How we manage smoldering multiple myeloma

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Abstract

Smoldering myeloma (SMM) is an asymptomatic stage characterized by bone marrow plasma cells infiltration between 10-60% in absence of myeloma-defining events and organ damage. Until the revision of criteria of MM to require treatment, two main prognostic models, not overlapping each other, were proposed and used differently in Europe and in US. Novel manageable drugs, like lenalidomide and monoclonal antibodies, with high efficacy and limited toxicity, improvement in imaging and prognostication, challenge physicians to offer early treatment to high-risk SMM. Taking advantage from the debates offered by SOHO Italy, in this review we will update the evidence and consequent clinical practices in US and Europe to offer readers a uniform view of clinical approach at diagnosis, follow-up and supportive care in the SMM setting.

Introduction

For long time, the two terms of Smoldering and Indolent myeloma were variably used in an undefined manner,1,2 until 2003 when the International Myeloma Working Group (IMWG) defined SMM as an asymptomatic stage of plasma cell disorder, defined by the presence of a serum monoclonal component of at least 30 g/L and/or more than 10% plasma cells in the bone marrow (BMPC),3 higher than those generally seen in monoclonal gammapathy of uncertain significance (MGUS), in absence of myeloma defining events, like hypercalcemia, renal failure, anemia, or bone disease (also collectively known as CRAB symptoms). In 2014, IMWG included BMPC>60%, elevated immunoglobulin free light chains (in which the involved light chains are 100 times more numerous than the uninvolved ones), and 2 or more bone focal lesions identified by magnetic resonance imaging (MRI)4 as additional myeloma-defining events, that address earlier patients at first-line treatment.

SMM accounts for about 15% of all the patients with newly diagnosed MM and it carries a higher risk of progression to symptomatic MM compared to MGUS.6,7 In the first 5 years after diagnosis the risk of progression to MM in SMM is approximately 10% per year and thereafter, differently from MGUS in which the rate of progression to MM is 1% per year, constant overtime.9 The difference in clinical behavior in SMM is due to genetic heterogeneity,10 as deciphered by application of novel technologies.11 While transcriptome trajectory is invariant,12 genomic events associated to progression from SMM through active MM can follow two main patterns, as revealed by whole-genome sequencing approach.11 The first, in which the sub-clonal architecture is retained and the progression is consequence of linear increase of disease burden; the second, due to a change of the sub-clonal architecture, in which progression is associated to stochastic additional complex genomic events.12,14 Like in active MM, cytogenetics can identify high-risk SMM patients8 and will likely be incorporated in future comprehensive models for risk stratification.15 As a whole, BMPC external factors, like microbiome composition16 or immune dysfunction,17,21 can play a role still to investigate.

Initial diagnostic work-up

While there are no significant differences between Italy and US in the initial diagnosis work-up, to exclude myeloma defining events, there are some emerging differences about the way to attribute risk class and further follow-up requirements. According to 2014 IMWG MM diagnostic criteria6 and 2016 ESMO guidelines,8 BM evaluation by aspirate and/or biopsy is the standard way to evaluate the number, immune phenotype (to check aberrancies like the absence of CD19 and/or CD45 expression, decreased expression of CD38, and overexpression of CD56) proliferation index22,23 and genetic aberrations (by FISH and/or conventional cytogenetics) of BMPC. Moreover, BM evaluation can provide additional information, like the presence of dysplastic hematopoiesis, an emerging prognostic factor for active MM.26 A BM evaluation should be offered to all patients, even if asymptomatic, with a serum monoclonal component higher than 1.5 g/dL, based on a large Italian study showing that the probability of detecting a plasma cell infiltration ≥10% in asymptomatic patients with a serum M-protein ≤15 g/L is 4.7% for IgG subtype.27 The absence of significant tumor burden with an M protein of <15 g/L and a normal FLC ratio seem to predict an MGUS-like behavior.28

In several European centers the evaluation is deferred in asymptomatic patients with apparent IgG MGUS if the serum M-protein is ≤15 g/L and without end-organ damage, until there is evidence of progression to symptomatic disease.29 Accordingly, the European Myeloma Network does not routinely recommend bone marrow evaluation when patients have a serum IgG M-protein ≤15 g/L or IgA M-protein ≤10 g/L without CRAB symptoms.29 A recent large retrospective series including patients presenting with low risk MGUS profile and no CRAB signs, confirmed that the risk of missing a diagnosis of SMM and MM by omitting bone marrow aspirate and biopsy was less than 1%. Thus, based on comorbidities, frailty,28 age and amount of monoclonal component bone marrow evaluation could be deferred, preferring clinical and laboratory monitoring.22,29

After the initial diagnosis of SMM, in our Center we repeat laboratory tests,21 including a hemogram, biochemistry tests, serum free
light chain (sFLC) ratio, serum and urine protein studies in 3 months to confirm the stabilization of the monoclonal component, as well as the absence of anemia, kidney impairment, and hypercalcemia. Shift from negative to positive urine immune-fixation and Bence Jones proteinuria are predictor markers of progression to active MM.\textsuperscript{30,32,33} Dynamic monitoring of sFLC\textsuperscript{34} and M component are helpful to identify evolving SMM type,\textsuperscript{35} with an emerging prognostic role.\textsuperscript{36} Based on the pioneering work of Dr. Dispenzieri and colleagues who evaluated disease progression in 273 SMM patients at Mayo Clinics, an involved/uninvolved FLC ratio of $\geq8$ is a significant risk factor for progression,\textsuperscript{37} and if sFLC ratio rises to $\geq100$, the 2 year risk of progression approaches $80\%$, thus to be considered a myeloma-defining event in the IMWG guidelines.\textsuperscript{38}

**Imaging: the emerging role of whole-body MRI**

Imaging is required in the initial work-up of any suspected plasma cell disorder,\textsuperscript{22,30} to collect detailed information about the BM involvement, by whole-body MRI\textsuperscript{39} and to early identify osteolytic bone lesions, preferentially by low-dose whole-body CT.\textsuperscript{40} In 20% SMM patients the X-rays scans is silent due to bone loss $\leq30\%$,\textsuperscript{40} thus whole-body CT screening for bone lesions can lead to change clinical management in almost one third of patients in the real-life setting.\textsuperscript{41} Latest IMWG guidelines recommended to perform WBCT (either CT alone or as part of an FDG-PET/CT protocol) as the first imaging technique at suspected SMM and, if these images are negative or inconclusive, to perform whole-body MRI.\textsuperscript{42} Indeed, 18F fluorodeoxyglucose (FDG) integrated with computed tomography (18F-FDG PET-CT) provides information more valuable than whole body X-rays for the assessment of myeloma bone disease in areas not covered by MRI.\textsuperscript{43,44}

Imaging can also provide prognostic additional information. Moulopoulos et al. first demonstrated that in patients with asymptomatic myeloma, time to progression (TTP) was shorter (16 vs 43 months) for patients with abnormal MRI (due to presence of focal, diffuse or variegated pattern) versus normal MRI.\textsuperscript{45} An abnormal marrow signal of MRI of the spine in a patient with SMM was associated with a significant factor for progression to symptomatic myeloma (median 15 months) and confirmed by similar findings in independent cohorts, leading to the new IMWG criteria to identify MM patients.\textsuperscript{38}

Since in MM imbalanced distribution of active lesions is frequently observed in medical imaging, associated to spatial heterogeneity,\textsuperscript{46,47} integrative imaging, like whole body MRI or immunoPET, can add valuable information diagnosis and prognosis. The preliminary results of immunoPET scans based on antibody-based radiotracers targeted for CXCR4, BCMA or CD38\textsuperscript{48} are shifting imaging from a metabolic toward a functional technique to monitor overttime and in different body areas potential therapeutic targets.\textsuperscript{44,48} The imaging biomarker speed of growth, defined as development of the total tumor volume over time as detected by whole-body MRI, can identify 63.2% of SMM patients who progress within 2 years, including a high-risk group with a 2-year progression rate of 82.5%.\textsuperscript{49} In newly-diagnosed MM significant splenic signal loss on diffusion-weighted MRI (DW-MRI) images, was seen in 24% patients and preserved in MGUS, reflecting increased tumor burden and associated to inferior outcome,\textsuperscript{50} but its role has never been tested in SMM.

### Risk assessment

After the diagnosis of SMM, it is necessary to evaluate the risk of progression to symptomatic disease, integrating several parameters that should be taken in account to predict the risk of progression to symptomatic MM and address potential therapeutic interventions.

#### The Level and the Type of Serum M Protein Concentration:

The size and type of the serum M-protein are two independent significant risk factors for progression in MM.\textsuperscript{2,6,51,52} In a large retrospective series, the median time to progression (TTP) in patients with a component $\geq4g/dL$ was 18 months vs 75 months in patients with a lower serum M-protein; the median TTP was significantly shorter in patients with IgA versus IgG M-protein;\textsuperscript{53} however, re-classifying SMM patients according to 2014 IMWG criteria for active MM, size and quality of M-protein have lost their prognostic meaning.\textsuperscript{8} Evolving changes in M-protein and hemoglobin,\textsuperscript{35,56} associated to FLC ratio $\geq8$, and BMPC $\geq20\%$ clearly identify those patients to requiring restaging with BM biopsy and imaging to validate progression.\textsuperscript{53}

#### Percentage of Bone Marrow Plasma Cells:

Based on two large independent series,\textsuperscript{6,37,54} BMPC $\geq20\%$ is associated to shorter time progression. This cut-off has been validated in a large series of patients with SMM diagnosed according to 2014 IMWG criteria for active MM and it is part of the 20/2/20 IMWG score.\textsuperscript{8}

#### Genomic and transcriptomic abnormalities

Genomic aberrancies are associated to increased risk of progression through active MM.\textsuperscript{14,55-57} Among findings available in clinics, the presence of del (17p13), t(4;14), +1q21 and hyperdiploidy is associated to inferior TTP.\textsuperscript{58,59} Based on a cohort of 331 patients with MGUS and SMM, Dhodapkar and colleagues identified a gene expression profiling (GEp70-gene signature) signature as an independent predictor of the risk of progression to MM.\textsuperscript{60} The same group identified four genes that can predict high risk of progression from smoldering to symptomatic MM.\textsuperscript{61} However, these techniques are note reproducible in all centers, require a specific expertise, and are burdened with technical issue such as the necessity to enrich neoplastic plasma cells and to avoid bone marrow hemodilution. Further efforts are required for quality control, harmonization and standardization before wider use in routine practice.\textsuperscript{62}

#### Immunophenotyping

The Spanish group found that 60% SMM patients have aberrancies in the immunphenotype of BMPCs similar to MM, where $>95\%$ of PCs are aberrant and only $<5\%$ of the detected PCs are normal, with a median TTP to symptomatic MM of 34 months.\textsuperscript{63} Similar aberrancies in the phenotype can be monitored also in peripheral blood, looking at circulating Plasma Cells (PBPC).\textsuperscript{63} Patients with high circulating PBPC have a higher risk to progress to active disease within 2 years compared with patients without high circulating PC (71 versus 25% respectively). However, the detection of circulating PC is still not standardized and difficult to reproduce,\textsuperscript{64} despite in the last years a terrific effort is challenging data interpretation and prospective clinical trial design of subsequent studies to incorporate and harmonize flow cytometry for\textsuperscript{65} disease assessment in both smoldering and active MM.\textsuperscript{52,63,66}

#### Immunoparesis

The suppression of one or more uninvolved immunoglobulins is a significant risk factor for progression in SMM, as shown by two independent large series. In the Mayo Clinics’ experience, the median TTP was 159 months for patients without immunoparesis, 89 months in those with a reduction of only one isotype, and 32 months in patients with reduction in two isotypes of uninvolved immunoglobulins. The Spanish group reported similar findings, with a median TTP of 31 months in SMM patients carrying one or more reduced
uninvolved immunoglobulins.23

**Serum-Free Light-Chain Ratio:** Based on the first work of the Mayo Clinic group, including 273 SMM patients, an involved/uninvolved FLC ratio of ≥ 2.8 is a significant risk factor for progression.37 When the involved/uninvolved FLC ratio rises to ≥ 100, the median TTP is only 15 months, and the 2-year risk of progression approaches 80%. Therefore, this can be considered as a biomarker of early progression and such patients are now classified as MM.38 However, recent studies suggest that this cut-off for sFLC may not confer as high a risk as initially defined,67 and additional factors should be added, thus conveying that a single biomarker cannot be predictive for evolutionary trajectory in SMM through progression to symptomatic MM.15

**Prediction models** In lack of a single reliable biomarker, clinical and laboratory findings should be integrated. To this end, several models and relevant scores have been developed and tested in clinical trials.15

In US the risk assessment of progression to MM in SMM is largely based on the Mayo Clinic (version 2007, 2008 developed before the 2014 update in the MM criteria4,22 and Arkansas models.

The Mayo 2007 score takes in account only two lab findings, BMPC ≥ 10% and serum M protein ≥ 3 g/dL to identify three groups of patients with the risk of progression to active MM at 5 years of 15%, 43% and 69% respectively. Adding FLC ratio > 8, the 5-year progression rates were 25%, 51%, and 76%, in the presence of one, two, or three risk factors respectively, in the Mayo 2008 score.37 Taking in account the 2014 update of the MM criteria the score has been further improved in the 20/2/20 Mayo 2018 version, combining the presence of BMPCs≥20%, a value of M-component ≥ 2 g/dL and sFLC ratio>20 to identify three groups of patients with the risk of progression to active MM at 5 years of 22.5%, 46.7% and 81.5% respectively.8

The Arkansas risk-stratification model is based on gene-expression of 4 genes, M protein ≥ 3 g/dL and albumin level <3g/dL to identify three groups of patients with the risk of progression to active MM at 2 years of 5%, 44.8% and 85.7% respectively.68

In Europe, the Spanish group proposed the PETHEMA score, developed before the 2014 update in the MM criteria6 on a cohort of 106 patients, combining the presence of aberrant BMPCs (aPCs/BMPC ≥ 95%) and immunopaesis to address the risk of progression to active MM at 5 years is 4%, 46%, and 72%, for patients with none, 1, or 2 risk factors respectively.21 The Danish group suggested a model derived form a population-based study, involving 297 patients, in which combining M protein ≥ 3 g/dL an immunopaesis could distinguish three groups of patients with the risk of progression to active MM at 5 years of 9%, 24% and 55% respectively.69

So far, the Mayo 2008 and the PETHEMA score, developed before the Mayo 2008 score.37 Thus most investigators use the 20/2/20 Mayo 2018 score based on parameters (M-protein size and the amount of BMPCs) available and reproducible in all centers.

**Follow up**

Outside the clinical trial setting, additional examinations should be recommended only in case of clinical evidence for progressive disease from the routine work-up. Subsequent follow-up should be individualized, based on risk of progression, evaluated by application of one of the above-mentioned scores and life expectancy.

The EMN and IMWG recommends follow-up 3 months after the initial SMM diagnosis, and if the results are stable, follow-up should be every 4-6 months for a year, and then every 6-12 months.

Since the likelihood of finding bone lesions at skeletal survey is very low for M-protein IgG ≤15 g/L (2%) and IgA ≤10 g/L (0.0%),27 in Europe imaging evaluation is not routinely recommended when patients have a serum IgG M-protein ≤15 g/L or IgA M-protein ≤10 g/L without bone pain,28 and for asymptomatic patients with limited life expectancy.29 In US, based on IMWG recommendations, imaging MRI is performed on an annual basis for at least 5 years and later based on clinical suspicion of progression, according to the findings of a large study at Mayo Clinics that suggested new cut-offs for prognostic variables to risk stratify SMM patients, the Mayo score 20/20/20, showing a stabilization of risk progression at 3%-5% per year beyond 5 years of follow-up.8

In our Center, we generally use the 20/20/20 Mayo 2018 prognostic scoring system,8 associated to CT-scan findings, evolving nature of the M-protein and sFLC, and Bence Jones proteinuria and distinguish SMM patients for further the follow-up in three categories:

- **low risk,** with a probability of progression at 5 years less than 10%, that should be followed similarly to MGUS patients, every 6 months in the first two years and then every 12 months

- **intermediate risk** with a probability of progression at 5 years less than 50%. They represent the true SMM patients that should be followed every 3-6 months

- **high risk,** with a probability of progression at 2 years more than 50%, for whom is under investigation the need of early treatment. Based on current evidences, outside of the clinical trial setting, treatment for SMM or MGUS is not recommended and treatment should be given only in case of symptomatic progression, as detected by the presence of one of the myeloma-defining events.4,22

In our Center, we propose at baseline CT-scan, bone marrow biopsy and aspirate to asymptomatic patients when M-component in serum is higher than 1 g/dL for IgA subtype and 15 g/L for IgG subtype27,29 and to all patients with Bence Jones proteinuria due to the increased probability to progress to high-risk SMM and active MM.32,33,71 Further imaging by CT-scan or MRI is performed every 18-24 months in lack of bone pain or if not differently clinically indicated.

The dynamic evaluation of additional lab findings can be helpful, including the increase of at least 25% of M-protein or s-FLC over time and hemoglobin reduction by at least 0.5 g/dL within the first year, that prompt us to reduce the follow up lag time to every 2 months, to detect the presence of one of the myeloma-defining events which require active anti-MM treatment. If after the second year of follow up M-protein, s-FLC and hemoglobin remain stable, the follow-up schedule can change to one visit per year. In addition, at least once a year we evaluate Pro-BNP and total urine protein to detect any cardiac or renal impairment that could lead to a diagnosis of amyloidosis.

**Clinical management and treatment**

Currently, management of SMM, especially of high-risk patients, is challenging, also because the available risk stratification models do not help to predict accurately the risk of progression. In the uncertainty to overtreat asymptomatic patients without improving quality of life or overall survival, waiting for mature results of completed or ongoing clinical trials (see below), no drugs are approved for the
treatment. For each individual patient a close observation remains the standard of care, taking in account the requirements of supportive and preventive measures to reduce the incidence of impaired bone mineral density, recurrent infections and cardiovascular disease and to optimize timing to start treatment when MM is diagnosed, even if the contribution of previous diagnosis of asymptomatic disease has been formally shown only for MGUS patients, and this approach reflects the importance of monitoring tumor load in a linear evolution from asymptomatic through active MM.

Supportive care

In MGUS and SMM patients there is an increased incidence of reduced bone mineral density, osteoporosis and atraumatic fractures, associate to lower levels of vitamin D. In these cases, beyond a careful evaluation of myeloma defining event by imaging as discussed above, supportive care should include monitoring and supplementation of vitamin D and calcium could be helpful, despite data from large prospective cohorts miss. In the past, early intervention with zoledronic acid did not show any advantage in increase overall survival, but they could still be used to prevent myeloma-related skeleton events.

Clinical implication of immunoparesis is the secondary antibody deficiency, whose biological contribution to MM evolution is still under investigation. As consequence of both innate and cellular immunity, immunosenescence, T-cell anergy and addiction of neoplastic plasma cells to TLR4 signaling, SMM patients have increased risk to develop bacterial and viral infections. In patients with active MM, both 13-valent pneumococcal conjugate vaccine (PCV13) and 23-valent pneumococcal polysaccharide vaccine (PPSV23) can increase anti-pneumococcal antibodies, and preliminary observations suggest that vaccination is negatively correlated with disease progression. Even if these preliminary observations have not maturely shown in the SMM setting, it is reasonable that a policy to improve the prevention of viral and bacterial infection should be tested in each single center and offered to all SMM patients with a positive anamnese for recurrent infections, including immunoglobulin replacement, as suggested by the Canadian group. We suggest that clinical evaluation and anamnestic aspects are fundamental to decide if may be helpful to prescribe or not substitutive therapy in MM. In our Center, we recommend seasonal flu vaccination and anti-pneumococcal vaccination, with either PCV13 or PPSV23 and offer sub-cutaneous, home delivered, immunoglobulin replacement when more than 3 infective episodes are registered in the previous 6 months, based on promising results of this approach in MM patients.

Since potentially clonal and dysplastic hematopoiesis may co-exist with MGUS and MM, associated with increased risk of atherosclerotic arterial disease, there is an emerging interest in defining the cardiovascular risk due to M-component. Despite data are not available for SMM, a retrospective series found an increase of cardiovascular events (coronary, peripheral and cerebrovascular) in both MGUS and MM patients, suggesting that the same could happen in SMM setting. In lack of any trial-derived evidence of specific prophylactic strategy to adopt, cooperative studies involving US and European Institutions of well-identified and classified SMM patients could clarify in a near future how to profile and manage cardiovascular risk in SMM.

Treatment options based on outcome goal: delay progression or curative attempt?

When ESMO guidelines have been released in 2016 only 15% MM patients could be cured and for this reason immediate treatment for patients with indolent myeloma could not be recommended, strongly encouraging enrollment in clinical trials for high-risk SMM. After failing of thalidomide in preventing progression through MM, in the last five years the scenario has been changed and more than 50 trials are ongoing to test the feasibility, safety and efficacy of drugs active in MM that alone or in combination could be offered to high-risk SMM. Both European and US groups have shown that the early addition of lenalidomide to treatment significantly prevents SMM progression to active MM.

However, there are still major concerns about study design, in particular primary endpoint (time to progression versus overall survival) and inclusion criteria, since the first trials included, in a variable proportion, patients who are classified as MM according to 2014 IMWG criteria, using uniform stratification risk models, to make the results comparable each other and the urgent need of additional surrogate endpoints, like achievement of minimal residual negativity.

There are two main strategies arising from the study designs: delay MM onset or eradicate MM cells in the attempt to offer a cure. According to the first goal, a gentle approach, fixed-term and steroid-free, has been proposed by US investigators; on the opposite, a most aggressive approach, including a total therapy, with induction, autologous stem cell transplantation (ASCT) and maintenance regimen with a curative intention is under investigation.

With the main goal to find a cure for MM, investigators from both the Spanish Myeloma Group in Europe and the Mayo Clinics in US, have shown that the early addition of lenalidomide to treatment significantly prevents SMM progression to active MM.

In the Spanish randomized phase 3 study early intervention consisting of nine cycles of lenalidomide– dexamethasone induction, followed by lenalidomide maintenance, compared with observation only in patients with high-risk SMM, defined according to the PETHEMA score, showed longer TTP and OS for the lenalidomide–dexamethasone group (median TTP: not reached vs. 21 months; 3-year OS: 94% vs. 80%). The PETHEMA trial demonstrated for the first time that early treatment with lenalidomide and dexamethasone delayed time to progression to active disease, and provided a significant improvement in overall survival, confirmed by the updated follow up at ten years presented at EHA 2020 (Abstract #EP950). However, major concerns raised from the inclusion criteria, based on the PETHEMA score that are not reproducible in all centers. In addition, in this study the bone lesions were evaluated by X-rays skeleton survey, reflecting the standard practice at that time, and that is probably one of the reasons of the exceptionally short median TTP of 24 months in the arm control. The ancillary substudy of the QUIREDEX trial support the importance of lenalidomide to delay the progression to MM due to recovery of T-cells activation and proliferation.

To better define the contribution of lenalidomide exposure to delay MM onset in SMM patients, reducing the bias associated to steroids, the E3A06 trial investigated continuous exposure to lenalidomide 25 mg versus observation, achieving in the experimental arm 91% 3- yrs PFS, confirming the promising role of lenalidomide in delay onset of MM-defining events or end-organ damage but confirming that the benefit of lenalidomide treatment is limited to high-risk SMM patients.

Other pilot trials are investigating the role of immunotherapy using monoclonal antibodies as single agents, including elotuzumab (anti-SLAMF7) tested in a phase II study, daratumumab (anti-CD38) tested in a phase II study, silvestimab (anti-IL-6) and pembrolizumab (anti PD-1).
extensively described in an excellent recent review,\textsuperscript{106} we recommend our readers for further details.

Additional single agents that more directly engage the immune system, tested in phase I-II studies, include pan-KIR2D inhibitor IPH2101,\textsuperscript{107} the anti-human anti-intercellular adhesion molecule-1 monoclonal antibody BI-505,\textsuperscript{108} rice bran arabinoxylan and curcumin.\textsuperscript{109,110}

The GEM-CESAR phase II single-arm clinical trial led by Spanish Myeloma Group enrolled 90 high-risk SMM (defined according to PETHEMA score) patients who received induction with six 4-week cycles of carfilzomib, lenalidomide and dexamethasone (KRd) regimen, followed by single ASCT, KRd consolidation and maintenance with lenalidomide. Preliminary results from 77 patients who completed induction, HDT-ASCT, consolidation, and 1 yr of maintenance, showed that 81% of patients achieved ≥ CR and 62% were MRD negative (Mateos. ASH 2019. Abstr 781).

The safety and efficacy of KRd regimen have been confirmed in a small cohort of high-risk SMM treated at MSKCC in New York, with more 90% of MRD-negative responses, but longer follow-up is required for definitive conclusions.\textsuperscript{111}

There are still open questions before to prime treatment to all SMM patients:
1. What characteristics of immune status, singularly or in cooperation, and mutational signatures co-vary with racial/ethnic differences for asymptomatic MM onset and how these factors influence progression to active MM?
2. Are there differences in immunological triggers (e.g. microbiote composition, dietary and life style) that could modify the evolution pattern and response to treatment?

Conclusions: unmet clinical needs and open questions

In conclusion, to manage each newly diagnosed SMM patient, it is necessary to identify the risk of progression to individualize follow-up schedule, taking in account all the available data, in a dynamic perspective. Waiting for the results of ongoing clinical trials enrolling SMM patients defined according to the 20/2/20 score, the primary goal of clinical management is delaying onset of CRAB symptoms and improving quality of life. Real-world life experiences will be needed in a near future, to explore the impact of advanced age, co-morbidities and the possibility to reduce drug dosage and exposure.

If early treatment could cure SMM patients, conveying sustained MRD negativity and longer overall survival, without giving unreasonable adverse events and secondary neoplasms, is a challenging paradigm of near future.

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