Monoclonal gammopathy of undetermined significance and Smoldering Multiple Myeloma: A review of the current understanding of epidemiology, biology, risk stratification and management of myeloma precursor disease

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Running title: MGUS and Smoldering Multiple Myeloma.

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Abstract

The term monoclonal gammopathy of undetermined significance (MGUS) was coined in 1978. The recent advances in our knowledge about MGUS and smoldering MM (SMM) have helped us better understand the pathogenesis of myeloma. It appears that myeloma evolves from a precursor state in almost all cases. We do not completely understand the multistep process from the precursor state to myeloma but studies including whole genome sequencing will continue to help in improving our understanding of this process. The process of transformation may not be linear acquisition of changes but rather a branched heterogeneous process. Clinical features that are prognostic of rapid transformation have been identified but no specific molecular markers have been identified. Even with recent advances, multiple myeloma remains an incurable disease in the vast majority and intervening at the precursor state provides a unique opportunity to alter the natural history of the disease. A limitation is that a vast majority of patients with precursor disease especially low risk MGUS will never progress to myeloma in their lifetime and treating these patients is not only unnecessary but may be potentially harmful. The challenge is to identify a subset of patients with the precursor state that would definitely progress to myeloma and in whom interventions will have a meaningful impact. As our understanding of the molecular and genetic processes improves, these studies will guide the selection of high-risk patients more appropriately and ultimately direct a tailored management strategy to either delay progression to symptomatic myeloma or even “cure” a person at this premalignant stage.
Introduction

Multiple myeloma is a plasma cell neoplasm characterized by multifocal proliferation of clonal, long-lived plasma cells associated with an overproduction of monoclonal gammaglobulin (1). In 1961, Jan Walderström described “essential benign hypergammaglobulinemia” as an asymptomatic condition wherein the monoclonal gammopathy is not associated with any symptoms (2). The term monoclonal gammopathy of undetermined significance (MGUS) was coined in 1978 (3) and smoldering multiple myeloma (SMM) in 1980 (4). It has always been recognized that some cases of MGUS progressed to symptomatic multiple myeloma but recent studies have shown that multiple myeloma is consistently preceded by MGUS (5, 6). This has given rise to the concept of a myeloma precursor disease and raised questions about the biologic events leading to progression of these precursor states to symptomatic myeloma. We will review the current understanding of the biology of these precursor states and also discuss trials looking at interventions.

Definition

In 2010 the International Myeloma Working Group (IMWG) defined MGUS by the presence of serum M-protein < 3g/dL, clonal plasma cell population in the bone marrow < 10%, and the absence of end-organ damage such as hypercalcemia (serum calcium ≥ 11.5 mg/dL), renal insufficiency (serum creatinine ≥ 2 mg/dL), anemia (hemoglobin value below the lower limit of normal by more than 2 g/dL or hemoglobin value < 10 g/dL) and lytic bone lesions (CRAB features) that can be attributed to the plasma cell proliferative disorder (7). Smoldering
multiple myeloma was defined by the presence of serum M-protein $\geq 3$ g/dL and/or clonal bone marrow plasma cells $\geq 10\%$ and the absence of CRAB features clinically.

Recently, 3 clinical subtypes of MGUS have been defined based on the type of immunoglobulin involved- non-IgM MGUS, IgM MGUS, and light-chain MGUS (8) and are characterized by a unique natural history in each subtype.

**Epidemiology**

In his initial description of monoclonal gammopathy, Jan Waldenström speculated that ‘essential benign hypergammaglobulinemia’ was more common than multiple myeloma (2). We now know that indeed MGUS is the most prevalent plasma cell disorder (9). In a large population based study in Olmsted County, MN, Kyle et al. analyzed serum samples of more than 75\% of residents, 50 years or older, within the county (9). They identified MGUS in 3.2\% of 21,463 patients tested. While the overall prevalence was noted to be 3.2\%, there was a significant age dependent increase in both sexes with the prevalence among persons 80 years of age or older 4 times as high as among those 50-59 years of age. In a subsequent study on a majority of the same patients from Olmsted County, Dispenzieri et al used the free light chain assay (FREELITE) and showed that 0.8\% of people older than 50 years had light chain-MGUS. The total MGUS prevalence including the light chain-MGUS cases was noted at 4.2\% (10). Other studies from across the globe have shown significant variation in the prevalence of MGUS (Table 1). The prevalence seems to be low in Mexico and among the Asian countries based on studies from Japan, Taiwan and Thailand (11-14) while much higher in Africans and African-Americans (15, 16).
In a study of 4 million veterans in VA hospitals across the nation, Landgren et al showed that the age-adjusted prevalence rate of MGUS was threefold higher for African American patients than for white patients (16). This study also showed that the rate of progression to multiple myeloma was similar among whites and African Americans.

The possible role of genetic factors in MGUS is suggested by the racial and ethnic differences mentioned above and also the increased prevalence of MGUS in blood relatives of persons with lymphoproliferative and plasma cell disorders. First-degree relatives of MM and MGUS patients were found to have a 2.6 fold risk of MGUS as compared to the general population (17).

Environmental factors have been evaluated and a study showed that exposure to pesticides increases the risk of MGUS (18). In a French study, the prevalence of monoclonal gammopathy was higher in the rural areas as compared to urban areas (19). A link between obesity and MGUS has also been suggested (20).

**MGUS consistently precedes multiple myeloma**

Since the early description of MGUS it was known that some cases of MGUS progressed to symptomatic myeloma but it was not clear whether all cases of myeloma are preceded by MGUS. In a study of more than 77,000 individuals, 55 to 74 years of age, from a cancer screening trial, Landgren et al found 71 patients who developed MM (5). The study showed that patients who eventually developed multiple myeloma consistently had MGUS in the years preceding development of multiple myeloma. A second study by Weiss et al found a
monoclonal gammopathy in 27 of 30 patients (90%) in sera 2 or more years before the diagnosis of myeloma (6).

**Biology of myelomagenesis- Precursor disease to symptomatic myeloma**

Studies looking at the epigenetic, genetic, transcriptional, and phenotypic changes within the transforming plasma cell as well as the microenvironment have improved our understanding of this process. The process of transformation, from a normal plasma cell to the premalignant MGUS/SMM state and finally to symptomatic multiple myeloma, involves several oncogenic events within the plasma cell as well as in the bone marrow microenvironment (Figure 1).

A recent study using SNP-based arrays compared MGUS, SMM and MM samples (21). They found copy number abnormalities in all stages. The incidence of genomic imbalance did increase from a median of 5/case for MGUS to 7.5/case for SMM and 12/case for MM. The study also noted certain genomic changes that were exclusive to MM including 11q and 21q gains and 16q and 22q deletions. Interestingly, the study found these abnormalities in a small subclone in MGUS patients indicating that most if not all of the chromosomal changes may be already present at the MGUS state.

Several studies have found varying rates of the different translocations between MGUS, SMM and MM (Table 2) (22-26). The rate of t(11;14) appears to be uniform from MGUS to MM, but there is some discrepancy in the rate of the other IgH translocations- t(4;14) and t(14;16) as well as del13q. Some studies have suggested that the incidence of these changes increases from MGUS to MM while other studies have indicated that the rate is the same among MGUS and MM patients. The role of 13q deletion is also not completely clear and some studies have
suggested that it may be an early event while others point to del13q as the next step in the pathogenesis of myeloma especially following IgH translocations (25, 27). The presence of these translocations in MGUS and SMM does not seem to affect the rate of progression in either condition, while in multiple myeloma, some of these translocations are associated with adverse outcomes (24, 28, 29). A recent study has shown that there is a clonal expansion of these genetically abnormal plasma cells from MGUS to SMM and MM (26). IgH translocations and 13q deletion were seen in a higher proportion of plasma cells in SMM compared to MGUS and in MM compared to SMM.

**Cyclin D overexpression as an unifying early event** - Using gene expression analyses, overexpression of the cyclin D genes appears to be one possible unifying event which is seen in almost all MM cases with or without an immunoglobulin translocation as compared to normal plasma cells (30). IgH translocations directly dysregulate Cyclin D1 or D3 (t(11;14) and t(6;14) respectively) and the C-MAF or MAFB transcription factors dysregulate Cyclin D2 (t(14;16) and t(14;20)) (31). In this study, 12 MGUS samples had a similar pattern of cyclin D dysregulation despite a lower proliferative index suggesting that cyclin D perturbation may indeed be an early and unifying event in plasma cell dyscrasias.

**MicroRNAs** are single stranded RNA molecules that regulate gene expression posttranscriptionally and are being implicated in a large number of cancers (32). A study comparing miRNA profiles of normal PC, MGUS, SMM and MM found overexpression of mir-21, mir-106~25 and mir181a and mir181b in MGUS and MM compared to normal PCs (33). The study also found mir-32 and mir17~92 clusters to be upregulated only in MM and not in any
other forms. Mir 17~92 and Mir 106~25 are known to have a role in B cell development as well as B cell lymphomas targeting PTEN, E2F1, Bcl2 and BIM (32, 33). The mir17 cluster has been shown to upregulated by the transcription factor c-Myc, which is considered a late event in myeloma progression (34, 35).

Cytogenetic and gene expression studies in myeloma precursor disease are limited by technical limitations in the ability to sort out the abnormal plasma cells for evaluation. The ratio of abnormal cells to normal plasma cells will be lower in a MGUS sample as compared to a MM sample if CD 138+ sorting is used.

With the advances in deep sequencing techniques, we are now able to study the whole genome of myeloma cells and compare that to the normal human genome. Several studies employing these techniques are beginning to shift our understanding of the pathogenesis of myeloma. These studies have revealed that the previously held dogma that cancer progression occurred through a linear cumulative acquisition of mutational changes may be too simplistic. A new model of clonal heterogeneity is beginning to emerge (36). In this model various subclones exist in a dynamic equilibrium and over time the subclonal populations flow under environmental evolutionary pressures with alternating dominance of various subclones (37-40). Most of these studies were done on patients with symptomatic MM and as similar studies involving MGUS and SMM emerge, our understanding of the pathogenesis of myeloma from these precursor states will continue to evolve.

**Role of microenvironment in progression of MGUS to MM** - The transition from MGUS to MM involves changes to the complex interaction with the microenvironment along with the genetic
changes described above. In MM there is an upregulation of osteoblast RANK-L expression and a decrease in osteoprotegerin (OPG) a decoy for RANK-L which inhibits osteoclast differentiation. This increases the ratio of RANK-L/OPG, which leads to osteoclast activation and development of the characteristic lytic lesions (41). Interestingly, although lytic bone lesions are not seen in MGUS, the RANK-L/OPG ratio is higher in MGUS subjects and they are at a higher risk of fractures compared to healthy controls (42, 43). The role of other pathways including Wnt/β-catenin involving activation of FRZB and Dickkopf 1 (DKK1), a Wnt inhibitor, is also being studied (44). The homing of MM cells to bone marrow (BM) stromal cell niches is essential for their survival. A recent study suggests that these BM stromal cell niches are limited and a progressive competition and replacement of normal BM cells by clonal plasma cells is associated with more advanced disease (45). The evasion of the immune system is an important step in the progression from MGUS to MM. Oligoclonal T cell expansion can be found in both MGUS and MM with lower disease burden states demonstrating a more robust T cell expansion (46, 47). A defect in the T cell function is seen during progression from MGUS to multiple myeloma (48, 49). Several cytokines and growth factors including IL-6, SDF-1, MIP-1α, IGF-1, VEGF and HGF have been implicated in myeloma pathogenesis and transition from MGUS (50, 51).

Risk of progression from precursor disease to symptomatic myeloma

It is clear from the description above that there are no major genetic differences between the plasma cells in MGUS and MM. Since the prevalence of MGUS/SMM is much higher than multiple myeloma, and several people with precursor disease will never progress to
symptomatic myeloma in their lifetime, it is important to identify patients who are at greatest risk for progression to myeloma. Several studies have tried to predict subgroups of precursor disease at highest risk of progression using different tools.

**Size of M protein**- In 1384 MGUS patients, the risk of progression to MM or a related disorder after 20 years was 14% with an initial protein level of 0.5 g/dL or less, 25% for 1.5 g/dL, 41% for 2 g/dL, 49% for 2.5 g/dL, and 64% with 3 g/dL (52). A progressive increase in the M-protein in the first year of follow up (evolving MGUS) has also shown to be prognostic (53).

**Type of immunoglobulin**- MGUS patients with IgM or IgA monoclonal protein have an increased risk of progression to disease as compared to patients with IgG protein (52).

**Serum free light chain (FLC) ratio and the Mayo clinic model**- In a study of 1148 MGUS patients, Rajkumar et al showed that an abnormal FLC assay was an independent risk factor for progression from MGUS to MM (54). For MGUS patients- a non-IgG isotype, M-protein concentration more than 1.5 g/dL and an abnormal free light chain ratio are considered adverse prognostic factors. At 20 years, the risk of progression in patients with 0, 1, 2 and 3 risk factors is 5, 21, 37 and 58% respectively (Table 3A). For SMM patients a M-protein \( \geq 3 \) g/dL, a FLC ratio outside the range of 0.125 to 8, and \( \geq 10\% \) plasma cells in the bone marrow are considered as adverse factors in this model (55, 56). The 5-year rate of progression in patients with 1, 2 and 3 risk factors was 25%, 51% and 76% respectively (Table 3C). Recently Rajkumar et al have proposed that SMM with \( >60\% \) plasma cells progress to multiple myeloma within 2 years in 95% cases and should be treated at diagnosis even in the absence of symptoms (57).
Flow cytometry and the Spanish model- Perez-Persona et al used immunophenotyping with multiparameter flow cytometry to identify aberrant plasma cell (aPC) in the BM of 407 MGUS and 93 SMM patients (58). A ratio of aPC/BMPC of >95% was shown to be an independent risk factor for progression in both MGUS and SMM. In a multivariate analysis, DNA aneuploidy (hypo or hyperdiploidy) was also noted to be a prognostic factor in MGUS and was combined with aPC/BMPC >95% to form a prognostic index. The presence of 0, 1 or 2 of these factors was associated with a progression risk of 2, 10 and 46% respectively in MGUS (Table 3B). The analysis identified immunoparesis as an independent prognostic factor in SMM. Using aPC/BMPC >95% and immunoparesis as the two factors the study found 5 year risk of 4, 46 and 72% in patients with 0, 1 or 2 factors respectively (Table 3D).

Other prognostic factors- Other studies have identified various factors that are prognostic for progression to symptomatic disease. Cesana et al proposed a prognostic index for MGUS based on the presence of BMPC infiltrate >5%, presence of Bence-Jones proteinuria, polyclonal serum Ig reduction, and ESR and showed that these features were associated with higher rate of transformation to myeloma (59). Whole body MRI has been shown to be more sensitive to a skeletal survey in detecting focal lesions and the presence of such focal lesions were an adverse prognostic factor for progression to multiple myeloma (60). An earlier study showed that an abnormal MRI was associated with a shorter time to progression compared to a normal MRI (1.5 vs 5 years) in SMM (61). The role of immunoparesis (suppression of uninvolved immunoglobulins) has been studied in progression and while for SMM immunoparesis is prognostic; in MGUS the value of immunoparesis is less clear (52, 55, 58, 59). A recent study also looked at each isotype-specific heavy and light chain in MGUS and suppression of the
uninvolved HLC (e.g., IgGλ suppression in an IgGκ MGUS patient) was shown to be prognostic for progression (62). In a study of 325 MGUS patients, the presence of circulating plasma cells was shown to be prognostic for progression (HR-2.1, p-value-0.03) compared to patients who did not have any circulating plasma cells (63). Age, sex, race, chromosomal translocations are not prognostic factors for progression from precursor disease to symptomatic myeloma.

**Intervention trials in myeloma precursor disease**

Despite all the recent advances in the treatment of multiple myeloma, it remains an incurable disease. The myeloma precursor conditions provide an opportunity to be able to intervene at an earlier stage to either delay or prevent progression altogether. Several trials have looked at early intervention in an attempt to change the natural history of multiple myeloma. These trials have produced mixed results and other than the PETHEMA trial have not shown an improvement in overall survival (Table 4A). A longer follow up will be necessary to ascertain if the benefits from early treatment are sustained without long term adverse effects. Several other studies testing novel drugs are ongoing for patients with SMM (Table 4B). The current standard of care based on the IMWG recommendations (Supplementary Fig-1) is to monitor patients with MGUS or SMM until they progress to MM before starting treatment (7).

**Conclusions**

The recent advances in our knowledge about MGUS and SMM have helped us better understand the pathogenesis of myeloma. It appears that myeloma evolves from a precursor state in almost all cases. We do not completely understand the multistep process from the precursor state to myeloma but studies including whole genome sequencing will continue to
help in improving our understanding of this process. The process of transformation may not be linear acquisition of changes but rather a branched heterogeneous process. Clinical features that are prognostic of rapid transformation to symptomatic disease have been identified but no specific molecular markers have been identified. Intervening at the precursor state provides a unique opportunity to alter the natural history of the disease. A limitation is that a vast majority of patients with precursor disease especially low risk MGUS will never progress to myeloma in their lifetime and treating these patients is not only unnecessary but may be potentially harmful. The challenge is to identify a subset of patients with the precursor state that would definitely progress to myeloma and in whom interventions will have a meaningful impact. As our understanding of the molecular and genetic processes improves, these studies will guide the selection of high-risk patients more appropriately and ultimately direct a tailored management strategy.
**Figure legends:**

Figure 1: Biology of myelomagenesis. Progression from a normal post germinal center B cell to symptomatic myeloma involves a series of genetic and phenotypic changes. Early genetic events can be categorized into two major types – hyperdiploid type and non-hyperdiploid type. These are unified by cyclin D dysregulation (30). The role of 13q appears to be less certain and it may be an early or late event. Secondary genetic changes include Ras mutations, NFκB pathway activating mutations, and inactivating mutations of p53, PTEN or RB pathways (1). Several other genetic changes also occur along the way including secondary translocations, increase in copy number abnormalities, HOXA9 overexpression and Myc upregulation (21, 36). The end result of these changes includes a clonal expansion of abnormal plasma cells that occupy BM stem cell niches (45). Lytic bone lesions are seen due to increased osteoclast activation resulting from RANKL signaling and osteoblast inhibition from DKK1 activity (41, 44). Immune evasion, paracrine and autocrine signaling mediated by cytokine and growth factors are important final steps (46, 51).
REFERENCES


71. Golombick T, Diamond TH, Manoharan A, Ramakrishna R. Monoclonal gammopathy of undetermined significance, smoldering multiple myeloma, and curcumin: a randomized, double-blind
placebo-controlled cross-over 4g study and an open-label 8g extension study. Am J Hematol. 2012;87:455-60.


Table 1: Worldwide incidence of MGUS

<table>
<thead>
<tr>
<th>Study Population</th>
<th>Age</th>
<th>No. of participants</th>
<th>Prevalence of MGUS (%) with 95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olmsted County, MN-2006 (9)</td>
<td>&gt;50</td>
<td>21,463</td>
<td>3.2 (3.0, 3.5)</td>
</tr>
<tr>
<td>Olmsted County, MN-2010 (10)</td>
<td>&gt;50</td>
<td>18,357</td>
<td>4.2 (3.9, 4.5)</td>
</tr>
<tr>
<td>Nagasaki City, Japan (11)</td>
<td>&gt;42</td>
<td>52,802</td>
<td>2.1 (1.9, 2.2)</td>
</tr>
<tr>
<td>Thailand (13)</td>
<td>&gt;50</td>
<td>3,260</td>
<td>2.3 (1.8, 2.8)</td>
</tr>
<tr>
<td>Ghana (15)</td>
<td>50-74</td>
<td>917</td>
<td>5.84 (4.27, 7.4)</td>
</tr>
<tr>
<td>Udine, Italy (64)</td>
<td>18-67</td>
<td>8,197</td>
<td>1.3</td>
</tr>
<tr>
<td>Finistere, France * (19)</td>
<td>&gt;30</td>
<td>30,279</td>
<td>1.1</td>
</tr>
<tr>
<td>General Hospital, Italy * (65)</td>
<td>-</td>
<td>102,000</td>
<td>0.7</td>
</tr>
<tr>
<td>Sweden * (66)</td>
<td>&gt;25</td>
<td>6,995</td>
<td>0.9</td>
</tr>
</tbody>
</table>

* These older studies did not use the modern definition of MGUS.
Table 2: Common cytogenetic abnormalities and their incidence seen in MGUS, SMM and MM (22, 24-27)*.

<table>
<thead>
<tr>
<th>Cytogenetic abnormality</th>
<th>Involved oncogene</th>
<th>MGUS%</th>
<th>SMM%</th>
<th>MM%</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgH translocations</td>
<td>See below</td>
<td>40-50%</td>
<td>40-50%</td>
<td>50-70%</td>
</tr>
<tr>
<td>t(11;14)(q13;q32)</td>
<td>CCND1 (cyclin D1)</td>
<td>10-25%</td>
<td>10-25%</td>
<td>15%</td>
</tr>
<tr>
<td>t(4;14)(p16;q32)</td>
<td>FGFR3 and MMSET</td>
<td>2-9%</td>
<td>3-13%</td>
<td>10-15%</td>
</tr>
<tr>
<td>t(14;16)(q32;q23)</td>
<td>C-MAF</td>
<td>2-5%</td>
<td>2-5%</td>
<td>2-5%</td>
</tr>
<tr>
<td>Other IgH translocations-</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>t(6;14)(p21;q32),</td>
<td>CCND3 (cyclin D3),</td>
<td>6-10%</td>
<td>1-10%</td>
<td>10%</td>
</tr>
<tr>
<td>t(14;20)(q32;q11) etc.</td>
<td>MAFB, etc.</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>13q deletion</td>
<td>Unknown</td>
<td>25-50%</td>
<td>35-50%</td>
<td>40-50%</td>
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<tr>
<td>Hyperdiploidy</td>
<td>Unknown</td>
<td>40-50%</td>
<td>40-50%</td>
<td>40-50%</td>
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</table>

Studies investigating the cytogenetic abnormalities in MGUS and SMM are limited by the small number of subjects in each group as well as by technical limitations in the ability to select abnormal plasma cells using CD138+ sorting methods. The numbers of subjects in each study are as follows- Ref 23- 123 High risk SMM; Ref 25- 62 MGUS and 10 SMM; Ref 26- 189 MGUS, 127 SMM and 400 MM; Ref 27- 90 MGUS, 102 high risk SMM and 373 MM; Ref 28- 147 MGUS, 39 SMM and 669 MM.
Table 3A: Risk Stratification Model for MGUS using Mayo clinic model (54)

<table>
<thead>
<tr>
<th>Model</th>
<th>No. of risk factors</th>
<th>20-year progression %</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayo Clinic model</td>
<td>0</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Risk factors: M-protein ≥</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.5g/dL, non IgG MGUS,</td>
<td>1</td>
<td>21</td>
<td>5.4</td>
</tr>
<tr>
<td>FLC ratio &lt;0.26 or &gt;1.65</td>
<td>2</td>
<td>37</td>
<td>10.1</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>58</td>
<td>20.8</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>20</td>
<td>NA</td>
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Table 3B: Risk Stratification Model for MGUS using Spanish (PETHEMA) model (58)

<table>
<thead>
<tr>
<th>Model</th>
<th>No. of risk factors</th>
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<th>Relative risk</th>
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<tr>
<td>Spanish (PETHEMA) model</td>
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<td>1</td>
</tr>
<tr>
<td>Risk factors: ≥ 95% aPC,</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DNA aneuploidy</td>
<td>1</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>46</td>
<td>23</td>
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<tr>
<td></td>
<td>Total</td>
<td>8.5</td>
<td>NA</td>
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Table 3C: Risk Stratification Model for SMM using Mayo clinic model (56)

<table>
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<th>Model</th>
<th>No. of risk factors</th>
<th>5-year progression %</th>
<th>Relative risk</th>
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<tbody>
<tr>
<td>Mayo Clinic model</td>
<td>1</td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td>Risk factors: M-protein ≥</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3g/dL, ≥ 10% BM plasma cells,</td>
<td>2</td>
<td>51</td>
<td>2.0</td>
</tr>
<tr>
<td>FLC ratio &lt;0.125 or &gt;8</td>
<td>3</td>
<td>76</td>
<td>3.0</td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>51</td>
<td>NA</td>
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Table 3D: Risk Stratification Model for MGUS using Spanish (PETHEMA) model (58)

<table>
<thead>
<tr>
<th>Model</th>
<th>No. of risk factors</th>
<th>5-year progression %</th>
<th>Relative risk</th>
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<tbody>
<tr>
<td>Spanish (PETHEMA) model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>46</td>
<td>11.5</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>72</td>
<td>18</td>
</tr>
<tr>
<td>Risk factors: ≥ 95% aPC, Immunoparesis.</td>
<td>Total</td>
<td>46</td>
<td>NA</td>
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Table 4a: Completed intervention studies for myeloma precursor disease

<table>
<thead>
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<th>Drug/s</th>
<th>Reference</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Melphalan and Prednisone</td>
<td>(67)</td>
<td>50 patients with SMM were randomized to receive melphalan and prednisone immediately upon diagnosis or at the time of disease progression. The study found no difference in the response rate or overall survival in the two groups.</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>(68)</td>
<td>A small single arm study of 16 subjects showed that thalidomide produced a PR or better in 6/16 subjects.</td>
</tr>
<tr>
<td>Thalidomide and pamidronate</td>
<td>(69)</td>
<td>In this phase 2 study, 76 SMM patients were administered daily thalidomide and monthly pamidronate. The study had a 50% discontinuation rate within the first 2 years due to adverse effects. Unexpectedly the study found that attaining a PR was associated with a shorter time to salvage therapy for disease progression.</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>(70)</td>
<td>A prospective, open label, randomized trial comparing zoledronic acid vs observation in 163 SMM patients. Monthly zoledronic acid for 1 year in SMM patients reduced the development of skeletal related events (SREs) at the time of progression (55.5% vs 78.3% p=0.041) but did not affect the time to progression to symptomatic disease (67 vs 59</td>
</tr>
</tbody>
</table>
months $p=0.83$).

<table>
<thead>
<tr>
<th><strong>Curcumin</strong> (71)</th>
<th>In a double-blind placebo controlled study, curcumin was shown to have a modest effect in decreasing the FLC ratio among a quarter of MGUS and SMM subjects but the effect on progression to symptomatic disease was not reported.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lenalidomide and dexamethasone</strong> (72)</td>
<td>A phase 3 PETHEMA trial of high risk SMM, randomized patients to induction with lenalidomide and dexamethasone followed by lenalidomide maintenance versus no treatment. After a median follow up of 32 months, 9 (15%) patients in the treatment arm and 37 (59%) patients in the observation arm had progressed (HR- 6.0; 95% CI (2.9-12.6); $p&lt;0.0001$). The estimated 3-year overall survival was 93% in the treatment arm and 76% in the observation arm ($p=0.04$).</td>
</tr>
</tbody>
</table>
Table 4b: Currently ongoing intervention studies for precursor disease (73)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Target/MOA</th>
<th>Study phase</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPH2101</td>
<td>Anti-KIR monoclonal Ab</td>
<td>2</td>
<td>Single arm study assessing response of drug in SMM and measuring toxicity.</td>
</tr>
<tr>
<td>BHQ880</td>
<td>Anti-Dickkopf (DKK1) Ab</td>
<td>2</td>
<td>Single arm study assessing response of drug in high risk SMM.</td>
</tr>
<tr>
<td>Elotuzumab</td>
<td>Anti-CS1 monoclonal Ab</td>
<td>2</td>
<td>Study looking at association between NK cell status and efficacy of Elotuzumab monotherapy in high risk SMM.</td>
</tr>
<tr>
<td>Slituximab</td>
<td>Anti-IL6 monoclonal Ab</td>
<td>2</td>
<td>Randomized, blinded, placebo controlled trial looking at one year PFS in high risk SMM.</td>
</tr>
<tr>
<td>MLN 9708 and dexamethasone</td>
<td>Proteasome inhibitor and steroid</td>
<td>2</td>
<td>A single arm study in high risk SMM with response rate as primary outcome and PFS and duration of response as secondary outcomes.</td>
</tr>
<tr>
<td>Lenalidomide</td>
<td>IMiD</td>
<td>3</td>
<td>A phase 3 randomized ECOG trial of lenalidomide vs observation in high risk SMM.</td>
</tr>
<tr>
<td>Drug Combination</td>
<td>Type</td>
<td>Study Information</td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>------</td>
<td>-------------------</td>
<td></td>
</tr>
<tr>
<td>Bortezomib</td>
<td>Proteasome inhibitor</td>
<td>Study looking at the effects of low dose (0.7 mg/m² i.v.) bortezomib on bone formation and natural history in SMM.</td>
<td></td>
</tr>
<tr>
<td>Carfilzomib, Lenalidomide and dexamethasone</td>
<td>Proteasome inhibitor, IMiD and steroid</td>
<td>Single arm study in high risk SMM assessing the safety and response rate of the triple drug combination in SMM.</td>
<td></td>
</tr>
</tbody>
</table>
Post germinal center B-cell → MGUS → Smoldering myeloma → Myeloma

Primary genetic events
- IgH translocations
- Hyperdiploidy
- Cyclin D dysregulation

Secondary genetic events
- NRAS (24%), KRAS (27%), BRAF (4%) mutations
- NFκB pathway mutations
- p53, PTEN, RB inactivation

13q deletion

Other genetic events
- Secondary translocations
- Copy number abnormalities
- HOXA9 overexpression
- MiRNA changes
- Myc upregulation

Phenotypic changes
- Increased RANKL/OPG ratio - Osteoclast activation
- Increased DKK1 activity - Osteoblast inhibition
- Increased homing of MM cells to BMSC niche
- Increased immune evasion
- Cytokine and growth factor changes

Figure 1:
Monoclonal gammopathy of undetermined significance and Smoldering Multiple Myeloma: A review of the current understanding of epidemiology, biology, risk stratification and management of myeloma precursor disease

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