ISSN 2231-2218

ASIAN JOURNAL OF PHARMACEUTICAL AND BIOLOGICAL RESEARCH

AJPBR

Indexed by:

ROAD Crossref Universal Impact Factor IMPACT FACTOR SEARCH

Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/
Universal IMPACT factor 7
SJIF 2022: 4.465
Volume 12 Issue 3
SEP-DEC. 2023

Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/
Universal IMPACT factor 7
SJIF 2022: 4.465
Volume 12 Issue 3
SEP-DEC. 2023

FEATURES OF CYTOGENETIC DISORDERS IN ACUTE LEUKEMIA

EGAMOVA SITORA KOBILOVNA
Bukhara State Medical Institute. Bukhara, Uzbekistan

Abstract. Cytogenetic analysis in acute myeloid leukemia (AML) and acute lymphoblastic leukemia (ALL) revealed a large number of non-random chromosomal abnormalities. In many cases, molecular studies of these abnormalities have identified specific genes involved in the process of leukemogenesis. The most common chromosomal aberrations are associated with specific laboratory and clinical characteristics and are currently used as diagnostic and prognostic markers to help the clinician choose the most effective treatment. Specific chromosomal aberrations and their molecular analogs have been included in the World Health Organization classification of hematologic malignancies and, together with morphology, immunophenotype, and clinical features, are used to identify various forms of the disease. This review summarizes current views on the clinical relevance of key cytogenetic findings in AML and ALL in adults.

Keywords: acute leukemia, diagnostics, cytogenetics, chromosomal aberrations.

Standard cytogenetic analysis is of greatest importance for the diagnosis of tumors of the hematopoietic system, the development of which is based on genetic changes in the precursor cell - the hematopoietic stem cell. As a rule, cytogenetic changes are represented by mutations of chromosomes. These include:

- translocation - exchange of sections of non-homologous chromosomes;
- inversion – rotation of individual sections of a chromosome by 180°C;
- insertion - insertion of a nucleotide sequence into any part of the chromosome;
- deletion - loss of the end section of the chromosome (terminal) and the internal section chromosomes (intercalary);
- appearance of additional chromosomes, etc.

Chromosomal mutations lead to inhibition of differentiation, disruption of cell cycle regulation mechanisms and uncontrolled proliferation. Genetic rearrangements are detected using the cytogenetic method during microscopic examination of metaphase plates (1,3).

The metaphase plate is a special way of isolating and localizing chromosomes during the process of cell division, in which the chromosomes are aligned so that their centromeres are perpendicular to the plane of the chromosome arm. After differential staining of metaphase chromosomes, a cross-striation unique to each pair of

chromosomes appears. The most commonly used technique for differential chromosome staining is G-differential staining (G-bands, Giemsabands) with Giemsa or Wright stain. Chromosome coloration is examined using light microscopy. Differential coloring of chromosomes makes it possible to describe the karyotype completely and to detect diagnostic, variant and additional rearrangements of the chromosomal apparatus of the cell. Typically 20–25 metaphases are karyotyped. The main disadvantage of this method is the absence in some cases of mitoses or the low quality of metaphase plates. sequence of G-bands obtained by differential staining of each chromosome, a unified cytogenetic classification and nomenclature was created (“An
International System for Human Cytogenetic Nomenclature", ISCN), according to which the karyotype is described (3).

Taking into account cytogenetic classification and nomenclature, the short and long arms of a chromosome are designated by the letters p and q, respectively. Translocation is denoted by the letter, after which the numbers of aberrant chromosomes are indicated in the first brackets, and the segments of these chromosomes involved in the translocation are indicated in the second brackets. Inversion is denoted by inv, insertion by ins, deletion by del. The normal karyotype of a man when calculating the metaphases indicated in square brackets is 46XY[20], for women - 46XX[20]. When describing a pathological karyotype, indicate the number of mitoses with an altered and normal karyotype, if any. For example, karyotype 46XY,t(9;22)[19] /46XY[1] is a karyotype of a man with a Philadelphia chromosome (Ph chromosome) in 19 out of 20 calculated metaphases, which, in terms of 100 metaphases, means the presence of 95% of tumor cells (2,4,5).

To date, several dozen different chromosomal abnormalities characteristic of acute leukemia have been identified; mostly these are translocations. Among them there are those that are found almost exclusively in certain morphological forms, others in various forms (5,6).

Cytogenetic features of acute myeloblastic leukemia. Changes in the number of chromosomes (anuplody) or their structure(pseudodiploidy), or both together, is observed in 50% of cases of acute myeloid leukemia(6,7).The most common anomalies are trisomy 8, monosomy 7, trisomy 21, loss of the X or Y chromosome. When treating acute myeloid leukemia with chemotherapeutic agents, as well as when using radiation therapy, a characteristic feature is partial or complete loss of chromosome 5(3.4).The most common chromosomal abnormalities and translocations in acute myeloid leukemia are presented in Table. 1.

Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/
Universal IMPACT factor 7
SJIF 2022: 4.465
Volume 12 Issue 3
SEP-DEC. 2023

Table 1. The most common chromosomal abnormalities in acute myeloid leukemia.

Chromosomal abnormality	**Clinical correlations**
Loss or gain of chromosomes	
Deletion of part or all of chromosome 5 or 7	Observed in patients with de novo acute myeloid leukemia (usually M1 and M2), as well as in patients treated with chemotherapy or radiation therapy, the prognosis is poor.
Trisomy 8	Characteristic of all types of acute myeloid leukemia, the prognosis is poor.
Trisomy 21	Most typical for types of acute myeloid leukemia M1, M7.
Trisomy13	Characteristic of biphenotypic leukemias
Monosomy 7	Observed in M2, M4, M5 variants of acute myeloid leukemia
Deletion (11)	Observed with options M5, M4, M2
Translocations	
t(8;21)	Present in 10% of patients with acute myeloid leukemia (more often with M2, M4 variants), in half of the cases it is combined with the loss of the Y chromosome in men or the X chromosome in women. High incidence of granulocytic sarcoma.
t(15;17)	It is observed in more than 70% of patients with acute promyelocytic leukemia, and the location of the retinoic acid receptor genes is disrupted; the prognosis is better.
t(9;22)	Present in 4% of patients with acute myeloid leukemia (usually with variant M1)

t(4;11)	Associated with acute monocytic leukemia (M5), especially common in children.
t(6; 9)	It is observed in 0.5% of patients with acute myeloid leukemia (variant M, M2, MJ, with an increased number of basophils in the bone marrow, and a poor response to treatment is typical.
t(6; 11) t(9; 11) t(11;17) t(11; 19)	Associated with acute monocytic leukemia; 11 q23 translocations are more common in children, characterized by a poor prognosis and disruption of the location of the MLL gene
Other structural abnormalities	
ιηv(16)(ρ13:q22); del(16)(q22);t(16:16)(p13:q22)t(8-16)(q11: q22)	Observed in acute myeloid leukemia with an increased number of eosinophils in the bone marrow

t(15;17)(q22;q21). The translocation is specific to acute promyelocytic leukemia (APL), in which it is observed in almost all cases (90-95%). The frequency of promyelocytic leukemia (ML) itself varies greatly in different regions of the world, ranging from 5 to 50% of all AML(1,2).Translocation t(15;17) was not detected in any hemoblastosis, except for APL and promyelocytic blast crisis CML. This translocation leads to the formation of a chimeric gene due to the fusion of a fragment of the PML gene from chromosome 15 with a fragment of the gene encoding the α-retinoic acid receptor (RARA) from chromosome 17(7.8).

Sometimes difficulties arise in the differential diagnosis between FAB variants M2 and M3 or M4. A standard cytogenetic study helps clarify the diagnosis, and in cases where the t(15;17) translocation cannot be detected, the diagnosis should be clarified using FISH or PCR(8,9).In addition, antibodies have now been developed to distinguish the MZ variant from other types of AML.

t(8;21)(q22;q22). Translocation is typical for the M2 variant and is very rarely observed for the M2 variant and is very rarely observed with M1, M4, M5. American researchers identify 6 morphological features of bone marrow cells, the combination of which is characteristic of AML with t(8;21) in contrast to myeloblastic leukemia

with other specific karyotype changes. In addition, with this anomaly, an increased content of eosinophils in the bone marrow is often observed.

Molecular genetic studies have shown that at t(8;21), breaks occur in two genes ETO (chromosome 8) and AML1 (chromosome 21). When the resulting DNA fragments merge, a chimeric gene is formed on chromosome 8: AML1-ETO. The products of this gene - RNA and protein - can be detected in 100% of patients(4.5).

inv(16)(p13;q22) and t(16;16)(p13;q22) These karyotype changes are characteristic of acute myelomonoblastic leukemia: M4Eo and M4, where they are detected with a frequency of 100% and 40%, respectively. Moreover, we are usually talking about inversion of chromosome 16, translocation t(16;16) is a much rarer anomaly. It is necessary to emphasize the close connection between the presence of inversion of chromosome 16 and the presence of abnormal eosinophils in the bone marrow, even in small numbers. In other words: the mentioned chromosomal rearrangements are found occasionally in various other morphological variants of AML (not only M4Eo and M4), however, almost all cases with inversion of chromosome 16 are characterized by the presence of abnormal eosinophils. The median survival for patients with inv(16) and t(16;16) was 18 months, and with the most intensive therapy - 27 months; 14% of patients were alive after 4 years from the start of treatment. Currently, the results of treatment of this form have improved significantly: complete remissions are achieved in 90%, and the median survival is 77 months.

t{3;3)(q21;q26) and inv(3)(q21q26). These chromosomal abnormalities are characteristic of AML and myelodysplasias, which occur with a unique clinical and hematological picture: increased than in patients with t(10;11).

Currently, it is recommended to perform a karyotype study in every patient with AML, since non-random chromosomal abnormalities have an independent prognostic value. At the same time, it is clear that each group of leukemias with identical karyotype changes is heterogeneous. In a group with a relatively good prognosis, the proportion of patients who live more than 5 years is significantly higher than in a group with a poor prognosis, but not all patients in each group will have the same life expectancy with the same type of treatment. For example, only 70-80% of patients with myeloid leukemia and the t(8;21) translocation survive the 5-year mark, but every the patient from the remaining 30% may live significantly less. All of the above is intended to emphasize the idea of the relative importance of cytogenetic prognosis in each specific case. On the other hand, the results of chromosomal analysis are very important when assessing the effectiveness of new therapeutic protocols, since the

Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/
Universal IMPACT factor 7
SJIF 2022: 4.465
Volume 12 Issue 3
SEP-DEC. 2023
cytogenetic characteristics of the group give an idea of the proportion of cases with a favorable and unfavorable prognosis (6,7).

Cytogenetic features of acute B-cell lymphoblastic leukemia. Cytogenetic studies reveal various chromosomal abnormalities in acute lymphoblastic leukemia. When analyzing the karyotype, pseudodiploidy may be detected (46 chromosomes with structural abnormalities, most often translocations). Hyperdiploidy, group I (from 47 to 50 chromosomes), hyperdiploidy group I (more than 50 chromosomes), hypodiploidy is not typical for acute lymphoblastic leukemia. Hyperdiploidy is most often detected in children.

With pre-B-ALL and much less often with pre-B-ALL. Translocations are very characteristic of ALL. Specific translocations are t(8;14) (in patients with B-cell ALL with morphological type) L3 with surface immunoglobulin); t(9;22) or Philadelphia chromosome; t(4;11); observed in pre-B-ALL). Translocation 1(4; 11) is most often observed in power cells with lymphoid and myeloid markers. The most important chromosomal abnormality in ALL is the t(9;22) translocation producing the chimeric BCR-ABL gene. With this translocation, the ABL gene moves from chromosome 9 to the breakpoint cluster region of chromosome 22. As a result, one of two abnormal protein kinases is synthesized - p210 or ρ 190. The p210 type is more common in chronic lymphocytic leukemia, and the p190 type is more common with ALL. Most often, t(9;22) is observed in patients with ALL, whose blasts have the CALL (CDIO) antigen. Characteristic common translocation for B-cell lymphocytic leukemia and Burkitt lymphoma for B-cell lymphocytic leukemia and Burkitt's lymphoma is t(8;14) (q24;q32), often t(2;8) (p11-13;q24) and t(8;22) (q24;q11).

The t(5;14) (q31;q32) translocation is often observed in B-ALL in combination with eosinophilia. This translocation is of great interest, as it causes changes in the immunoglobulin heavy chain and interleukin-3 genes. Assumed to be uncontrollable This cell growth is the result of activation of the interleukin-3 gene. Table 2 summarizes the most common chromosomal abnormalities in ALL.

Table. 2. The most characteristic chromosomal abnormalities in acute B-cell lymphoblastic leukemia.

Immunophenotype	Chromosomal abnormality	Genes involved in the pathological process
V-ALL	t(4;11)(q21;q23) t(5;14)(q31;q32) t(8;14) (q24;q32)	 IL3,Igh c-myc, Igh

Asian journal of Pharmaceutical and biological research 2231-2218
http://www.ajpbr.org/
Universal IMPACT factor 7
SJIF 2022: 4.465
Volume 12 Issue 3
SEP-DEC. 2023

Pre-V-ALL	t(2;8) (p1l;q24) t(8;22)(q24;q11) t(1;19)(q23;p13)	c-myc, Igκ c-myc, Igλ Prt, E2A

Note:*IL3—interleukin 3; Igh—immunoglobulin heavy chain; k and λ - light chains of immunoglobulins.*

Cytogenetic features of acute T-cell lymphoblastic leukemia. In patients with acute T-cell lymphoblastic leukemia Various chromosomal translocations have been identified that affect the T-cell receptor genes, consisting of α-, β-, γ-, δ-subunits. The most characteristic is damage to chromosome 14q11 of the α/β chain of the T-cell receptor. Translocation t(l;14) (p13;q11) occurs in approximately 25%, at(1;14) (p34;q11) - in 3% of children with the T-cell variant of acute lymphoblastic leukemia. Damage in chromosome 7(q32-q36), at the f region of the T-cell receptor β-subunit gene, is often observed in T-cell ALL, but not in β-cell ALL. Breakpoints in the t(10;14) (q24;q11) translocations damage the T-cell receptor α subunit and terminal deoxynucleotidyl transferase (TdT) genes. The most typical chromosomal abnormalities in T-cell lymphoblastic leukemia are presented in Table 3.

Table.3. Characteristic chromosomal abnormalities in T-cell acute lymphoblastic leukemia.

Chromosomal abnormalities	**Genes involved in the pathological process**
t(11,14)(p13,q11)	tcl-2,TCRa
t(1,14)(p34,q11)	TCRac-myc,TCRa
t(8,14) (q24,q11)	tcl-3,TCRa
t(10,14)(q24,q11)	TCRa
t(1,14) (p32,q11)	TCRa
t(14,14)(q11,q32)	TCRβ
t(7,9) (q35,q34)	TCRp
t(7,14)(q35-36,q11)	TCRγ
t(7,7)(p15,q11)	TCRγ
t(7,14)(p15,q11)	TCRa, tcl-1
inv(14) (q11,q32)	

Designations: TCRa, β, γ - genes of T-cell receptor subunits.

In various immunophenotypic variants of acute lymphoblastic leukemia, in 10% of cases, a deletion of the short arm of chromosome 9 is observed involving sections

p21 and 22. The α- and β 1-interferon genes are localized in this region. This deletion results in the loss of a tumor suppressor gene, which may be the interferon gene (7,5).

The most well-known specific abnormalities in ALL are the following:
t(9;22)(q34;q11). Translocation is observed in 20-30% of adults and 5-10% of children with ALL. With standard cytogenetic analysis, the translocation between chromosomes 9 and 22 in ALL is indistinguishable from that in CML. At the molecular level, in approximately half of the cases in adults and in 20% of children, the changes are the same as in CML; in other patients, the break in chromosome 22 (BCR gene) is located closer to the centromere. The resulting chimeric protein is P190 BCR/ABL has higher protein kinase activity than P210 BCR/ABL, characteristic of CML (2.8)
t(1;14)(p32-34;q11). A relatively rare translocation characteristic of T-cell ALL. At the molecular level, the formation of a chimeric gene from fragments of two genes was discovered - the T-cell receptor gene (localized in 14q11) and the TAL(1p32) gene. Interestingly, the TAL gene is expressed only in leukemic, but not in normal lymphoid progenitor cells. It has been established that in approximately 5-25% of cases with T-cell acute leukemia, interstitial deletions occur in the short arm of chromosome 1, as a result of which the 5th end of the TAL gene is connected to another gene - SCL, located closer to the centromere than the TAL gene. As a result, the chimeric SCL-TAL gene is formed. In all these cases, as well as in t(1;14), the TAL gene is activated. Such leukemias have a relatively favorable course: 3-year survival rate is 60-70%.
t(4;11)(q21 ;q23). A specific chromosomal translocation that can be detected in various types of acute leukemia. Most often it occurs in ALL and biphenotypic ALL. This translocation is most typical for children under 1 year of age (more than 50% of the total number of ALL); in leukemia in infants up to six months, it is found even more often, and in children older than one year and in adults with ALL, its frequency is 10-15%. At the molecular level, this translocation revealed breaks in the MLL (11q23) and AF4 (4q21) genes. When the resulting fragments merge, chimeric genes are formed. It is generally accepted that the chimeric gene formed on chromosome 11 plays a decisive role in the development of leukemia. Currently, very sensitive molecular probes have been developed that can detect almost all MLL gene rearrangements. Leukemias with the t(4;11) translocation or other translocations involving the chromosomal region 11q23 (MLL gene) are characterized by high leukocytosis and have extremely unfavorable prognosis. In adult patients, the prognosis is almost the same as with Ph-translocation; in children under one year of

age, it is even worse. The worst prognosis is observed in infants under six months of age, in whom acute leukemia occurs with t(4;11). Thus, the median relapse-free course of treatment monitoring is not an absolutely independent diagnostic criterion. It should be used in conjunction with other clinical and laboratory tests (3.6).

The importance of cytogenetic diagnosis of tumors of hematopoietic tissue is due to the specific and prognostic nature of a number of chromosomal abnormalities. The specific nature of cytogenetic abnormalities means the predominant or absolute combination of the anomaly with a certain immunophenotype of tumor cells. For example: t(9;22) is an absolute criterion for chronic myeloid leukemia, t(15;17) is for acute promyelocytic leukemia. Today, the most reliable prognostic value in relation to the curability (curability) of acute leukemia is precisely the cytogenetic abnormalities that underlie acute leukemia and relate to anomalies of a favorable, intermediate and unfavorable prognosis.

Conclusion. The karyotype is critical for the evaluation of acute leukemia at diagnosis. Cytogenetic abnormalities found in acute leukemia are one of the strongest independent prognostic factors. This influences the choice of treatment in clinical trials. All chromosomes can be targeted; common chromosomal abnormalities are recurrent and can be associated with a well-defined cytological type. In 40% of cases the karyotype is normal and should be associated with molecular biology studies that can clarify the prognosis. The usefulness of the karyotype is more limited during patient follow-up due to its limited sensitivity, but it is still useful in the clinical management of relapse.

REFERENCES.

1. Arber DA, Borowitz MJ, Cessna M, et al. Initial diagnostic workup of acute leukemia: guideline from the College of American Pathologists and the American Society of Hematology // Arch Pathol Lab Med. 2017. 141:1342–1393.
2. Döhner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel // Blood. 2017. 129:424–447
3. Egamova SK Algoritm for the diagnosis of acute leukemia // British medical journal. London, 2021.-№2. R.160-174.
4. Egamova SK, Boboev KT A case of acute lymphoblastic leukemia with translocation t(1;7)(q41;p22), t(4;12)(q34;q23), +mar. British medical journal. London, 2022.-№1. R.273-277.
5. Egamova SK, Boboev KT Prognostic significance of genetic mutations in patients with acute leukemia. NeuroQuantology, 2022.- Volume 20. P.1093-1097

6. Egamova SKCytogenetically normal acute myeloid leukemia.Asian journal of Pharmaceutical and biological research.No. 12 (1). R.118-121

7. Egamova SK Significance of standard cytogenetic analysis in the diagnosis of acute leukemia.Asian journal of Pharmaceutical and biological research.No. 12 (2). R.208-213

8. Papaemmanuil E, Gerstung M, Bullinger L, et al. Genomic classification and prognosis in acute myeloid leukemia // N Engl J Med. 2016. 374:2209–2221.

9. Walter RB, Othus M, Burnett AK, et al. Resistance prediction in AML: analysis of 4601 patients from MRC/ NCRI, HOVON/SAKK, SWOG and MD Anderson Cancer Center // Leukemia.2015. 29:312–320.