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CYTOGENETICALLY NORMAL ACUTE MYELOID LEUKEMIA

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Abstract. In recent years, a number of somatically acquired mutational changes have been identified in patients with acute myeloid leukemia (AML). Most of these genetic changes occur in normal-karyotype AML, representing the largest cytogenetic subgroup (40–50%) of AML. These molecular data not only provide new insight into the pathogenesis of AML, but also have clinical implications. In this review, we will discuss the most important gene changes, including mutations in the TP53 gene and mutations in the tyrosine kinase domain (TKD) of the FLT3 gene. These gene mutations have become important prognostic markers and now allow us to separate cytogenetically normal (CN)-AML into distinct prognostic subgroups. In addition, these mutant molecules are potential targets for molecular therapy.

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

Acute myeloid leukemia is a molecularly heterogeneous group of malignant neoplasms [1,4]. Cytogenetics and PCR diagnostics have traditionally been used to stratify patients with AML into three main categories based on risk: favorable, intermediate and unfavorable [5,6]. 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, those with monosomic karyotype) should undergo allogeneic hematopoietic stem cell transplantation (HSCT) [3]. However, the decision to treat patients in the intermediate risk category More recently, the discovery of several gene mutations associated with CN-AML has led to three important advances in the field of AML. First, the improvement of the molecular definition of «AML with recurrent genetic abnormalities» of the World Health Classification (WHO). Indeed, in 2008 this category was expanded to include NPM1 mutated AML and CEBPA mutated AML as provisional units, allowing more than 50% of AML to be classified based on the underlying genetic lesion. Second, the identification of molecularly defined subgroups of patients with different prognosis within CI-AML. Third, the ability to use certain mutations that are very common and stable (eg, NPM1 mutations) to monitor minimal residual disease in about 60% of CN-AML cases [7,9].

Purpose of the study. To study the frequency of gene mutations in cytogenetically normal AML.

Materials and methods. 46 patients with AML aged 18–68 years were examined. The material for a complex cytogenetic study was bone marrow cells obtained by sternal puncture, as well as peripheral blood cells of patients. Cytogenetic preparations were stained with the differential GTG method. At least 20 metaphase plates were analyzed in each study. The karyotype pathology was interpreted in accordance with the International Nomenclature for Differentially Segmented

Chromosomes (ISCN, 2013). The material for analysis of the mutational status of the FLT3-TKD and TP53 genes was genomic DNA. Isolation of genomic DNA from peripheral blood was performed using AmpliSense RIBO-prep kits (Russia, Moscow). Mutation analysis was performed by real-time PCR.

Research results. Karyotype changes were determined in 12,5% (14) of patients with AML, 87% (32) had a normal karyotype. Depending on the karyotype at the onset of the disease, patients were divided into prognostic risk groups: favorable (n=6), intermediate (n=35) and unfavorable (n=5). The frequency of detection of FLT3 gene mutations did not differ significantly depending on the prognostic group: in the group of patients with a favorable prognosis, it was 1,2% (n=1), in the group of patients with an intermediate prognosis - 6.0% (n=5) and in group of patients with poor prognosis – 2,4% (n=2) (p>0.05). Results The frequency of detection of mutations in the TP53 gene: in the group of patients with a favorable prognosis was absent, in the group of patients with an intermediate prognosis – 13,4% (n=11) and in the group of patients with an unfavorable prognosis – 2,4% (n=2) (p >0,05).

Most studies have shown that mutations in the tyrosine kinase domain (TKD) of the FLT3 gene give an unfavorable prognosis [2,8,13]. This is especially true for AML patients with a normal karyotype. FLT3 activating mutations tend to be more common in individuals with a normal karyotype. However, they have also been reported in patients with t(15;17) typical of acute promyelocytic leukemia (APL), the t(6;9) translocation found in a rare form of AML with basophilia, and also with some other recurrent cytogenetic abnormalities [9] . Clinical trials have shown that FLT3-TKD is closely associated with leukocytosis, high blast counts, normal cytogenetics, and t(15;17) [11].

Mutations *TP53* are the most common single gene anomaly identified to date in AML in adults, accounting for about 30% of all AML and 50-60% of CI-AML [4,5]. TP53 mutations in AML are very stable over the course of the disease, appearing in relapses even many years after the initial diagnosis, in patients with more than one relapse, and even in relapses occurring in extramedullary sites. The presence of TP53 mutations has become an important favorable prognostic factor also in elderly (>60 years) patients with AML. This effect has recently been described even in octogenarians [8,15]. Notably, the favorable prognostic impact of TP53 mutations in elderly patients with AML occurs independently of FLT3-TKD status. Thus, the search for TP53 mutations is a valuable analysis for the selection of those elderly patients who

Summary. For patients with AML, the karyotype is the strongest predictor of treatment outcome. AML with a normal karyotype is usually categorized as "intermediate risk". Treatment outcomes for AML with a normal karyotype are highly heterogeneous. Accordingly, there has recently been interest in using molecular markers to stratify the risk of these patients. New technologies available, such as gene expression profiling, have increased our knowledge of potentially

altered genes and their predictive impact. It is anticipated that these newly recognized molecular markers will soon become part of the diagnostic/prognostic screening of AML patients with normal cytogenetics.

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