SMOLDERING MULTIPLE MYELOMA

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Abstract

Smoldering multiple myeloma (SMM) is an asymptomatic clonal plasma cell disorder. SMM is distinguished from monoclonal gammopathy of undetermined significance (MGUS) by a much higher risk of progression to multiple myeloma (MM). There have been major advances in the diagnosis, prognosis, and management of SMM in the last few years. These include a revised disease definition, identification of several new prognostic factors, a classification based on underlying cytogenetic changes, and new treatment options. Importantly, a subset of patients who were previously considered SMM are now reclassified as MM, based on biomarkers that identify patients with an 80% or higher risk of progression within 2 years. SMM has assumed greater significance based on recent trials which show that early therapy can be potentially beneficial to patients. As a result, there is a need to accurately diagnose and risk-stratify patients with SMM, including routine incorporation of modern imaging and laboratory techniques. In this review, we outline current concepts in diagnosis and risk-stratification of SMM, and provide specific recommendations on management of SMM.
Smoldering multiple myeloma (SMM) is an asymptomatic clonal plasma cell disorder. Kyle and Greipp initially described the entity as an intermediate stage between monoclonal gammopathy of undermined significance (MGUS) and multiple myeloma (MM) based on 6 patients with increased bone marrow plasma cells ≥10% who remained stable for 5 or more years without chemotherapy. SMM has since been well characterized, and high-risk subsets of SMM are increasingly recognized as the optimal phase of MM evolution to test early treatment strategies.

SMM is distinguished from MGUS primarily for clinical reasons since the risk of progression to malignancy in the first 5 years following diagnosis is different; 10% per year in SMM versus 1% per year in MGUS. SMM is biologically heterogeneous; it is a clinically-defined entity comprised of a subset of patients with biological premalignancy (i.e., MGUS) and a subset with CRAB-(hypercalcemia, renal failure, anemia, lytic bone lesions)-negative and/or other MDE-(myeloma defining events)-negative malignancy (i.e., MM). It includes patients who behave like MGUS with a very low rate of progression, as well as those who develop clinical symptoms and end-organ damage within the first two years of diagnosis. Unfortunately, at the current time, there is no single pathologic or molecular feature that reliably can be used to distinguish patients with SMM who have only clonal premalignant plasma cells from those with clonal malignant myeloma cells.

DEFINITION

SMM is defined by the presence of a serum monoclonal (M) protein of ≥ 3g/dl and/or 10-60% clonal bone marrow plasma cells (BMPC) with no evidence of end-organ damage (i.e. CRAB criteria) or other MDE. It is distinguished from MGUS based on the level of serum M protein.
and the percentage of clonal BMPCs (Table 1). The disease definition of SMM was recently updated to exclude patients with bone marrow plasma cells of 60% or higher, serum involved/uninvolved FLC ratio of $\geq 100$, and those with 2 or more focal lesions (typically indicating focal bone marrow abnormalities) on magnetic resonance imaging. Such patients have an approximately 40% per year risk of progression and are now considered as MM.

Light chain SMM is a subtype of SMM in which there is monoclonal free light chain (FLC) excess with no expression of immunoglobulin heavy chain (IgH). This entity is characterized by excess secretion of monoclonal FLC in the urine (Bence Jones proteinuria) (Table 1).

**CLINICAL PRESENTATION AND COURSE**

By definition, SMM is an asymptomatic condition. At this time, there is no population-based registry of SMM patients. Based on available single-center registries, the typical age at SMM diagnosis is approximately 50-70 years. Because SMM is asymptomatic, newly diagnosed patients are typically diagnosed when an M protein is discovered on laboratory testing as part of the work-up of a variety of disorders. Unlike MGUS which is present in approximately 2-3% of the general population over the age of 50, SMM is a relatively uncommon clinical entity. A recent study based on the Swedish Myeloma Registry, a prospective observational registry designed to document real-world treatment and outcomes in newly diagnosed MM patients, 14% of the patients were SMM.

The clinical course of SMM was reported by Kyle and colleagues in a retrospective study of 276 patients seen at the Mayo Clinic between 1970-1995. In this study, the risk of progression to malignancy was 10% per year for the first 5 years. After 5 years, the risk of
progression decreased to 3% per year for the next 5 years, and approximately 1% per year thereafter. Thus 50% of patients with newly diagnosed SMM progress within the first 5 years, and these patients probably have early MM without CRAB features. In contrast, approximately one-third of patients with newly diagnosed SMM will not progress in the first 10 years following diagnosis, and these patients probably have a premalignant state (biologic MGUS) even though the clonal BMPC percentage or M protein levels are higher than that specified in the clinical definition of MGUS.\textsuperscript{3,6,20}

**RISK FACTORS FOR PROGRESSION**

The prognosis of SMM varies considerably, and it is possible to more accurately estimate risk of progression using a variety of prognostic variables. Although the variables listed below were studied prior to recent changes to the definition of SMM, the effect of such changes on the estimates is likely to be minimal since the proportion of patients upstaged from SMM to MM on the basis of the new criteria are relatively small (10-15%).\textsuperscript{7}

**M protein concentration**

In the above mentioned retrospective study of 276 patients with SMM seen at Mayo Clinic, Kyle and colleagues found that the size of the serum M protein was a significant risk factor for progression of SMM (P<0.001).\textsuperscript{1} The median TTP in patients with markedly elevated serum M protein (\(\geq 4\text{gm/dL}\)) was 18 months compared with 75 months in those with serum M protein less than 4gm/dL, P<0.001. Similar results have also been reported by the Spanish group in a study of 93 patients with SMM.\textsuperscript{21} In light chain SMM, the risk of progression is higher based on the level of the urinary M protein. In a study by Kyle and colleagues, the 5 year risk of progression of
light chain SMM was 19% with urinary M protein 0.50–0.99 gm/24 hours versus 39% with urinary M protein $\geq$1.0 gm/24 hours.\textsuperscript{15}

**M protein type**

The type of M protein also influences the risk of progression in SMM. Kyle and colleagues found that TTP is significantly shorter in patients with IgA M protein compared with IgG M protein, median 27 months versus 75 months, respectively, $P=0.004$.\textsuperscript{1} In a recent study, the risk of progression in patients with light chain SMM was found to be lower with median TTP of 159 months; probability of progression was 28%, 25%, and 56% at 5, 10, and 15 years respectively.\textsuperscript{15}

**Immunoparesis**

Suppression of one or more uninvolved immunoglobulins (immunoparesis) is seen in over 80% of patients; approximately 50% of patients have suppression of two uninvolved immunoglobulin isotypes.\textsuperscript{1} In the Mayo Clinic study of 276 patients with SMM, immunoparesis was a significant risk factor for progression to MM or related disorder.\textsuperscript{1} The median TTP was 159 months in patients with normal levels of uninvolved immunoglobulins, 89 months in those with a reduction in one isotype, and 32 months in patients with reduction in 2 isotypes of uninvolved immunoglobulins, $P=0.001$. The same effect was also seen in a Spanish study of SMM, where a decrease in one or two of the uninvolved immunoglobulins was a significant prognostic parameter in SMM; median TTP not reached with normal immunoglobulins versus 31 months with reduction in one or more uninvolved immunoglobulins, $P<0.01$.\textsuperscript{21} Suppression of uninvolved immunoglobulins has also been found to be a risk factor for progression in light chain SMM.\textsuperscript{15}
Serum FLC ratio

The serum FLC assay (Freelite®, The Binding Site Limited, Birmingham, U.K.) measures free kappa and lambda light chains that circulate unbound to immunoglobulin heavy chains. The normal ratio FLC kappa/lambda ratio is 0.26-1.65. In clonal plasma cell disorders, there is excess production of one FLC type (the clonal component, referred to as the “involved” light chain) and this leads often to an abnormal FLC ratio. Dispenzieri and colleagues studied 273 patients with SMM seen at the Mayo Clinic from 1970 to 1995. An involved/uninvolved FLC ratio of ≥8 was a significant risk factor for progression, hazard ratio, 2.3; 95% CI, 1.6-3.2, P<0.001. Median TTP was 30 months in patients with an involved/uninvolved FLC ratio of ≥8 compared with 110 months for those with FLC ratio less than 8. The risk of progression in the first 2 years following diagnosis is approximately 40% in patients with an involved/uninvolved FLC ratio of ≥8.

The risk of progression associated with abnormal FLC ratio is a continuum. Thus, 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%. Such patients are now considered as MM.

Change in Monoclonal Protein Level

A key variable that could potentially identify patients with a high risk of progression is change in M protein levels over time. However, such studies have been hampered by the fact that patients with SMM have not been uniformly followed at specified intervals outside of clinical trials. In one study of 53 patients with SMM, patients with a progressive rise in M protein (evolving type) had a higher risk of progression compared to those with stable M protein levels. In this study, the evolving type was defined as an increase in the serum M protein level by ≥10% on two
successive evaluations. Patients with an evolving type of SMM had a 65% probability of progression to MM or related disorder in the first 2 years. TTP was 1.3 years versus 3.9 years in the evolving versus non-evolving types of SMM, respectively, \( P = 0.007 \). A recent study by the Southwest Oncology Group (SWOG) found that patients with an M protein of \(<3 \text{gm/dL}\) which increased to an M protein level of \(\geq 3 \text{ g/dL}\) over 3 months was associated with a risk of progression of approximately 50% at 2 years.\(^{28}\)

However, in the observation arm of the Spanish trial of SMM,\(^5\) patients with a rise in M protein of \(\geq 25\%\) over two successive evaluations did not have a significant increase in risk of progression compared with patients without such an increase; 2-year risk, 69% versus 75%, respectively (M.V. Mateos, personal communication).

We do believe that a rise in M protein level, especially over a short period of time is of concern, and we await more data on how best to incorporate such a finding in the management of SMM.

**Extent of Bone Marrow involvement**

The risk of progression in SMM increases with the extent of bone marrow involvement. In the Mayo Clinic study, the median TTP was 117, 26 and 21 months for patients with BMPC <20%, 20-50% and \(>50\%\) respectively, \(P<0.001\).\(^1\) Subsequent studies show that the risk of progression increases dramatically when the BMPC is \(\geq 60\%\), with a 2-year risk of progression of approximately 90%, and such patients are now considered as MM.\(^9,10\) BMPC estimate is done on either the bone marrow aspirate or biopsy examination, and in the event of a discrepancy the higher of the two values should be used.\(^7\)
Immunophenotype

Immunophenotyping with multiparametric flow cytometry is useful in determining prognosis in SMM by accurately distinguishing and quantitating BMPCs with malignant potential from normal PCs.\textsuperscript{5} Aberrant phenotype is defined by the absence of CD19 and/or CD45 expression, decreased expression of CD38, and overexpression of CD56. In MGUS, a substantial proportion of plasma cells are polyclonal and exhibit normal immunophenotype, whereas in MM almost all plasma cells seen (>95%) are clonal and have an aberrant immunophenotype.\textsuperscript{21,29,30} In a study of 93 patients with SMM, Perez-Persona and colleagues found 60% of patients with SMM have an aberrant immunophenotype similar to MM (>95% PCs aberrancy; <5% of the detected PCs are normal).\textsuperscript{21} The risk of progression in such patients was significantly higher compared to those who had a lower rate of aberrancy in the detected BMPC population; median TTP was 34 months versus not reached for patients with 95% or greater versus less than 95% aberrant PC, respectively, P<0.001.

Tumor genetic abnormalities

Table 3 provides the classification of SMM based on underlying cytogenetic abnormalities.\textsuperscript{31,32} The Mayo Clinic group recently analyzed the prognostic influence of cytogenetic abnormalities in a series of 351 patients with SMM.\textsuperscript{31} Patients with t(4;14) and/or del(17p) were defined as high risk SMM. These patients had a significantly shorter median TTP (24 months) compared with patients with trisomies (intermediate-risk), other cytogenetic abnormalities including t(11;14) (standard-risk) and no cytogenetic abnormalities (low-risk). Similar results have also been reported by Neben and colleagues in a study of 249 patients with SMM.\textsuperscript{32}
Dhodapkar and colleagues have assessed the value of gene expression profiling (GEP) signatures in 331 patients with MGUS and SMM. An increased risk score (>−0.26) based on a 70-gene signature (GEP70) was an independent predictor of the risk of progression to MM. Further studies are needed to determine incremental value of GEP compared with other more readily available risk factors discussed earlier.

**Circulating Plasma Cells**

Bianchi and colleagues studied 91 patients with SMM who were tested for circulating PCs using an immunofluorescent assay. High level of circulating PCs was defined as absolute peripheral blood PCs >5000 x 10⁶/l and/or >5% cytoplasmic immunoglobulin (Ig) positive PCs per 100 peripheral blood mononuclear cells. Patients with high circulating PCs were significantly more likely to progress to active disease within 2 years compared with patients without high circulating PCs, 71 versus 25%, respectively, P=0.001. However the methods that have been published for estimating circulating PCs are not universally available and cut-points using multiparametric flow cytometric methods are needed.

**Imaging**

Magnetic resonance imaging is of prognostic value in SMM. Moulopoulos and colleagues studied the prognostic value of spinal MRI in 38 patients with newly diagnosed asymptomatic MM. Bone marrow abnormalities were detected in 50 of patients, including diffuse, variegated, and focal changes. Patients with abnormal MRI bone marrow changes had a median TTP of 16 months versus 43 months for those with normal MRI studies, P<0.01. Further, median TTP was shorter in patients with focal lesions (6 months) compared with those who had diffuse (16
months) or variegated pattern (22 months). In a more recent study of 149 patients with SMM, Hillengass and colleagues detected focal lesions in 28% of patients using whole-body MRI (wb-MRI), and the presence of such lesions was associated with an increased risk of progression to MM. In the same study, the authors also confirmed the adverse prognostic effect of diffuse bone marrow changes detected on MRI imaging, hazard ratio of 3.5, P<0.001.

Of importance, in the study by Hillengass and colleagues, 15% of patients had more than one focal lesion on wb-MRI imaging. The median TTP in such patients was 13 months, and the 2-year progression rate was 70%. Similar findings have also been found in a study reported by Kastritis and colleagues, and in a study by Dhodapkar and colleagues. Patients with more than one focal lesion are now defined as MM, and should not be considered as SMM.

Data are limited on the role of PET-CT imaging in predicting risk of progression in SMM. However, patients with focal lesions with increased uptake on PET-CT with underlying osteolytic destruction are not considered SMM; they are defined as having MM. In contrast, we need data on the prognostic value of focal lesions that show increased uptake without underlying bone changes. The finding of an increased uptake on PET-CT without bone destruction is not adequate to be considered as an MDE.

**Plasma cell proliferative rate**

A high proliferative rate of clonal PCs is associated with high risk of progression in SMM. In one study, 175 patients with SMM were studied to determine the predictive value of plasma cell proliferative rate measured using a slide-based immunofluorescence method, the plasma cell labeling index (PCLI). The median TTP was 1.2 years in patients with PCLI ≥1 versus 2.6
years with PCLI <1, P<.001. The PCLI is limited by lack of availability in the clinical setting. We are awaiting data from proliferative rate assessed using flow cytometric methods.

**Risk-stratification of SMM**

Two models that have been well studied and subsequently validated in a prospective trial are the one proposed by the Mayo Clinic group and another proposed by the Spanish Myeloma group. The Mayo Clinic model uses the size of the serum M protein and the extent of bone marrow involvement. These two variables are used to classify SMM into 3 risk groups: group 1 with serum M protein $\geq$ 3 g/dL and $\geq$ 10% BMPCs, group 2 with $< 3$ g/dL M protein and $\geq$ 10% BMPCs, and group 3 with M protein $\geq$ 3 g/dL but BMPCs $< 10\%$. The median TTP to symptomatic MM are significantly different among the 3 groups: 2, 8 years, and 19 years, respectively. The probability of progression at 15 years is 87%, 70%, and 39%, respectively. The model developed by the Spanish myeloma group uses the presence 2 risk factors in patients with SMM who have $\geq$10% BMPCs: presence on an aberrant plasma cell immunophenotype in $>95\%$ of clonal PCs and immunoparesis (reduction in one or more uninvolved immunoglobulins by more than 25% compared to normal). Patients with both risk factors abnormal have a median TTP of 23 months, compared to 73 months when only one risk factor is present (either aberrant plasma cell or immunoparesis) and not reached when neither risk factor is present. In a recent randomized trial patients were considered high risk if they met either the Mayo Clinic or the Spanish Myeloma group criteria for high risk SMM. The trial showed that patients meeting these criteria had a median TTP of 24 months, confirming the validity of these criteria.

The Mayo Clinic and Spanish models enable initial risk stratification of SMM that can then be refined using additional prognostic factors. For example, Dispenzieri and colleagues
have shown that the prognostic value of the initial Mayo Clinic model can be improved by adding the serum FLC ratio as a variable. Each model appears to identify unique patients as high risk, with some but not complete overlap. We feel that the classification of high risk SMM is critical, and should be based on all available data on a given patient rather than a restricted set of variables. Table 2 provides revised criteria for high risk SMM that incorporates the Mayo Clinic and Spanish Myeloma criteria, as well as other risk factors that have been well studied and identify patients with a similar risk of progression (~50% risk of progression within 2 years). Patients defined as high risk SMM using these criteria need close follow up and are candidates for clinical trials investigating the value of early therapy.

**DIAGNOSTIC EVALUATION**

Baseline studies should include complete blood count, serum creatinine, serum calcium, skeletal survey, serum protein electrophoresis with immunofixation, 24 hour urine protein electrophoresis with immunofixation, and serum FLC assay. Specialized imaging with either an MRI of the spine and pelvis (or ideally whole body MRI) or (18) F-fluorodeoxyglucose positron emission tomography with computerized tomography (PET-CT) is also recommended to exclude MM. Bone marrow examination is required, and should include fluorescent in situ hybridization (FISH) studies to detect high risk cytogenetic abnormalities, and plasma cell immunophenotyping by multiparametric flow cytometry to enable accurate risk stratification (Table 2).

The M protein, serum FLC levels, complete blood count, calcium, and creatinine should be re-evaluated every 3-4 months. In high risk patients, follow up should continue indefinitely, and should include periodic imaging studies to rule out asymptomatic progression. In low risk
patients, follow up can be reduced to once every 6 months after the first 5 years. In both groups, development of symptoms suggestive of MM or related disorders should be carefully pursued.

In patients with baseline abnormalities on MRI, an increase in number and/or size of focal lesions in follow-up has diagnostic and prognostic value. Therefore, in patients with MRI showing diffuse infiltration, solitary focal lesion, or equivocal lesions, follow-up examinations in 3-6 months are strongly recommended.

**TREATMENT**

The standard of care for SMM has been observation. However it is well recognized that the term SMM encompasses patients with early malignancy (MM) that is still asymptomatic, patients with premalignancy who are at high risk of progression, as well as patients with premalignancy where the progression rate is more in line with MGUS rather than that reported for SMM. The International Myeloma Working Group (IMWG) has revised diagnostic criteria for MM, and a subset of patients with early malignancy are now considered as MM and treated as such. But clearly not all patients with early malignancy can be captured by the new IMWG criteria. SMM still includes a high risk subgroup (Table 2) with an approximately 50% risk of progression within 2 years, and these patients need to be considered for clinical trials testing early therapy.

The rationale for observation as the standard of care for SMM over the years has been the lack of clear data from randomized trials of an overall survival or quality of life benefit with early therapy, the toxicity of therapy in an asymptomatic patient population, and the fact that some patients can be free of progression for many years without any therapy. There is also a
concern that early therapy may increase the risk of selecting resistant clones. We therefore need to accurately identify patients who are most likely to benefit from intervention. Although, there are still no laboratory methods to definitively differentiate clonal premalignancy (biologic MGUS) from clonal malignancy (biologic MM), we now have several biomarkers that help us identify the patients with SMM who are at the greatest risk of progression.44

**Early studies**

Three small studies compared early therapy with melphalan and prednisone (MP) versus observation or MP treatment at the time of progression.45-47 These studies found no significant improvement in overall survival with early therapy.

**Bisphosphonates**

In a small trial, no significant antitumor effect was seen with pamidronate.48 In a subsequent randomized trial, pamidronate administration (60-90 mg once a month for 12 months) was compared to observation in 177 patients with SMM.49 There was no improvement in TTP or overall survival with pamidronate. However, a reduction in skeletal-related events (SRE) was noted with pamidronate compared with observation, SRE rate at progression 39% versus 73%, respectively, P=0.009. In another randomized trial 163 patients with SMM were randomized to zoledronic acid (4 mg once a month for 12 months) versus observation.50 There was no significant difference in TTP, median TTP 67 months versus 59 months with zoledronic acid and observation, respectively, P = 0.8312. However, as with pamidronate, a reduction in the rate of SREs was noted, 56% versus 78%, respectively, P=0.041.

**Thalidomide**
Two small phase II trials initially evaluated the role of thalidomide in patients with SMM.\textsuperscript{51,52} However, therapy was limited by the development of neuropathy in most patients. In a subsequent phase 2 trial of 76 eligible patients with SMM, thalidomide was combined with pamidronate.\textsuperscript{53} However, a reduction in dose of thalidomide due to adverse events was needed in 86\% of patients within the first 2 years.

In a randomized trial, Witzig and colleagues compared thalidomide plus zoledronic acid versus zoledronic acid alone in 68 patients with SMM.\textsuperscript{54} TTP was superior with thalidomide plus zoledronic acid versus zoledronic acid alone, median TTP 2.4 years versus 1.2 years, respectively, $P=0.02$. PR or better was seen in 37\% versus 0\%, respectively, $P<0.001$. However, there were no significant differences in TTP to symptomatic MM, 4.3 versus 3.3 years, respectively, or overall survival, 5-year survival 74\% versus 73\%, respectively.

**Lenalidomide**

In a recent randomized trial, the Spanish Myeloma Group tested the combination of lenalidomide and low-dose dexamethasone (Rd) versus observation in 120 patients with high risk SMM.\textsuperscript{5} TTP was significantly longer in patients treated with Rd compared with the observation group, median TTP not reached versus 21 months, $P<0.001$. Ninety percent of patients treated with Rd achieved a PR, including 26\% who achieved a CR. Symptomatic disease developed in 13 patients (23\%) assigned to Rd versus 47 patients (76\%) assigned to observation. Overall survival was longer with Rd compared with observation, 3-year survival rate 94\% vs. 80\%, respectively, $P=0.03$. This study shows for the first time that the overall survival of high-risk SMM patients can be improved by effective early treatment.
Although the Spanish study results are of importance, there are some limitations which affect generalizability. For example, a high proportion of patients who progressed from SMM to MM within the first 6 months were diagnosed MM due to lytic bone lesions, and it is possible that with routine MRI or PET-CT imaging studies these patients can be identified at baseline. Second, we also need to determine whether patients identified as high risk using other criteria listed on Table 2 besides the ones used in this trial benefit in a similar manner to therapy. Third, some have argued that waiting for end-organ damage in the control arm rather than initiating therapy at the time of biologic progression (as was done in the treatment arm with the addition of dexamethasone) may have biased the trial in favor of early therapy. Although this criticism could be the subject of a subsequent phase III trial, at the time the Spanish trial was conducted the standard of care in the control arm was indeed observation until end-organ damage occurs. The trial thus showed that such an approach is not optimal for high risk patients, and provided the impetus for eliminating the reliance on CRAB features as a requirement to start therapy. Finally, the trial was not designed for regulatory purposes and therefore results need to be reproduced by other studies. In line with this, a randomized trial being conducted by the Eastern Cooperative Oncology Group (ECOG) comparing lenalidomide to observation will be of value.

**Combination therapy**

Some patients with high risk SMM are interested in more aggressive treatment options targeting stringent CR, minimal residual disease (MRD) negative state, and possible cure. Landgren and colleagues have recently reported on 12 patients with high risk SMM on a phase II trial using carfilzomib (a second generation proteasome inhibitor), lenalidomide, and dexamethasone (KRd). In an interim analysis, 7 of 12 patients (58%) achieved CR or stringent CR. Among
these 7 patients, 6 were MRD negative on a sensitive multiparametric flow cytometry assay.
Additional patients are being enrolled, and further results are awaited.

**Recommendations for therapy**

The standard of care for SMM remains observation until development of symptomatic MM.\(^3,38,41,42\) The updated IMWG diagnostic criteria for MM allows us now to initiate therapy prior to end-organ damage based on specific biomarkers, and also allows the use of sensitive imaging criteria to diagnose MM including PET-CT and MRI.\(^7\) Thus patients with high risk SMM who are being observed can be initiated on therapy without waiting for CRAB features to appear.

We recommend that patients with high risk SMM (Table 2) be offered clinical trials testing early intervention. These patients need close follow up indefinitely as discussed earlier.\(^44\) Selected high risk SMM patients with multiple risk factors or evidence of biologic progression (rising M protein level) can be considered for therapy. There are no specific factors to make this determination, and clinical judgment is needed. If therapy is chosen, peripheral blood stem cells should be collected for cryopreservation after approximately 4 cycles of therapy.\(^57,58\) Patients treated with Rd also need appropriate thromboprophylaxis.\(^58,59\) When possible it is important for these patients to be referred to centers specializing in MM therapy. Patients with low-risk SMM who are stable and free of progression after 5 years can be followed less often.

Bisphosphonates (pamidronate or zoledronic acid) administered using the MM dosing schedule (once a month) are not recommended for patients with SMM. Once-yearly bisphosphonate used for the treatment of osteoporosis is appropriate. More frequent dosing every 3-4 months can be considered for selected high risk SMM patients.
FUTURE DIRECTIONS

SMM is an excellent setting to test the impact of several new treatment options in development. This includes the oral proteasome inhibitor ixazomib,\textsuperscript{60,61} elotuzumab,\textsuperscript{62} daratumumab,\textsuperscript{63} and pomalidomide.\textsuperscript{64} Studies using both molecular-based (e.g. VDJ sequencing) and multiparametric flow cytometry-based MRD detection are needed to compare sensitivity, feasibility, and other important aspects.

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Authorship Contributions and Disclosure of Conflicts of Interest

Contribution: S.V.R. wrote the first draft of the paper after reviewing literature and discussion with co-authors O.L. and M.V.M. All authors listed on the paper reviewed the draft, provided detailed input and comments, and contributed to the final paper. All authors approved the final paper.

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References


Table 1. Monoclonal Gammopathy of Undetermined Significance and Smoldering Multiple Myeloma

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Disease Definition</th>
<th>Progression Rate</th>
<th>References</th>
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<tbody>
<tr>
<td>Non-IgM Monoclonal gammopathy of undetermined significance</td>
<td>Both criteria must be met:</td>
<td>1% per year</td>
<td>7</td>
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<tr>
<td></td>
<td>• Serum monoclonal protein (IgG or IgA) &lt;3gm/dL and clonal bone marrow plasma cells &lt;10%, and</td>
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<tr>
<td></td>
<td>• Absence of myeloma defining events or amyloidosis</td>
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<tr>
<td>Smoldering multiple myeloma*</td>
<td>Both criteria must be met:</td>
<td>10% per year in first 5 years. Light chain smoldering multiple myeloma has a lower progression rate of 5% per year</td>
<td>7,15</td>
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<tr>
<td></td>
<td>• Serum monoclonal protein (IgG or IgA) ≥3gm/dL or urinary monoclonal protein ≥500 mg per 24 hours and/or clonal bone marrow plasma cells 10%-60%, and</td>
<td></td>
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</tr>
<tr>
<td></td>
<td>• Absence of myeloma defining events or amyloidosis</td>
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* Note that the term smoldering multiple myeloma excludes patients without end-organ damage who meet revised definition of multiple myeloma, namely clonal bone marrow plasma cells ≥60% or serum free light chain (FLC) ratio ≥100 (plus measurable involved FLC level ≥100 mg/L), or more than one focal lesion on magnetic resonance imaging.
Table 2. Definition of High Risk Smoldering Multiple Myeloma*

<table>
<thead>
<tr>
<th>Bone marrow clonal plasma cells ≥10% and any one or more of the following:</th>
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<tbody>
<tr>
<td>Serum M protein ≥30g/L</td>
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<tr>
<td>IgA SMM</td>
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<tr>
<td>Immunopareshis with reduction of two uninvolved immunoglobulin isotypes</td>
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<tr>
<td>Serum involved/uninvolved free light chain ratio ≥8 (but less than 100)</td>
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<tr>
<td>Progressive increase in M protein level (Evolving type of SMM)†</td>
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<tr>
<td>Bone marrow clonal plasma cells 50-60%</td>
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<tr>
<td>Abnormal plasma cell immunophenotype (≥95% of bone marrow plasma cells are clonal) and reduction of one or more uninvolved immunoglobulin isotypes</td>
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<tr>
<td>t (4;14) or del 17p or 1q gain</td>
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<tr>
<td>Increased circulating plasma cells</td>
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<tr>
<td>MRI with diffuse abnormalities or 1 focal lesion</td>
</tr>
<tr>
<td>PET-CT with focal lesion with increased uptake without underlying osteolytic bone destruction</td>
</tr>
</tbody>
</table>

SMM, smoldering multiple myeloma; M, monoclonal; MRI, magnetic resonance imaging; PET-CT, positron emission tomography-computed tomography

* Note that the term smoldering multiple myeloma excludes patients without end-organ damage who meet revised definition of multiple myeloma, namely clonal bone marrow plasma cells ≥60% or serum free light chain (FLC) ratio ≥100 (plus measurable involved FLC level ≥100 mg/L), or more than one focal lesion on magnetic resonance imaging. The risk factors listed in this Table are not meant to be indications for therapy; they are variables associated with a high risk of progression of SMM, and identify patients who need close follow up and consideration for clinical trials

† Increase in serum monoclonal protein by ≥25% on two successive evaluations within a 6 month period
Table 3. Cytogenetically Defined Risk-Based Classification of Smoldering Multiple Myeloma

<table>
<thead>
<tr>
<th>Risk</th>
<th>Cytogenetic Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>High-Risk</td>
<td>t(4;14) del(17p) 1q gain</td>
</tr>
<tr>
<td>Intermediate-Risk</td>
<td>Trisomies without IgH translocation</td>
</tr>
<tr>
<td>Standard-Risk</td>
<td>Other IgH translocations including t(11;14), t(14;16) and t(14;20)</td>
</tr>
<tr>
<td></td>
<td>Presence of trisomies and IgH translocation, except t(4;14) Monosomy13/del(13q)</td>
</tr>
<tr>
<td>Low-Risk</td>
<td>No abnormalities (normal or insufficient)</td>
</tr>
</tbody>
</table>

IgH, immunoglobulin heavy chain

Smoldering multiple myeloma

S. Vincent Rajkumar, Ola Landgren and María-Victoria Mateos

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