The progression from MGUS to smoldering myeloma and eventually to multiple myeloma involves a clonal expansion of genetically abnormal plasma cells

Lucía López-Corral1*, Norma C. Gutierrez1*, Maria Belén Vidriales1, Maria Victoria Mateos1, Ana Rasillo2, Ramón García-Sanz1, Bruno Paiva1, Jesús F. San Miguel1.

1Servicio de Hematología, Hospital Universitario. Centro de Investigación del Cáncer-IBMCC (USAL-CSIC), Salamanca, Spain.

2Centro de Investigación del Cáncer-IBMCC (USAL-CSIC), Servicio General de Citometría y Departamento de Medicina, Universidad de Salamanca, Salamanca, Spain.

*LLC and NCG contributed equally to this work

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Running title: Expansion of genetically abnormal PC from MGUS to SMM and MM

Corresponding author:
Jesús F. San Miguel
Hospital Universitario de Salamanca
Paseo de San Vicente 58-182
37007 Salamanca, Spain
Tel: +34 923291384
Fax: +34 923294624
Email: sanmigiz@usal.es

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TRANSLATIONAL RELEVANCE

Previous studies have shown that PCs from MGUS and MM have the same cytogenetic abnormalities than MM. We now show in the present study that a major difference among these three entities is the number of PC with genetic abnormalities that increases from MGUS to SMM and to MM. This finding was found for IGH translocations, 13q and 17p deletions, and 1q gains using fluorescence in situ hybridization. We have ruled out using multiparametric flow cytometry the possibility that the increase of PC with genetic abnormalities during the evolving stages of monoclonal gammopathies, was due to dilution of the clonal PC by residual polyclonal PC. Our results confirmed that only a fraction of the clonal PC present in MGUS carried the cytogenetic abnormality. These findings highlight the potential clinical importance of follow-up quantification of the population of PC with genetic abnormalities in the premalignant conditions of MM.
ABSTRACT

Purpose: Genetic aberrations detected in multiple myeloma (MM) have also been reported in the premalignant conditions, monoclonal gammopathy of undetermined significance (MGUS) and smoldering MM (SMM). Our aim was to investigate in depth the level of clonal heterogeneity of recurrent genetic abnormalities in these conditions.

Experimental Design: Immunoglobulin heavy chain (IGH) translocations, 13q14 and 17p13 deletions, and 1q21 gains using fluorescence in situ hybridization (FISH) were evaluated in 90 MGUS, 102 high-risk SMM and 373 MM. To this end, we not only purified plasma cells (PC) for the FISH analysis (purity >90%), but subsequently we examined the correlation between the proportion of PC with cytogenetic changes and the number of clonal PC present in the same sample, as measured by multiparametric flow cytometry.

Results: We observed a significant difference between the proportion of clonal PC with specific genetic abnormalities in MGUS compared with SMM, and in SMM compared with MM. Thus, the median proportion of PC with IGH translocations globally considered, t(11;14) and 13q deletions was significantly lower in MGUS than in SMM, and in SMM than in MM (IGH translocations: 34% vs. 57% vs. 76%; t(11;14): 38% vs. 61% vs. 81% and 13q deletion: 37% vs. 61% vs. 74% in MGUS, SMM and MM, respectively). For t(4;14) the difference was significant in the comparison between MGUS/SMM and MM and for 1q between MGUS and SMM/MM.

Conclusions: This study demonstrates that the progression from MGUS to SMM, and eventually to MM, involves a clonal expansion of genetically abnormal PC.
INTRODUCTION

Multiple myeloma (MM) is a clonal plasma cell (PC) disorder that remains an incurable disease accounting for approximately 10% of all hematological cancers. Although it was believed that approximately only one-third of newly diagnosed MM patients had a history of previous monoclonal gammopathy of undetermined significance (MGUS) (1), recent epidemiological studies have demonstrated that MM evolves from a premalignant condition in most, if not all, patients (2, 3). Although, smoldering MM (SMM) is also considered to be an asymptomatic precursor of active MM (4, 5), the rate of progression of these two premalignant conditions to symptomatic MM greatly differ. Thus, while MGUS evolves to MM or a related malignancy at a rate of 1% per year (1), the cumulative probability of progression to active MM or amyloidosis in SMM is 10% per year in the first five years (6).

Consistent with the clinical evolution of PC dyscrasias as a progression from premalignant to malignant entities, the current pathogenic models assume that MM develops through a multistep transformation from normal PC to MGUS, which implies PC immortalization and, subsequently, the transformation to active MM, where clonal PC cause end-organ damage (7-10). Several studies indicate that most genetic changes reported in MM are already present in MGUS (11-16). It is intriguing to see that this also applies to those changes associated with poor outcome in MM, such as t(4;14), t(14;16) and 17p deletion, which have also been found in MGUS, but apparently have no prognostic influence (12-15, 17). However, the frequency of the genetic abnormalities in MGUS and SMM compared with in MM is not well established. Two studies have compared these frequencies (12, 14), showing that the incidence of 13q deletion and t(4;14) is lower in MGUS than in MM, with discrepant results for SMM. In addition, Chiecchio et al not only found a different incidence of genetic abnormalities, but also a significantly lower proportion of PC carrying 13q deletion in MGUS than in SMM and MM, while they did not detect any variation for IGH rearrangements (14). One explanation for this could be that the lower tumor burden of MGUS affects the final PC purity. Another possibility is that the coexistence of clonal and polyclonal PC within the PC (CD138 population) compartment in MGUS may have contributed to the underestimation of genetically abnormal PC (14, 15).

To shed further light on this matter we have investigated in depth the level of clonal heterogeneity of the recurrent genetic abnormalities in a series of 565 patients with monoclonal gammopathies (90 MGUS, 102 SMM and 373 MM). To do so we not only purified PC for the FISH analysis, but subsequently investigated the correlation between the proportion of PC with cytogenetic changes and the number
of clonal PC present in the same sample, as assessed by multiparametric flow cytometry (4, 18). We reasoned that if we were able to demonstrate that the frequency of cytogenetic changes even in the clonal population (excluding the polyclonal one) was lower in premalignant entities (MGUS and SMM) than in symptomatic MM, this would indicate a progressive accumulation of the genetically abnormal PC during the multistep evolution of MM. In order to avoid misclassification or overlapping entities we decided to focus on MGUS patients with more than one year of stable follow-up, high-risk SMM and symptomatic MM using well establish criteria (4, 19, 20).
PATIENTS AND METHODS

Patients

Samples for this study were obtained from patients with MGUS (n=90), high-risk SMM (102) and newly diagnosed MM (n=373), according to the International Myeloma Working Group criteria (19). All patients were studied at diagnosis before any intervention. High-risk SMM was defined as the presence of >10% PC in bone marrow (BM) and a monoclonal component IgG ≥3 g/dL, IgA ≥2 g/dL or Bence Jones proteinuria ≥1 g/24 h together with absence of CRAB (Calcium increase, Renal Insufficiency, Anemia, Bone lesions) (20). Patients meeting either but not both of these two criteria were also included in the study if they met the additional criteria of having ≥95% phenotypically aberrant PC in the BM PC compartment (aPC/BMPC) and immunoparesis (4).

The study was approved by the research ethics committees of all participating centers and written informed consent was obtained from all patients in accordance with the Helsinki Declaration. The main clinical and laboratory characteristics of these patients are shown in Supplementary Table 1.

Cytogenetic analysis

In all the BM samples CD138-positive PC isolation was carried out using the AutoMACs automated separation system (Miltenyi-Biotec, Auburn, CA, USA). Purity was >95% in all MM and SMM cases, and >90% in MGUS patients. The systematic screening for genomic aberrations in our institution includes interphase fluorescence in situ hybridization (FISH) studies for detecting IGH rearrangements (LSI IGH dual-color, break-apart rearrangement probe; Abbott Molecular/Vysis, Des Plaines, IL, USA), 13q (LSI 13, RB1 13q14) and 17p deletions (LSI p53, 17p13.1) (Abbott Molecular/Vysis) as previously described, and 1q gains (ON 1q21/SRD 1p36, Kreatech Diagnostics, Amsterdam). Those MM samples with IGH translocations were explored for t(11;14)(q13;q32), t(4;14)(p16;q32) and t(14;16)(q32;q23) with the corresponding dual-color, dual-fusion translocation probes from Abbott Molecular/Vysis. The interphase FISH procedure has been described previously in detail (21). A total of 200 interphase nuclei were analyzed using the scoring criteria recommended by the manufacturer. The cut-off level for the identification of IGH translocations (fusion/break-apart probes) and 1q gains was set at 10% and at 20% for numerical abnormalities, as recommended by the European Myeloma Network (EMN) FISH workshop.
**Immunophenotypic studies and sorting of BMPC**

Immunophenotypic analyses were performed using the following monoclonal antibody combinations (FITC/PE/PerCP-Cy5.5/APC) to identify aberrant antigen expression in PCs: CD38/CD56/CD19/CD45, CD38/CD27/CD45/CD28 and β2microglobulin/CD81/CD38/CD117 (4, 18). For specific cases, additional staining for cytoplasmatic Ig light chains was used to determine the polyclonal or monoclonal nature of the PC. The cIgM/cIgA staining was performed in a four-color tube including simultaneous surface staining for CD38 plus either CD45, CD56 or CD19, depending on the type of antigenic aberration. We first identified PCs on the basis of their uniquely bright intensity for CD38 and intermediate side scatter (SSC). Once PCs had been identified, we focused our analysis on the PC compartment, and within it, we discriminated between PCs with normal and aberrant phenotypes corresponding to polyclonal and clonal PCs, respectively, as we previously demonstrated (22-24). The underexpression of CD19, CD27, CD38, CD45, and/or CD81; overexpression of CD28 and/or CD56 and asynchronous expression of CD117 were used to identify aberrant phenotypes in PCs (22, 25).

The following data were recorded for each case: (i) total percentage of PCs among all nucleated BM cells and (ii) percentage of phenotypically aberrant (clonal) plasma cells within the BMPC compartment. We have identified PC based on high CD38 expression and SSC characteristics, that were easily distinguished from B cells precursor (CD38high but SSC low) and from monocytes (weaker CD38 and brighter CD45) (26). We want to stress that in previous studies we did not found differences between the CD38/CD138/SSC and the CD38/SSC identification and enumeration PC approaches (27).

In a group of 18 monoclonal gammopathies samples, immunophenotypically aberrant PC and polyclonal PC were sorted using a FACSARia flow cytometer (Becton Dickinson Biosciences) equipped with 3 laser lines and 13 fluorescence detectors, for further FISH analysis. Reanalysis of the sorted immunophenotypically aberrant PC showed a purity above 98% (28).

Statistical analyses was done using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). The X² and Fisher’s exact tests were used to measure associations between genetic abnormalities and other categorical variables. The Wilcoxon rank sum test was used for continuous variables. Values of P<0.05 were considered to be statistically significant.
RESULTS

Frequency of chromosomal abnormalities in the three subgroups of plasma cell dyscrasias

We observed at least one of the chromosomal abnormalities explored by FISH in 43 of the 90 MGUS (48%), 78 of the 102 SMM (76%) and 257 of the 373 MM (69%). These differences were only statistically significant for the comparison between MGUS and either SMM or MM. When we analyzed the frequency of specific chromosomal abnormalities with respect to the type of monoclonal gammopathy, we found that IGH translocations globally considered, 13q and 17p deletions were significantly less frequent in MGUS than in both symptomatic MM and SMM, the latter two subgroups of patients having similar frequencies (Table 1). In fact, these three genetic abnormalities were present respectively in 24%, 22% and 1% of MGUS compared with 41%/36%, 42%/40% and 8%/8% of SMM/MM (Table 1). Upon looking for differences between the subtypes of IGH translocation, only a borderline difference was found in t(4;14), which was present in 4% of MGUS but in 12% of SMM and 10% of MM (p=0.06) (Table 1). The frequency of 1q gains was significantly lower in MGUS (29%) as compared to MM (42%).

Proportion of PC bearing genetic abnormalities

We next wanted to determine not only if there was a difference in the incidence of cytogenetic abnormalities with respect to the underlying diagnosis, but also whether the number of PC with cytogenetic abnormalities varied between MGUS, SMM and MM, for those cases with genetic aberrations. Our results showed that the median proportion of PCs with IGH translocations globally considered, t(11;14) and 13q deletions was significantly lower in MGUS than in SMM, and in SMM than in MM status (IGH: 34% vs. 57% vs. 76%; t(11;14): 38% vs. 61% vs. 81% and 13q deletion: 37% vs. 61% vs. 74% in MGUS, SMM and MM, respectively) (Table 2). A similar pattern was observed for 17p deletion with median values of 35% vs. 48% vs. 62% in MGUS, SMM and MM, although the differences were not statistically significant. Differences in the proportion of PC exhibiting t(4;14) were also found when comparing MM (83%) with both SMM (59%) and MGUS (48%), although there was no significant difference between MGUS and SMM (Table 2). Furthermore, the median proportion of PC carrying 1q gain was significantly lower in MGUS than in MM (both asymptomatic and symptomatic diseases) (Table 2). Figures 1 and 2 illustrate this gradual change from MGUS to SMM and MM.

To rule out the possibility that the increase of PC with genetic abnormalities during the evolving stages of monoclonal gammopathies was due to dilution of the clonal PC by residual polyclonal PC, which are present at higher numbers in MGUS
than in MM, we used multiparametric flow cytometry to quantify the number of phenotypically aberrant and normal PCs in MGUS and then correlated the results from the FISH analysis with the flow cytometry data. Our results confirmed that only a fraction (<50% in most cases) of the clonal PC present in MGUS carried the cytogenetic abnormality. This was observed for all the chromosomal changes to a greater or lesser extent. Figure 3 illustrates the disparity between the percentage of clonal PC assessed by flow cytometry and the proportion of PC genetically abnormal for the IGH rearrangement, t(11;14), t(4;14), 13q deletion and 1q gains. Although there were 14 MGUS cases with more than one chromosomal abnormality, we did not observe a predominant abnormal clone that enabled us to infer that one of the abnormalities was a primary genetic aberration.

Since the monoclonal antibody (CD138) used for selecting the PC subsequently analyzed by FISH was not included in the flow cytometry panel and this fact could interfere in the correlation between FISH analysis and flow cytometry results, we performed FISH studies on the clonal PC sorted by flow cytometry in a group of 18 monoclonal gammopathies. Ten of the 18 samples showed cytogenetic lesions and the analysis of the cytogenetically abnormal cases confirmed that only a proportion of clonal PC identified by flow cytometry (purity>98%) displayed the genetic abnormality.

Finally, we had the opportunity to analyze sequentially three MGUS patients and five SMM who progressed to symptomatic MM. The genetic abnormalities of this set of patients are described in Table 3. The five patients (two MGUS and three SMM) who already had chromosomal abnormalities at diagnosis showed a higher percentage of PC bearing the genetic aberration at the time of transformation into symptomatic MM. The proportion was doubled in one case, trebled in another two, and increased six-fold in one case.
DISCUSSION

Our results support the hypothesis that the number of genetically abnormal PC increases from MGUS to SMM and to MM. This observation was seen not only in those abnormalities considered secondary events, like 13q deletions, but also in IGH translocations, which are supposed to occur early in the disease pathogenesis (29, 30).

The present study shows that chromosomal abnormalities recurrently found in MM are also present in MGUS, including those abnormalities considered to be secondary genetic events, such as 13q and 17p deletions, and 1q gains, and even those associated with poor outcome, such as 17p, t(4;14) and t(14;16). Interestingly, we found seven MGUS patients with genetic abnormalities associated with dismal outcome -four with t(4;14), two with t(14;16) and one with 17p deletion- and none of them have progressed after a median follow-up of 45 months (range: 22-55 months).

Regarding the frequency of chromosomal abnormalities in the three plasma cell dyscrasias, our study revealed a significantly lower frequency of chromosomal changes at MGUS than at SMM and MM stage. In this setting, the incidence of IGH translocations globally considered was significantly lower in MGUS than in SMM and MM, which is not consistent with the results of Chiecchio et al, who reported the presence of illegitimate IGH rearrangements at the same frequency in patients with MGUS as with MM. In keeping with previous reports we observed a similar prevalence of t(11;14) in the three stages (12, 14). However, although differences were not significant, we also observed, like Chiecchio et al and Avet-Loiseau et al, a lower percentage of PC displaying t(4;14) in MGUS than in MM, for both symptomatic and asymptomatic diseases. Regarding 13q deletion, its frequency progressively increased from MGUS to MM as reported in previous studies (12, 14). Although 17p deletion is a very rarely described abnormality in MGUS (13, 14), it was found in one MGUS case. In the present study, the classical panel of FISH probes was extended to explore chromosome 1 abnormalities. We described 1q gains in 29% of MGUS, a significantly lower proportion than in both active and asymptomatic MM (41% and 42% respectively). This observation is consistent with the findings of Bochtier et al (13), but not with Hanamura data that did not detect 1q gains in MGUS (31). The lack of any significant difference between the incidence of genetic abnormalities in SMM and MM could be due to the fact that the patients with SMM included in this study had a high risk of progression to symptomatic MM.

Recent data suggest that for prognostication in MM, even more important than the presence or absence of a particular cytogenetic abnormality is the number of PC
carrying such abnormality (32). Accordingly, this could be also important in the progression from MGUS to SMM and to MM, with a progressive accumulation of PC carrying the chromosomal abnormality (Figures 1 and 2). In this regard, we observed a significant difference between the proportion of PC with genetic abnormalities in MGUS compared with SMM, and in SMM compared with MM. This was observed for IGH translocations globally considered, t(11,14) and 13q deletion. In addition, for t(4;14) there was a significant difference between MGUS/SMM and MM and for 1q between MGUS and SMM/MM. Further studies are needed to determine whether the progression from pre-malignant stages to MM is influenced by the clonal expansion of genetically abnormal PC. Findings supporting evidence for this hypothesis would justify a FISH analysis along the evolution of genetically abnormal MGUS and SMM, not to identify new genetic changes but to quantify the population of genetically abnormal PC. It is important to emphasize that although the SMM analyzed in the present study had a high risk of progressing to MM and, therefore, great biological similarities between the two entities should be expected, the percentage of PC with genetic abnormalities differed markedly between SMM and symptomatic MM. A study analyzing the influence of the proportion of genetically abnormal PC on the risk to progression of high-risk SMM would be of interest. This hypothesis is also supported by the five cases in which we had the opportunity to perform sequential studies during the evolution from both MGUS and SMM into symptomatic MM identifying a marked increase in the proportion of PC with the genetic abnormality.

The lower frequency of some of the abnormalities in MGUS than in MM, as well as the lower proportion of PC with genetic abnormalities could be explained by the low number of PC in MGUS, which would lead to the true incidence of genomic abnormalities being underestimated. The efficiency of immunomagnetic cell selection has enabled the number of PC exhibiting the chromosomal abnormality to be accurately measured. However, the enrichment can be significantly affected when the tumoral population is very small. To avoid the possibility of contamination of the total cellularity of BM affecting the results, we selected only those MGUS samples in which the final PC recovery was above 90%. Another factor that could play a part in determining the lower proportion of PC with cytogenetic abnormalities in MGUS is the lower percentage of clonal PC (normal and clonal PC coexist in MGUS samples). This possibility was suggested by Chiecchio et al in order to explain the lower proportion of PC with 13q abnormality that they observed in MGUS as compared to SMM/MM (14). Therefore, we considered the possibility that the smaller proportion of genetic abnormalities found in MGUS compared to MM simply reflects contamination of the samples with normal PC, which lack
chromosomal aberrations. To explore this, we examined the correlation between the proportions of phenotypically abnormal PC and of those with genetic abnormalities. Interestingly, in most MGUS cases, chromosomal abnormalities were present in a relatively low proportion of clonal PC (Figure 3). On the other hand, the smaller percentage of PC with genetic abnormalities observed in SMM compared with MM also implies that the results are not affected by technical limitations, since the contamination by normal PC in high-risk SMM is very small and comparable to overt MM. This demonstrates for the first time that the progressive increase in the proportion of PC with genetic abnormalities in the subsequent steps from MGUS to MM is a genuine effect that cannot be attributed to the underestimation of genetically abnormal PC in MGUS.

To summarize, our results show that the progression from MGUS to SMM, and eventually to MM, involves a clonal expansion of genetically abnormal PC. One explanation for this is that cytogenetic abnormalities all arise as secondary events, occurring early on disease pathogenesis but not at the very beginning (15), similarly to what has been proposed for chronic myeloid leukemia (33-35). In a further step, these abnormalities would confer a proliferative advantage leading to a clonal selection (an enrichment in PC with genetic abnormalities).
FIGURE LEGENDS

Figure 1: Median percentage of PC with genetic abnormalities in MGUS, SMM and MM. The number of PC bearing cytogenetic abnormalities increases from MGUS to SMM and to MM. PC: plasma cells; MGUS: monoclonal gammopathy of undetermined significance; SMM: smoldering multiple myeloma; MM: multiple myeloma.

Figure 2: Distribution of PC proportions with genetic abnormalities in MGUS, SMM and MM.

Figure 3: Comparison of proportion of clonal PC by flow cytometry and percentage of PC with chromosomal abnormalities in MGUS patients. PC: plasma cells; aPC: abnormal plasma cells; BMPC: bone marrow plasma cells.
ACKNOWLEDGMENTS

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Table 1: Frequency of genetic abnormalities in MGUS, SMM and MM patients

<table>
<thead>
<tr>
<th>Genetic Abnormalities</th>
<th>MGUS (n=90) Number of patients (%)</th>
<th>SMM (n=102) Number of patients (%)</th>
<th>MM (n=373) Number of patients (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgH abnormality</td>
<td>22/90 (24%)</td>
<td>42/102 (41%)</td>
<td>133/373 (36%)</td>
<td>P=0.01 (MGUS vs SMM) P=0.04 (MGUS vs MM)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>t(11;14)</td>
<td>9/90 (10%)</td>
<td>16/102 (16%)</td>
<td>52/373 (14%)</td>
<td>NS</td>
</tr>
<tr>
<td>t(4;14)</td>
<td>4/90 (4%)</td>
<td>12/102 (12%)</td>
<td>36/373 (10%)</td>
<td>NS</td>
</tr>
<tr>
<td>t(14;16)</td>
<td>2/90 (2%)</td>
<td>5/101 (5%)</td>
<td>9/373 (2%)</td>
<td>NS</td>
</tr>
<tr>
<td>Other</td>
<td>7/90 (8%)</td>
<td>9/102 (9%)</td>
<td>36/373 (10%)</td>
<td>NS</td>
</tr>
<tr>
<td>13q deletion</td>
<td>20/90 (22%)</td>
<td>42/101 (42%)</td>
<td>151/373 (40%)</td>
<td>P=0.004 (MGUS vs SMM) P=0.001 (MGUS vs MM)</td>
</tr>
<tr>
<td>17p deletion</td>
<td>1/89 (1%)</td>
<td>8/102 (8%)</td>
<td>29/373 (8%)</td>
<td>P=0.04 (MGUS vs SMM) P=0.02 (MGUS vs MM)</td>
</tr>
<tr>
<td>1q gain</td>
<td>23/79 (29%)</td>
<td>40/98 (41%)</td>
<td>149/358 (42%)</td>
<td>P=0.04 (MGUS vs MM)</td>
</tr>
</tbody>
</table>

Abbreviations: NS, not significant.
<table>
<thead>
<tr>
<th>Genetic Abnormalities</th>
<th>MGUS (n=90) Percentage of PC (%) Median (range)</th>
<th>SMM (n=102) Percentage of PC (%) Median (range)</th>
<th>MM (n=373) Percentage of PC (%) Median (range)</th>
<th>p value</th>
</tr>
</thead>
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<tr>
<td><strong>IgH abnormality</strong></td>
<td>34 (12-73)</td>
<td>57 (28-90)</td>
<td>76 (11-100)</td>
<td>P&lt;0.001 (MGUS vs SMM) P&lt;0.001 (MGUS vs MM) P=0.007 (SMM vs MM)</td>
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<tr>
<td><strong>t(11;14)</strong></td>
<td>38 (12-72)</td>
<td>61 (24-88)</td>
<td>81 (13-100)</td>
<td>P=0.042 (MGUS vs SMM) P&lt;0.001 (MGUS vs MM) P=0.003 (SMM vs MM)</td>
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<td><strong>t(4;14)</strong></td>
<td>48 (21-69)</td>
<td>59 (32-88)</td>
<td>83 (35-100)</td>
<td>P=0.008 (MGUS vs SMM) P=0.007 (SMM vs MM)</td>
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<td><strong>t(14;16)</strong></td>
<td>30 (25-36)</td>
<td>58 (35-72)</td>
<td>76 (15-91)</td>
<td>NS</td>
</tr>
<tr>
<td>Other</td>
<td>30 (12-55)</td>
<td>72 (38-90)</td>
<td>73 (11-90)</td>
<td>P=0.008 (MGUS vs SMM) P=0.001 (MGUS vs MM)</td>
</tr>
<tr>
<td><strong>13q deletion</strong></td>
<td>37 (20-79)</td>
<td>61 (22-93)</td>
<td>74 (20-100)</td>
<td>P=0.004 (MGUS vs SMM) P&lt;0.001 (MGUS vs MM) P=0.007 (SMM vs MM)</td>
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<td><strong>17p deletion</strong></td>
<td>35 (35-35)</td>
<td>48 (32-100)</td>
<td>62 (20-95)</td>
<td>NS</td>
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<tr>
<td><strong>1q gain</strong></td>
<td>43 (10-91)</td>
<td>63 (14-94)</td>
<td>70 (11-100)</td>
<td>P=0.03 (MGUS vs SMM) P=0.005 (MGUS vs MM)</td>
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Abbreviations: NS, not significant.
<table>
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<tr>
<th>Disease at diagnosis</th>
<th>% of PC with genetic abnormalities</th>
<th>Disease at progression</th>
<th>% of PC with genetic abnormalities</th>
<th>TTP (months)</th>
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<tr>
<td>1. <strong>MGUS</strong></td>
<td>No abnormalities</td>
<td><strong>MM</strong></td>
<td>Rb deletion (68%)</td>
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<td>2. <strong>MGUS</strong></td>
<td>Rb deletion (25%)</td>
<td><strong>MM</strong></td>
<td>Rb deletion (76%)</td>
<td><strong>28</strong></td>
</tr>
<tr>
<td>3. <strong>MGUS</strong></td>
<td>t(11;14) (12%)</td>
<td><strong>MM</strong></td>
<td>t(11;14) (73%)</td>
<td><strong>38</strong></td>
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<tr>
<td>4. <strong>SMM</strong></td>
<td>1q gain (78%)</td>
<td><strong>MM</strong></td>
<td>1q gain (92%)</td>
<td><strong>17</strong></td>
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<td>5. <strong>SMM</strong></td>
<td>Rb deletion (31%)</td>
<td><strong>MM</strong></td>
<td>Rb deletion (62%)</td>
<td><strong>14</strong></td>
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<td>6. <strong>SMM</strong></td>
<td>No abnormalities</td>
<td><strong>MM</strong></td>
<td>No abnormalities</td>
<td><strong>17</strong></td>
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<tr>
<td>7. <strong>SMM</strong></td>
<td>No abnormalities</td>
<td><strong>MM</strong></td>
<td>No abnormalities</td>
<td><strong>24</strong></td>
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<td>8. <strong>SMM</strong></td>
<td>17p deletion (24%)</td>
<td><strong>MM</strong></td>
<td>17p deletion (80%)</td>
<td><strong>14</strong></td>
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