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To Study The Frequency Distribution Of Chromosomal Abnormalities And Its Relationship With Driver Somatic Mutations In Patients With Acute Myeloid Leukemia.

Musashaykhova Shakhnoza Mamirbekovna

Associate Professor of the Department of Family Doctor Training, Andijan State Medical Institute, Andijan, Republic of Uzbekistan. (musashayxov1989@mail.ru), (ORCID: 0000-0001-9158-976X)

Salokhiddinov Zukhriddin Salokhiddinovich

Head of the Department of Family Doctor Training, Professor, Andijan State Medical Institute, Andijan, Republic of Uzbekistan. (zuxriddinsaloxiddinov45@gmail.com), (ORCID: 0000-0002-1033-9177)

Djumabayeva Svetlana Eduardovna, Soliyev Dilmurod Kodirovich, Soliyev Alisher Kodirovich, Valiyeva Madina Yunusovna, Ahmadaliyeva Umida Kobuljanovna, Usmonova Umida Iminjanovna, Kodirov Dilshod Adhamovich, Yaminova Nafisa Haydaraliyevna.

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Abstract: The peripheral blood of 145 patients with AML who were in inpatient treatment at the Republican Specialized Scientific and Practical Medical Center of Hematology of the Ministry of Health of the Republic of Uzbekistan served as the material for molecular genetic research. Clinical and laboratory studies were performed at the Republican Specialized Scientific and Practical Medical Center of Hematology of the Ministry of Health of the Republic of Uzbekistan.

The study demonstrated a significantly higher frequency of NPM1 mutation distribution in patients with normal karyotypes compared to patients with chromosomal disorders (35.3% versus 9.4% with $\chi 2=7.0$; OR=0.2; p=0.01; 95% CI: 0.06-0.65).

Statistical processing of the results was performed using the standard OpenEpi V.9.2 application software package.

Key words: mutation, genetic marker NPM1, hemorrhage, thrombocytopenia, blast cells.

INTRODUCTION.

Acute myeloblastic leukemia (AML) — is a clonal malignant disease characterized by ineffective hematopoiesis. Most AML patients have various cytogenetic and molecular genetic lesions that are combined with certain biological and clinical features of the disease [3,7,8]. Approximately 50-60% of de novo patients and 80-95% of patients with secondary AML show chromosomal changes. It should be noted that structural cytogenetic aberrations are the most common markers and occur in about 40% of cases of AML de novo. A fairly large group of patients with a normal karyotype (NC-AML), formally classified as an intermediate risk, is extremely heterogeneous in relation to the prognosis of the course of the disease. Currently, only some mutations characterized by a known prognostic value are included in the current prognostic classifications of AML, in particular t (8;21), NPM1 and BRAF [6,9,10].

Classical karyotype analysis reveals chromosome changes in about half of AML patients. Many chromosomal aberrations are independent prognostic factors and are included in the modern classification of AML

published by the World Health Organization (WHO) [5]. Patients with normal karyotype (NC), according to the international classification, belong to an intermediate risk group. However, it is well known that the clinical picture and prognosis of the disease in this group of patients are very different. Identification of mutations in patients with NC allows not only to identify categories of patients with a certain prognosis, but also to understand the molecular pathogenesis of the disease. More than 85% of NC-AML patients have genome mutations [1,4]. Some of these mutations not only complement the prognostic information, but also provide a potential basis for the development of new targeted therapy capabilities. Although some mutations are already included in the current WHO classification and recommendations of European experts, a more detailed study of the molecular architectonics of leukemia is needed [2, 11].

RESEARCH MATERIALS AND METHODS.

The peripheral blood of 145 patients with AML who were in inpatient treatment at the Republican Specialized Scientific and Practical Medical Center of Hematology of the Ministry of Health of the Republic of Uzbekistan served as the material for molecular genetic research. Clinical and laboratory studies were performed at the Republican Specialized Scientific and Practical Medical Center of Hematology of the Ministry of Health of the Republic of Uzbekistan.

In the main study group of patients, the median age was 44.6±1.2 years. In particular, in male patients the average age was 47.2±1.9 years, in female patients the median age was 42.2±1.5 years. The median age was higher in men compared to the female sex.

Mutation testing was carried out on a Rotor-Gene Q device (Quagen, Germany), using a commercial test kit from Syntol LLC (Russia).

Statistical processing of the results was performed using the standard OpenEpi V.9.2 application software package

THE RESULTS OBTAINED AND THEIR DISCUSSION.

In the course of our study, 83 patients out of 145 studied patients underwent cell karyotyping. In accordance with the objectives of the study, we conducted a karyotype analysis using standard cytogenetic examination (SSI) in patients with AML.

During a standard cytogenetic study, karyotype changes were detected in 32 patients out of 83 (38.6%) patients, whereas in 51 patients (61.4%) chromosomal aberrations were not detected (karyotype 46XX or 46XX).

In male patients, 19 out of 39 (48.7%) patients had chromosomal abnormalities, and 20 patients (51.3%) had no karyotype abnormalities. And in the group of female patients, chromosomal aberrations were detected in 13 of 44 (29.5%) patients, as well as in 31 patients (70.5%), no karyotype changes were detected. Chromosomal aberrations were reported most frequently among men compared to the female sex. In young patients, a karyotype disorder was detected in 33.3% of cases (22 out of 66), a normal karyotype was detected in 66.7% (44 out of 66) patients, respectively. In elderly patients, chromosomal abnormalities were reported in 10 out of 17 patients (58.8%), a normal karyotype was detected in 7 out of 17 patients (41.2%).

Thus, chromosomal aberrations were recorded most often among men and in elderly patients.

During the study, mutations t (8;21) were detected in 9.7% (14 out of 145) patients, however, a mutation of this gene was not detected in 90.3% of cases, respectively. Only single mutations were found in 5 out of 14 (35.7%) patients. In 9 out of 14 (64.3%) patients, mutations were of a combined nature. Statistically, mutations of this genetic marker were significantly more often detected in patients with an altered karyotype – in 6 (18.8%) of the 32 examined patients in relation to patients without them (-2=0.1; OR=1.2; p=0.7; 95%CI:0.39–3.98). In the group of patients with a favorable karyotype, mutations t (8;21) were detected only in 15.7% of patients (see Table 1).

Table 1
Differences in the frequency of gene mutation factor t (8, 21) in the groups of patients with normal and altered karyotypes.

The factor	The number of examined				χ2	p	OR	95%CI
	Altered karyotype		Normal karyotype					
	n	%	n	%				
is available	6	18.8	8	15.7	0.1	p = 0.7	1.2	0.39 – 3.98
no	26	81.2	43	84.3	0.1	p = 0.7	0.8	0.25 – 2.59

Mutations in the inv gene (16;9) were found in 4 (2.8%) of 145 patients with AML. This mutation was not registered in 141 (97.2%) out of 145. In all cases, the mutation of the above-mentioned gene was of a combined nature.

When studying patients depending on the karyotype, it was found that the greatest detection of mutations in the inv gene (16, 9) was detected in the group of patients with a normal karyotype – in 3 (5.9%) of 51 patients. In the group of patients with chromosomal aberrations, the occurrence of mutation of the studied gene was found in 1 out of 32 patients (3.1%). Despite this, differences in the frequency of inv gene mutation (16, 9) in patients with normal karyotype and with altered karyotype were not statistically significant (χ2=0.3; OR=0.5; p=0.6; 95%CI:0.05–5).

The presence of mutations of the BRAF genetic marker was statistically significantly associated in patients with chromosomal aberrations in relation to patients with a normal karyotype (12.5% vs. 2.0%). In the presence of this mutation, the risk of developing chromosomal abnormalities is significantly higher (7.1 times) compared with patients without a mutation of this gene (χ2=3.9; OR=7.1; p=0.05; 95%CI:1-50.81) (see Fig. 1).

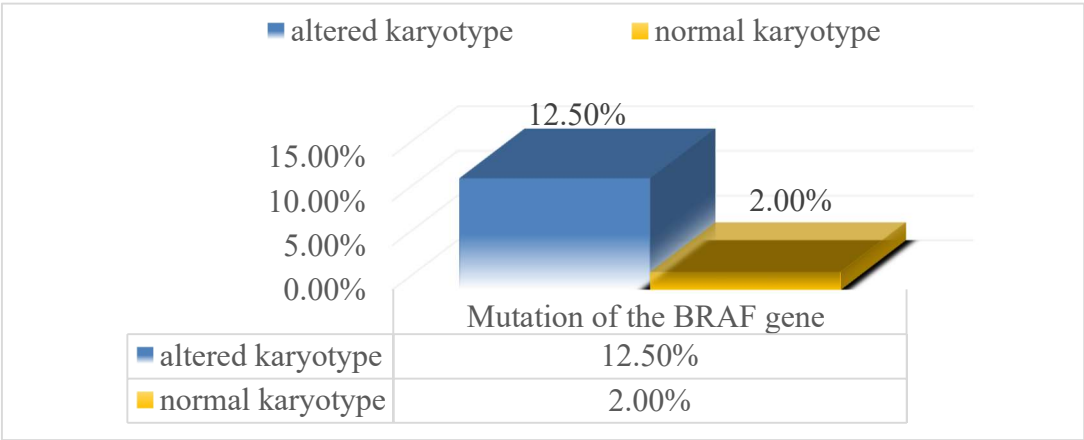

Figure 1. Frequency of distribution of the genetic marker BRAF and its relationship with chromosomal abnormalities in patients with AML.

In the study, mutations in the NPM1 gene were detected in 17.2% of patients, and in 82.8% of cases this mutation was not registered.

Single mutations of the NPM1 gene were detected in 16 out of 25 patients. The remaining 9 out of 25 patients had combined mutations.

The study demonstrated a significantly high frequency of distribution of the NPM1 mutation in patients with a normal karyotype in relation to patients with chromosomal abnormalities (35.3% vs. 9.4% at -2=7.0; OR=0.2; p=0.01; 95%CI:0.06–0.65).

CONCLUSION.

Thus, in the course of a standard cytogenetic study, karyotype changes were detected in 38.6% of patients, whereas in 61.4% of cases, chromosomal aberrations were not detected. Chromosomal aberrations were reported most frequently among men and in elderly patients. In patients with a normal karyotype, insertions in the NPM1, inv genes are more often detected (16;9), however, mutations in the t (8;21) and BRAF genes were more common in patients with an altered karyotype.

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