Similarly, trials investigating the effect of bisphosphonate showed no clear antitumoral effects; bisphosphonate was shown to have a positive effect on the bone metabolism as a significant reduction in the incidence of skeletal-related events was reported.[52–54] One of the first agents showing to

Table 5 Overview of the SMM risk stratification models

Risk model	High-risk patients, no of patients/no high-risk patients	Risk factors	Definition of high risk	TTP for high-risk patients	References
Mayo Clinic	276/27	BMPC ≥10% M-protein ≥3 g/dL	All RF	5-year: 69%	20
Mayo Clinic	273/78	BMPC ≥10% M-protein ≥3 g/dL	All RF	5-year: 76%	26
Spanish Myeloma Group	93/39	≥95% aberrant PCs within BMPCs Immunoparesis	All RF	5-year: 76%	32
SWOG S0120	105/14	Elevated 4-gene expression score Monoclonal protein ≥3 g/dL Serum albumin <3.5 g/dL	4-gene expression score ≥ 9.28	2-year: 86%	11
PENN	135/NA	BMPC ≥10% SFLCR ≥50 Serum albumin ≤3.5 g/dL	2–3 RF	2-year: 81%	46
Heidelberg	248/44	del(17p13); t(4;14) or +1q21 Monoclonal protein ≥2 g/dL	All RF	3-year: 59%	9
Czech Myeloma Group	287/NA	Immunoparesis Monoclonal protein ≥2.3 g/dL Involved: uninvolved SFLC >30	All RF	2-year: 79%	47
Danish Myeloma Group	321/42	Immunoparesis Monoclonal protein ≥3 g/dL	All RF	2-year: 38%	27
Barcelona	207/67	Evolving pattern Serum M-protein ≥3 g/dL Immunoparesis	ALL RF	2-year: 80%	48
Japanese	301/NA	Beta 2-microglobulin ≥2.5 mg/L M-protein increment rate >1 mg/dL/d	2 RF	2-year: 67.5%	49
Mayo evolving model	190/19	Evolving change in monoclonal protein level (eMP) Evolving change in hemoglobin (eHb) ≥20% BMPCs	3 RF	2-year: 90.5%	29

Abbreviations: BMPC, bone marrow plasma cell; NA, not available; PCs, plasma cells; RF, risk factors; SFLCR, serum free light chain ratio; SMM, smoldering multiple myeloma; TTP, time-to-progression.

have a beneficial effect in SMM patients was thalidomide. A Phase II trial showed partial responses in a third of the patients.[55] However, thalidomide treatment was associated with significant toxicity.[56,57] A later Phase III trial,[58] conducted by the Mayo Clinic, compared thalidomide plus zoledronate versus zoledronate alone. The authors reported a response rate of 37% in the thalidomide arm (whereas no responses were seen in the zoledronate arm). Furthermore, the authors showed no significant difference in the TTP to MM (4.3 vs. 3.3 years) or in OS (74% vs. 73% at 5 years).[58] Based on these clinical trials, bisphosphonates are recommended only for SMM patients with osteoporosis.[59]

The benefits of early treatment were reported for the first time in a Phase III randomized trial (NCT00480363) performed by the Spanish Myeloma Group.[60] One hundred and nineteen high-risk SMM patient fulfilling the Mayo and/or Spanish criteria were included in the study. The treatment arm included lenalidomide plus dexamethasone in the induction phase followed by lenalidomide alone in maintenance and was compared to the observation arm. The primary endpoint, TTP, was significantly longer in patients in the treatment than in the observation arm (not reached vs. 21 months; $P<0.001$). Fifty-three out of 62 (86%) patients in the observation group progressed to symptomatic MM compared with 22 out of 57 (39%) patients in the treatment group. Furthermore, OS was longer in the treatment arm compared to the observation arm (3-year survival rate, 94% vs. 80%, $P<0.03$). This study demonstrated for the first time that the OS of high-risk SMM patients can be improved by early treatment without significant side-effects. Despite the relevance of the results, some of its design problems have to be noted such as: 1) a high proportion of patients who progressed from SMM to MM within the first 6 months and might have been identified with routine MRI or PET-CT studies at baseline; 2) the median age of the control group

was higher than the treatment group; 3) lack of crossover in the control arm at the time of biological progression; 4) design not fitted for regulatory purposes. Promising positive effects of early intervention have also been shown in an interventional Phase II study that tested the combination of carfilzomib, lenalidomide, and dexamethasone. Twelve high-risk SMM patients achieved at least near-complete response. Minimal residual disease (MRD) negativity was found in 11 out of 12 patients by flow cytometry and in 9 out of 12 by next-generation sequencing (NGS). This result highlights the methodologic differences between both platforms with the expected increased sensitivity of NGS. Furthermore, there was no significant association found between the degree of PET-CT response and clinical outcome or PFS.[61]

Current trials such as CESAR (NCT02415413) and ASCENT (NCT03289299) offer early treatment for high-risk SMM aiming in achieving sustained MRD-negative status and eradicating the disease. The debate around controlling the disease through continuous oral therapy versus the intensive therapy approaches, including high-dose therapy and transplantation with the possibility of "cure" is very controversial. The success of those approaches will probably depend on combinations of effective agents used and risk features of SMM. Finally, current trials are investigating the impact of early intervention with many novel agents or their combinations (Table 6).

Management recommendation/follow-up

The follow-up strategy for patients with SMM should be adapted to their risk of progression. As shown by the prospectively validated Mayo Clinic and Spanish models, the risk profile and TTP can differ significantly between the SMM subsets of patients. The risk assessment models differ, and each patient's risk of progression should probably be defined based on all the available data rather than with use of a restricted model. In general, SMM patients can be categorized into low, intermediate, and high risk of progression.

SMM patients with low risk of progression can be treated like patients with MGUS. The risk of progression in that group at 5 years is only 8%. This group should be followed up annually. Patients at intermediate risk of progression display some high risk factors. The risk of progression in this cohort is estimated at 42% in 5 years. In the first year, patients should be followed every 3–4 months to exclude disease progression and then every 6 months. The high-risk patients require a closer follow-up, i.e., every 2–3 months.

Table 6 Overview of selected clinical trials for SMM patients

ClinicalTrials.gov Identifier	Trial design	Interventional drug	Primary outcomes
NCT02279394	Phase II	Elotuzumab, lenalidomide, dexamethasone	TTP at 2 years
NCT02903381	Phase II	Nivolumab, lenalidomide dexamethasone	TTP at 2 years
NCT02916771	Phase II	Ixazomib, lenalidomide, dexamethasone	2-years PFS rate
NCT02603887	Phase I	Pembrolizumab	ORR
NCT02415413	Phase II	Carfilzomib, lenalidomide, dexamethasone	Efficacy by Flow-CR at day 100 post ASCT
NCT01484275	Phase II	Siltuximab	1-year PFS rate
NCT02943473	Phase II	Ibrutinib	TTP at 1 year
NCT01718899	Phase I/IIa	PVX-410, a multi-peptide cancer vaccine	Safety and toxicity
NCT02784483	Phase I	Atezolizumab (anti-PD-L1)	Prevalence of anti-SOX2 reactive T-cells after anti-PDL1 therapy
NCT03236428	Phase I	Daratumumab	Proportion of patients in deep response at 2-year time
NCT02697383	Phase I	Ixazomib, dexamethasone	ORR at 1 year
NCT02886065	Phase Ib	PVX-410 (a multi-peptide cancer vaccine), durvalumab, +/– lenalidomide	Safety and toxicity
NCT02960555	Phase II	Isatuximab	ORR at 6 months
NCT02492750	Phase I/II	Anakinra, lenalidomide dexamethasone	Safety and toxicity, MTD, TTP at 2 years
NCT02240537	Phase I	BBMPI03, an oncofetal antigen multi-peptide immunotherapy	Safety and tolerability, DLT, MTD, and OBD

Note: Data from Muchtar et al[62] and Mateos et al[63].

Abbreviations: ASCT, autologous stem cell transplantation; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; OBD, optimal biologic dose; ORR, objective response rate; PFS, progression-free survival; SMM, smoldering multiple myeloma; TPP, time-to-progression.

In our institution, we perform a comprehensive SMM workup (Table 2) including both PET-CT and WB-MRI. We also plan to extend it by adding immunprofiling and next generation flow cytometry in the near future. Currently, the risk of progression of individual patients is being discussed at the multidisciplinary meeting. Although we believe in the need of exploring early treatment, we do not treat high-risk SMM patients outside of the clinical trials. We are convinced that the translational studies including genetic and epigenetic factors, protein and phenotype analysis will help us define the subpopulation of patients that will benefit from the therapy, hopefully completely eradicating the progression to symptomatic disease.

Future directions

Until recently, treatment was reserved for symptomatic myeloma patients. This paradigm is now being challenged, as there is increased risk of progression into MM of certain SMM patient cohorts. In addition, there is now availability of novel, targeted drugs that may provide a more personalized treatment to SMM patients, combined with an acceptable side-effect profile.

Successful identification and validation of prognostic SMM to MM transition markers, such as CPCs, genetic and/or proteomic profiles will inform and direct novel clinical trials that will be able to identify those SMM patients who will benefit from early intervention.

Acknowledgment

DB would like to acknowledge funding from the Irish Cancer Society.

Disclosure

POG has research support from Janssen and Celgene. The other authors report no conflicts of interest in this work.

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