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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

Amit Agarwal¹ and Irene Ghobrial²

¹Division of Hematology/Oncology, University of Arizona, Tucson, AZ

²Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA

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 Waldenström 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 ≥ 3 g/dL and/or clonal bone marrow plasma cells ≥ 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-1 α , 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 ≥ 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 $\geq 60\%$ 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 $\geq 95\%$ 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 $\geq 95\%$ 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 $\geq 95\%$ 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 $\geq 5\%$, 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 (eg IgG λ suppression in a IgG κ 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Anderson KC, Carrasco RD. Pathogenesis of myeloma. *Annu Rev Pathol*. 2011; 6:249–74. [PubMed: 21261519]

2. Waldenstrom J. Studies on conditions associated with disturbed gamma globulin formation (gammopathies). *Harvey Lect.* 1960; 56:211–31. [PubMed: 14004528]
3. Kyle RA. Monoclonal gammopathy of undetermined significance. Natural history in 241 cases. *Am J Med.* 1978; 64:814–26. [PubMed: 645746]
4. Kyle RA, Greipp PR. Smoldering multiple myeloma. *N Engl J Med.* 1980; 302:1347–9. [PubMed: 7374679]
5. Landgren O, Kyle RA, Pfeiffer RM, Katzmann JA, Caporaso NE, Hayes RB, et al. Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study. *Blood.* 2009; 113:5412–7. [PubMed: 19179464]
6. Weiss BM, Abadie J, Verma P, Howard RS, Kuehl WM. A monoclonal gammopathy precedes multiple myeloma in most patients. *Blood.* 2009; 113:5418–22. [PubMed: 19234139]
7. Kyle RA, Durie BG, Rajkumar SV, Landgren O, Blade J, Merlini G, et al. Monoclonal gammopathy of undetermined significance (MGUS) and smoldering (asymptomatic) multiple myeloma: IMWG consensus perspectives risk factors for progression and guidelines for monitoring and management. *Leukemia.* 2010; 24:1121–7. [PubMed: 20410922]
8. Rajkumar SV, Kyle RA, Buadi FK. Advances in the diagnosis, classification, risk stratification, and management of monoclonal gammopathy of undetermined significance: implications for recategorizing disease entities in the presence of evolving scientific evidence. *Mayo Clin Proc.* 2010; 85:945–8. [PubMed: 20884827]
9. Kyle RA, Therneau TM, Rajkumar SV, Larson DR, Plevak MF, Offord JR, et al. Prevalence of monoclonal gammopathy of undetermined significance. *N Engl J Med.* 2006; 354:1362–9. [PubMed: 16571879]
10. Dispenzieri A, Katzmann JA, Kyle RA, Larson DR, Melton LJ 3rd, Colby CL, et al. Prevalence and risk of progression of light-chain monoclonal gammopathy of undetermined significance: a retrospective population-based cohort study. *Lancet.* 2010; 375:1721–8. [PubMed: 20472173]
11. Iwanaga M, Tagawa M, Tsukasaki K, Kamihira S, Tomonaga M. Prevalence of monoclonal gammopathy of undetermined significance: study of 52,802 persons in Nagasaki City, Japan. *Mayo Clin Proc.* 2007; 82:1474–9. [PubMed: 18053454]
12. Lee LN, Jan IS, Tien HF, Lin JS, Lo SC, Cheng WC. Laboratory and clinical characterization of monoclonal gammopathy in Taiwanese. *J Formos Med Assoc.* 2002; 101:91–7. [PubMed: 12099210]
13. Watanaboonyongcharoen P, Nakorn TN, Rojnuckarin P, Lawasut P, Intragumtornchai T. Prevalence of monoclonal gammopathy of undetermined significance in Thailand. *Int J Hematol.* 2012; 95:176–81. [PubMed: 22234527]
14. Ruiz-Delgado GJ, Ruiz-Arguelles GJ. Genetic predisposition for monoclonal gammopathy of undetermined significance. *Mayo Clin Proc.* 2008; 83:601–2. author reply 2–3. [PubMed: 18452695]
15. Landgren O, Katzmann JA, Hsing AW, Pfeiffer RM, Kyle RA, Yeboah ED, et al. Prevalence of monoclonal gammopathy of undetermined significance among men in Ghana. *Mayo Clin Proc.* 2007; 82:1468–73. [PubMed: 18053453]
16. Landgren O, Gridley G, Turesson I, Caporaso NE, Goldin LR, Baris D, et al. Risk of monoclonal gammopathy of undetermined significance (MGUS) and subsequent multiple myeloma among African American and white veterans in the United States. *Blood.* 2006; 107:904–6. [PubMed: 16210333]
17. Vachon CM, Kyle RA, Therneau TM, Foreman BJ, Larson DR, Colby CL, et al. Increased risk of monoclonal gammopathy in first-degree relatives of patients with multiple myeloma or monoclonal gammopathy of undetermined significance. *Blood.* 2009; 114:785–90. [PubMed: 19179466]
18. Landgren O, Kyle RA, Hoppin JA, Beane Freeman LE, Cerhan JR, Katzmann JA, et al. Pesticide exposure and risk of monoclonal gammopathy of undetermined significance in the Agricultural Health Study. *Blood.* 2009; 113:6386–91. [PubMed: 19387005]
19. Saleun JP, Vicariot M, Derooff P, Morin JF. Monoclonal gammopathies in the adult population of Finistere, France. *J Clin Pathol.* 1982; 35:63–8. [PubMed: 6801095]

20. Landgren O, Rajkumar SV, Pfeiffer RM, Kyle RA, Katzmann JA, Dispenzieri A, et al. Obesity is associated with an increased risk of monoclonal gammopathy of undetermined significance among black and white women. *Blood*. 2010; 116:1056–9. [PubMed: 20421448]
21. Lopez-Corral L, Sarasquete ME, Bea S, Garcia-Sanz R, Mateos MV, Corchete LA, et al. SNP-based mapping arrays reveal high genomic complexity in monoclonal gammopathies, from MGUS to myeloma status. *Leukemia*. 2012
22. Lopez-Corral L, Mateos MV, Corchete LA, Sarasquete ME, de la Rubia J, de Arriba F, et al. Genomic analysis of high risk smoldering multiple myeloma. *Haematologica*. 2012
23. Avet-Loiseau H, Facon T, Daviet A, Godon C, Rapp MJ, Harousseau JL, et al. 14q32 translocations and monosomy 13 observed in monoclonal gammopathy of undetermined significance delineate a multistep process for the oncogenesis of multiple myeloma. *Intergroupe Francophone du Myelome. Cancer Res*. 1999; 59:4546–50. [PubMed: 10493504]
24. Fonseca R, Bailey RJ, Ahmann GJ, Rajkumar SV, Hoyer JD, Lust JA, et al. Genomic abnormalities in monoclonal gammopathy of undetermined significance. *Blood*. 2002; 100:1417–24. [PubMed: 12149226]
25. Chiecchio L, Dagrada GP, Ibrahim AH, Dachs Cabanas E, Protheroe RK, Stockley DM, et al. Timing of acquisition of deletion 13 in plasma cell dyscrasias is dependent on genetic context. *Haematologica*. 2009; 94:1708–13. [PubMed: 19996118]
26. Lopez-Corral L, Gutierrez NC, Vidriales MB, Mateos MV, Rasillo A, Garcia-Sanz R, et al. The progression from MGUS to smoldering myeloma and eventually to multiple myeloma involves a clonal expansion of genetically abnormal plasma cells. *Clin Cancer Res*. 2011; 17:1692–700. [PubMed: 21325290]
27. Avet-Loiseau H, Facon T, Grosbois B, Magrangeas F, Rapp MJ, Harousseau JL, et al. Oncogenesis of multiple myeloma: 14q32 and 13q chromosomal abnormalities are not randomly distributed, but correlate with natural history, immunological features, and clinical presentation. *Blood*. 2002; 99:2185–91. [PubMed: 11877296]
28. Fonseca R, Blood E, Rue M, Harrington D, Oken MM, Kyle RA, et al. Clinical and biologic implications of recurrent genomic aberrations in myeloma. *Blood*. 2003; 101:4569–75. [PubMed: 12576322]
29. Gertz MA, Lacy MQ, Dispenzieri A, Greipp PR, Litzow MR, Henderson KJ, et al. Clinical implications of t(11;14)(q13;q32), t(4;14)(p16.3;q32), and -17p13 in myeloma patients treated with high-dose therapy. *Blood*. 2005; 106:2837–40. [PubMed: 15976175]
30. Bergsagel PL, Kuehl WM, Zhan F, Sawyer J, Barlogie B, Shaughnessy J Jr. Cyclin D dysregulation: an early and unifying pathogenic event in multiple myeloma. *Blood*. 2005; 106:296–303. [PubMed: 15755896]
31. Hurt EM, Wiestner A, Rosenwald A, Shaffer AL, Campo E, Grogan T, et al. Overexpression of c-maf is a frequent oncogenic event in multiple myeloma that promotes proliferation and pathological interactions with bone marrow stroma. *Cancer Cell*. 2004; 5:191–9. [PubMed: 14998494]
32. Visone R, Croce CM. MiRNAs and cancer. *Am J Pathol*. 2009; 174:1131–8. [PubMed: 19264914]
33. Pichiorri F, Suh SS, Ladetto M, Kuehl M, Palumbo T, Drandi D, et al. MicroRNAs regulate critical genes associated with multiple myeloma pathogenesis. *Proc Natl Acad Sci U S A*. 2008; 105:12885–90. [PubMed: 18728182]
34. O'Donnell KA, Wentzel EA, Zeller KI, Dang CV, Mendell JT. c-Myc-regulated microRNAs modulate E2F1 expression. *Nature*. 2005; 435:839–43. [PubMed: 15944709]
35. Avet-Loiseau H, Gerson F, Magrangeas F, Minvielle S, Harousseau JL, Bataille R. Rearrangements of the c-myc oncogene are present in 15% of primary human multiple myeloma tumors. *Blood*. 2001; 98:3082–6. [PubMed: 11698294]
36. Chapman MA, Lawrence MS, Keats JJ, Cibulskis K, Sougnez C, Schinzel AC, et al. Initial genome sequencing and analysis of multiple myeloma. *Nature*. 2011; 471:467–72. [PubMed: 21430775]
37. Egan JB, Shi CX, Tembe W, Christoforides A, Kurdoglu A, Sinari S, et al. Whole-genome sequencing of multiple myeloma from diagnosis to plasma cell leukemia reveals genomic initiating events, evolution, and clonal tides. *Blood*. 2012; 120:1060–6. [PubMed: 22529291]

38. Keats JJ, Chesi M, Egan JB, Garbitt VM, Palmer SE, Braggio E, et al. Clonal competition with alternating dominance in multiple myeloma. *Blood*. 2012; 120:1067–76. [PubMed: 22498740]
39. Walker BA, Wardell CP, Melchor L, Hulkki S, Potter NE, Johnson DC, et al. Intracлонаl heterogeneity and distinct molecular mechanisms characterize the development of t(4;14) and t(11;14) myeloma. *Blood*. 2012; 120:1077–86. [PubMed: 22573403]
40. Bahlis NJ. Darwinian evolution and tiding clones in multiple myeloma. *Blood*. 2012; 120:927–8. [PubMed: 22859708]
41. Roodman GD. Pathogenesis of myeloma bone disease. *Leukemia*. 2009; 23:435–41. [PubMed: 19039321]
42. Politou M, Terpos E, Anagnostopoulos A, Szydlo R, Laffan M, Layton M, et al. Role of receptor activator of nuclear factor-kappa B ligand (RANKL), osteoprotegerin and macrophage protein 1-alpha (MIP-1a) in monoclonal gammopathy of undetermined significance (MGUS). *Br J Haematol*. 2004; 126:686–9. [PubMed: 15327520]
43. Kristinsson SY, Tang M, Pfeiffer RM, Bjorkholm M, Blimark C, Mellqvist UH, et al. Monoclonal gammopathy of undetermined significance and risk of skeletal fractures: a population-based study. *Blood*. 2010; 116:2651–5. [PubMed: 20610813]
44. Tian E, Zhan F, Walker R, Rasmussen E, Ma Y, Barlogie B, et al. The role of the Wnt-signaling antagonist DKK1 in the development of osteolytic lesions in multiple myeloma. *N Engl J Med*. 2003; 349:2483–94. [PubMed: 14695408]
45. Paiva B, Perez-Andres M, Vidrales MB, Almeida J, de las Heras N, Mateos MV, et al. Competition between clonal plasma cells and normal cells for potentially overlapping bone marrow niches is associated with a progressively altered cellular distribution in MGUS vs myeloma. *Leukemia*. 2011; 25:697–706. [PubMed: 21252988]
46. Perez-Andres M, Almeida J, Martin-Ayuso M, Moro MJ, Martin-Nunez G, Galende J, et al. Characterization of bone marrow T cells in monoclonal gammopathy of undetermined significance, multiple myeloma, and plasma cell leukemia demonstrates increased infiltration by cytotoxic/Th1 T cells demonstrating a skewed TCR-Vbeta repertoire. *Cancer*. 2006; 106:1296–305. [PubMed: 16475149]
47. Halapi E, Werner A, Wahlstrom J, Osterborg A, Jeddi-Tehrani M, Yi Q, et al. T cell repertoire in patients with multiple myeloma and monoclonal gammopathy of undetermined significance: clonal CD8+ T cell expansions are found preferentially in patients with a low tumor burden. *Eur J Immunol*. 1997; 27:2245–52. [PubMed: 9341766]
48. Dhodapkar MV, Krasovsky J, Osman K, Geller MD. Vigorous premalignancy-specific effector T cell response in the bone marrow of patients with monoclonal gammopathy. *J Exp Med*. 2003; 198:1753–7. [PubMed: 14638846]
49. Dhodapkar MV, Geller MD, Chang DH, Shimizu K, Fujii S, Dhodapkar KM, et al. A reversible defect in natural killer T cell function characterizes the progression of premalignant to malignant multiple myeloma. *J Exp Med*. 2003; 197:1667–76. [PubMed: 12796469]
50. Mahtouk K, Moreaux J, Hose D, Reme T, Meissner T, Jourdan M, et al. Growth factors in multiple myeloma: a comprehensive analysis of their expression in tumor cells and bone marrow environment using Affymetrix microarrays. *BMC Cancer*. 2010; 10:198. [PubMed: 20465808]
51. Podar K, Richardson PG, Hideshima T, Chauhan D, Anderson KC. The malignant clone and the bone-marrow environment. *Best Pract Res Clin Haematol*. 2007; 20:597–612. [PubMed: 18070708]
52. Kyle RA, Therneau TM, Rajkumar SV, Offord JR, Larson DR, Plevak MF, et al. A long-term study of prognosis in monoclonal gammopathy of undetermined significance. *N Engl J Med*. 2002; 346:564–9. [PubMed: 11856795]
53. Rosinol L, Cibeira MT, Montoto S, Rozman M, Esteve J, Filella X, et al. Monoclonal gammopathy of undetermined significance: predictors of malignant transformation and recognition of an evolving type characterized by a progressive increase in M protein size. *Mayo Clin Proc*. 2007; 82:428–34. [PubMed: 17418070]
54. Rajkumar SV, Kyle RA, Therneau TM, Melton LJ 3rd, Bradwell AR, Clark RJ, et al. Serum free light chain ratio is an independent risk factor for progression in monoclonal gammopathy of undetermined significance. *Blood*. 2005; 106:812–7. [PubMed: 15855274]

55. Kyle RA, Remstein ED, Therneau TM, Dispenzieri A, Kurtin PJ, Hodnefield JM, et al. Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. *N Engl J Med*. 2007; 356:2582–90. [PubMed: 17582068]
56. Dispenzieri A, Kyle RA, Katzmann JA, Therneau TM, Larson D, Benson J, et al. Immunoglobulin free light chain ratio is an independent risk factor for progression of smoldering (asymptomatic) multiple myeloma. *Blood*. 2008; 111:785–9. [PubMed: 17942755]
57. Rajkumar SV, Larson D, Kyle RA. Diagnosis of smoldering multiple myeloma. *N Engl J Med*. 2011; 365:474–5. [PubMed: 21812699]
58. Perez-Persona E, Vidriales MB, Mateo G, Garcia-Sanz R, Mateos MV, de Coca AG, et al. New criteria to identify risk of progression in monoclonal gammopathy of uncertain significance and smoldering multiple myeloma based on multiparameter flow cytometry analysis of bone marrow plasma cells. *Blood*. 2007; 110:2586–92. [PubMed: 17576818]
59. Cesana C, Klersy C, Barbarano L, Nosari AM, Crugnola M, Pungolino E, et al. Prognostic factors for malignant transformation in monoclonal gammopathy of undetermined significance and smoldering multiple myeloma. *J Clin Oncol*. 2002; 20:1625–34. [PubMed: 11896113]
60. Hillengass J, Fechtner K, Weber MA, Bauerle T, Ayyaz S, Heiss C, et al. Prognostic significance of focal lesions in whole-body magnetic resonance imaging in patients with asymptomatic multiple myeloma. *J Clin Oncol*. 2010; 28:1606–10. [PubMed: 20177023]
61. Wang M, Alexanian R, Delasalle K, Weber D. Abnormal MRI of spine is dominant risk factor for early progression of asymptomatic multiple myeloma. *Blood*. 2003; 102:687a.
62. Katzmann JA, Clark R, Kyle RA, Larson DR, Therneau TM, Melton LJ 3rd, et al. Suppression of uninvolved immunoglobulins defined by heavy/light chain pair suppression is a risk factor for progression of MGUS. *Leukemia*. 2012
63. Kumar S, Rajkumar SV, Kyle RA, Lacy MQ, Dispenzieri A, Fonseca R, et al. Prognostic value of circulating plasma cells in monoclonal gammopathy of undetermined significance. *J Clin Oncol*. 2005; 23:5668–74. [PubMed: 16110026]
64. La Raja M, Barcobello M, Bet N, Dolfini P, Florean M, Tomasella F, et al. Incidental finding of monoclonal gammopathy in blood donors: a follow-up study. *Blood Transfus*. 2012; 10:338–43. [PubMed: 22507857]
65. Malacrida V, De Francesco D, Banfi G, Porta FA, Riches PG. Laboratory investigation of monoclonal gammopathy during 10 years of screening in a general hospital. *J Clin Pathol*. 1987; 40:793–7. [PubMed: 3114329]
66. Axelsson U, Bachmann R, Hallen J. Frequency of pathological proteins (M-components) om 6,995 sera from an adult population. *Acta Med Scand*. 1966; 179:235–47. [PubMed: 4160039]
67. Hjorth M, Hellquist L, Holmberg E, Magnusson B, Rodger S, Westin J. Initial versus deferred melphalan-prednisone therapy for asymptomatic multiple myeloma stage I--a randomized study. Myeloma Group of Western Sweden. *Eur J Haematol*. 1993; 50:95–102. [PubMed: 8440364]
68. Rajkumar SV, Dispenzieri A, Fonseca R, Lacy MQ, Geyer S, Lust JA, et al. Thalidomide for previously untreated indolent or smoldering multiple myeloma. *Leukemia*. 2001; 15:1274–6. [PubMed: 11480571]
69. Barlogie B, van Rhee F, Shaughnessy JD Jr, Epstein J, Yaccoby S, Pineda-Roman M, et al. Seven-year median time to progression with thalidomide for smoldering myeloma: partial response identifies subset requiring earlier salvage therapy for symptomatic disease. *Blood*. 2008; 112:3122–5. [PubMed: 18669874]
70. Musto P, Petrucci MT, Brinchen S, Guglielmelli T, Caravita T, Bongarzone V, et al. A multicenter, randomized clinical trial comparing zoledronic acid versus observation in patients with asymptomatic myeloma. *Cancer*. 2008; 113:1588–95. [PubMed: 18683218]
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. [PubMed: 22473809]
72. Mateos, M.; López-Corral, L.; Hernandez, M.; Giraldo, P.; Rubia, JDL.; Arriba, Fd, et al. ASH. Vol. 2012. San Diego: 2012. Smoldering Multiple Myeloma (SMM) At High-Risk of Progression to Symptomatic Disease: A Phase III, Randomized, Multicenter Trial Based On Lenalidomide-

Dexamethasone (Len-Dex) As Induction Therapy Followed by Maintenance Therapy with Len Alone Vs No Treatment.

73. ClinicalTrials.Gov. [cited; Available from: www.clinicaltrials.gov

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).

Table 1

Worldwide incidence of MGUS

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

^{*} 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)*.

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

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)

Model	No. of risk factors	20-year progression %	Relative risk
Mayo Clinic model	0	5	1
	1	21	5.4
Risk factors: M-protein	2	37	10.1
	3	58	20.8
1.5g/dL, non IgG MGUS, FLC ratio <0.26 or >1.65	Total	20	NA

Table 3B

Risk Stratification Model for MGUS using Spanish (PETHEMA) model (58)

Model	No. of risk factors	5-year progression %	Relative risk
Spanish (PETHEMA) model	0	2	1
	1	10	5
	2	46	23
Risk factors: 95% aPC, DNA aneuploidy	Total	8.5	NA

Table 3C

Risk Stratification Model for SMM using Mayo clinic model (56)

Model	No. of risk factors	5-year progression %	Relative risk
Mayo Clinic model	1	25	1
	2	51	2.0
	3	76	3.0
Risk factors: M-protein			
3g/dL, 10% BM plasma cells, FLC ratio <0.125 or >8	Total	51	NA

Table 3D

Risk Stratification Model for MGUS using Spanish (PETHEMA) model (58)

Model	No. of risk factors	5-year progression %	Relative risk
Spanish (PETHEMA) model	0	4	1
	1	46	11.5
	2	72	18
Risk factors: 95% aPC, Immunoparesis.	Total	46	NA

Table 4a

Completed intervention studies for myeloma precursor disease

Drug/s	Reference	Comments
Melphalan and Prednisone	(67)	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.
Thalidomide	(68)	A small single arm study of 16 subjects showed that thalidomide produced a PR or better in 6/16 subjects.
Thalidomide and pamidronate	(69)	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.
Zoledronic acid	(70)	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 months $p=0.83$).
Curcumin	(71)	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.
Lenalidomide and dexamethasone	(72)	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); $p<0.0001$). The estimated 3-year overall survival was 93% in the treatment arm and 76% in the observation arm ($p=0.04$).

Table 4b

Currently ongoing intervention studies for precursor disease (73)

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