GENETIC FEATURES OF ACUTE MYELOID LEUKEMIA WITH t(8;21) IN ADULTS

Egamova Sitora Kabilovna
Bukhara State Medical Institute, Bukhara, Uzbekistan

Resume

Acute myeloid leukemia (AML) is a molecularly heterogeneous group of malignant neoplasms. Cytogenetics and PCR diagnostics have traditionally been used to stratify patients with AML into three main categories based on risk: favorable, intermediate and unfavorable. This predictive category has an important influence on treatment decisions. In general, there was agreement that AML patients with favorable recurrent cytogenetic changes, eg, inv(16) and t(8,21), should be treated with conventional therapy, while patients at low risk (eg, hose with monosomic karyotype) should undergo allogeneic hematopoietic stem cell transplantation (HSCT). However, the decision to treat patients belonging to the intermediate risk category, which mainly includes AML with normal cytogenetics, has been difficult due to the high clinical and molecular heterogeneity of this group (constituting 40-50% of all cases of AML in adults).

Keywords: acute myeloid leukemia, cytogenetics, karyotype, prognosis.

Acute leukemias are the most common malignant diseases and the proportion of acute myeloid leukemia is 15–20% of all hemoblastoses. Modern intensive polychemotherapy based on the use of high doses of cytosine arabinoside (Ara-C) and anthracyclines allows achieving complete remission in more than 90% of patients and long-term survival in 50–60% with AML [1,2,3]. An aberrant karyotype and the corresponding abnormal genes resulting from fusion of chromosome regions, replacement and loss of gene regions are detected on average in 70–80% of patients with AML [10,11]. The most common karyotypic anomaly in AML is the t(8;21)(q22;q22) translocation, first described by Rowley in 1973 [7,12,13]. This aberration occurs in 4–5% of adults with AML [2,6,11]. The essence of this translocation is that the AML1 gene (Acute Myeloid Leukemia) from the long arm of the 21st chromosome is transferred to the region of the ETO (Eight-Twenty-One) gene located on the long arm of the 8th chromosome. The AML gene (now RUNX1) encodes the transcriptional regulatory factor CBFα, which, in combination with CBFα, activates the transcription of genes that control myeloid differentiation. As a result, the chimeric RUNX1/ETO gene and its product, the CBFα-ETO protein, are formed, which inhibits the transcription of differentiating factors in myeloid cells [5, 13]. The chimeric AML1/ETO transcript can also occur in patients with t(2;21;8)(p12;q22;q22), t(8;10;21) (q22;q26), t(6;8;21)(p22;q22;q22), which are considered as a variant of t(8;21) and in some cases are detected in patients with a normal karyotype [12,13]. Purpose of the study. To analyze the genetic features of AML patients with t(8;21).

Materials and Methods

AML was diagnosed based on the detection of 20% or more leukemic myeloid blasts in a bone marrow or blood aspirate and classified based on the FAB criteria [43]. Stratification into risk groups was carried out on the basis of data from chromosomal analysis and molecular biological studies. The standard risk group included patients with t(15.17)(q22;q21) and t(8.21)(q22;q22) with CBF□(AML1)/ETO. High-risk group — patients with (-5/5q-), (-7/7q) and complex karyotype All other patients with normal karyotype belonged to the medium-risk group.

Results

Chromosomal analysis was carried out in 46 patients. Cytogenetic anomalies were found in 10 (21.7%) patients. A molecular biological study was performed in 42 (91.3%) patients out of 46. Abnormal transcripts were found in 3 (6.5%) patients. Chromosome analysis revealed translocation t(8;21)(q22;q22) in 2 (4.3) patients out of 46. An abnormal AML1/ETO transcript was detected in 1 (2.1%) patient. The clinical characteristics of patients in the study group were as follows: the median number of leukocytes was $18.6x10^9$/l (3–$109.5x10^9$/l), the median number of blast cells in the bone marrow was 66.5% (19.5–88%). Splenomegaly was noted in 14/46 (30.4%) patients. Neuroleukemia was detected in 8 (17.3%) patients, extramedullary lesions were also found in 8 patients (in 7 with localization in the facial area - orbit, zygomatic bone, eyelids). In 4 patients, neuroleukemia was combined with the presence of extramedullary lesions. Interestingly, the worst results in our study were obtained in patients in the t(8;21) group with potentially adverse anomalies, in which the probability of survival was 0. Similar trends were found in other study groups.

CONCLUSIONS

Thus, taking into account the high probability of recurrence, patients in this group can be regarded as candidates for allogeneic stem cell transplantation in the first remission. These data once again confirmed that with the use of modern therapy within the group with t(8;21) there are different sub-variants of the disease, the prognosis of which is determined by additional factors. Accordingly, in order to identify a truly favorable group of patients with t(8;21), an all-embracing diagnosis is necessary - chromosomal analysis and an extended molecular genetic study in order to identify all significant prognostic factors. This will be the next step towards more differentiated treatment.

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