MultipleMyelomaHub

General MM

Risk stratification in smoldering multiple myeloma (SMM)

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Smoldering multiple myeloma (SMM) is a key topic in the field of multiple myeloma (MM) and currently there is a lot of stimulating discussion on how to define high-risk SMM and when to intervene. This was discussed at recent congresses such as the 5th World Congress on Controversies in Multiple Myeloma (COMy), the American Society of Clinical Oncology (ASCO) meeting and the European Hematology Association (EHA) meeting.

The MM Hub is focusing on SMM as this month's educational theme, and this article will provide an overview of risk stratification strategies for SMM provided by Professor Shaji Kumar, Mayo Clinic, Rochester, US, who presented on the topic of risk stratification of SMM at COMy[1] and Professor Maria-Victoria Mateos, University Hospital Salamanca, Salamanca, ES, who presented an updated risk stratification protocol for SMM during ASCO.[2]

Risk stratification of SMM

SMM was first described in 1980 when Robert Kyle and Philip Greipp published an article in the *New England Journal of Medicine*, describing six patients who had symptoms of MM, without disease progression, who remained stable for >five years and did not have end organ damage that is typical of MM.[1]

SMM is distinct from monoclonal gammopathy of undetermined significance (MGUS) due to a higher risk of progression to active MM disease. For patients at high-risk of progressing from SMM, the main questions raised are; "should this subset of patients be treated as having MM?".[1]

Defining MM[1]

The classical definition of MM is based on the CRAB symptoms of hypercalcemia (C), renal insufficiency (R), anemia (A) and lytic bone disease (B). This definition was subsequently expanded to include three additional results, defined by the International Myeloma Working Group (IMWG), which indicate a high risk of progression:

- Bone marrow plasma cell (BMPC) percentage ≥60%
- Involved: uninvolved free light chain (FLC) ratio >100
- Two or more lesions on the spine, detected by MRI or PET

Using these updated criteria, it is possible to identify patients with a risk of progression of ≥80% over two years.[1] It is this population of patients for whom treatment is required.

Defining SMM

SMM is traditionally defined as an asymptomatic disease with an increased clonal burden, the presence of:

- Serum monoclonal protein IgG or IgA ≥3 g/dL or
- Urinary monoclonal (M) protein ≥500mg per 24 hours or
- Clonal BPMC of 10–60%
- No traditional CRAB features

Risk of progression from SMM to MM

Unlike MGUS which has a 1% risk of progression year on year, SMM carries a 15% risk within the first three years since diagnosis, which lowers to 3% between years three and 10, and drops to 1% at 10 years post-diagnosis.[1] As SMM progresses into MM, there is an associated increase in M protein and BMPC percentage, as well as the development of end organ damage. Professor Kumar commented that this progression is a quantitative effect, over time. However, there are also qualitative genomic changes that occur over this time period within the plasma cells.

Table 1. Prognostic risk factors for 50% risk of progression in SMM[1,2]

Quantitative	Qualitative	Both
Serum M protein ≥30g/L or progressive increase in M protein level	Fluorescence *in situ* hybridization (FISH) abnormalities t(4;14), del(17p) or 1q gain	Serum involved/uninvolved FLC ratio abnormality ≥8 but <100
Clonal BMPC 50–60%	Mutations	Immunoparesis with reduction of two uninvolved immunoglobulin isotypes
MRI with diffuse bone marrow abnormalities or one focal lesion	Genome expression profile (GEP)	Circulating tumor cells
Increased circulating plasma cells	Proliferation rate	Evolving phenotypes
PET-CT with focal lesion and increased uptake without underlying osteolytic bone destruction	Abnormal plasma cell immunophenotype (≥95% of BMPCs are clonal) and reduction of ≥one uninvolved immunoglobulin isotype	

Evolving parameters[1]

Professor Kumar stated that the current stratification system is dynamic and can be adapted depending on new data and patient characteristics. Factors that have an evolving role in this process include M-protein level and MRI findings.

Risk stratification models

There are two main models for risk assessment in SMM:[2]

1. The Mayo risk model is based on plasma cells bone marrow infiltration, serum M-component level, and serum FLC ratio
2. The Spanish risk model uses aberrant plasma cells (aPCs) by immunophenotype and immunoparesis

Table 2. Comparison of currently used risk models for SMM[2]

Mayo risk model*			**Spanish risk model**	
Subgroups	Risk of progression at five years	Risk of progression at 10 years	Subgroups	Risk of progression at two years
One risk factor	25%	50%	No adverse factors	5%
Two risk factors	51%	65%	>95% aPC /BMPC or immunoparesis	35%
Three risk factors	76%	84%	>95% aPC/BMPC and immunoparesis	50%

* Risk factors: BMPC >10% with M-spike >3 g/dL and FLC ratio >8 or <0.125

The Mayo Clinic revised risk stratification for SMM is based on the 20/20/20 criteria; BMPC >20%, M spike >20g/L and FLC ratio >20. Subsequently, patients are stratified as low-risk (absence of any of these factors), intermediate-risk (one factor present) or high-risk (two or more factors present).[1]

Both models were validated in the phase III trial QuiRedex which compared lenalidomide + dexamethasone (Rd) with observation alone in 119 patients with high-risk SMM. The Mayo risk model identified a hazard ratio (HR) for progression of 0.21 (95% CI, 0.10–0.40, $p< 0.0001$), whilst the Spanish risk model identified a HR of 0.27 (95% CI, 0.15–0.46, $p< 0.0001$) in these patients.[3]

In 2014, the IMWG redefined patients with SMM who had BMPC ≥60%, or a serum FLC ratio ≥100 or 1 focal lesion by MRI, as having MM. As such, the remaining categories and criteria needed to be reassessed and amended accordingly.[2,4]

Revised risk stratification: Spanish myeloma group[2]

During ASCO 2019, Professor Maria-Victoria Mateos presented an updated risk stratification model, incorporating the 2014 IMWG criteria. Professor Mateos and colleagues conducted a multicenter retrospective study (N= 2004) on patients with SMM diagnosed after 1st January 2004. Patients had not progressed within six months, had baseline data from diagnosis, a follow-up of ≥1 year and did not participate in a therapeutic trial for SMM. The study aimed to identify factors associated with increased risk of progression at two years.

Univariate Cox regressions were conducted for each factor, with cut-off points identified for each. Following this, a stepwise regression to fit multivariate Cox model was done. Using proposed cut-off categories, the authors found three factors associated with increased risk of progression (**Table 3**).

Table 3. Risk factors associated with an increased risk of progression[2]

	Proposed cut-off	Analysis	HR (95% CI) *vs* low risk	*p* value
Serum M protein	2 g/dL	>2 *vs* ≤2	1.99 (1.62–2.45)	<0.0001
Serum FLC ratio	20	>20 *vs* ≤20	2.04 (1.65–2.52)	<0.0001
BMPC %	20%	>20 *vs* ≤20	2.26 (1.83–2.79)	<0.0001

The patients in the study (n= 1151) were stratified into low, intermediate and high-risk categories based on the presence of these factors (0, 1, and 2 or more, respectively). The patients in the high-risk group had a higher rate of progression (**Table 4**). In the high-risk group, the presence of 2, or 3, risk factors did not add to the model.[2]

Table 4. Progression rates for different stratified subgroups[2]

Number of risk factors	Classification	N	HR	*p*	2-year progression
0	Low	424	Reference	-	5%
1	Intermediate	312	2.25 (1.68-3.01)	<0.001	17%
≥2	High	415	5.63 (4.34-7.29)	<0.001	46%

This model also incorporated cytogenetic factors; translocation (4;14) (t[4;14]), t(14;16), 1q gain or deletion of 13q, by defining them as an additional risk factor, as shown in **Table 5**.

Table 5. Progression rates for different stratified subgroups, including cytogenetics[2]

Number of risk factors	Classification	N	HR	2-year progression

0	Low	232	Reference	8%
1	Low-intermediate	322	2.25 (1.62–3.11)	21%
2	Intermediate	253	3.69 (2.68–5.09)	37%
≥3	High	145	7.52 (5.36–10.54)	59%

This revised 2/20/20 model has been validated in this analysis and can be universally applied, though future efforts will focus on incorporating cytogenetic abnormalities and those without FLC based on availability of testing.[2]

Revised risk stratification: Mayo group[1,4]

Based on the IWMG definition of ultra-high risk SMM, Professor Kumar and colleagues conducted an analysis, having excluded patients who were redefined based on this criterion.

Using BMPC >20%, FLC ratio >20 and high-risk cytogenetics defined as del(17p), t(4;14) or hyperdiploidy, patients were stratified as low, intermediate and high-risk (having 0, 1 and 2 or more factors respectively).

The median time to progression (TTP) was:

- Low: not reached (NR, [95% CI, 33.3 months–NR])
- Intermediate: 63.0 months (95% CI, 29.8–NR)
- High: 14.5 months (95% CI, 10.7–25.4)
- This was statistically significant with a *p* value of <0.0001

Future perspectives[1]

To date, two phase III trials have shown that prevention approaches can improve survival. The question now is how treatment options should be applied to each subgroup? Professor Kumar stated it is likely that high-risk patients SMM will be treated with MM strategies, though more data is required.

Conclusion

Since SMM is a transitional state between MGUS and MM, it generally contains a mixture of patients with MGUS with polyclonal yet benign BMPCs and, patients with MM with malignant BMPCs. As such, no specific biomarker exists and it is not possible to morphologically identify SMM. The evolving definition of SMM will likely continue, based on latest data and advances in the field. This is necessary to ensure patients receive the best, and most appropriate care.

References

1. Kumar S. Risk stratification in smoldering multiple myeloma. 5th World Congress on Controversies in Multiple Myeloma (COMy). 2019 May 16. Oral presentation.

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3. Mateos M.V. *et al.* Lenalidomide plus dexamethasone versus observation in patients with high-risk smouldering multiple myeloma (QuiRedex): long-term follow-up of a randomised, controlled, phase 3 trial. Lancet Onc. 2016. DOI: 10.1016/S1470-2045(16)30124-3

4. Lakshman A. *et al.* Risk stratification of smoldering multiple myeloma incorporating revised IMWG diagnostic criteria. Blood Cancer J. 2018 Jun 12. DOI: 10.1038/s41408-018-0077-4
