Clinical and biologic implications of recurrent genomic aberrations in myeloma


Nonrandom recurrent chromosomal abnormalities are ubiquitous in multiple myeloma (MM) and include, among others, translocations of the immunoglobulin heavy chain locus (IgH). IgH translocations in MM result in the up-regulation of oncogenes, and include more commonly t(11;14)(q13;q32), t(4;14)(p16;q32), and t(14;16)(q32;q23). Based on the recurrent nature of these translocations and their finding since the early stages of the plasma cell (PC) disorders, we hypothesized that they would confer biologic and clinical variability. In addition, deletions of 13q14 and 17p13 have also been associated with a shortened survival. We used cytoplasmic Ig–enhanced interphase fluorescent in situ hybridization to detect deletions (13q14 and 17p13), and translocations involving IgH in 351 patients treated with conventional chemotherapy entered into the Eastern Cooperative Oncology Group clinical trial E9486/9487. Translocations were frequently unbalanced with loss of one of the derivative chromosomes. The presence of t(4;14)(p16;q32) (n = 42; 26 vs 45 months, P < .001), t(14;16)(q32;q23) (n = 15; 16 vs 41 months, P = .003), −17p13 (n = 37; 23 vs 44 months, P = .005), and −13q14 (n = 176; 35 vs 51 months, P = .028) were associated with shorter survival. A stratification of patients into 3 distinct categories allowed for prognostication: poor prognosis group (t(4;14)(p16;q32), t(14;16)(q32;q23), and −17p13), intermediate prognosis (−13q14), and good prognosis group (all others), with median survivals of 24.7, 42.3, and 50.5 months, respectively (P < .001). This molecular cytogenetic classification identifies patients into poor, intermediate, and good risk categories. More importantly it provides further compelling evidence that MM is composed of subgroups of patients categorized according to their underlying genomic aberrations. (Blood. 2003;101:4569-4575)

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Introduction

Genetic and cytogenetic abnormalities define subgroups of hematologic neoplasms, and accordingly have been associated with unique biologic, clinical, and prognostic features. Recent studies with interphase fluorescent in situ hybridization (FISH) indicate that all multiple myeloma (MM) cells harbor chromosome abnormalities. Interphase FISH–detected chromosomal abnormalities studies have also been associated with dissimilar outcomes in some reports.

We and others have proposed that specific cytogenetic abnormalities can identify groups of MM patients with unique clinical and biologic features. Abnormalities of chromosome 13 (Δ13), monosomy representing 85% of them, have an adverse prognosis in MM when detected by metaphase analysis and interphase FISH. Likewise, deletions of 17p13.1, the genomic locus of the p53 tumor suppressor gene, have been associated with an adverse patient outcome. Translocations involving immunoglobulin heavy chain locus (IgH) (14q32) are seen in 50% to 60% of MM patients, and involve an array of nonrandom recurrent chromosomal partners, but their prognostic significance has not been tested. The 3 most common IgH translocations in MM are t(4;14)(p16.3;q32), t(11;14)(q13;q32), and t(14;16)(q32;q23). In this paper we evaluate and integrate the clinical and biologic relevance of the most common cytogenetic abnormalities. To do so we used interphase FISH in a large cohort of MM patients who have had long duration of follow-up.

Patients and methods

Patient characteristics

Patients enrolled in the Eastern Cooperative Oncology Group (ECOG) E9486 and its associated correlative laboratory clinical trial E9487 (N = 561) had newly diagnosed MM and have been described in detail elsewhere. They were randomized to receive treatment with conventional chemotherapy variations. The median overall survival for the whole group was 40.5 months. Patients have extensive follow-up information with the minimum follow-up of survivors being 96 months (range, 96-138 months), resulting in negligible censoring. A total of 351 patients were included in this study for our analysis (Table 1), as previously described by us, and appeared to be no different from the larger cohort of patients when all relevant biologic and prognostic factors are considered (data not shown). Pertinent clinical and prognostic features are available for the majority of the patients including, among others, the plasma cell labeling index (PCLI),...
separately reported regarding the t(11;14)(q13;q32) and validation, and scoring procedures as described previously by us. 19,21 We probe from Vysis (Downers Grove, IL). We used standard hybridization, Chesi et al.23 To test for 17p13.1, we used a locus specific that localize to 16q23, and BAC clones 10205 and 10206 described by (BAC) clones (356D21 and 484H2; Research Genetics, Huntsville, AL).

Table 1. Baseline clinical and laboratory descriptive features of patients by abnormality

<table>
<thead>
<tr>
<th>Variable</th>
<th>All (n = 351)</th>
<th>t(4;14)(p16;q32) (n = 42)</th>
<th>t(14;16)(q32;q23) (n = 15)</th>
<th>t(11;14)(q13;p12) (n = 53)</th>
<th>Δ13 (n = 176)</th>
<th>Del 17p13.1 (n = 37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, y (range)</td>
<td>63 (35-84)</td>
<td>59 (35-74)</td>
<td>58 (41-75)</td>
<td>62 (35-80)</td>
<td>62 (35-82)</td>
<td>64 (40-78)</td>
</tr>
<tr>
<td>Sex, male/female, %</td>
<td>62/38</td>
<td>55/45</td>
<td>47/53</td>
<td>68/32</td>
<td>57/43</td>
<td>54/46</td>
</tr>
<tr>
<td>ECOG PS, %</td>
<td>0 to 1</td>
<td>86</td>
<td>90</td>
<td>100</td>
<td>91</td>
<td>88</td>
</tr>
<tr>
<td>Plasmacytoma, %</td>
<td>2 to 4</td>
<td>14</td>
<td>10</td>
<td>0</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Lytic bone lesions, %</td>
<td>Yes</td>
<td>10</td>
<td>12</td>
<td>13</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Hypercalcemia, %</td>
<td>Yes</td>
<td>61</td>
<td>62</td>
<td>54</td>
<td>62</td>
<td>60</td>
</tr>
<tr>
<td>Serum M component, %</td>
<td>Present, 1 or more g/dL</td>
<td>83</td>
<td>90</td>
<td>73</td>
<td>72</td>
<td>78</td>
</tr>
<tr>
<td>Urine M component, %</td>
<td>Absent</td>
<td>17</td>
<td>10</td>
<td>27</td>
<td>28</td>
<td>22</td>
</tr>
<tr>
<td>Light chain type, %</td>
<td>Present, detectable</td>
<td>72</td>
<td>69</td>
<td>67</td>
<td>68</td>
<td>76</td>
</tr>
<tr>
<td>Creatinine, mg/dL†</td>
<td>Absent</td>
<td>25</td>
<td>24</td>
<td>33</td>
<td>30</td>
<td>20</td>
</tr>
<tr>
<td>β2-microglobulin, mg/dL‡</td>
<td>Unknown</td>
<td>3</td>
<td>7</td>
<td>0</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>β2-microglobulin to SI units:</td>
<td>X</td>
<td>63</td>
<td>48</td>
<td>40</td>
<td>60</td>
<td>59</td>
</tr>
</tbody>
</table>
| Bone marrow research samples were obtained (in that order), and cytospin slides were stored for future use (at 70°C). Aspirate samples were enriched for monoclonal cells using the Ficol method. To improve on the specificity of the scoring process we combined interphase FISH with immune-fluorescent detection of the cytoplasmic-immunoglobulin light-chain20 (Figure 1).

Probes

β2-microglobulin, C-reactive protein, and serum level of soluble interleukin-6 receptor (sIL-6R). These patients did not have conventional karyotype analysis requested at the time of study entry, and it is thus not available for comparison.

Bone marrow samples

Institutional review board (IRB) approval, informed consent, and bone marrow research samples were obtained (in that order), and cytospin slides were stored for future use (at 70°C). Aspirate samples were enriched for monoclonal cells using the Ficol method. To improve on the specificity of the scoring process we combined interphase FISH with immune-fluorescent detection of the cytoplasmic-immunoglobulin light-chain20 (Figure 1).

Probes

We used previously reported sets of probes to detect Δ13, t(11;14)(q31;q32), and t(4;14)(p16.3;q32).19,21,23 This same cohort of patients has been separately reported regarding the t(11;14)(q13;q32) and Δ13.13,24 To detect t(14;16)(q32;q23) we used the same 1q42 chromosome probes previously described by us,21 in combination with 2 bacterial artificial chromosome (BAC) clones (356D21 and 484H2; Research Genetics, Huntsville, AL) that localize to 1q23, and BAC clones 10205 and 10206 described by Chesi et al.23 To test for 17p13.1, we used a locus specific probe (LSI) p53 probe from Vysis (Downers Grove, IL). We used standard hybridization, validation, and scoring procedures as described previously by us.19,21 We scored 100 cells for each one of the abnormalities and recorded the percentage of cells with abnormal patterns (with special attention to the number of fusions detected for the translocations).

Statistical analysis

Descriptive and survival analysis. To test for association between abnormalities, or between abnormalities and other patient categoric treatment characteristics or response to treatment, the Fisher exact test was used.24 To test for difference in PCLI and β2-microglobulin between patients with and without an abnormality, a Wilcoxon rank sum test was used.25 The distribution for overall and progression-free survival was estimated using the method of Kaplan and Meier.26 The log-rank test was used to test for differences in survival between groups.27 We decided to score 100 cells per patient to evaluate positivity and evidence of clonal heterogeneity.

Multiple regression model. A Bayesian analysis was used to evaluate the contribution of genetic abnormalities to survival.28 This analysis allowed us to include all of the studied patients in the model, even the patients with missing data. The following clinical prognostic factors (cut-off points), dichotomized according to previously reported studies, were included in the model: PCLI (< 1% vs ≥ 1%), bone marrow PC percentage (< 30% vs ≥ 30%), serum creatinine (< 152.5 vs ≥ 152.5 μM), albumin (< 30 vs > 30 g/L), hemoglobin (< 100 vs > 100 g/L), β2-microglobulin (< 2.7 vs ≥ 2.7 mg/dL), soluble IL-6 receptor (< 270 vs ≥ 270 ng/mL), C-reactive protein (< 2 vs ≥ 2 mg/dL), serum monoclonal protein (< 10 vs ≥ 10 g/L), and stage (I-II vs III).

A Weibull distribution was used to model time to death.29 The regression coefficients and the shape parameter were given “noninformative” normal and gamma priors, respectively. Prior distributions for the covariates were assumed to be binomial (P, 1) with P distributed as uniform (0, 1). The BUGS program (Bayesian inference using the Gibbs sampling algorithm)29 was used to estimate the coefficients and obtain 95% credible confidence intervals (CIs). We performed an initial 500 burn-in of iterations.
Results

Prevalence of the abnormalities

The prevalence of chromosomal abnormalities among the 351 patients tested are as follows: t(4;14)(p16;q32) (42/332 patients, 12.7%), t(14;16)(q32;q23) (15/323 patients, 4.6%), t(11;14)(q13;q32) (53/336 patients, 15.8%), deletions 17p13.1 (37/345 patients, 10.7%), and Δ13 (176/325 patients, 54.2%). The prevalence of the abnormalities was not significantly different according to the stage of the disease or age, except for Δ13, which appeared to be more common among stage III patients (P < .014). A strong association was noted between Δ13 and the t(4;14)(p16.3;q32) as we have previously reported (38/42 patients; P < .001), but this association was not present in patients with t(14;16)(q32;q23) (8/13 patients) or t(11;14)(q13;q32) (24/51 patients). A significant positive correlation between deletion 17p13.1 and t(14;16)(q32;q23) was observed (5/15 patients, 33%; P = .018), and was suggested for t(4;14)(p16;q32) (8/42 patients, 20%). In contrast 17p13.1 deletions had a lower incidence in patients with t(11;14)(q13;q32) (P = .027).

Translocation patterns and relations

In this cohort of patients all translocations were mutually exclusive; that is, there were no patients with 2 coexistent translocations. However, many patients had combinations of a translocation and deletion(s) of 17p13.1 and/or Δ13. The median percentage of cells with an abnormality was more than 80% for all abnormalities. IgH translocations were usually seen in more than 95% of cells. Deletions 17p13.1 were seen in less than 50% of cells in 11 (30%) of 37 cases. Using the specific sets of probes we found that of 348 evaluable patients, 139 (40%) had 1 chromosomal abnormality detected, 77 (22%) had 2, and 10 (3%) had 3. Using these probes, a total of 122 patients had no abnormalities detected. Prognostic features including the PCLI and β2-microglobulin

Patients had unique biologic and prognostic features according to their baseline prognostic features (Table 1). The PCLI was significantly higher among patients with Δ13 (P = .03), t(14;16)(q32;q23) (P = .02), or deletion 17p13.1 (P = .01). Serum levels of β2-microglobulin appeared to be significantly higher in patients with deletion 17p13.1 (P = .03). Deletions of 17p13.1 were significantly associated with hypercalcemia (P = .009) and soft-tissue plasmacytomas (P = .0053). The use of light chain was favored in patients with t(14;16)(q32;q32) (P = .05). Serum levels of sIL6-R were higher in patients with Δ13 (P = .003), t(4;14)(p16.3;q32) (P = .025), t(14;16)(q32;q23) (P = .009), and deletions of 17p13.1 (P = .006). Patients with t(4;14)(p16.3;q32) were significantly more likely to have a serum monoclonal protein higher than 30 g/L (P = .019). Light-chain only disease was slightly more common among those patients with t(11;14)(q13;q32) (28% among patients with t(11;14)(q13;q32) and 16% in those without t(11;14)(q13;q32); Fisher exact, P = .04). The IgA isotype was slightly more common among patients with the t(4;14)(p16.3;q32) but was not significant (P > .2). No trend was observed among patients with t(14;16)(q32;q23).

Balanced versus unbalanced translocations

A predominant pattern of one fusion signal was seen in only 56 (51%) of 110 patients with evidence of a translocation by the fusion strategy. When one considers only cases in which the predominant pattern was seen in more than 90% of the clonal cells the total was 34 patients (33% of all IgH translocations). This is remarkably different than previous assumptions of balanced translocations in MM (Table 2). In a recent study by Keats et al that used reverse transcriptase–polymerase chain reaction (RT-PCR)–based strategies, they found that up to one third of patients with the t(4;14)(p16.3;q32) have unbalanced IgH translocations.30

Response to treatment

Among patients evaluable for response, those with Δ13 had a lower likelihood of an objective response than those without the abnormality (Table 3). Otherwise there were no major differences noted.
Survival analysis

On the univariate analysis, patients with t(4;14)(p16.3;q32), t(14;16)(q32;q23), deletions of 17p13.1, and ∆13 had a significantly worse overall survival (Figure 2 and Table 3). Progression-free survival was significantly worse in patients with t(4;14)(p16.3; q32), t(14;16)(q32;q32), and ∆13, and was of marginal significance in patients with deletions of 17p13.1 (Table 3).

Multiple regression model

When adjusting for the clinical factors that were statistically significant, as well as for other genetic abnormalities, t(4;14)(p16.3; q32) and t(14;16)(q32;q23) had the highest hazard ratios (1.78 and 1.67, respectively), t(4;14)(p16.3;q32) being statistically significant and t(14;16)(q32;q23) marginally significant. Deletion of 17p13.1 was marginally significant with an intermediate hazard ratio (1.34) with respect to the other 4 genetic abnormalities (Table 4). ∆13 were also statistically significant, with a hazard ratio equal to 1.28. These results were similar to those obtained using the Cox regression model for only the 275 cases with complete data. The hazard ratios (95% CI) of the genetic abnormalities in the Cox regression model, which also included creatinine, PCLI, and bone marrow PC percentage as covariates, were 1.69 (1.15-2.49) for t(4;14)(p16.3;q32), 1.42 (0.75-2.66) for t(14;16)(q32;q23), 1.47 (0.97-2.20) for −17p13.1, 1.35 (1.04-1.74) for ∆13, and 0.94 (0.66-1.34) for (t11;14)(q13;q32).

Prognostic groups

The 3 hierarchic groups identified 3 distinct prognostic groups (log-rank, P < .001). The groups are as follows: poor prognosis group—patients with t(4;14)(p16.3;q32) and/or t(14;16)(q32;q23) and/or deletion 17p13.1 (n = 66); intermediate prognosis—patients with ∆13, but not t(4;14)(p16.3;q32), t(14;16)(q32;q23), or deletion 17p13.1 (n = 103); and good prognosis—patients with only t(11;14)(q13;q32) or none of the abnormalities tested (n = 106). Their median survival times were 24.7 months, 42.3 months, and 50.5 months, respectively (Figure 3).

Discussion

Summary

In this study we find subgroups of MM patients classified according to their underlying cytogenetic abnormalities and show that these abnormalities alone can establish prognostic categories. Our study provides conclusive clinical evidence that MM is not a single uniform disorder, but rather a group of disorders, which can be defined by their underlying cytogenetic anomalies supported by this biologic variability.31 Patients with the t(4;14)(p16.3;q32), t(14;16)(q32;q23), and deletion of 17p13.1 have a significantly worse prognosis that others. We suspect this observation is likely due to the up-regulation of specific oncogenes involved in these translocations and to loss of the tumor suppressor gene p53.22 We previously demonstrated that chromosomal abnormalities define unique presenting factors for MM and may be associated with specific features such as the oligosecretory variant, λ light chain usage, or ploidy status.7,8

Biology of IgH translocations in general

Between 50% to 60% of MM patients harbor IgH translocations,31,33 and these translocations have been detected since the very early stages of the PC neoplasms (ie, monoclonal gammapathies of undetermined significance [MGUS]).34,35 This is consistent with IgH translocations being primary events, as is seen in the mouse plasmacytoma model in which they result in c-myc upregulation.36 Of interest, all IgH translocations in MM appear to be up-regulating proliferation genes.12 We conclude that while translocations may be an early and important step,34,35 they are not sufficient in humans for malignant transformation and more likely result in the initial clone-immortalizing event. It is important to note that the translocations that impart a poor prognosis in the active MM stage have no known effect on prognosis when they are detected in MGUS. In fact we have found that patients with MGUS

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**Table 2. Prevalence of unbalanced translocations**

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Patients with predominantly one signal</th>
<th>All patients with each translocation</th>
<th>Patients with one signal, %</th>
<th>Patients/number of fusions</th>
<th>Percent of cells with only one fusion more than 90%</th>
<th>Patients/number of fusions</th>
<th>Percent of cells with only one fusion more than 75%</th>
<th>Patients/number of fusions</th>
<th>Percent of cells with only one fusion more than 75%</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(4;14)(p16.3; q32)</td>
<td>14</td>
<td>35</td>
<td>40</td>
<td>3/14</td>
<td>21</td>
<td>6/14</td>
<td>43</td>
<td>5/14</td>
<td>36</td>
</tr>
<tr>
<td>t(11;14)(q13;q32)</td>
<td>35</td>
<td>53</td>
<td>66</td>
<td>25/35</td>
<td>71</td>
<td>4/35</td>
<td>11</td>
<td>6/35</td>
<td>17</td>
</tr>
<tr>
<td>t(14;16)(q32; q23)</td>
<td>7</td>
<td>15</td>
<td>47</td>
<td>6/7</td>
<td>86</td>
<td>1/7</td>
<td>14</td>
<td>0/7</td>
<td>0</td>
</tr>
<tr>
<td>Total patients with each translocation</td>
<td>56</td>
<td>34</td>
<td>11</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

**Table 3. Overall Survival (OS), progression-free survival (PFS), and objective response (OR) to treatment by abnormality**

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Median OS with abnormality, mo (95% CI)</th>
<th>Median PFS with abnormality, mo (95% CI)</th>
<th>OR* with abnormality, n(%), P</th>
<th>5-y OS rate with abnormality, %</th>
<th>5-y OS rate without abnormality, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(4;14)(p16.3; q32)</td>
<td>332</td>
<td>26 (21-33)</td>
<td>45 (39-50)</td>
<td>&lt;0.001</td>
<td>17 (13-21)</td>
</tr>
<tr>
<td>t(14;16)(q32; q23)</td>
<td>323</td>
<td>16 (13-22)</td>
<td>41 (37-48)</td>
<td>0.003</td>
<td>9 (6-13)</td>
</tr>
<tr>
<td>t(11;14)(q13;q32)</td>
<td>336</td>
<td>50 (37-60)</td>
<td>39 (36-44)</td>
<td>0.332</td>
<td>33 (28-45)</td>
</tr>
<tr>
<td>Deletion 17p13</td>
<td>345</td>
<td>23 (20-36)</td>
<td>44 (39-49)</td>
<td>0.005</td>
<td>17 (11-24)</td>
</tr>
<tr>
<td>∆13</td>
<td>325</td>
<td>35 (29-41)</td>
<td>51 (41-57)</td>
<td>0.028</td>
<td>25 (21-29)</td>
</tr>
</tbody>
</table>

*The number of patients evaluable for response may be slightly smaller than N given in column 2.
Table 4. Multivariate Bayesian analysis for survival using the Weibull proportional hazards model (n = 351)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>Standard error</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>-10.760</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>(4;14)(p16.3;q32)*</td>
<td>0.574</td>
<td>0.179</td>
<td>1.78 (1.23-2.50)</td>
</tr>
<tr>
<td>(14;16)(q32;q23)*</td>
<td>0.513</td>
<td>0.286</td>
<td>1.67 (0.92-2.83)</td>
</tr>
<tr>
<td>Deletion 17p13*</td>
<td>0.291</td>
<td>0.188</td>
<td>1.34 (0.92-1.93)</td>
</tr>
<tr>
<td>≥13</td>
<td>0.244</td>
<td>0.119</td>
<td>1.28 (1.01-1.61)</td>
</tr>
<tr>
<td>t(11;14)(q13;q32)*</td>
<td>-0.213</td>
<td>0.163</td>
<td>0.81 (0.58-1.11)</td>
</tr>
<tr>
<td>Creatinine, 2 or more vs less than 2 mg/dL†</td>
<td>0.580</td>
<td>0.165</td>
<td>1.79 (1.29-2.44)</td>
</tr>
<tr>
<td>PC labeling index, 1% or higher vs less than 1%</td>
<td>0.441</td>
<td>0.123</td>
<td>1.55 (1.22-1.97)</td>
</tr>
<tr>
<td>C-reactive protein, 2 or more vs less than 2 mg/dL</td>
<td>0.435</td>
<td>0.175</td>
<td>1.54 (1.09-2.16)</td>
</tr>
<tr>
<td>Bone marrow involvement, 30% or higher vs less than 30%</td>
<td>0.354</td>
<td>0.116</td>
<td>1.43 (1.14-1.79)</td>
</tr>
</tbody>
</table>

NA indicates not applicable.
*Present versus absent.
†Convert creatinine to SI units: multiply mg/dL × 76.25 = μM.
breakpoints at 16q23. A possible tumor suppressor role is being sought for this gene, which spans several hundred kilobases at 16q32 and is located at the fragile site Fra16D. C-maf, has been shown to have transforming activity in chicken fibroblasts. The t(14;16)(q32;q23) is observed in 25% of human MM cell lines but is seen in only 5% of primary MM samples. In one of these human MM cell lines, KMS-11, the 16q23 breakpoint places c-maf at more than 700 kb of the IgH enhancer in the translocated allele, without evidence of intervening deletion or inversion (R.F., unpublished observations, September 2001). This highlights the possibility that oncogenes other than those described to date may be up-regulated by any IgH translocation, other than those currently believed important for pathogenesis.

**Chromosome 13 abnormalities**

Our study confirms that ∆13 have a negative impact on prognosis. Others and we have found that ∆13 detected by FISH is an independent prognostic variable on a multivariate analysis. The genes associated with the negative prognostic implications of ∆13 have yet to be defined. Detailed molecular analysis has revealed that in the majority of cases ∆13 are indicative of monosomy. While a minimally deleted region has been postulated as being in 13q14, other sites may be involved as well. The role of ∆13 in the pathogenesis of MM is still being elucidated. In the setting of widespread genomic instability, chromosome 13 is almost never seen as trisomic, suggesting clonal intolerance to the gain.

**Deletion of 17p13.1 (p53)**

Deletions at the p53 locus also confer an adverse prognosis, even when they are observed in only a small proportion of patients. While most other abnormalities (ie, IgH translocations and ∆13) have not associated with the negative prognostic implications of ∆13 have yet to be defined. Detailed molecular analysis has revealed that in the majority of cases ∆13 are indicative of monosomy. While a minimally deleted region has been postulated as being in 13q14, other sites may be involved as well. The role of ∆13 in the pathogenesis of MM is still being elucidated. In the setting of widespread genomic instability, chromosome 13 is almost never seen as trisomic, suggesting clonal intolerance to the gain.

**Therapeutic implications**

As targeted therapy evolves, different treatment interventions will have variable success, depending on the underlying genetic nature of the clone. For instance, the development of effective MMSET or FGFR3 small molecule inhibitors may allow for patients with t(4;14)(p16.3;q32) to become a better prognostic category. The use of inhibitors of the cyclin D1/CDK pathways, such as flavopiridol, seems especially suited for patients with t(11;14)(q13;32). It is also worth noting that it appears that specific treatments may be better tailored for patients with specific chromosomal abnormalities. A comparison of our results (in patients treated with conventional chemotherapy) with those of Moreau et al (in patients treated with high-dose therapy) suggests that high-dose chemotherapy provides little, or no, survival advantage for patients with ∆13 or t(4;14)(p16.3;q32). In contrast it appears that high-dose chemotherapy provides a significant survival increment for patients with t(11;14)(q13;32). While these observations are speculative for now, as they are based on a retrospective comparison, they are highly provocative and in need of confirmation in prospective clinical trials.

**Statistical aspects**

A Bayesian approach was used in this study to assess the impact of genetic abnormalities on survival, adjusting for known clinical prognostic factors. The advantage of the Bayesian analysis is that it allows all subjects to be included in the model, even those that have missing data in their covariates. In our study sample 22% of subjects had missing data, either in the genetic abnormalities or in the clinical variables. Imputation of missing data is done in the Gibbs sampling framework by treating missing values as additional unknown quantities and randomly selecting values from their conditional distributions. Conditional distributions are a function of the observed individual data and the current sampled values of the other missing data for a particular individual. There was no indication of random “missingness” in our data, one of the assumptions of the Bayesian analysis. Also, the assumptions of Weibull distribution, proportional hazards, and adequacy of the multivariate model were assessed with satisfactory results. When the results of the Bayesian approach (which included all of the 351 studied patients) were compared with those of the Cox proportional hazards regression (which included only the 275 patients with complete data), the hazard ratios were similar. Differences were observed mostly for the genetic abnormalities with the smallest prevalence: t(14;16)(q32;q23) and −17p13.

It is important to cautiously interpret the hierarchical group survival analysis, as patients in the poor prognosis group could have more abnormalities than patients in the intermediate or good prognosis groups. For instance, patients in the poor prognosis group could possibly have ∆13 deletion in addition to one or more of the poor prognosis abnormalities. To make sure this was not the only reason that patients in the poor prognosis group did poorly, we switched the order of the hierarchical grouping. In the new grouping, patients with ∆13 were in one group; patients with any of the 3 (t(4;14)(p16.3;q32), t(14;16)(q32;q23), deletion 17p13.1) poor prognosis abnormalities, but not ∆13 were in another group; and patients with only t(11;14)(q13;q32) or none of the 5 tested abnormalities were in the third group. While the median survival times differed slightly from the originally hierarchical grouping, the trend in median survival times was the same. Patients with the poor prognosis abnormalities (t(4;14)(p16.3;q32), t(14;16)(q32;q23), and deletion 17p13.1) did worse than patients with ∆13, and those patients did worse than patients with only t(11;14)(q13;q32) or none of the 5 tested abnormalities. We thus conclude that patients with t(4;14)(p16.3;q32), t(14;16)(q32;q23), or deletion 17p13.1 seem to make up a poor prognosis group.

**References**


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