Smoldering Multiple Myeloma requiring treatment – time for a new definition?

Short title: Redefining smoldering MM

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ABSTRACT

Smoldering multiple myeloma (SMM) bridges the gap between monoclonal gammopathy of undetermined significance (MGUS) – a mostly pre-malignant disorder – and active multiple myeloma (MM). Until recently, no interventional study in patients with SMM showed improved overall survival with therapy as compared to observation. A report from the PETHEMA-GEM group described both fewer myeloma related events and better overall survival among patients with high-risk SMM patients who were treated with lenalidomide and dexamethasone. This unique study has prompted us to review current knowledge about SMM, and address the following questions: 1) are there patients currently defined as SMM, who should be treated routinely? 2) should the definitions of SMM and MM be reconsidered? 3) has the time come when not treating is more dangerous than treating; and 4) could unintended medical harm result from overzealous intervention? Our conclusion is that those patients with the highest risk SMM -- extreme bone marrow plasmacytosis, extremely abnormal serum immunoglobulin free light chain ratio, and multiple bone lesions detected only by modern imaging -- be reclassified as active MM, such that they can receive MM appropriate therapy and the paradigm of careful observation for patients with SMM can be preserved.
INTRODUCTION

Smoldering multiple myeloma (SMM) was initially recognized in the 1980’s.\textsuperscript{1} It bridged the gap between monoclonal gammopathy of undetermined significance (MGUS) – a mostly pre-malignant disorder – and active multiple myeloma (MM). The classification of SMM is based on levels of circulating monoclonal immunoglobulin, bone marrow plasmacytosis and end organ damage. Until the International Myeloma Working Group (IMWG) classification system was developed (Table 1), definitions had varied.\textsuperscript{2} The minimum and maximum thresholds for immunoglobulin, bone marrow plasmacytosis, presence of bone lesions, and degree of anemia have varied by the study.\textsuperscript{1,3} The common theme across these studies was the universal recognition that there were asymptomatic patients, who exceeded the limits of the definition of MGUS, who could remain without end-organ damage for years, and who out-survived MM patients with higher tumor burden and/or end-organ damage. Studies performed in the 1980s assessing the role of observation versus early intervention in these patients revealed no prolongation of survival with treatment.\textsuperscript{4-6} Studies performed over the next two decades assessing bisphosphonate and/or thalidomide usage also did not show any clear advantage to instituting therapy in these asymptomatic patients other than fewer skeletal-related events.\textsuperscript{7-14} However, a recent report from the PETHEMA-GEM group described both fewer CRAB (calcium increased, renal dysfunction, anemia and bone lesions) events as well as better overall survival among \textit{high-risk} SMM patients treated with lenalidomide and dexamethasone.\textsuperscript{15}
This article will try and address the following three questions. First, should the definition of SMM be reconsidered such that those patients who are considered to have the highest risk SMM be added into the active MM category in order to preserve the doctrine that SMM is an entity that can be observed without therapy? Second, has the time come when not treating is more dangerous than treating? Third, alternatively, could unintended medical harm result from over zealous intervention?

DEFINITIONS OF SMM

Approximately 8–20% of patients with multiple myeloma are recognized by chance without significant symptoms. Kyle and Greipp first used the term ‘smoldering myeloma’ in 1980 (Table 1). This expression referred to those patients who satisfied the following criteria: 1) M protein greater or equal to 30 g/L; 2) bone marrow plasmacytosis of greater than or equal to 10%; 3) no end organ damage; and 4) no progression of disease at 5 years. At the same time Alexanian et al. explored the use of the term ‘indolent’ myeloma (IMM), an entity that allowed for up to 3 lytic bone lesions, a minimum bone marrow plasmacytosis of 15%, and distinct minimum and maximum thresholds for IgG and IgA. Over time Alexanian also separated the SMM (or asymptomatic MM) from the IMM assigning a maximum value of M-spike of 45 g/L for the former category. Subsequent to the SMM and the IMM classifications came that of evolving MM, which was defined as an M-protein that abruptly increases when symptomatic MM develops. There was considerable overlap between DSS IA and SMM. It was not until 2003, when there was
international consensus about the definitions of plasma cell disorders, that the
criteria for SMM were established. Most subsequent publications have used this
more uniform definition.

DEFINING RISK IN SMM

As shown in Table 2, many investigators have evaluated the risk of
progression among patients with SMM. In most of the earlier studies, ‘high-risk’
patients had annual progression rates as high as 25-40%, depending on the risk
criteria applied, and had survival rates comparable to patients with active
myeloma. Several of these risk-factors, especially those that related to tumor
mass, may be useful to identify patients with the most ‘advanced’ disease rather
than those with the most aggressive biology.

The most commonly identified risk factor for progression to active myeloma
in the era before the 2003 IMWG criteria was the number of bone lesions. The
realization that patients with lytic lesions were among the patients with the shortest
time to requiring systemic therapy contributed to the decision of excluding those
patients with lytic bone lesions from the modern SMM definition (Table 2). The size
of the M-spike and the degree of plasmacytosis were also consistent risk factors
(Figure 1A, 1B). The IgA isotype, the presence of proteinuria, an
abnormal serum immunoglobulin free light chain ratio (Figure 1B, 1C),
circulating plasma cells by slide based immunofluorescence, a high proliferative
rate of bone marrow plasma cells, immunoparesis, a high percentage of bone
marrow plasma cells with aberrant flow cytometry (Figure 1D), and an
abnormal MRI (Figure 1E),\textsuperscript{27,32-34} have all also been recognized as risk factors for progression. Bone marrow plasmacytosis as a risk factor is a relatively complex parameter given the variability of estimation depending on the source of the sample.\textsuperscript{35} Computed tomography and magnetic resonance imaging (MRI) reveal specific lesions in 40\% of Durie-Salmon stage (DSS) I myeloma patients.\textsuperscript{36} Among asymptomatic multiple myeloma patients with normal radiographs, 50\% have tumor-related abnormalities on MRI of the lower spine.\textsuperscript{37}

Two groups have recently reported the impact of interphase FISH on risk of progression (Table 2, Figure 1F, 1G).\textsuperscript{38,39} Both found that the presence of deletion 17p or t(4;14) is associated with the shortest time to progression and that trisomies were a risk factor for progression from SMM to MM. The Mayo paper addressed this peculiar finding of trisomies being a SMM risk factor—but a well-accepted favorable prognostic factor in active MM—by assessing overall survival in the SMM cohort.\textsuperscript{38} OS from the time of SMM diagnosis for the trisomy SMM patients was comparable to that of those patients with either normal FISH or with standard risk abnormalities such as t(11;14) and deletion 13/13q. This was in stark contrast to outcomes for the deletion 17p and t(4;14) patients who had inferior OS both from the time of SMM diagnosis and from active MM diagnosis (Figure 2). The Heidelberg group also found that gains of 1q21 were a risk factor for progression among patients with SMM. These authors made an effort to relate FISH abnormalities with other reported risk factors, most notably tumor burden and found that risk of the high risk FISH was independent of tumor burden on multivariate analysis with the greatest impact among those patients with lower tumor burden.\textsuperscript{39}
There are less data about the risk of abnormal metaphase cytogenetics in SMM,\textsuperscript{40} in part because they are normal in 70\% of patients with newly diagnosed MM; however, abnormal metaphase cytogenetics are a reflection of proliferative myeloma\textsuperscript{41} and are also a risk factor for progression.\textsuperscript{42}

RESULTS OF INTERVENTIONAL THERAPEUTIC TRIALS

As mentioned, the purpose of the SMM construct was to bridge the gray zone between MGUS and MM (Figure 3). The separation was useful for management since SMM patients had a risk of progression many times greater than MGUS and hence needed more frequent follow-up than MGUS. Similarly, SMM patients were distinguished from MM since they could be observed without therapy until evidence of disease progression. This strategy was aimed at avoiding unnecessary side-effects and cumulative exposure of alkylating drugs, which were found to be associated with MDS and acute leukemia.\textsuperscript{43-46} Patients with DSS I disease, who also meet the criteria for smoldering or asymptomatic myeloma, could be managed expectantly. Median progression-free survival in asymptomatic DSS I patients, observed without any therapy, ranged from 12 to more than 48 months.\textsuperscript{4,5,22,47}

Melphalan: Two small randomized clinical trials were reported in the 1990s, comparing immediate institution of melphalan and prednisone to initiation only once patients progressed from SMM to symptomatic MM (Table 3). Neither of these trials demonstrated a survival advantage, although they were not adequately powered to make definitive conclusions.\textsuperscript{4-6}
Bisphosphonates: The next class of drug evaluated in SMM patients in prospective clinical trials—1 small pilot\textsuperscript{7} and 2 randomized controlled trials—was single agent bisphosphonate (Table 3).\textsuperscript{8,9,10} Neither of the randomized trials demonstrated improved TTP or OS, but both demonstrated fewer skeletal related events with bisphosphonate use. Patients using bisphosphonate also had higher rates of symptomatic hypocalcemia, fever, and osteonecrosis of the jaw.

Thalidomide: Thalidomide with or without bisphosphonate has been studied in patients with SMM in phase 2 trials and one underpowered randomized controlled trial (Table 3).\textsuperscript{11-14,48} Eligibility criteria varied among trials as did response rates, PFS, and OS. In the Mayo Clinic randomized controlled trial,\textsuperscript{48} 82\% were DSS 1A, but 63\% were high risk according to the Mayo Clinic SMM risk classification as defined by Dispensieri et al.\textsuperscript{25} There was a significant improvement in PFS in the thalidomide/zoledronic acid arm as compared to the zoledronic acid alone arm (29 months versus 14 months), but no difference in PFS as defined by CRAB events (49 months versus 40 months, \(p=0.18\)) or in overall survival (6-year OS > 70\%).\textsuperscript{48} The overall response rate was 37\% for the thalidomide containing arm and none with zoledronic acid group. Thalidomide was poorly tolerated with 80\% of the thalidomide group developing grade 1-2 peripheral neuropathy and 74\% with grade 1-2 fatigue in the thalidomide/zoledronic acid arm. The patients treated with zoledronic acid alone also had adverse effects including grade 1-2 fatigue in 52\% and grade 1-2 peripheral neuropathy in 18\%. The outcomes of this phase 3 trial differed slightly from its phase 2 predecessors in that time to progression was shorter than that of Barlogie\textsuperscript{11} or Rajkumar\textsuperscript{12,13} (29 months versus 4-year EFS 60\%).
versus 35 months, respectively). Part of the discrepancy may relate to the fact that the Barlogie study allowed for all risk SMM patients and that the Rajkumar phase 3 study allowed for patients with IMM to enter. Another discrepancy between these studies is that patients in the Barlogie study who achieved a PR or better had a shorter TTP than the non-responders, in contrast to the findings of the two Mayo led trials. Indeed, Barlogie’s study was concerning in that it implied that treatment with thalidomide may actually select for more aggressive myeloma clones to emerge under the selective pressure of the drug.

*Lenalidomide:* The most provocative study for patients with SMM is that of the PETHEMA-GEM group. These authors reported on 119 patients with high-risk SMM managed in an open-label randomized controlled trial by either observation or lenalidomide and dexamethasone. The lenalidomide and dexamethasone patients received 9 months of induction (28 day cycles of lenalidomide 25 mg per day days 1-21 and dexamethasone 20 mg days 1-4 and 12-15) followed by 15 months of single agent lenalidomide (10 mg days 1-21 every month). The high-risk population was defined by the presence of both bone marrow plasma cells greater than 10% and M protein > 30g/L or, if only one criterion was present, patients had a proportion of aberrant (defined as absence of CD19 and/or CD45 expression, over expression of CD56, or weak expression of CD38) plasma cells within the total bone marrow plasma cell compartment by immunophenotyping of ≥ 95% as well as immunoparesis (reduction under the lower normal limit of either of the uninvolved immunoglobulins).
Patients in the abstention arm were more likely to develop symptomatic disease (76% versus 23%). The overall response rate during induction therapy was 79%, including 65% partial responses, 11% very good partial responses, 14% complete responses and 7% stringent complete responses. In the treatment group, there were no grade 4 adverse events, but there was 1 death due to pneumonia and 12% of patients had SAEs as compared to 3% in the observation arm. Most AEs were grade 1-2. Rates of diarrhea or constipation were 37% (versus 5% in observation arm) and rash occurred in 32%. There were only 3 deep venous thromboses. Seventeen of 57 patients (30%) in the treatment arm withdrew due to toxicity or choice as compared to 3 (4.8%) in the observation arm. A potential impact in quality of life needs to be excluded.

With a median follow-up of 40 months, the treated patients had a superior 3-year survival without progression to symptomatic disease (77% versus 30%, p<0.001) and a superior 3-year OS (94 versus 80%, p=0.03) from the time of registration. A major limitation in interpreting this study was the difference in how asymptomatic biochemical progression was handled in the 2 groups. In the observation arm, full CRAB progression was required for patients to receive anti-myeloma therapy, whereas in the treatment arm, asymptomatic biochemical progression (>25% increase of monoclonal component) during maintenance lenalidomide was sufficient to warrant salvage with dexamethasone (or re-escalation of lenalidomide). Forty-two percent (24/57) in the intervention group, who developed asymptomatic biochemical progression, were not counted as events in
the Kaplan-Meier curves; rather 18 had dexamethasone added, and an unspecified fraction had their lenalidomide dose re-escalated according to protocol. Finally, the cause for the large discrepancy of discontinuation due to “choice” between the intervention arm versus abstention arm (23% versus 5%) could be attributed at least in part to patients’ or treating physicians’ reluctance to tolerate asymptomatic biochemical progression in patients for whom therapy had already begun, i.e. lenalidomide and dexamethasone. These questions and the design of the study do not allow us to clearly determine if a preemptive strategy may be equally beneficial with less toxicity than a prophylactic strategy.

Moreover, this difference in managing asymptomatic biochemical progression events may explain the relatively high 3-year mortality of 20% in the control arm. Historically, this rate of 3-year mortality is seen in the elderly, but 3-year mortality for patients with newly diagnosed active myeloma who are transplant eligible is closer to 10-15%. Another caveat is that lenalidomide-dexamethasone was not used consistently as salvage for the abstention group upon progression.

Questions that require clarification before this strategy can be adopted for even high-risk patients include: 1) Could some of the excess mortality in the observation arm relate to the protocol requirement that CRAB be reached before instituting therapy? 2) Was there a difference in follow-up compliance and intensity / frequency of de facto testing between the intervention and observation arms? Providing these clarifications will allow this very important study to shed light on
questions that extend beyond its primary and secondary objectives.

RETHINKING THE DEFINITION OF SMM AND TIMING OF THERAPY

Some have argued that SMM is not a unique biologic state, but rather a heterogeneous entity comprising some patients with biological premalignancy (MGUS) and some with true malignancy who are yet to declare clinical end-organ damage.\textsuperscript{56,57} With the advent of multiple novel markers of disease—from MRI to PET/CT to flow phenotype to FISH cytogenetics—and of newer (and presumably safer) anti-myeloma therapies, should the definition of SMM be reconsidered? We believe so. Patients who are considered to have the highest risk SMM should be moved into the active MM category in order to preserve the doctrine that SMM is an entity that can be observed without therapy (Figure 3). The time has come when not treating a subset of what has up to now been considered high-risk SMM is more dangerous than treating. Our group has previously shown that even among patients with MGUS, the transition to MM can be unexpected and associated with end-organ damage in 40% of patients who do progress.\textsuperscript{58} In other studies among patients with SMM who are observed until CRAB, the rates of renal failure were 11-13% and SRE 58-73%.\textsuperscript{9,20} In yet another study, 32% of the clinical progressions were severe as defined as need for RBC transfusion, dialysis, or treatment for a pathologic fracture.\textsuperscript{59}

Also worthy of consideration is the question of whether some of the lowest risk SMM patients should be shifted into the MGUS category in order to reduce
anxiety and intensity of follow-up since the absence of risk factors predicts not only for a longer time to progression, but also for a superior overall survival. To date, annual rates of progression in the “low-risk” SMM are reduced from approximately 10% per year to 3-5% per year (Figure 1H). Although this is a significant reduction, these rates of progression are still slightly higher than that of high risk MGUS.\textsuperscript{60}

As the questions about treating groups of SMM patients are considered, there must be agreement about acceptable rates of “overtreatment” and “under-treatment” of patients.\textsuperscript{61} Figure 1 illustrates 2-year progression rates for several recent SMM risk assessments. Most systems contain high-risk groups with 2-year TTP rates of less than 60% (Table 2). The four exceptions are bone marrow plasmacytosis of \textgreater60\%\textsuperscript{27,62}, serum immunoglobulin free light chain ratio greater than 100 (Figure 1C)\textsuperscript{26,27}, circulating plasma cells by slide based immunofluorescence,\textsuperscript{29} and more than 1 focal lesion on whole body MRI (Figure 1E).\textsuperscript{34} Bone marrow plasmacytosis of 60\% affects 2-8% of all SMM patients, yields a median TTP of 7-15 months\textsuperscript{27,62} and had a specificity of 95.5\% for progression at 18 months.\textsuperscript{27} The involved FLC/uninvolved FLC of 100 or greater captures approximately 7-15\% of the SMM population and had a specificity of 98\% for progression at 18 months.\textsuperscript{27} With a median TTP of 13-15 months, a 2-year TTP of 79\% and a 5-year TTP of 94\%,\textsuperscript{26,27} shifting these populations into the active MM category would also be reasonable (Figure 4) though it would be of interest to know how many of these “high-risk” SMM had smoldering LC myeloma.\textsuperscript{63} More than one focal lesion on whole body MRI, which affected 15\% of SMM patients in one study, had a high predictive value for progression to active multiple myeloma with a
median time to progression of 13 months and a 2-year TTP of 70%.

Diffuse marrow infiltration pattern was also significant on multivariate analysis. Both of these MRI variables made M protein concentration of 40 g/L and bone marrow infiltration of greater than or equal to 20% insignificant in the multivariate model. Figure 4 summarizes our interpretation of the changing definitions for SMM and active MM.

In terms of other appealing candidates to help redefine SMM and active MM, circulating plasma cells as detected by slide based immunofluorescence captures 15% of SMM patients and yielded a median TTP of 12 months, but this test is not readily available. We therefore await data on a more accessible circulating plasma cell risk system using flow cytometry. Patients with high-risk FISH (deletion 17p, t(4;14), and gain 1q21) might be considered as active myeloma and be candidates for early treatment, but these groups are too heterogeneous for us to make that recommendation.

**CONSENSUS RECOMMENDATIONS ON TREATMENT**

Recent work from our institution shows that there has been stage migration among those patients being treated as active myeloma, suggesting that patients are being treated at an earlier time point during their disease course. It is possible but not proven that some of the improved survival seen in epidemiologic studies may be in part a function of physicians being more willing to treat patients earlier which potentially exaggerates the beneficial impact of novel therapies over the past 15 years. The question remains, however, whether treating
sooner than later improves QOL and/or overall survival. Observation as practiced in the PETHEMA-GEM study in patients with “high-risk” SMM was associated with an unacceptable early mortality that was significantly decreased by early treatment with lenalidomide and dexamethasone. As mentioned early, some of the benefit—both survival and time to symptomatic disease—observed in this study may relate to the protocol design: treating biochemical progression and a 30% drop-out rate by “choice” in the treatment arm; and strict adherence fulfilling a CRAB criterion prior to instituting therapy in the observation arm.

There are additional caveats that limit the generalizability of the PETHEMA-GEM study. First, the trial results apply not to all patients with SMM, but only to “high-risk” SMM patients as defined by the trial criteria. Forty percent of patients enrolled did so purely based on the flow-based definition of plasma cell immunophenotype, a methodology that is not available in most institutions and that requires considerable expertise to interpret the results even if the technology were available. Second, the authors did not use lenalidomide-dexamethasone as universal salvage for the abstention trial universally. Third, reviewing Figure 1 and Table 2, one sees that this strategy may result in overtreatment of approximately 40% of patients at 3 years, 30% of patients at 4 years, and 20% of patients at 5 years. Fourth, the costs of intervention also need to be considered. Although the “cost” of under treatment is partially captured—more bone lesions and renal failure and now a suggestion of inferior overall survival—the “cost” of overtreatment is less clear. With the simplest of regimens, i.e. lenalidomide plus dexamethasone, the annual cost of therapy is approximately $100,000 USD, not including the extra
monitoring required for patients on active therapy and management of adverse
events.\textsuperscript{68, 69} Part of the “cost” of overtreatment may include increased side-effects,
which may translate into inferior quality of life. Finally, long-term safety data for
protracted lenalidomide use is limited. The potential of this last “cost” would be
abrogated if physicians choose to treat according to the method of the PETHEMA-
GEM study—i.e. only 2 years of lenalidomide followed by observation until
progression—a practice gaining favor in light of concerns of the potential risk of
cumulative risk of secondary primary malignancy.\textsuperscript{70-72}

After reviewing all the data, taking into account the risks and benefits of
observation, as well as the risks and benefits of intervention, our recommendations
for the management of SMM patients are shown in Figure 4. Clearly, there is room
for still finding better predictors, but for now we recommend changing the
definition of active MM, in the absence of CRAB, to include: 1) patients with bone
marrow plasmacytosis greater than or equal to 60%; 2) a ratio of involved to
uninvolved FLC of greater than or equal to 100; or 3) whole body MRI
demonstrating greater than one focal lesion. In these patients the risk of
progression in the first 2-3 years is 80% or higher. Once defined as having active
MM, these patients should receive therapy appropriate for any newly diagnosed
patient and one such therapy now supported with Phase 3 evidence would be
lenalidomide plus dexamethasone as used in the PETHEMA-GEM interventional
arm, though the combination is not FDA approved in the United States as first line
therapy. The cost of performing whole body MRI on all patients with SMM with the
intent of treating only those with more than 1 focal lesion on MRI would be much
less expensive than treating a SMM patient who did not require treatment for 2 years or more. Limitations to using wbMRI are that many institutions do not have an algorithm to perform or interpret the test and that payment for the test may not be reimbursed by insurance providers. PET/CT may be a nice alternative to WbMRI since PET/CT has a superior sensitivity to standard bone radiographs, is faster and more comfortable for the patient, and can be used in patients with implanted pacemakers and defibrillators. 73-75 We recommend that all other patients with SMM be observed without therapy every 3-6 months and encouraged to participate in clinical trials. Although the PETHEMA- GEM trial shows that a subset of these patients, those with both bone marrow plasma cells greater than 10% and M protein > 30g/L, could benefit from therapy, we do not recommend intervention at this point until further confirmatory evidence emerges though it is important that these data be shared with patients. We would recommend that our recommendations be considered by International Myeloma Working Group to arrive at an international consensus.

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All authors contributed to the design, writing, and review of the manuscript.

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10.4065/84.2.114.

Table 1. Definitions of SMM (asymptomatic)/IMM/Evolving MM

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>%BMPC, (M-protein, g/L ), [other criteria]</th>
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<td>&gt;=10, (And &gt;= 30), [no anemia, hypercalcemia, or renal insufficiency]</td>
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<td></td>
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<td>No bone, 25 m</td>
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<td>Overall survival</td>
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<td>• lytic bone lesions or osteoporosis with compression fracture</td>
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<td></td>
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<td>• Symptomatic hyperviscosity, amyloidosis, or &gt;2 bacterial infections/12 m</td>
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<td>&gt;10 g/dL, Calcium &lt; 12 mg/dL, no more than solitary bone lesion]</td>
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<td>OS 58 m^76</td>
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<td>“Indolent MM”: &gt;=15%, (AND IgG&gt; 25 g/L or IgA &gt; 10 g/L), [Hb&gt;10.0 g/dL; &lt; 3 lytic bone lesions; no painful compression fx]</td>
<td>Not available</td>
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<td>-------------</td>
<td>--------------------------------------------------------------------------</td>
<td>--------------------</td>
<td></td>
</tr>
<tr>
<td>Alexanian, 1988</td>
<td>16</td>
<td>Indolent MM: &gt;=10 (*AND &gt;= 45 g/dL), [or Hb &lt;10.5]</td>
<td>Not available, 8 mo</td>
<td></td>
</tr>
<tr>
<td>Rosinol 2003</td>
<td>53</td>
<td>Evolving MM: &gt;=10, (*AND &gt;= 30 g/L (or LC excretion 1 g/24 hr), [Hb &gt;10 g/dL, no bone lesions, renal, or hypercalcemia]</td>
<td>Evolving (n=22) Non-evolving (n=26) TTP Non-evolving: 47 m Evolving: 16 m Overall Survival All from Dx: 98 m All from Rx: 42 m</td>
<td></td>
</tr>
<tr>
<td>Cesana 2002</td>
<td>127</td>
<td>1 year stability required 11-19% (*OR IgG 35-69 g/L, IgA 21-69 g/L, BJ proteinuria 1 g/24 hrs), [No bone lesions, anemia, hypercalcemia, and renal insufficiency]</td>
<td>BMPC &gt;10%; IgA M-protein; proteinuria Not given</td>
<td></td>
</tr>
</tbody>
</table>
Table 2: Prognostic factors for progression of SMM to active MM

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>%BMPC, (M-protein, g/L), [other criteria]</th>
<th>Risk factors</th>
<th>Median TTP and OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wisloff, 1991</td>
<td>71</td>
<td>&gt;=10 (*OR IgA &gt; 15, IgG &gt;30, Bj proteinuria &gt; 1 g/24 hours)</td>
<td>Lytic bone lesions; BMPC &gt;20%</td>
<td>TTP 26 mo; OS 45 mo</td>
</tr>
<tr>
<td>Dimopoulos, 1993</td>
<td>95</td>
<td>&gt;15 (*AND serum M protein &lt;45 g/L), [Any lytic bone lesion was exclusionary; &gt; Hb 10.5 g/dL]</td>
<td>Protein risk: M protein &gt; 30 g/L or proteinuria &gt; 50 mg/24 hrs</td>
<td>TTP: 26 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Low (n=27): no factor</td>
<td>Low: 61 m</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intermediate (n=43): either protein characteristic</td>
<td>Intermediate: 25 m</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High (n=25): Lytic bone lesions and/or both protein risk characteristics</td>
<td>High: 10 m</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TTP: 26 mo Low: 61 m Intermediate: 25 m High: 10 m OS from SMM (from Rx)</td>
<td>TTP: 26 mo Low: 61 m Intermediate: 25 m High: 10 m OS from SMM (from Rx)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Low: 89 m (35 m) Intermediate: 92 m (31 m) High: 57 m (41 m)</td>
<td>Low: 89 m (35 m) Intermediate: 92 m (31 m) High: 57 m (41 m)</td>
</tr>
<tr>
<td>Witzig, 1994</td>
<td>57</td>
<td>&gt;10, (not stated), [No CRAB]</td>
<td>Circulating cells by PBLI (n=14)</td>
<td>TTP: 48 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0 factor (n=38)</td>
<td>0: &gt;50 m</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 factor (n=35)</td>
<td>1: 26 m</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;1 factor (n=18)</td>
<td>&gt;1 factor: 6 m</td>
</tr>
<tr>
<td>Facon, 1995</td>
<td>91</td>
<td>&gt;15% (*AND DSS I)</td>
<td>Hb &lt;12 g/dL; BMPC &gt;20%; M protein &gt;30 g/L (IgG) or &gt;25 g/L (IgA)</td>
<td>TTP: 48 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0 factor (n=38)</td>
<td>0: &gt;50 m</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 factor (n=35)</td>
<td>1: 26 m</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>&gt;1 factor (n=18)</td>
<td>&gt;1 factor: 6 m</td>
</tr>
<tr>
<td>Moulopoulos, 1995</td>
<td>38</td>
<td>&gt;10 (Or M-spike &gt; 25 -45 g/L or Bj &gt;150 mg/dL), [Hb &gt; 10.5 g/dL;</td>
<td>Abn MRI</td>
<td>TTP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Abn MRI</td>
<td>Normal MRI: 43 m</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Abn MRI: 16 m</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>No lytic bone lesions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>M protein &gt;30 g/L; IgA M protein; Proteinuria &gt;50 mg/24 h</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low (n=16): none</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate (n=65): one</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High (n=20): 2 or more</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TTP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low: 95 m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate: 39 m</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High: 17 m</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>OS from Dx (from Rx)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low: 89 m (26 m)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate: 87 m (34 m)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High: 51 m (32 m)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Kyle, 2007</th>
<th>276</th>
<th>IMWG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>M protein &gt;=30; BMPC &gt;=10%</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Group A: M protein only</strong> (n=27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Group B: BMPC only</strong> (n=143)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Group C: Both</strong> (n=106)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2-yr TTP (5-yr TTP)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A: 6% (15%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B: 22% (43%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C: 45% (69%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Perez-Persona, 2007</th>
<th>273</th>
<th>IMWG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>95% aberrant BMPC</strong> (absence of CD19 and/or CD45 expression, over expression of CD56, or weak expression of CD38); <em>immunoparesis of the uninvolved immunoglobulins</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Neither</strong> (n=28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Either</strong> (n=39)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Both</strong> (n=39)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Median TTP (5-yr TTP)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neither: NR (4%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Either: 73 m (46%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both: 23 m (72%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dispenzie, 2008</th>
<th>273</th>
<th>IMWG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>M protein &gt;=30; BMPC &gt;=10%; involved FLC/uninvolved FLC &gt;=8</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 high (n=81)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 high (n=114)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 high (n=78)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2-yr TTP (5-yr TTP)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1: 12% (25%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2: 27% (51%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3: 52% (76%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td>IMWG</td>
<td>Parameters</td>
</tr>
<tr>
<td>-----------</td>
<td>------</td>
<td>------------</td>
</tr>
<tr>
<td>Hillengass 2010</td>
<td>IMWG</td>
<td>Whole body MRI Low (n=126): no or 1 focal lesion High (n=23): &gt;1 focal lesion</td>
</tr>
<tr>
<td>Rajkumar 2011</td>
<td>IMWG</td>
<td>BMPC &gt;=60% (n=21)*</td>
</tr>
<tr>
<td>Larsen 2013</td>
<td>IMWG</td>
<td>Involved FLC/uninvolved FLC &lt;100 (n=496)</td>
</tr>
<tr>
<td>Bianchi 2013</td>
<td>IMWG</td>
<td>High: Slid e based &gt;5X 10^6/L or &gt;5% PC/100 clg MNC</td>
</tr>
<tr>
<td>Rago 2013</td>
<td>IMWG</td>
<td>Hb &lt;=12.5</td>
</tr>
<tr>
<td>Madan 2010</td>
<td>IMWG</td>
<td>PCLI &lt; 1%</td>
</tr>
<tr>
<td>Rajkumar 2013</td>
<td>IMWG</td>
<td>FISH Low: (n=53), normal or insufficient; Standard: (n=106), t(11;14), maf translocations, other/unknown translocations, or deletion 13/13q; Intermediate: (n=148), trisomies alone; High: (n=44), t(4;14) or deletion 17p</td>
</tr>
<tr>
<td>OS from SMM (from Rx)</td>
<td>Low, 135 m (60 m)</td>
<td>Standard, 147 m (77 m) Intermediate, 135 m (86 m)</td>
</tr>
<tr>
<td>Author</td>
<td>N</td>
<td>Source</td>
</tr>
<tr>
<td>---------</td>
<td>-----</td>
<td>--------</td>
</tr>
<tr>
<td>Kastritis 17</td>
<td>96</td>
<td>IMWG</td>
</tr>
<tr>
<td>Neben 2012 39</td>
<td>246</td>
<td>IMWG</td>
</tr>
</tbody>
</table>

* The estimate of bone marrow plasmacytosis was according to the methods of Rajkumar et al, i.e. using the highest estimate from the aspirate or the bone marrow as the estimate.
Table 3: Treatment trials for patients with smoldering multiple myeloma

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study</th>
<th>Therapy</th>
<th>N</th>
<th>TTP</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hjorth 1993</td>
<td>RCT</td>
<td>Initial vs delayed MP</td>
<td>50 SMM and IMM</td>
<td>12 mo</td>
<td>No difference</td>
</tr>
<tr>
<td>Riccardi 5,6</td>
<td>RCT</td>
<td>Initial vs delayed MP</td>
<td>145 DSS I</td>
<td>~12 m</td>
<td>No difference 64 vs 71 m</td>
</tr>
<tr>
<td>Peest 1995</td>
<td>Obs</td>
<td>Delayed MP</td>
<td>54 DSS I</td>
<td>2-yr PFS 75%</td>
<td>Tumor specific OS 80% at 60 m</td>
</tr>
<tr>
<td>Martin 2002</td>
<td>Pilot</td>
<td>Pamidronate</td>
<td>5 SMM and 7 IMM</td>
<td>2-yr TTP 25%</td>
<td></td>
</tr>
<tr>
<td>Musto 2003 / D'Arena 2011</td>
<td>RCT</td>
<td>Pamidronate vs observation</td>
<td>177 SMM</td>
<td>5-year PFS 53% both arms; SRE 74% v 39%, p=0.009</td>
<td>Median OS 46 and 48 months</td>
</tr>
<tr>
<td>Musto 2008</td>
<td>RCT</td>
<td>Zolendronate vs obs x 1 yr</td>
<td>163 SMM</td>
<td>TTP: 67 vs 59 m, p=NS SRE: 55% v 78%, p=0.04</td>
<td>OS not different</td>
</tr>
<tr>
<td>Barlogie 2008</td>
<td>Phase 2</td>
<td>Thalidomide pamidronate</td>
<td>76 SMM</td>
<td>4-yr EFS 60%</td>
<td>4 yr OS 91%</td>
</tr>
<tr>
<td>Rajkumar 2001</td>
<td>Ph 2</td>
<td>Thalidomide</td>
<td>19 SMM and 10 IMM</td>
<td>Median 35 m</td>
<td>OS: 86 m OS from Rx: 49 m</td>
</tr>
<tr>
<td>Weber 2003</td>
<td>Ph 2</td>
<td>Thalidomide</td>
<td>28 high-risk SMM</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Witzig 2013</td>
<td>RCT</td>
<td>Thalidomide +ZA vs ZA</td>
<td>68 SMM</td>
<td>29 m versus 14 m</td>
<td>6 yr &gt;70%</td>
</tr>
<tr>
<td>Lust 2009</td>
<td>Ph 2</td>
<td>IL-1 receptor antagonist +/- dex</td>
<td>47 SMM and IMM</td>
<td>37 mo</td>
<td></td>
</tr>
<tr>
<td>Golombick 2009</td>
<td>X-over</td>
<td>Curcumin vs placebo</td>
<td>17 SMM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mateos 2013</td>
<td>RCT</td>
<td>Len+dex x 9 m → len maintenance x 15 m versus Observation</td>
<td>119 SMM</td>
<td>2-yr PFS: 92 vs 50%, p&lt;0.001</td>
<td>3 yr OS: 93 vs 76%, p=0.04</td>
</tr>
</tbody>
</table>
FIGURE LEGENDS

Figure 1. Risk of SMM progression to active MM according to different prognostic systems as compared to risk of progression of MGUS to active MM. Gray shading includes 2-year time point.

A. SMM risk based on BMPC >=10%, M-protein >=30g/L \(^{21}\) - bold solid, both above threshold; solid, BMPC >=10%, but M-protein < 30g/L; dash, BMPC <10% but M-protein >=30g/L.

B. SMM risk based on BMPC >=10, M-protein >=30g/L, and involved FLC/ uninvolved FLC >=8 \(^{25}\) - bold solid, all 3 factors above threshold; solid, any 2 factors above threshold; dashed, any 1 factor above threshold

C. SMM risk based on involved FLC/ uninvolved FLC >=100 \(^{26}\) - bold solid, above threshold; solid, below threshold

D. SMM risk based on (absence of CD19 and/or CD45 expression, over expression of CD56, or weak expression of CD38) and immunoparesis of either of the uninvolved immunoglobulins \(^{31}\) - bold solid, both risk factors present; solid, either risk factor present; dashed, neither risk factor present

E. SMM risk based on presence (bold solid) or absence (solid) of 1 or more focal lesion on whole body MRI \(^{34}\)
F. SMM risk based on FISH – bold solid Del 17p, or t(4;14); solid, trisomies alone; dashed any other iFISH abnormality; dotted, normal or insufficient iFISH

G. SMM risk based on high risk iFISH (del 17p, t(4;14), +1q21, or hyperdiploidy) and high tumor burden (M-protein >=20 g/L). – bold solid, both high risk factors present; solid, iFISH low risk and tumor high risk; dashed, FISH high and tumor low; dotted, both low risk

H. MGUS risk of progression to MM based on M-protein >=30 g/L, abnormal rFLC, and heavy chain IgA or IgM – bold solid, all risk factors present; solid, 2 risk factors present; dashed, 1 risk factor present; dotted, no risk factor present.

Figure 2. Distribution and outcomes based on FISH abnormalities among patients with smoldering multiple myeloma (SMM).

A. No iFISH abnormalities, white; standard risk: t(11;14), t(14;16) or t(14;20) or other/unknown IgH or del 13/13q, light gray; intermediate risk: trisomy w/o IgH translocation, dark gray; high risk: t(4;14) or del (17p), black. Solid, progression from SMM to multiple myeloma; stippled, overall survival from SMM diagnosis.

B. Duration of time patient lives with labels ranging from MGUS to SMM to active MM are in part related to iFISH. Although individuals harboring trisomies (ii) appear to progress more rapidly through their diagnosis of SMM than patients with normal FISH or non-t(4;14) translocations (i), they survive much longer than those patients with deletion 17p (iii) and about as long as patients with normal or non-t(4;14) translocations (i)
**Figure 3.** Present, future and ideal state for distribution of patients with MGUS, SMM, and MM

**Figure 4.** Algorithm for reclassifying SMM and active MM

BMPC, bone marrow plasma cells; CRAB, calcium high, renal insufficiency, anemia, bone lesions; MGUS, monoclonal gammopathy of undetermined significance; MM, multiple myeloma; SMM, smoldering multiple myeloma

* Consider including patients with following FISH: deletion 17p, t(4;14), and 1q21 gains as active MM; this population could account for as many as 30% of SMM patients

§ Consider using more than FDG avid lesion on PET/CT in lieu of MRI
Figure 2A

Solid: Progression from SMM
Patterned: OS from SMM diagnosis

Mo to progression or death

Normal
Standard risk
Intermediate risk
High-risk

13%
15%
42%
30%
i  Standard risk SMM, standard risk MM

ii  High risk SMM, standard risk MM (trisomies in the absence of translocations)

iii  High risk SMM, High risk MM (deletion 17p, t(4;14), gain 1q21)
Figure 3

Present state

Future state

Ideal State?

MGUS

Active Multiple Myeloma

Smoldering multiple myeloma

Smoldering multiple myeloma
Figure 4

Active MM

No CRAB, but BMPC ≥ 10% and / or M protein ≥ 30 g/L

BMPC <10%

High-risk MGUS

BMPC ≥60%

Active MM

2-3% of patients

Yes

BMPC ≥10%

Active MM

As many as 15% of patients

No

WbMRI § > 1 focal lesion

SMM

BMPC ≥10%*

iFLC/uFLC ≥ 100

No

Yes

OBserve

As many as 15% of patients

Active MM

TREAT

As many as 15% of patients

Active MM

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Smoldering multiple myeloma requiring treatment: time for a new definition?