


To the editor:

Genotype-phenotype correlation in cases of juvenile myelomonocytic leukemia with clonal RAS mutations

In a recent issue of Blood, Matsuda et al reported 11 children with juvenile myelomonocytic leukemia (JMML) and clonal NRAS or KRAS mutations.1 Three patients showed improvement of various clinical and laboratory features over a 2- to 4-year period without chemotherapy or hematopoietic stem cell transplantation (HSCT). The authors correlate the comparatively mild course with a specific mutation predicting a glycine-to-serine substitution at position 12 in the NRAS or KRAS protein (G12S), and suggest that “no chemotherapy may be a recommended management” for JMML patients with NRAS/KRASG12S.

We have some reason to believe that these conclusions are premature. Available data do not support that RASG12S has weaker oncogenic activity than substitutions with valine, arginine, or aspartic acid. Interestingly, the authors show that myeloid progenitor cells from their patients with G12S respond to granulocyte macrophage–colony stimulating factor (GM-CSF) in a comparable manner as other mutants (Figure 1B in Matsuda et al). Others reported that HRASG12S led to focus induction in NIH3T3 cultures with a similar potency as substitutions with arginine or aspartic acid.2,3

We argue that the clinical course observed in the 3 children is not uncommon in JMML cases with similar hematologic features and age. The European Working Group of Myelodysplastic Syndromes in Childhood (EWOG-MDS) has previously shown that platelet count 33 × 10^9/L or more and hemoglobin F less than 15% at diagnosis identifies a prognostically favorable subgroup in JMML with a 40% to 70% probability of survival at 2 to 4 years without HSCT.4 The relatively favorable course in the Matsuda patients is also because all 3 were less than 1 year old at diagnosis.5 It is known that infants with JMML without severe thrombocytopenia at diagnosis may experience transient improvement even without treatment.3

To examine whether RASG12S is overrepresented in JMML patients with less aggressive disease (defined as survival ≥ 3 years without HSCT), we reviewed the clinical and molecular data of 216 cases collected in the EWOG-MDS registry, excluding patients

Table 1. Clinical characteristics of patients with JMML and clonal RAS mutations surviving long-term without HSCT

<table>
<thead>
<tr>
<th>Case number</th>
<th>Mutation</th>
<th>Age, y</th>
<th>Sex</th>
<th>Liver, cm</th>
<th>Spleen, cm</th>
<th>WBC, 10^9/L</th>
<th>Mono, 10^9/L</th>
<th>Hb, g/L</th>
<th>Plt, 10^9/L</th>
<th>HbF, %</th>
<th>Outcome (time from diagnosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SC047</td>
<td>NRAS c.G35T (codon 12 Gly &gt; Val)</td>
<td>0.1</td>
<td>M</td>
<td>0</td>
<td>7</td>
<td>23.7</td>
<td>5.2</td>
<td>102</td>
<td>54</td>
<td>10</td>
<td>alive without HSCT (4.5 y)</td>
</tr>
<tr>
<td>I013</td>
<td>NRAS c.G38A (codon 13 Gly &gt; Asp)</td>
<td>1.7</td>
<td>M</td>
<td>2</td>
<td>2</td>
<td>22.2</td>
<td>2.4</td>
<td>103</td>
<td>40</td>
<td>1.3</td>
<td>alive without HSCT (5.5 y)</td>
</tr>
<tr>
<td>D175</td>
<td>NRAS c.G35C (codon 12 Gly &gt; Ala)</td>
<td>0.7</td>
<td>F</td>
<td>4</td>
<td>7</td>
<td>18.6</td>
<td>1.3</td>
<td>96</td>
<td>75</td>
<td>3.1</td>
<td>alive without HSCT (8.8 y)</td>
</tr>
<tr>
<td>D028</td>
<td>NRAS c.G35A (codon 12 Gly &gt; Asp)</td>
<td>0.4</td>
<td>M</td>
<td>3</td>
<td>5</td>
<td>57.4</td>
<td>8.0</td>
<td>112</td>
<td>192</td>
<td>8.3</td>
<td>alive without HSCT (21.5 y)</td>
</tr>
<tr>
<td>CZ011</td>
<td>NRAS c.G35A (codon 12 Gly &gt; Asp)</td>
<td>0.5</td>
<td>M</td>
<td>5</td>
<td>2</td>
<td>57.6</td>
<td>11.5</td>
<td>100</td>
<td>162</td>
<td>6.0</td>
<td>dead without HSCT (3.3 y)</td>
</tr>
<tr>
<td>D278</td>
<td>NRAS c.C181A (codon 61 Gin &gt; Lys)</td>
<td>0.5</td>
<td>M</td>
<td>2</td>
<td>4</td>
<td>62.5</td>
<td>13.1</td>
<td>87</td>
<td>68</td>
<td>n.d.</td>
<td>alive with HSCT (7.0 y)</td>
</tr>
</tbody>
</table>

Liver and spleen sizes are given in cm below the costal margin. Leukemic clones in all patients had a normal karyotype. WBC indicates white blood cell count; Mono, monocytes; Plt, platelet count; Hb F, fetal hemoglobin; and nd, not done.
with Noonan syndrome. Fifty patients were not given HSCT within the first 3 years from diagnosis. Of these, 17 survived this period. Six of 17 carried a clonal RAS mutation (Table 1). It is evident that there is no appreciable difference in clinical features between the 3 patients reported by Matsuda (included in Table 1 for convenience) and our 6 patients. However, all 6 patients in our group had substitutions other than G12S. Overall, only 1 of 216 children had a G12S mutation. This patient received early HSCT, so the evaluation of his spontaneous course is precluded. However, he presented with 60% hemoglobin F, which is usually associated with an aggressive form of the disorder.

We agree that sporadic patients with JMML enjoy long-term survival without intervention. However, in the absence of reliable markers that prospectively identify those rare cases, and in view of the clear superiority of HSCT over other treatment modalities (probability of 10-year survival 0.39 vs 0.06 without HSCT),3,6 the EWOG-MDS recommends prompt HSCT for every patient with JMML, except children with Noonan syndrome.7 Importantly, the relapse incidence dramatically increases with age (from 18% in children ≤ 2 years old to 73% in patients ≥ 4 years old).5 Although we are not convinced that NRAS/KRASG12S is a useful marker for treatment decisions, we thank Matsuda and colleagues for stimulating this discussion and illustrating the need to continue the search for accurate prognostic markers in JMML.

Response:

Evaluation of relationship between the genetic abnormalities and disease phenotype is required in juvenile myelomonocytic leukemia

In their letter, Flotho et al comment on our recently published paper on spontaneous improvement of hematologic abnormalities in patients having juvenile myelomonocytic leukemia with specific RAS mutations.2 Although we are not convinced that NRAS/KRASG12S is a useful marker for treatment decisions, we thank Matsuda and colleagues for stimulating this discussion and illustrating the need to continue the search for accurate prognostic markers in JMML.

References


Conflict-of-interest disclosure The authors declare no competing financial interests.

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