Myelodysplastic Syndromes

NRAS, FLT3 and TP53 mutations in patients with myelodysplastic syndrome and a del(5q)

Mutations of the NRAS and TP53 genes and internal tandem duplication (ITD) of the FLT3 gene are among the most frequently observed molecular abnormalities in the myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML). We sought to determine the incidence of these abnormalities in patients with MDS and a 5q deletion. NRAS and FLT3 mutations are uncommon in MDS patients with a 5q deletion and TP53 mutation is associated with the more advanced MDS subtypes.

Table 1. MDS patients with mutations in the TP53 gene.

<table>
<thead>
<tr>
<th>Pt</th>
<th>Sex/Age</th>
<th>FAB</th>
<th>Karyotype</th>
<th>Exon</th>
<th>Codon</th>
<th>Type</th>
<th>Nucleotide</th>
<th>Amino Acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>KB</td>
<td>F/82</td>
<td>RAEB</td>
<td>45XX,-7,-22, del(5)(q13?q33),t(6;12)(q13;p12),+mar</td>
<td>6</td>
<td>192</td>
<td>nonsense</td>
<td>C → T</td>
<td>Gln → stop</td>
</tr>
<tr>
<td>KB</td>
<td>F/82</td>
<td>RAEB</td>
<td>45XX,-7,-22, del(5)(q13?q33),t(6;12)(q13;p12),+mar</td>
<td>6</td>
<td>220</td>
<td>missense</td>
<td>A → G</td>
<td>Tyr → Cys</td>
</tr>
<tr>
<td>DS</td>
<td>F/85</td>
<td>RAEB</td>
<td>45XX,del(5)(q13?q33),-7, del(12)(p11?p12)</td>
<td>7</td>
<td>238</td>
<td>missense</td>
<td>G → A</td>
<td>Cys → Tyr</td>
</tr>
<tr>
<td>DS</td>
<td>F/85</td>
<td>RAEB</td>
<td>45XX,del(5)(q13?q33),-7, del(12)(p11?p12)</td>
<td>7</td>
<td>248</td>
<td>missense</td>
<td>G → T</td>
<td>Arg → Leu</td>
</tr>
<tr>
<td>BL</td>
<td>M/58</td>
<td>RAEB</td>
<td>43-45,XY,del(5)(q31), del(7)(p11?p22),q17,del(20)(q13)?3,</td>
<td>8</td>
<td>273</td>
<td>missense</td>
<td>G → A</td>
<td>Arg → His</td>
</tr>
</tbody>
</table>

RAEB, refractory anemia with excess of blasts. These mutations have all been previously reported in a variety of human cancers and are documented in the TP53 Mutation Database (http://p53.free.fr).
Letters to the Editor

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References

Myelodysplastic Syndromes

Prognostic factors in myelodysplastic and myeloproliferative types of chronic myelomonocytic leukemia: a retrospective analysis of 83 patients from a single institution

We analyzed independent prognostic factors associated with survival and risk of evolution to acute leukemia in our series of 83 patients with previously untreated chronic myelomonocytic leukemia (CMML), with the aim of testing the validity of the stratification based on white blood cell (WBC) count, in myeloproliferative and myelodysplastic types of the revisited WHO classification.

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From 1989 to 2001, 643 adults were diagnosed with myelodysplastic syndromes (MDS) at our Institution; 83 (12.4%) of these had primary CMML. According to the limit of WBC count of 13×10^9/L, 46 had a myelodysplastic (MD) type and 37 a myeloproliferative (MP) type. The median follow-up of patients was 38 months. Bone marrow (BM) dysplasia was assessed according to previously established FAB criteria.1 Cytogenetic studies were available for 48 patients. Different prognostic scores (Bournemouth, modified Bournemouth, Spanish, IPSS, Gonzalez-Medina score, Dusseldorf score, MDAPS)1-4 were evaluated for risk distribution and relative impact on survival prediction. Clinical and hematologic features, tested for survival and rate of transformation to acute myeloid leukemia (AML), were compared by the χ^2 and Wilcoxon rank sum tests. Univariate analysis was estimated using Cox regression models. p values <0.05 were regarded as statistically significant in two-tailed tests. SPSS software (version 10.00, SPSS, Chicago, USA) was used for statistical analyses. Significant independent variables were used to develop a multivariate model by the Cox method in order to identify independent prognostic relationships. The differences between the MD and MP groups were sex ratio, WBC, monocyte, platelet and lymphocyte count and hemoglobin level.

Trilineage dysplasia was evident in 35 MD (76%) and in 17 MP patients (46%) (p=0.005). A normal karyotype was observed in 38 patients (80%) while in 10 patients a +8 (4 MD and 1 MP patients), a del (13) (2 patients), a del (16) (2 patients), a -7 (1 patient) were identified.

Median survival was 20 and 17.4 months for MD and MP patients, respectively (p=0.007). The disease progression rate was higher for the MP type (29.7%) than for the MD type (15.2%, p=0.001). The median duration of the pre-acute leukemic phase was 16 and 14 months in the MP and MD variants, respectively (p=NS). At the time of our analysis, 12 patients with MD type (26%) and 19 with MP type (51%) had died (p=0.005). Death was related to AML progression (45%) or hemorrhagic (19%) and/or septic complications of BM failure (19%). Other causes of death were heart failure in 7 old patients receiving marked transfusional support (12%), liver failure (3%), and second neoplasia (2%). Survival after evolution into AML was 1.5 and 2 months for patients with MP and MD variants, respectively (p=NS). Twenty-one MP patients received hydroxyurea to control leukocytosis and 5 patients whose disease evolved into AML received intensive induction treatment. Transfusion requirements were higher in MP patients than in MD patients (59% vs 26%; p=0.003); the frequency of infections and hemorrhages was not significantly different in the two groups (p=NS). Only 6/14 patients with hemorrhages required platelet transfusions.

Sex, WBC > 13×10^9/L, lymphocytes >2.5×10^9/L, platelets <100×10^9/L, and trilineage dysplasia were individually associated with shorter survival (Table 1). These parameters were entered in a multivariate analysis, but only trilineage dysplasia had independent prognostic value for survival (p=0.02).

BM blasts >5%, WBC count, neutrophils and lymphocytes >2.5×10^9/L, and presence of peripheral blood blasts, associated with AML progression in univariate analyses, were tested in a multivariate analysis but only the lymphocyte count had an independent prognostic value (p=0.01).

All scoring systems applied, except IPSS, stratified