p53 Lesions in Leukemic Transformation

TO THE EDITOR: Myeloproliferative neoplasms have an inherent tendency toward leukemic transformation. The genetic mechanisms of transformation remain largely unknown. We analyzed biopsy specimens of myeloproliferative neoplastic tissue from 330 patients for chromosomal aberrations associated with leukemic transformation (the analysis was performed with the use of Genome-Wide Human SNP [single-nucleotide polymorphism] Array, Affymetrix). Of those patients, 308 had chronic-phase myeloproliferative neoplasms and 22 had postmyeloproliferative-phase neoplasm secondary acute myeloid leukemia (AML). Among these 22 patients, 1 carried the myeloproliferative leukemia virus oncogene (MPL) W515L and all others carried the Janus kinase 2 gene (JAK2) V617F mutation. Amplifications of chromosome 1q were significantly associated with transformation to AML (0.32% in patients with chronic-phase myeloproliferative neoplasms and 18.18% in patients with secondary AML; P<0.001). The minimal amplified region on chromosome 1q (201.0 to 204.5 Mbp) harbored MDM4 (Fig. 1A), a potent inhibitor of p53 often amplified in several types of cancer. This observation led us to investigate the involvement of the p53 pathway in postmyeloproliferative-neoplasm AML.

We sequenced the TP53 gene from all patients in whom leukemic transformation had occurred and found that 6 patients (27.3%) carried somatic mutations. Three of the patients had independent mutations in TP53, and another 3 had biallelic mutations. The mutations were C135S, M246K, N239D, and S261T. The results are presented in Table 1.

<table>
<thead>
<tr>
<th>Patient</th>
<th>TP53 Mutations</th>
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<tr>
<td>8</td>
<td>C135S</td>
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<tr>
<td>17</td>
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<td>17</td>
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dent mutations on both TP53 alleles, and 2 had homozygous mutations because of an acquired uniparental disomy of chromosome 17p. One patient had only one mutated TP53 allele (Table 1). None of the patients with TP53 mutations had amplification of chromosome 1q. The phenomenon of mutual exclusivity of TP53 mutations and MDM4 amplifications has been also observed in solid tumors.2

Among the 22 patients with postmyeloproliferative-neoplasm AML, 10 (45.5%) had evidence of a p53-related defect mediated by TP53 gene mutations or gains of chromosome 1q (Table 1). We detected monoallelic TP53 mutations (R283C and E298K) in 2 of 65 patients with chronic-phase myeloproliferative neoplasms, indicating that low mutation frequency is associated with this condition (3.1%). Thus, in our cohort, TP53 mutations were strongly associated with transformation to AML in patients with myeloproliferative neoplasms (P=0.003). Recent reports have implicated IDH1/2, LNK, and IKZF1 in this transformation.3-5 We found one mutation in IDH1 and one in IDH2 in postmyeloproliferative-neoplasm AML but no LNK mutations (Table 1). In our cohort, TP53 mutations and 1q gains were the most frequent lesions associated with postmyeloproliferative-neoplasm AML.

Tissue samples from chronic-phase myeloproliferative neoplasms were available from two of the patients who carried biallelic TP53 mutations and whose condition had progressed to secondary AML. Patient 8 carried both TP53 mutations in the chronic phase, but in a smaller clone; in Patient 17, only one of the two mutations was present in the chronic phase (Fig. 1B). The fact

<table>
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<th>Patient No.</th>
<th>JAK2</th>
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* UPD denotes uniparental disomy.
that TP53 mutations were detectable in both patients during the chronic phase suggests that TP53 mutations may predict leukemic transformation in myeloproliferative neoplasms.

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.


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CORRECTIONS

Telemonitoring in Patients with Heart Failure (December 9, 2010;363:2301-9). In Table 1 (page 2305), the data for white race were incorrect. In the Telemonitoring column, the number of patients should have been 414, rather than 413, and in the Usual Care column, the number and percentage should have been 401 (48.5), rather than 402 (48.6). The article is correct at NEJM.org.

Tourette’s Syndrome (December 9, 2010;363:2332-8). In the final paragraph (page 2337), the third to last sentence, beginning “For combined . . . ,” should have ended, “. . . although this agent is not approved by the FDA for Tourette’s syndrome,” rather than “. . . although this agent is not approved by the FDA for these conditions.” We regret the error. The article is correct at NEJM.org.

CORRECTIONS