Cytogenetic Disorders During Tumor Progression in Leukemia

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The successes in studying the karyotype of malignant tumors as well as the achievements in molecular biology and molecular genetics have considerably deepened our knowledge concerning the role of chromosomal disorders in oncogenesis [1-4]. Recognition of clonal origin of leukemias [5] has stimulated the interest in studying the formation and development of cytogenetically marked leukemic clones during development of leukemias.

The purpose of this investigation was to analyze the pathogenetical and clinical significance of karyotypic peculiarities in different stages of the leukemic process.

Chromosomal analysis employing the G-banding technique was carried out in 394 patients with preleukemia (PL), secondary leukemia, different stages of chronic myeloid leukemia (CML), and different variants of leukemia (AL).

The group with PL consisted of 95 patients with firm cytopenia and either hypo-, normo- or hypercellular bone marrow with erythropoietic disorders. Cytogenetic examinations revealed only normal diploid metaphases, but increased percentages of aneuploid and polyploid cells and structural aberrations, i.e., instability of the karyotype and clonal anomalies.

Karyotypic instability manifested both in quantitative and structural aberrations. Quantitative disorders were common for patients with bone marrow hypoplasia, whereas structural aberrations were more often observed during erythropoietic disorders (Table 1).

Both chromosomal and chromatid types of aberrations were found, including breaks, fragments, deletions, chromatid exchanges, marked chromosomes, and, sometimes plural aberrations.

We observed transformation into acute leukemia in 13 out of 88 patients (14.8%). It was found that in patients with karyotypic instability, the frequency of subsequent emergence of abnormal clones and leukemic processes is reliably higher (36.4%) than in patients with normal karyotype (1.8%).

These data suggest that karyotypic instability may provide a favorable background, or even be the first step, for the formation of leukemic clones. The discovery of abnormal clones may be interpreted as evidence of the leukemic process, even without clinical manifestations. During tumor progression, we observed an increase in the percentage of abnormal clones cells as well as the appearance of new clones. The majority of patients with leukemia that developed after preceding preleukemic disorders had clonal abnormalities.

The second group investigated included patients with secondary leukemia that developed as a complication of different neoplastic diseases, treated by chemo- or radiotherapy, 11 months to 8 years after diagnosis of the primary tumor. In 11 out of 13 such patients, abnormal clones were found. Quantitative and structural aberrations of chromosomes 7, 5, 3, and 17 were charac-
<table>
<thead>
<tr>
<th>Investigated group</th>
<th>Karotype</th>
<th>Total no. of metaphases</th>
<th>Metaphases with quantitative abnormalities (%)</th>
<th>Metaphases with structural abnormalities (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hypodipl. (range)</td>
<td>Hyperdipl. (range)</td>
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<tr>
<td>Bone marrow hypoplasia (n=51)</td>
<td>Normal (n=34)</td>
<td>1320</td>
<td>7.4 (1-10)</td>
<td>0.15 (0-2.5)</td>
</tr>
<tr>
<td></td>
<td>Unstable (n=14)</td>
<td>550</td>
<td>13.5 (7-20)</td>
<td>8.0 (3-20)</td>
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<td></td>
<td>Clonal abnormalities (n=3)</td>
<td>56</td>
<td>% of cells of abnormal clones; 48, 27, 43</td>
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<tr>
<td>Erythropoietic disorders (n=44)</td>
<td>Normal (n=21)</td>
<td>630</td>
<td>7.1 (2-9)</td>
<td>0.5 (0-2.5)</td>
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<tr>
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<td>Unstable (n=19)</td>
<td>604</td>
<td>15.2 (5-34)</td>
<td>7.1 (0-13)</td>
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<tr>
<td></td>
<td>Clonal abnormalities (n=4)</td>
<td>85</td>
<td>% of cells of abnormal clones: 75, 27, 16, 33</td>
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*Hypodipl:* hypodiploidy; *hyperdipl:* hyperdiploidy; *polydipl:* polydiploidy; *aberr:* aberrations.
teristic of this group. Abnormal clones were often observed on the background of bone marrow hypoplasia and karyotypic instability.

The investigations carried out in different stages of CML enabled us to study chromosomal disorders regularly during tumor progression. In 95% of patients with the developed stage of CML, only t(9;22) was found, and neither additional quantitative nor structural aberrations were observed. Supplementary chromosomal abnormalities, both clonal (2PH, + 8, + 9, + 21, i17q) and random (instability), were found in 48% of patients during the period preceding the blast crisis.

The rise of new clones, constituting the basis of blast crisis, was observed more often on the background of karyotypic instability and presented evidence of transformation into the new malignant stage. In the terminal stage of CML, the new abnormal clones were found in 68% of investigated cases.

Thus, our research has shown that karyotypic instability might be considered as a risk-factor of leukemic clone development, or as the first step in their formation. The appearance of abnormal clones can be regarded as a basic differential-diagnostic criterion for revealing early stages of acute leukemia.

The study of AL itself has shown the presence of abnormal clones with non-random chromosomal disorders in 58% of patients, 63% in acute lymphocytic leukemia (ALL) and 55.6% in acute nonlymphocytic leukemia (AnLL). In AnLL, mostly with hypo- or pseudodiploidy, chromosomes 5, 7, 8, and 21 were damaged most often, while for ALL, hyperdiploidy with rearrangement of chromosomes 6, 9, 8 and 21 was most common.

The correlation between normal and abnormal metaphases plays a certain role in course of disease and is one of the significant prognostic factors.

The discovery of chromosomal disorders preceding manifestation of AL, the nonrandom chromosome changes in abnormal clones formed during the preblastic stage of CML, the presence of some specific chromosome aberrations in AL, and the correlation between chromosomal disorders and the course of leukemia point out the important role of chromosomal disorders in leuke-mogenesis.

References