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Review Article

Is It Possible to Predict Tumor Progression Through Genomic Characterization of Monoclonal Gammopathy and Smoldering Multiple Myeloma?

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Abstract. The study of monoclonal serum proteins has led to the generation of two major theories: one proposing that individuals who had monoclonal proteins without any symptoms or evidence of end-organ damage have a benign condition, the other one suggesting that some individuals with asymptomatic monoclonal proteins may progress to multiple myeloma and thus are affected by a monoclonal gammopathy of undetermined significance (MGUS). Longitudinal studies of subjects with MGUS have supported the second theory. Subsequent studies have characterized and defined the existence of another precursor of multiple myeloma, smoldering multiple myeloma (SMM), intermediate between MGUS and multiple myeloma. Primary molecular events, chromosome translocations, and chromosome number alterations resulting in hyperploidy, required for multiple myeloma development, are already observed in myeloma precursors. MGUS and SMM are heterogeneous conditions with the presence of tumors with distinct pathogenic phenotypes and clinical outcomes. The identification of MGUS and SMM patients with a molecularly defined high risk of progression to MM offers the unique opportunity of early intervention with a therapeutic approach on a low tumor burden.

Keywords: MGUS; Monoclonal gammopathy; Clinical classification; Molecular classification.

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Introduction. Multiple myeloma (MM) is a disorder of the monoclonal plasma cells. It is the second most common hematologic malignancy, and its incidence is increasing. The current estimated annual incidence rate (AIR) is very different in the various countries; high-income countries reported the highest incidence: Australia and New Zealand with an incidence (AIR 4.86 [4.66-5.07]), Northern America (4.74 [4.69-4.79]), and northern Europe (3.82 [3.71-3.93]) The lowest incidences were observed in western Africa (0.81 [0.39-1.66]), Melanesia (0.87 [0.55-1.37]), and southeastern Asia (0.96 [0.73-1.27]). In the USA, the incidence was 7.7 per 100,000 inhabitants (2019), with a 126% increase since 2000, when the incidence was 6.1 per 100,000.[1] MM may originate from the evolution of precursor conditions, including monoclonal gammopathy of undetermined significance (MGUS) and smoldering multiple myeloma (SMM).

Patients with precursors to MM are dichotomized as having MGUS or SMM based on monoclonal protein concentrations or plasma cell percentage in the bone marrow. The current diagnostic criteria for MGUS imply the presence of a serum monoclonal protein (M protein) at a concentration of <3g/dL, bone marrow with <10% monoclonal plasma cells, and absence of end-organ damage (lytic bone lesions, anemia, hypercalcemia, kidney impairment, hyperviscosity) related to the proliferation of plasma cells. Diagnostic criteria for SMM imply the presence of serum M protein (IgG or IgA) ≥ 3g/dL or urinary M protein ≥ 500mg/24h and/or 10%-59% clonal plasma cells in the absence of end-organ damage attributable to the plasma cell disorder.[1,2]

Genetic Alterations in MGUS. MGUS occurs in about 3% of individuals 50 years of age or older.[2] This estimate was based on the current routine methodology based on serum protein electrophoresis supplemented by immunofixation. However, recently developed mass spectrometry (MS)-based approaches have allowed a markedly greater sensitivity in the detection and quantification of M-proteins, showing that the prevalence of MGUS might be two/three times higher than previously estimated using serum protein electrophoresis.[3-5] Interestingly, the mass spectrometry evaluation allowed to distinguish two types of MGUS: monoclonal gammopathies below the clinical immunofixation electrophoresis detection level (>0.2 g/L) defined as monoclonal gammopathy of indeterminate potential (MGIP, predominantly of immunoglobulin M isotype); monoclonal gammopathies with higher M protein concentrations, defined as mass-spectrometry MGUS.[5] The prevalence of MGIP among 7622 participants increased with age: 19%] for individuals aged <50 years, 29% for those aged ≥50 years, and 37% for 946] for those aged ≥70 years.[4] However, the large discrepancy between the prevalence of MGIP and MGUS in the general population (particularly in older individuals) and the relative rarity of myeloma indicates that evolution in myeloma requires very complex and subtle rare mechanisms.

A few risk factors have been involved in MGUS development, including age, male, sex, Black or African American race, and family history. The definition of a category of MGUS patients with an M protein of 0.2 g/dL and identified as MS-MGUS allows us to show an epidemiological link between MGUS and obesity and heavy smoking.[6]

A fundamental study by Kyle and coworkers explored the long-term follow-up of 1384 subjects with MGUS; MGUS progression was observed in 11% of these patients; the risk of progression was estimated at 10% at 10 years, 18% at 20 years, 28% at 30 years, 36% at 35 years and 36% at 40 years.[2] Among patients with IgM MGUS, the presence of two risk factors, such as high serum M-protein (≥1.5 g/dL) and an abnormal serum-free light-chain ratio (ratio of kappa to lambda free light chains), was associated with a risk of progression at 20 years of 55%, compared to 41% in those with one adverse risk factor and 19% in patients without any of the two risk factors[2] (**Table 1**, **Figure 1**). Among patients with non-IgM MGUS, the presence of two risk factors was associated with a risk of progression at 20 years of 30%, 20% among those with one risk factor and 7% in those without neither risk factor.[2] Importantly, individuals with MGUS have a shorter survival rate than those without MGUS in a control population matched for age and sex.[2]

Table 1. Absolute risk of progression of MGUS to myeloma or related disorders based on the serum FLC ratio. From Blood 2005. Modified.

	Normal ratio 0.26-1.65*	**Abnormal ratio < 0.26 or > 1.65**
Absolute risk of progression, % of patients (95% CI)		
Time of follow-up		
5 y	**2.5 (1.3-3.8)**	**8 (4.8-11)**
10 y	**5.3 (3.2-7.4)**	**16.7 (11.4-21.7)**
15 y	**6.6 (4-9.8)**	**29.9 (21.1-37.8)**
20 y	**12.6 (4.5-20.7)**	**35 (23.6-45)**
Cumulative annual rate of progression, %/y	**0.6**	**1.8**
Cumulative annual rate of progression, after adjusting for competing risk of death, %/y	**0.3**	**0.8**

It is of interest to note that there are three different asymptomatic conditions characterized by clonal expansion of blood cells: MGUS, monoclonal B-cell lymphocytosis (MBL), and clonal hematopoiesis (CH). All these three conditions are associated with an increased risk of hematologic cancers; particularly, each condition has an annual progression rate of about 1-2% per year, with MGUS progressing to MM, MBL to chronic lymphocytic leukemia, and CH to myeloid neoplasia. Furthermore, all three premalignant conditions are associated with adverse outcomes. A common feature of all these states is their consistent heterogeneity at the mutational level, including a set of gene abnormalities acquired by apparently stochastic processes, driving changes in biological behavior, and generation of multiple clonal propagating units in the competition. Screening on non-hematological patients showed that there is no association between these three premalignant conditions, thus supporting their independent origin.[7]

Initial oncogenic events commonly displayed by MGUS and MM are characterized by at least one of seven primary immunoglobulin heavy chain gene translocations at q32 or by hyperploidy (about 50% of cases) related to trisomy of several chromosomes (3, 5, 7, 9, 11, 15, 19 and 21) .[8-10] Dysregulation of the G_1-S

Table 2. Risk-stratification models to predict progression of monoclonal gammopathy of undetermined significance to myeloma or related disorders. From Blood 2005 and NEJM 2018 (Modified).

Risk group	No. Patients Blood 2005=1148 NEJM=1384 IgM=210 IgG+IgA=1129	Absolute risk of progression at 20 years, % ---------- Blood 2005 I NEJM 2018 I gM IgG-IgA	Absolute risk of progression at 20 years accounting for death as a competing risk, %
Addition of FLC ratio to known prognostic categories			
Low risk (serum M protein < 15 g/L and IgG subtype)			
Normal FLC ratio	449 769	5	2
Abnormal FLC ratio	142 (24%) 379 (33%)	27	12
Intermediate risk (either serum M protein ≥ 15 g/L or non-IgG subtype)			
Normal FLC ratio	278	22	9
Abnormal FLC ratio	184 (39%)	37	17
High risk (serum M protein ≥ 15 g/L and non-IgG subtype)		(All Pts) 34 33	
Normal FLC ratio	42	37	23
Abnormal FLC ratio	53 (56%)	58	27
Risk stratification model incorporating all 3 predictive factors			
Low risk (serum M protein < 15 g/dL, IgG subtype, normal FLC ratio [0.26-1.65])	449	5 7	2
Low-intermediate risk (any 1 factor abnormal)	420	21 19 20	10
High-intermediate risk (any 2 factors abnormal)	226	37 41 30	18
High risk (all 3 factors abnormal)	53	58 50	27

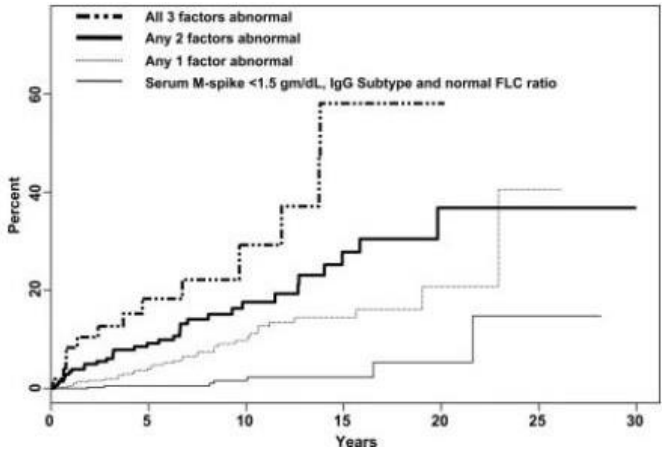

Figure 1. Risk of progression of MGUS to myeloma or related disorder using a risk-stratification model that incorporates the FLC ratio and the size and type of the serum monoclonal protein. The top curve illustrates risk of progression with time in patients with all 3 risk factors, namely an abnormal serum kappa- lambda FLC ratio (0.26 or 1.65), a high serum monoclonal protein level (15 g/L), and non–IgG MGUS; the second gives the risk of progression in patients with any 2 of these risk factors; the third curve illustrates the risk of progression with one of these risk factors; the bottom curve is the risk of progression for patients with none of the risk factors. Rajkumar et al, Blood. 2005;106: 812-7

cell-cycle transition through overexpression of the cyclin D gene is an event observed in both non-hyperploid and hyperploid MGUS; it is an early event in MM development.[8]

The analysis of the clonality of copy number alterations (CNAs), including those related to whole chromosomes or segments of chromosomes, was carried out by Samur et al. in 164 samples.[11] 30.5% of the MGUS were classified as hyperploid, and in these tumors, gains in chromosomes 19 (95%), 15 (86%), and 9 (87%) were the most frequent events; in the non-hyperploid group, del 13 was the most frequent event (21%), followed by the gain of 1q (13%).[11] Importantly, the most recurrent CNAs observed in hyperploid MGUS are also observed in hyperploid MM, thus confirming the occurrence of these events very early in the disease process, while the majority of subclonal deletions (deletions targeting 1q, 6q, 8p, 12p, 12q, 14q, 16p, 16q and 17p) detected in MM patients, were not observed in MGUS patients, thus suggesting that they are late events.[11]

CNAs are frequently observed in MGUS patients, and their number is lower than that observed in MM;

furthermore, the number of CNAs is higher in MGUS patients who progress to MM compared to those who did not progress to MM.[12]

Amplification of the chromosomal region 1q21 is the most recurrent chromosomal gain observed in MM; its frequency is higher in MM (40%) than in MGUS (25%) patients, and its presence is associated with a higher risk of progression of MGUS to MM.[13] Several candidate oncogenes are contained in region 1q21, and one of them, *ILF2*, plays a relevant role in MM development, progression, and drug resistance.[14] ILF2 promotes its oncogenic effects in MM cells through interaction with APOBECC3B, potentiating its DNA cytosine deaminase activity, thus favoring DNA genomic instability.[15] 1q21 gain/amplification has a negative prognostic value.[16]

The frequency of 1p deletions is much lower in MGUS (about 5%) than in MM (about 30%).[11] This deletion implies the loss of two tumor suppressor genes, *CDKN2C* and *FAM46C*.[17] Particularly, the deletion of 1p32.3, which involves loss of *CDKN2C*, is associated with adverse overall survival.[18]

Complete loss of chromosome 13 is more frequent in MM than in MGUS patients. However, the frequency of chromosome loss in MGUS is associated with the presence of some specific IgH translocations, such as t(4;14) and t(14;16) translocations, but absent in other IgH translocations, such as t(6;14) and t(11;14)(16).[19]

The clonality analysis of the CNAs in MGUS was carried out by Samur et al. in 164 samples.[11] 30.5% of MGUS were classified as hyperdiploid, and in these tumors, gains in chromosomes 19 (95%), 15 (86%), and 9 (87%) are the most frequent events; in the nonhyperdiploid group, del 13 was the most frequent event (21%), followed by the gain of 1q (13%).[11] Importantly, the CNAs observed in hyperdiploid MGUS are also observed in hyperdiploid MM, thus confirming the occurrence of these events very early in the disease process; in contrast the majority of subclonal deletions (deletions targeting 1q, 6q, 8p, 12p, 12q, 14q, 16p, 16q and 17p) detected in MM patients, were not observed in MGUS patients, thus suggesting that they are late events.[11]

Whole exome sequencing studies have shown the presence of non-synonymous mutations and copy number alterations in 97% and 60% of MGUS cases, respectively; somatic mutations in MGUS were markedly less frequent than in MM.[20] Few genes were similarly mutated in MGUS and MM; IGH translocations are present in similar frequency in MGUS and MM; *MYC* translocations and *TP53* mutations are not observed in MGUS, thus indicating that these alterations are drivers of progression to MM.[20]

Studies of characterization of molecular alterations of MGUS and MM suggest a classification of MGUS into monoclonal gammopathy and early multiple myeloma (eMM): monoclonal gammopathy is characterized by the presence of canonical IGH translocations and hyperploidy, while additional genetic abnormalities are observed in eMM and MM, such as mutations in driver genes, copy number alterations, *MYC* translocation, complex genetic events.[21] MGUSs classified as monoclonal gammopathy have a low risk of progression to MM, while those classified as eMM have a high risk of MM progression.[21] These conclusions were supported by whole genome sequencing studies of MGUS, SMM, and MM, showing that cases with a non-progressing, clinically stable myeloma precursor condition are characterized by later initiation in the life of patients and by the absence of myeloma-defining genomic events, including chromotripsis, templated insertion, mutations in driver genes, and canonical APOBEC mutational activity.[22] Particularly in stable myeloma precursor condition, the tumor mutational burden, as well as the prevalence of structural variants and copy number alterations [such as del(14q), del(16q), del(17p), del(1p12), amp(1q24), del(6q25), del(8p), amp(8q24)] are observed at a significantly lower number compared with progressive myeloma precursor condition.[20] None of the stable myeloma precursor condition cases displayed any structural variant involving the MYC hotspot.[22]

The molecular analysis of IgM MGUS and Waldenstrom macroglobulinemia (WM) showed a similar mutational profile, with quantitative differences in the mutational frequencies higher in WM than in IgM MGUS.[23] *MYD88* was the gene most frequently mutated in both WM (85%) and IgM MGUS (47%).[21] The somatic $MYD88^{L265P}$ mutation determines the constitutive activation of NF-kB and stimulation of B-lymphoid proliferation. The *MYD88* mutation is an early event during WM development, as supported by its high frequency in IgM MGUS patients. The presence of *MYD88* mutations and high serum M-protein concentration (1g/dL or higher) identified a subpopulation of high-risk IgM MGUS patients, with a 38% risk of transformation at 10 years.[24]

IgM MGUS is a premalignant condition for Waldenstrom macroglobulinemia and other B-cell malignancies and very rarely for MM. It is defined by the presence of a monoclonal protein at a level below 3g/dL with plasmocytic bone marrow infiltration below 10%.[25]

The gene encoding the chemokine receptor CXCR4, involved in the homing of B-lymphoid cells in the bone marrow, is mutated in a minority of IgM MGUS (5-10%), compared to a higher frequency of mutations observed in WM (20-25%).[26] *CXCR4* mutation is usually a subclonal event and occurs late during WM development.[26]

Moreno and coworkers have investigated *MYD88* and *CXCR4* mutations by droplet digital polymerase chain reaction (ddPCR) in 101 IgM MGUS and 69 SWM (smoldering Waldenstrom macroglobulinemia).[27] Importantly, ddPCR was more sensitive than standard

PCR for the detection of *MYD88*^{L265P} mutations in both IgM MGUS (64% vs. 39%) and in SWM (82% vs. 73%); the *MYD88* mutation burden was markedly higher in SWM (5.36%) and WM (11%) than in IgM MGUS (1.13%); the *MYD88* mutation burden correlated with the serum M-protein size, the serum IgM concentration, the infiltration of the BM by histological evaluation of the percentage of BM clonal B-cells by flow cytometry.[25] The two most frequent *CXCR4* mutations were C1013G and C1013A; *CXCR4* C1013G was positive in 35% and 43% of patients with IgM MGUS and SWM, respectively; the median *CXCR4* C1013G mutation distribution in both IgM MGUS and SWM was 0.4% and suggested a subclonal pattern for *CXCR4* mutations; *CXCR4* C1013A mutation was more rarely observed (2/54 IgM MGUS and 3/42 SWM).[27]

Several biological features of MGUS are helpful in stratifying the risk for progression of MGUS to symptomatic disease. Among them, the most relevant is represented by the size of the BM plasma cell clone and M-protein levels. Several risk stratification models predicting MGUS progression to MM have been proposed; these models take into account serum M-protein levels (>15g/L), aberrant phenotype in >95% BM plasma cells, non-IgG subtype and abnormal FLC (free light chains) ratio as predictive of MGUS progression risk factors.[28] Mayo Clinic MGUS is one of the most adopted risk stratification models and implies the stratification into low, low-intermediate, high-intermediate, and high with increasing absolute risk of progression at 20 years.[29] Although these prognostic models have proven their utility, they have not been useful for identifying cases with MGUS with low- and intermediate-risk who may have undergone malignant transformation.

MM development is characterized by progressive stromal alterations mainly characterized by reduced hematopoietic support, decreased osteoblast differentiation and function, and increased osteoclast activity. A recent study showed that abnormalities of stromal cells already occur in MGUS, such as the presence of a high number of senescent cells and a reduced osteogenic differentiation capacity and hematopoietic support.[30] Furthermore, RNA sequencing studies have shown the expression of a broad spectrum of differentially expressed genes, including genes of the BMP/TGF-signaling pathway, present in MGUS and increasing in SMM and MM.[30]

Transition from MGUS to SMM and MM. Several studies have attempted to define the molecular changes that drive the transition from MGUS to SMM and from SMM to MM. Comparisons of unpaired MGUS/SMM and MGUS/MM samples have shown that MGUS and SMM display a consistent similarity with MM; however, many mutations are present in a lower proportion of malignant plasma cells.[19,31] Thus, Lopez-Corral, using FISH, observed that the proportion of plasma cells bearing IgH translocations, t(11;14), and 13q deletions was significantly lower in MGUS than in MM.[28] Furthermore, the same authors showed a progressive increase in the incidence of CNAs from MGUS to SMM and MM (median 5, 7.5, and 12 per case, respectively). Furthermore, it was shown that CNAs, such as 11q and 21q gains together with 16q and 22q deletions, apparently exclusive on MM cases, are, in fact, found as minor subclones in MGUS.[31]

In agreement with these findings, paired-sample studies based on the analysis of a few patients evaluating the evolution of genetic abnormalities in the transition from MGUS to SMM[10] or from high-risk SMM to MM[32] have identified most genetic abnormalities required for these tumor evolutions in the premalignant stages, with the clinically dominant subclone already present in SMM.

The ensemble of these studies suggested that intraclonal heterogeneity is an early event in the development and occurs at stages anterior to MM. Whole exome sequencing studies of five paired cases with the evolution from MGUS to SMM and five with the evolution from SMM to MM further supported this model of MM development, showing that MM development is mainly characterized by the phenomenon of clonal stability, with the highly transformed subclonal populations observed in MM being already present at the stages of precursor lesions (MGUS and SMM).[33]

Bolli et al. reported the analysis of 10 SMM patients progressing to MM by whole-genome analysis of 10 paired SMM and MM samples; the analysis of the genomic landscape, including mutational profile and structural rearrangements, showed a similarity between the SMM stage and the MM stage.[34] Paired sample analysis showed two different patterns of progression: 60% of SMM patients evolved according to a spontaneous evolution process implying a change in subclonal composition from SMM to MM in a branching pattern, reflecting a spontaneous evolution model where without any external selective pressure from treatment, acquisition of new genetic abnormalities confer a proliferative advantage to a subclone at expense of others; 40% of patients progressed following a static progression model, where all subclones were equally represented in both SMM and MM samples, without any significant change in their subclonal structure.[34]

Gene Mutations in SMM. The iStopMM study, a nationwide screening study for multiple myeloma precursors in which all residents of Iceland 40 years or older are involved, showed a prevalence of SMM in the total population of 0.53% (0.67% in men and 0.39% in women); its prevalence increased in both sexes with age.[35] In 193 individuals with SMM, the mean M-protein concentration was 0.62g/dL, and the median age was 70

years.[35]

Several studies have explored the genetic alterations observed in SMM and the genetic changes that underline its transition to MM. Using whole genome sequencing, Bolli et al. showed that the genomic landscape, including mutational profile and structural rearrangements at the SMM stage, is very similar to that observed in MM.[34] Paired sample analysis showed two patterns of progression: a static model, implying the maintenance of the subclonal architecture during SMM progression to MM, and the progression being related to the progressive achievement of a sufficient disease burden; a spontaneous evolution model implying changes at the level of subclonal composition.[31] The analysis of mutational signatures suggested a major role of APOBEC cytosine deaminases in disease progression.[34]

It was estimated that patients with SMM have a higher risk of progression to MM (10%/year) compared to those with MGUS (1%/year).[36]

Prognostic models are unable to fully capture the risk of SMM progression since also some patients evaluated as intermediate- or low-risk can still progress to MM. The study of genomic profiles may help to define better the risk of progression in SMM patients. Thus, Bustoros et al., through whole genome sequencing of 214 patients with SMM, identified some genetic predictors of SMM progression: thus, alterations of the MAPK pathway (*KRAS* and *NRAS* mutations), the DNA repair pathway (deletion p17, *TP53*, and *ATM* mutations) and *MYC* (translocations and copy number alterations) are independent risk factors of progression after accounting for clinical risk staging.[37]

Boyle et al. reported the results of a study involving the analysis of 82 patients with SMM by targeted sequencing and comparing these results with those observed in newly diagnosed MM and showed a lower frequency of driver gene mutations in SMM compared to MM, a lower frequency on *NRAS* and *FAM46C* mutations and fewer adverse translocations, del(1p), del(14q), del(16q) and del(17p) in SMM than in MM, suggesting a possible role of these genetic alterations as drivers of the transition to MM; biallelic inactivation of tumor suppressor genes is markedly less frequent in SMM; mutations in *KRAS* are associated with a shorter time to progression.[38] The analysis of clonal heterogeneity showed that changes in subclonal architecture precede progression, and clonal diversity is a marker of time to progression.[38]

Bustoros et al. reported the results of an integrative genetic analysis on 214 SMM patients using an unsupervised binary matrix factorization clustering approach to identify molecular subtypes. Using this approach, they identified six distinct genetic subtypes of SMM (**Figure 2**).[39]

A hyperdiploid genotype characterizes cluster 1 (hyperdiploid-like 1) and is significantly enriched in *NRAS*, *TRAF3*, and *MAX* mutations. Cluster 2 (hyperdiploid-like 2) is characterized by a high frequency of hyperdiploidy (69%), frequent arm-level deletions, including 16q, 6q, 1p, 17p, 4q, 18q, and 20q and the IgH translocations t(14;20) and enrichment in mutations of *NRAS*, *BRAF*, *TP53*, *ATM*, *MAFB* and *CDKN2C* genes. Cluster 3 (translocation-like 1) is enriched in hypodiploid tumors (<45 chromosomes) and is characterized by the presence of t(4;14) which upregulates FGFR3 and MMSET genes, copy number losses of 14q, 1p, 8p, 10p, 11q, 12p, and 17p and by mutations in *DIS3*, *MAF*, *TGFR3*, *PRKD2*, *PRDM1* and

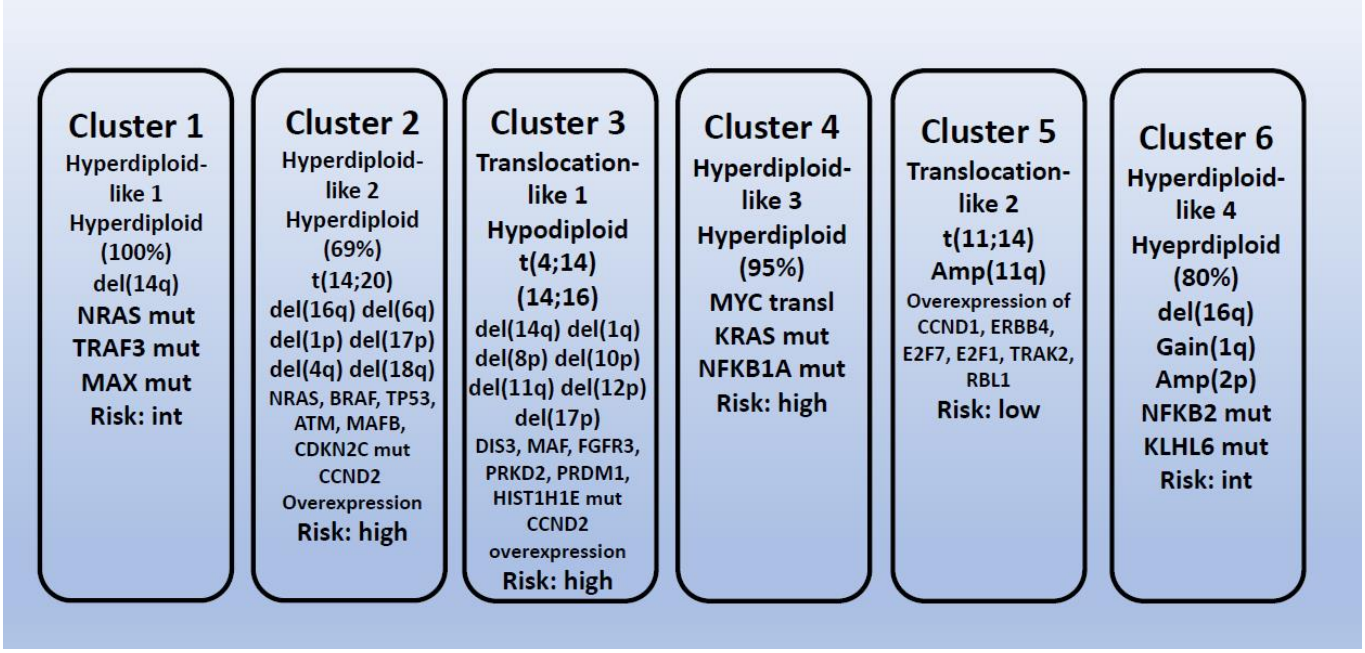

Figure 2. Molecular classification of SMM into six different clusters associated with different molecular abnormalities, according to Bustoros et al.

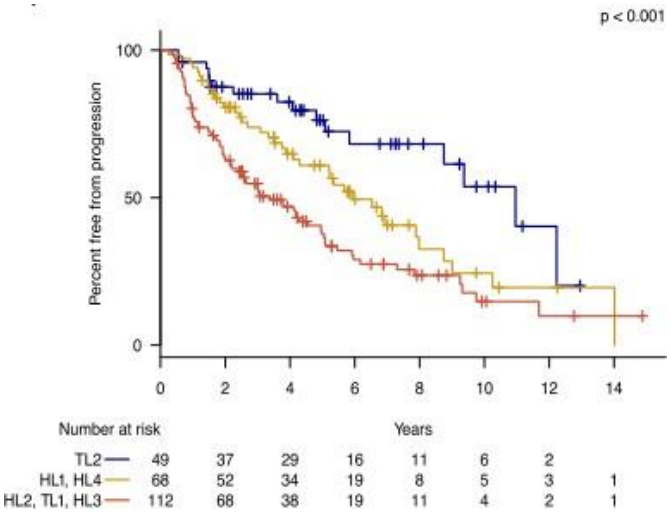

Figure 3. Kaplan-Meier curves for analysis of TTP in patients belonging to the three genetic risk groups of the combined cohort(n=229); log-rankpvalue=0.0002. From Bustoros et Al. Nature Communications | (2022) 13:3449

HIST1H1E. Cluster 4 (hyperdiploid-like 3) is characterized by the presence of hyperdiploid tumors that harbor mutations in *KRAS* and *NFKB1A* genes and by *MYC* translocations. Cluster 5 (translocation-like 2) is characterized by overexpression of *CCND1*, *ERBB4*, *E2F7*, *E2F1*, *TRAK2*, *RBL1* and downregulation of *DUSP4*, *TRAF6*, *PRKD3*, *CCDC6*, and *ZNF844*. Cluster 6 (hyperdiploid-like 4) is characterized by hyperdiploidy, is enriched in *NFKB2* and *KLHL6* mutations, and copy gains in 2p.[39] Clusters 2, 3, and 4 are associated with an increased risk of progression to active MM (**Figure 3**).[39]

Patients developing MM post-SMM (P-SMM) during clinical surveillance were presenting with a lower disease burden, reduced level bone disease, and potentially irreversible myeloma-defining events.[40]

Various clinical risk models have attempted to evaluate the risk of SMM progression. The Mayo risk evaluation criteria stratified SMM patients into risk categories depending on no risk factors (low-risk), one risk factor (low-risk), and two or more risk factors (high-risk); risk factors include free light chain ratio >20, M-protein concentration >2g/dL, BMPC percentage >20%.[41] This risk evaluation system was updated by the International Myeloma Working Group (IMWG), including some cytogenetic markers [t(4;14), t(14;16), gain(1q) and del(13/13q)].[42] More recently, the PANGEA model, based on the evaluation of M-protein levels, free light chain ratio, age, creatinine concentration, BMPC percentage, and hemoglobin trajectories, improved the prediction of SMM progression compared with the two other models.[43] Other models of SMM stratification have been proposed, but there is significant discordance between them.[44]

Interestingly, Diamond and coworkers have performed a whole genomic sequencing analysis on 27 high-risk SMM (HR-SMM) patients treated with carfilzomib, lenalidomide, and dexamethasone; after a median follow-up of 52.8 months, median PFS was not reached and 51.9% of patients achieved sustained MRD negativity.[45] The genomic features of these patients were similar to those of ND-MM for that concerns the frequency of t(4;14), t(14;16), and t(14;20); mutations of *NRAS* were lower in HR-SMM than in ND-MM, as well as gene abnormalities at *MYC* locus and gains of 1q; furthermore, aberrations of tumor suppressor genes, such as *CDKN2C*, *CYLD*, *TENT5C*, *FUBP1*, *MAX*, *NCOR1*, *NF1*, *NFKBIA*, *PRMD1*, *RB1*, *RPL5* and *TRAF3* were less frequent in HR-SMM than in ND-MM.[42] Interestingly, the genomic features were correlated with the treatment outcomes: gain 1q, t(4;14) and *MYC* dysregulation through loss of *MAX* were associated with failure to achieve MRD negativity; inactivation of *CYLD*, *BREBBP*, *MAX*, and t(4;14), APOBEC expression, and chromotripsis all were associated with HR-SMM progression; presence of any or more than one of these features was associated with progression.[45]

SMM is considered a heterogeneous disease entity which includes patients with consistently variable risk of progression to MM; thus, in a subset of patients, the disease is comparable to MGUS and exhibits a low rate of MM progression, while in another subset of patients, is considered as an early MM, with progression to symptomatic MM within 2 years. The Mayo 2018 20/2/20 system classifies SMM patients into three subgroups, low-, intermediate- and high-risk, based on the presence of 0, 1 or 2 or >2 risk factors, respectively, including >20% bone marrow plasma cells, monoclonal protein >2g/dL, and free light chain ratio >20.[41] The 2020 International Myeloma Working Group risk stratification model further widened the separation of SMM patients into four subgroups incorporating cytogenetic abnormalities into the Mayo Clinic 2018 model.[42] The approach to high-risk SMM patients varies among clinicians; while some advocate early interventions, others reserve treatment at progression to MM. A recent survey of 146 different clinicians showed that 92% of them did not recommend routine treatment for high-risk SMM patients based on a single time point assessment, instead preferring active surveillance.[46] The active and frequent surveillance of these patients is important because it was recently estimated that about 70% of HR-SMM patients progress to MM in a follow-up of 3.9 years.[47]

A recent study strongly supports the important role of longitudinal evaluation of the evolution of risk biomarkers over time.[48] Aklhagi et al. retrospectively evaluated the prognostic impact of risk stratification in 398 SMM patients, who were analyzed at the Memorial Sloan Kettering Cancer Center. They observed that risk stratification based on the evaluation of biomarkers reflecting disease burden at the time of diagnosis was unable to predict tumor progression in about 50% of

SMM patients who progressed to MM during the first year.[45] In fact, among these rapidly progressing patients, only 43% had a baseline M-protein ≥2.2 g/dL, and 43% had an FLCr ≥26; furthermore, among these progressor patients, 29% had a baseline M-protein <1.6 g/dL and 26% had baseline FLCr <11.3.[48] However, the evolution of these two biomarkers over time was predictive of risk of progression to MM; thus, evolving changes in M-protein and FLCr were associated with a higher risk of progression from SMM to MM: for patients with low-risk baseline stratification, the presence of evolving M-protein (≥0.3 g/dL increase) and eFLCr (≥50% increase), had a median time to progression of 25 months, similar to that observed in patients with a baseline high-risk.[48]

Abdallah et al. have reported the analysis of the mode of progression in 406 SMM patients evaluated at the Mayo Clinic.[49] With a median follow-up of 3.9 years, 72% of the high-risk SMM patients who did not receive treatment in the SMM phase progressed to MM; 11% of the high-risk patients who received treatment at the SMM stage progressed to MM.[49] The median time to progression in the high-risk SMM patients was 2.6 years, compared to 7.0 years in the non-high-risk patients.[49] Finally, a high proportion (45%) of patients with high-risk SMM on active surveillance develop end-organ damage at progression.[49]

Two different strategies have been proposed for the treatment of HR-SMM: either low-intensity regimens, such as lenalidomide and dexamethasone, or intensive regimens with the aim of cure.[46] The ensemble of the studies carried out until now do not support the early intervention with intensive treatment strategies in SMM as the optimal path to curing myeloma.[50] Interestingly, the Immuno-PRISM trial evaluated the safety and the efficacy of Teclistamab, a bispecific anti-CD38, and anti-CD3 monoclonal antibody, in comparison to lenalidomide and dexamethasone for the treatment of high-risk SMM patients.[51] In the Teclistamab cohort, a 100% overall response (with 87% of CR and 13% of very good partial responses) rate was observed, compared to 66% in the control arm treated with lenalidomide and dexamethasone.[51] 100% of the patients treated with Teclistamab achieved an MRD-negative status.[51] It is of interest to note that the ORR observed in high-risk SMM patients was higher than that previously observed from R/ MM patients treated with Teclistamab (100% vs 63%, respectively).

Conclusions. The development of new techniques for the analysis of genomic alterations occurring in MM and its precursors, MGUS and SMM, have greatly contributed to defining the acquired genomic abnormalities involved in tumor initiation and progression. MGUS and SMM are heterogeneous conditions with the presence of tumors with distinct pathogenic phenotypes and clinical outcomes. The identification of SMM patients with a molecularly defined high risk of progression to MM offers the unique opportunity of early intervention with a therapeutic approach on a low tumor burden using drugs such as bispecific antibodies with a good safety profile.

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