To the editor:

Differential prognosis impact of IDH2 mutations in cytogenetically normal acute myeloid leukemia

Mutations in the genes isocitrate dehydrogenase 1 and 2 (IDH1/IDH2) have been recently identified in gliomas and acute myeloid leukemia (AML). We and others reported that IDH1R132 mutations were associated with normal karyotype and nucleophosmin 1 gene (NPM1) mutations. In a large cohort of 1450 AML patients, Schnittger et al showed a general unfavorable impact of IDH1 mutation in AML. Other studies, focused on cytogenetically normal (CN) AML, suggested that this effect would be principally observed in CN-AML with favorable genotype, that is, with NPM1 mutation without internal tandem duplication of FLT3 gene (FLT3-ITD). The prognosis impact of IDH2 mutations is not clearly defined. Two major host spots of IDH2 mutations have been reported in AML, IDH2R172 mutations, homologous to IDH1R132 mutations,

Table 1. Frequency and prognostic impact of IDH2 gene mutations in CN-AML

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Age range, y</th>
<th>Frequency</th>
<th>IDH2R172 mutation</th>
<th>Prognosis</th>
<th>Frequency</th>
<th>Prognosis</th>
<th>IDH2R140 mutation</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marcucci et al\textsuperscript{3}</td>
<td>358</td>
<td>19-83</td>
<td>4%</td>
<td></td>
<td>CR</td>
<td>16%</td>
<td>NC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thol et al\textsuperscript{4}</td>
<td>272</td>
<td>≤ 60</td>
<td>1.1%</td>
<td></td>
<td>No impact</td>
<td>11%</td>
<td>No impact</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paschka et al\textsuperscript{5}</td>
<td>338</td>
<td>16-60</td>
<td>NC</td>
<td></td>
<td>NC</td>
<td>NC</td>
<td>NC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Boissel et al\textsuperscript{6}</td>
<td>213</td>
<td>17-70</td>
<td>6%</td>
<td>CR, RR, OS</td>
<td></td>
<td>—</td>
<td>—</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abbas et al\textsuperscript{7}</td>
<td>353</td>
<td>15-77</td>
<td>14%†</td>
<td></td>
<td>No impact</td>
<td>14%†</td>
<td>No impact</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chou et al\textsuperscript{8}</td>
<td>155†</td>
<td>18-90</td>
<td>NC</td>
<td></td>
<td>OS</td>
<td>NC</td>
<td>OS</td>
<td></td>
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</tr>
</tbody>
</table>

ND indicates not done; NC, not communicated; CR, complete remission; OS, overall survival; —, not done; and RR, risk of relapse.
\textsuperscript{a}All IDH1 mutations.
\textsuperscript{†}All IDH2 mutations.
\textsuperscript{‡}Patients with prognosis analysis.
were found in 1.1%-6% CN-AML (Table 1).3,5,7 IDH2R140 mutations have been identified in 11%-16% CN-AML patients.3,7 Two recent publications in Blood by Thol et al7 and Abbas et al8 reported no prognosis impact of these mutations analyzed together, whereas a third publication by Chou et al9 reported a favorable impact (Table 1). However, other studies focusing on IDH2R172 suggested that this mutation may be associated with a poor prognosis in CN-AML (Table 1).3,5

To investigate these discrepancies further, we screened 205 patients with CN-AML treated in the Acute Leukemia French Association (ALFA)-9802 and ALFA-9801 trials for the presence of IDH2R140 mutations. The detection of IDH2R140 mutations was performed using the FastStart Taq DNA Polymerase Kit (Roche) and the primers IDH2-F (5′-TGAAGATGCGGTGCTGAT-3′) and IDH2-R (5′-GGGTGAAGACCATTTTGA-3′).

These patients were already screened for IDH1R132 and IDH2R172 mutations.5 IDH2R172 and IDH2R140 mutations were identified in 12 and 18 patients (6% and 9%, respectively). The absence of IDH2R140 mutations in complete remission samples (18 paired specimens) confirmed that these mutations were acquired and not polymorphisms. IDH1 and IDH2 mutations were all exclusive. Unlike IDH2R172 mutations, which were homogeneously present among FAB subtypes, we found a significant association of IDH2R140 mutations with FAB-M1 subgroup (50%, P = .04). Unlike IDH2R172 mutations, which were not detected in the presence of other gene mutations (NPM1m, FLT3-ITD, CEBPαm),5 IDH2R140 mutations were associated with NPM1m in 11 patients, with FLT3-ITD in 3 patients, and with CEBPαm in 2 patients.

The outcome of patients with CN-AML and IDH2R140 mutations was better than those observed in patients with IDH2R172 mutations. Complete remission rates were 100%, 58%, and 85% in the IDH2R140, the IDH2R172, and the IDH2wt group, respectively (P = .007 by Fisher exact test). The 5-year risk of relapse was 48%, 100%, and 61% (P = .03 by log rank test). This difference in response to treatment had a direct impact on overall survival (OS), as 5-year OS rates were 67%, 0%, and 43% in each of this subgroup (P = .004).

Thus, the disease profile of IDH2R140 mutations differed significantly from this observed in the context of IDH2R172 mutations. The unfavorable prognosis observed in IDH2R172 patients was also noted by Marcucci et al, who also reported specific gene and microRNA signatures associated with this mutation.3 The functional impact of both IDH2 mutations on IDH2 enzyme activity is not known. However, consistent differences in associated mutations may contribute to explain the differences in related outcome. Even if the frequencies of IDH2R140 and IDH2R172 mutations are relatively low, their prognostic impacts have to be analyzed separately.

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References

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