International Journal of Education, Social Science & Humanities.
Finland Academic Research Science Publishers
ISSN: 2945-4492 (online) | (SJIF) = 7.502 Impact factor
Volume-11| Issue-6| 2023 Published: |22-06-2023|

THE RANGE OF FUNCTIONAL MUTATIONS AND THEIR CONTRIBUTION TO THE FORMATION OF BLAST CELLS AND THE DEVELOPMENT OF LEUKEMIA (LITERATURE REVIEW)

https://doi.org/10.5281/zenodo.8031331

Fazilova Sharifa Mirkhamidovna
PhD Senior Lecturer, Department of Military Field Therapy and Hematology, Urgench branch of the Tashkent Medical Academy E-mail; fazilova sharifa@mail.ru
Matkarimova Dilfuza Soburovna
Doctor of medical sciences professor Department of Hematology, Transfusiology and Laboratory work, of the Tashkent Medical Academy E-mail; asdf123-as@yandex.ru

Summary
The main important factor in the structure of hemoblastosis and the pathogenesis of leukemia is the occurrence of mutations in these genes. Thus, the detection of molecular genetic changes in the tumor clone, as well as the comprehensive assessment of the main signaling pathways in tumor cells, not only allows understanding tumor biology, but also provides new information in patients with acute leukemia requires additional scientific research to help develop diagnostic and treatment criteria.

Key words.
hemoblastosis, mutations, allows, requires

Prevalence. Acute leukemia (AL) - tumor disease bone marrow, often colloquially referred to as "blood cancer", in its natural course inevitably leading to death [28]. The hereditary predisposition to the development of malignant tumors has been known for a long time, only after the rediscovery of Mendel's laws in 1900, a scientific explanation of this fact became possible. By this time, it was already known that tumor cells have an altered set of chromosomes. Teodor Boveri contributed to the understanding of the genetics of cancer: he suggested that there are chromosomes that stimulate cell division and there are chromosomes thatinhibit. Today we know that both types of genes do exist.

In OL, the normal hematopoiesis: excessive production of abnormal immature blood cells, usually progenitors leukocytes(blast cells), which, multiplying and accumulating in the bone marrow, interfere with the production and functioning of normal blood cells, which causes the main symptoms of the disease. OL occupy a leading place in the structure of the incidence of hemoblastoses, accounting for

approximately 1/3 of their total number. The incidence of AL is on average 3-5 cases per 100,000 population. In 75% of cases, the disease is diagnosed in adults, in 25% in children [21]. The structure of occurrence of acute leukemia largely depends on age. So, in the age group up to 15 years, the ratio of acute lymphoblastic leukemia (ALL): acute myeloid leukemia (AML) is 4:1, in the age group from 15 to 35 years - 1:1.5, and in the age group over 35 years - 1:8. In the age period from 2 to 5 years, when the so-called infantile peak of the age-related incidence of acute leukemia is formed, boys get sick more often than girls. At the age of 10-13 years, the incidence of acute leukemia has approximately the same level [5,14]. The first peak of the incidence of ALL is observed at the age of 3-4 years, the increase in the disease in adults is observed at about 40-50 years, the peak incidence is at 84 years [2]. The median age of patients with acute non-lymphoblastic leukemia is 60-65 years, with acute lymphoblastic leukemia 10 years [13]. The ratio between male and female is 1:4. In Europe, 8,10,000 new cases of ALL are diagnosed each year among adults, with an incidence rate of 1.3 in men and 0.9 in women. According to the National Cancer Institute, the incidence rate of ALL (2010-2014) in the United States was 1.7 per 100,000 population [17, 19, 20]. acute lymphoblastic leukemia for 10 years [13]. The ratio between male and female is 1:4. In Europe, 8,10,000 new cases of ALL are diagnosed each year among adults, with an incidence rate of 1.3 in men and 0.9 in women. According to the National Cancer Institute, the incidence rate of ALL (2010-2014) in the United States was 1.7 per 100,000 population [17, 19, 20]. acute lymphoblastic leukemia for 10 years [13]. The ratio between male and female is 1:4. In Europe, 8,10,000 new cases of ALL are diagnosed each year among adults, with an incidence rate of 1.3 in men and 0.9 in women. According to the National Cancer Institute, the incidence rate of ALL (2010-2014) in the United States was 1.7 per 100,000 population [17, 19, 20].

The geographic differences in hematological malignancies may be partly explained by the quality and access to health care systems associated with resource levels, although there is likely a role for etiological factors, including gene-environment interactions.

According to literary sources, pesticides were used on a large scale in the countries of the post-Soviet space, including in the Republic of Uzbekistan, for this purpose pesticides were used, which led to an environmental disaster. According to the results of 30 studies from 2001 to 2010 the incidence rate per 100,000 population in Andijan region was 13.8%, in Samarkand 12.3%, in Bukhara 9.1%, in Namangan 8.1%. Including in the first five years (2001-2005) of adult patients with leukemia - 323 people (40.1%) in the second five years (2006-2010) - 482 (59.9%)

patients, when comparing incidence rates clearly it can be seen that the incidence in each five-year period increases by an average of 1.5 times. Among children, these figures also increased as in adults: in the 1st five-year period 61 (42%) patients, in the 2nd five-year period - 84 (58%).

In Russia, leukemia incidence rates are variable, with the highest incidence rates recorded in the Penza (11.2 per 100,000 men and 7.7 per 100,000 women) and Murmansk (10.4 and 10.3 per 100,000, respectively) regions. The lowest rates are observed in men in the Primorsky and Khabarovsk Territories (2.4–3.1 per 100,000) and in women in Kalmykia, Saratov, Jewish Autonomous and Magadan Regions (1.4–2.3 per 100,000) [24, 7].

In Kazakhstan, the incidence rate in children from 2.8%ooo (1997) to 3.2%ooo in 2006, and the incidence of leukemia in children in the structure of malignant neoplasms was 32.0±0.34%. In Tajikistan, the standardized incidence rate of acute leukemia in the country as a whole was 2.04 per 100,000 population [12,11].

Distributions of geographical features play an important role in the formation of the epidemiological characteristics of a particular nosological unit. The impact of climatic factors, as well as exogenous carcinogens (chemical and agricultural agents, physical impact) directly proportionally affect the incidence of malignant neoplasms in a particular region. In almost all localizations, the incidence in the city, as the focus of greater exposure to carcinogenic agents, is higher compared to the incidence in rural areas.

Establishment of the molecular mechanisms of action of various enzymes, the structure of the human, animal and plant genome was a fundamental revolution in biology, which has a significant impact on the development of medicine in the 21st century. Thousands of genes are being discovered, their functional significance and role in various diseases are being established, unique opportunities are emerging for elucidating the cause of many hereditary and oncological diseases, for monitoring environmental influences, 9 pharmacogenetics and predictive medicine are expected to develop rapidly [16].

In 2016, the two nosological forms described above were included by the experts of the World Health Organization (WHO) as preliminary classification units in the B-lymphoblastic leukemia/lymphoma section of the modern classification of tumors of hematopoietic and lymphoid tissues [23].

The introduction of massive parallel sequencing methods (whole genome, exome, and transcriptome sequencing) made it possible to conduct detailed studies of the genome, which, together with the determination of the gene expression profile, greatly expand the understanding of the pathogenesis of AL and its

International Journal of Education, Social Science & Humanities.
Finland Academic Research Science Publishers
ISSN: 2945-4492 (online) | (SJIF) = 7.502 Impact factor
Volume-11| Issue-6| 2023 Published: |22-06-2023|

heterogeneity. Based on research, it is possible not only to determine the molecular genetic markers of the disease, but also to isolate new subtypes of OL, which are subsequently included in modern classifications of tumors of hematopoietic and lymphoid tissues [6].

Despite the successes of recent decades, the overall mortality rate from AL remains quite high [25]. The study of the mechanisms of development, progression of acute leukemia, as well as the search for early diagnostic and targeted therapeutic approaches is a priority in modern oncohematology.

Results of studies indicating the contribution of tumor suppressor genes (antioncogene, tumor suppressor) in the development of AL. Protein products of suppressor genes (antioncogenes) can also encode miRNAs. Suppressor genes are usually found in inactivating mutations that are phenotypically manifest in the formation of tumors.

With the discovery of new subtypes of OL, the pathogenesis of the disease continues to be actively studied. Recent studies using massive parallel sequencing have revealed in patients with OL a spectrum of somatic mutations in genes involved in numerous signaling pathways that regulate transcription, lymphoid differentiation, cell cycle, chromatin structure modification, epigenetic regulation, as well as TP53-, RAS/RAF/ MEK/ERK -, JAK/STAT-, NOTCH-, PI3K/AKT/mTOR-, Wnt/β-catenin-dependent signal transduction [27].

Common mechanisms of activation of these cascades during leukemoid genesis include the occurrence of mutations in the genes - kinases and cytokine receptors that form these cascades. Interest in the study of activating mutations in the genes that form the above signaling pathways is due to two clinical aspects. Firstly, the accurate identification of genetic changes and their combinations contributes to a more rigorous stratification of patients into risk groups, and secondly, the detection of anomalies that can be targeted allows the introduction of new treatment methods into clinical practice. The significance of activating mutations in the NRAS, KRAS, JAK2, CRLF2 genes in patients treated according to the protocols of Russian multicenter studies is unknown. Another important subject of research is the mutational status of the TP53 gene. Although disorders of the TP53 gene have been described in many tumors, they are quite rare in ALL, with the exception of relapses of ALL and ALL with a hypoploid karyotype [15]. It is noteworthy that more than half of the mutationsArg72Pro the TP53 gene in patients with ALL with a hypoploid karyotype is detected in non-tumor cells, which suggests the hereditary nature of these mutations, and in this case, leukemia can be considered a manifestation of LiFraumeni syndrome (LF) [17]. For some

tumor foci, the quality of studies was related to the size of the genetic association, mainly in cancers of the cervix, head and neck, stomach and lungs. However, the quality of the study did not significantly explain the observed heterogeneity. Meta-regression showed that a significant part of the observed heterogeneity is responsible for ethnic, allelic frequency and genotyping method. The results indicate that ethnicity and histological and anatomical sites may modulate the Arg72Pro penetrant in relation to cancer susceptibility. This meta-analysis indicates the importance for more good quality studies and that the covariant responsible for heterogeneity should be controlled to obtain a more conclusive answer about Arg72Pro function in cancer [18,4,8].

According to Francisco G. et al. [9], when studying the effect of mutations in the TP53 gene, only 8% of the studied patients showed changes in the genotype, but the results showed that mutations in the TP53 gene in ALL patients do not affect the hematological response during chemotherapy, but clearly correlated with early disease recurrence and poor survival.

These data are important for understanding the genetic pathogenesis of AL. At the same time, patients with different types of program therapy experience relapses of the disease [30].

International experts are strongly advised to include patients in clinical trials and save biological samples so that they can be compared in the future with the results of therapy and establish a correlation between laboratory data and the outcome of the disease. The use of the principles of "evidence-based" medicine in such a field as hematology is necessary, since, perhaps, in no other area of \u200b\u200b medical knowledge one has to constantly face critical situations and make critical decisions. In addition, according to the results of a registration study performed by the Russian OL Research Group in a number of regions of the Russian Federation, the median age of diagnosis of AML is 53 years, which is more than 10 years less than in Western countries. These indicators indicate both the insufficient diagnosis of AML in patients of the older age group and the shorter life expectancy of the population in our country and although AML is classified as an organ disease, the social significance of the treatment of this most formidable disease of the blood system determines the need to organize adequate specialized care that involves the interaction of many medical disciplines, a combination of clinical, laboratory, instrumental and scientific studies, the continuity of inpatient and outpatient care. Moreover, AML remains the main indication for allogeneic bone marrow transplantation as the most effective treatment for leukemia. Every year, the number of transplanted patients in the world is increasing both due to the

International Journal of Education, Social Science & Humanities.
Finland Academic Research Science Publishers
ISSN: 2945-4492 (online) | (SJIF) = 7.502 Impact factor
Volume-11| Issue-6| 2023 Published: |22-06-2023|

establishment of cooperation between transplant and hematological centers, an increase in the number of transplant centers, and due to the expansion of indications for elderly patients due to the emergence of new low-intensity conditioning regimens. [29]. The clinical picture of acute leukemia is very variable and there is currently no clear understanding of the molecular genetic mechanisms involved in the clinical manifestation of the course of the disease. The process of oncogenesis includes pathological changes, both at the molecular and cellular levels, so leukemic clones are characterized by various disturbances in cellular homeostasis, as a result of destabilization of the genome structure and an imbalance in the processes of proliferation and apoptosis. The rapid development of studies on the role of apoptosis and proliferation in the development of malignant neoplasms stimulated the development of new therapeutic and diagnostic measures for diseases of the hematopoietic system [22,26].

Diagnosis of acute leukemia consists of two stages. The first of them (stage 1) is the determination of immature (blast) cells in the bone marrow punctate. If their number exceeds 20% of all nuclear cells in the sample, the patient has acute leukemia, otherwise the diagnosis of acute leukemia is excluded. The second stage (stage 2) is to determine whether the detected blast cells belong to one or another subtype of leukocytes and to determine the degree of their maturation. Depending on the nature of blast cells, acute leukemias are divided into lymphoblastic (ALL) and myeloid (AML), and each of these types is divided into subgroups depending on the stage of maturation of blast cells (T-ALL 1-4, B-ALL 1-4, OML M0-M7). This subgroup is actually a diagnosis according to the so-called. Franco-American-British (FAB) classification [31]. Despite the fact that the modern classification of leukemia takes into account the presence of various mutations, if it is impossible to conduct appropriate studies, the diagnosis according to the FAB classification allows, if necessary, to prescribe treatment. It is necessary to develop fundamentally new approaches to create multiparameter molecular diagnostics, which should become universally available for research groups and clinics [3].

Conclusion. Summarizing the above, it can be concluded that in the structure of the incidence of hemoblastoses the main significant factor in the pathogenesis of leukemia is the occurrence of mutations in genes.

Thus, the identification of molecular genetic changes in the tumor clone, as well as a comprehensive assessment of key signaling pathways in tumor cells, not only provides insight into the biology of the tumor, but also opens up new opportunities forpredicting the early development and treatment of the disease,

which will lead to a decrease in its relapses, complications and an increase in the quality of life of patients with AL.

BIBLIOGRAPHY

1. Alieva M.D., V.G. Polyakova, G.L. Mentkevich, S.A. Mayakova. – M.: Pediatric oncology. National leadership; ed. Publishing group RONTS, 2012. - 681 p.
2. Baranova, O.Yu. Possibilities of modern therapy of acute non-lymphoblastic leukemias in adults / O.Yu. Baranova, M.A. Volkova // Russian medical journal. - 2001. - V. 9, No. 22. - S. 999
3. Bogdanov, A.N. A case of acute lymphoblastic leukemia with t(9; 22) translocation and several additional rearrangements / A.N. Bogdanov, O.V. Sarzhevsky, S.N. Kolyubaeva // Hematology and transfusiology. - 2008. - No. 3. - S. 35-38.
4. Demidova, I.A. Using molecular biological methods to determine genetic disorders in myeloid leukemia and monitor minimal residual disease / I.A. Demidova // Oncohematology. - 2007. - No. 4. - S. 17-26.
5. Zaridze, D.G. Epidemiology of leukemia in children / D.G. Zaridze // Archive of Pathology. –1997. - T. 59, No. 5. - S. 65-70.
6. Zarubina K.I., 2021.
7. Omarova, K.O. Epidemiological features of acute myeloid leukemia in Kazakhstan [Electronic resource] / K.O. Omarova, Zh.B. Sauranbaeva // Ecology and health of children. - 2000. - Astana. - Access mode: http://pediatrics.med.kz/conf/2000/ec108.html
8. Rumyantseva A.G. - M .: A practical guide to childhood diseases. Hematology/oncology of childhood; ed. Medpraktika, 2002. - P.468.
9. Savchenko V.G., Parovichnikova E.N. Afanasiev B.V. "National clinical guidelines for the diagnosis and treatment of adult acute myeloid leukemia" Gematol. and transfusiol. Russia 2014 v56 №1
10. Saliev D. Dynamics of the spread of leukemia in Karakalpakstan and in five regions of Uzbekistan over the last two five-year periods (2001-2005 and 2006-2010) / D. Saliev, K.K. Saliev // Bulletin of Hematology. - 2014. - T. 10, No. 2. - S. 133-136.
11. Usenova A.A., - Bishkek 2016.- Article 8-9.
12. Khairoeva, N.A. Medico-statistical monitoring of acute leukemia in children of the Republic of Kazakhstan / N.A. Khairoeva: Author. diss. ... cand. honey. Sciences. - Almaty, 2010. - S. 9-10.

13. Khodzhieva G.B., M.K. Rakhmatov, J.M. Khasanov, K.Z. Urakov, 2018.

14. Chissova V.I., S.L. Daryalova. - M.: Publishing house "News", Selected lectures on clinical oncology: ed. 2000. - 256 p.

15. Fazoil I. A., Novichkova G. A., Kuznetsova S. A. "A method for the differential diagnosis of acute leukemia using a cell biochip" Russia 2017.12.18.

16. Arber DA et al., 2016.

17. Chan, GCF Current Status of Acute Lymphoblastic Leukaemia in Children / GCF Chan, CH Pui // J. Peadiatr. - 2003. - No. 8. - R. 170-183.

18. Comeaux EQ, 2017.

19. David, A. Rates and Trends of Pediatric Acute Lymphoblastic Leukemia - United States, 2001–2014 / A. David, S. Jane Henley, Lori A. Pollack, // Morbidity and Mortality Weekly Report. - 2017. - Vol. 66. - R. 950-954.

20. Descher, B. Acute myeloid leukemia: epidemiology and etiology / B. Descher, M. Lubbert // Cancer. - 2006. - No. 107. - R. 2099-2107.

21. Evangelisti C., A. Cappellini, M. Oliveira, 2021; R. Fragoso, J.T.Barata, A. Bertaina, 2019; F. Locatelli, 2020.

22. Francisco, G. Arg72Pro TP53 polymorphism and cancer susceptibility: a comprehensive meta-analysis of 302 case-control studies / G. Francisco, PR Menezes, J. Eluf-Neto et al. // Int. J. Cancer. - 2011. - Vol. 129, No. 4. - R. 920-930.

23. Groves FD, BTWatkins, DJRoberts, TCTucker, T. Shen, TJFlood, 2019).

24. Gusstafsson, G. Sex and other prognostic factors in acute lymphoblastic leukemia in childhood / G. Gusstafsson, A. Kreuger // The American J. of pediatric Hematology/oncology. - 1983. - Vol. 5. - R. 243-250.

25. Harrison C.J., 2019; H.Inaba, 2019.

26. Hellström A., D. Ley, I. Hansen-Pupp, B. Hallberg, 2018.

27. Holmfeldt L., Wei L., Diaz-Flores E., Walsh M., Zhang J., Ding L., et al. 2019; Hsiao MH, Yu AL, Yeargin J., Ku D., Haas M. 2020.

28. Jerchel IS, AQHoogkamer, IMAriës, EMSteeghs, 2020; JMBoer, NJBesselink, A.Boeree, 2021.

29. Swerdlow, S., Campo, E., Harris, N. L, Jaffe, ES, Pileri, SA, Stein, H., ... & Vardiman, JW (2008). WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues 4th Ed.

30. Tian, X. Association between TP53 Arg72Pro polymorphism and leukemia risk: a meta-analysis of 14 case-control studies / X. Tian, D. Shundong, S. Jing // Published online. - 2016. - Vol. 6, No. 3. - R. 1152.

31. Yeoh, EJ Classification, subtype discovery, and prediction of outcome in pediatric acute lymphoblastic leukemia by gene expression profiling / EJ Yeoh, ME Ross, SA Syurtleff et al. // Cancerctl. - 2002. - Vol. 1. - R. 133-143.