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# THE ROLE OF CLINICAL-HEMATOLOGICAL AND CYTOGENETIC CHARACTERISTICS IN THE PROGRAM THERAPY OF B-CELL LEUKEMIA IN CHILDREN IN THE REPUBLIC OF KAZAKHSTAN

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## ABSTRACT

***Relevance:*** *The study of immunological and molecular genetic characteristics of leukemia in children and the influence of biological features of the tumor population of acute B-cell lymphoblastic leukemia (B-ALL) on the effectiveness of therapy is particularly relevant for the Republic of Kazakhstan.*

***The study aimed to*** *evaluate the effectiveness of modern program chemotherapy in children depending on the biological characteristics of B-cell leukemias.*

***Methods:*** *The study analyzed the data of 154 children aged six months to 15 years with primary B-ALL on inpatient treatment at the Scientific Center of Pediatrics and Pediatric Surgery JSC (Almaty, the Republic of Kazakhstan) in 2016-2018. When determining events, we were guided by the criteria of the protocols of the ALL-BFM group.*

***Results:*** *The age groups most exposed to B-ALL were 3-7 years old (43.5%), reflecting the so-called infant peak. In the clinical picture of this type of ALL, intoxication syndrome accompanying the period of manifestation was present in 75.3% of patients. The clinical polymorphism of the debut period determined the most diverse list of diagnoses of "masks." Damage to organs and systems, in the form of liver failure, was detected in 41 (26.6%) children, with the development of respiratory failure in 12 (7.8%), cardiovascular failure in 5 patients (3.2%), acute kidney injury in 3 (1.9%), CNS damage in 5 (3.2%) patients. With B-ALL, the distribution of immunological variants was determined as follows: B1 – 9 (5.8%), B2 – 123 (79.8%), B3 – 18 (11,7%), B4 – 4 (2,6%) and leukemia of B-cell lymphoma was noted in one (0.6%) patient. From the group of quantitative anomalies, hyperploidy was detected in 12 (7.8%) cases. Among qualitative anomalies, t(12;21) (p13;q22) was determined in 6 (3.9%) patients and was a favorable prognostic factor (remission was recorded). Trisomy of chromosome 21 with Down syndrome in 3 (1.9%) patients with combined anomalies (isochromosome 7, trisomy 4, 6, 15, 17, translocation t(9; 22) (q34;q11) was detected in 1.3%. Translocations t(1;19)(q23;p13.3) in 5.8% and del 9-chromosome defect in 3.2% of cases.*

***Conclusion:*** *The response to therapy and long-term prognosis are largely determined by biological factors such as cytogenetic features of the tumor, sensitivity to prednisone, as well as the degree of aggressiveness, which manifests itself in the form of pronounced symptoms of lymphoproliferation and hyperleukocytosis. The research has shown the high efficiency of modern ALL-BFM program therapy in children.*

***Keywords:*** *children, acute B-cell lymphoblastic leukemia, blast cells, immunophenotyping, cytogenetic study.*

***Introduction:*** Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer [1]. ALL means a heterogeneous group of hematological malignancies characterized by abnormal proliferation of immature lymphoid cells. It is the most commonly diagnosed childhood cancer, with an almost 80% cure rate. Despite favorable survival rates in pediatric population, some patients develop resistance to therapy, relapse of the disease, and clonal evolution of cells, which determines a poor prognosis of the disease.

Leukemia is caused by abnormal changes in the lymphoid lineage of blood cells that can affect the bone marrow, blood, and extramedullary sites, causing bone and joint pain, fatigue and weakness, swollen lymph nodes, pale skin, easy bleeding or bruising, fever, or infection.

The currently used classification system for hemoblastoses is based on a combined analysis of clinical and biological data (cytology, immunophenotype, and cell cytogenetics) [2, 3]. ALL can be classified into acute B-cell lymphoblastic leukemia (B-ALL) (85% of cases) and T-ALL types. An oncological lineage of mature B cells indicates a rapidly growing Burkitt's lymphoma or acute leukemia from B cell progenitors [4].

Recent advances in molecular biology and new technologies resulted in a significantly better understanding of ALL pathophysiology. In some patients, environmental risk factors interacted with hereditary genetic susceptibility. Chromosomal and genetic anomalies play a significant role in the pathological differentiation and proliferation of lymphoid precursor cells. New findings

in molecular genetics, pharmacology, and related fields shall change the B-ALL diagnostics and treatment [5]. The intensive development of next-generation sequencing in the last decade has expanded the study of genomic changes. New technologies allowed detecting molecular changes such as point mutations and characterizing epigenetic or proteomic profiles. Newly researched subtypes of this disease are characterized by genetic changes, including changes in chromosomes, sequence mutations, and changes in the number of DNA copies. These genetic abnormalities are used as diagnostic, prognostic, and predictive disease biomarkers.

Next-generation sequencing during leukemogenesis has proven the B-ALL heterogeneity. This emphasizes the diversity of the pathogenesis of a malignant clone, predetermines the nature of the clinical course of the tumor, differences in susceptibility or resistance to chemotherapy, and opens up prospects for targeted treatment [6].

Thus, the pronounced heterogeneity of the studied pathology attaches great importance to diagnosing molecular genetic changes in patients for the prognosis of the tumor process [7]. The analysis of these studies is important for understanding the theoretical foundations of the development of leukemia, optimizing the results of tumor pathology chemotherapy by establishing a linear affiliation, the stage of cell maturity, accurately determining the variant of leukemia, and stratifying into program risk groups [8, 9].

***Materials and Methods:*** A retrospective analysis of the case histories of 154 children aged six months to 15 years with primary B-ALL who were hospitalized at the Scientific Center of Pediatrics and Pediatric Surgery JSC (Almaty, Kazakhstan) in 2016-2018 was carried out. The analysis of clinical and laboratory data and the dependence of the response to therapy on the level of leukocytosis, lymphoproliferative syndrome (LPS), cytogenetic changes, and completeness of the response to the cytoreduction phase with prednisolone was performed. The effectiveness of specialized therapy was measured by 5-year event-free survival (EFS) and overall survival (OS) calculated using the Kaplan-Meier method. The therapy results were assessed by the number of patients who achieved complete remission and are in complete long-term remission, as well as by the number of induction deaths and deaths in remission. The minimum follow-up period for the entire group of patients with ALL was 23 months.

***Results:*** The age and gender analysis of patients showed the boys-to-girls ratio in the B-ALL group of 1.16:1 (53.8%, n=83: 46.1%, n=71). Most children with B-ALL were 3-7 years old (43.5%, n=67) or below three years (22.7%, n=35). This corresponds to the so-called infant peak noted by other researchers [10, 11]. Children of the older age groups, 7-10 and 10-15 years old, accounted for 15.6%, respectively. The nationality analysis revealed a significant predominance of children of Kazakh nationality – 77.9%. Representatives of Slavic peoples were second in terms of incidence and accounted for 20.8% of cases.

Clinically, in 75.3% of patients with B-ALL, the intoxication syndrome during the period of manifestation was manifested by weakness, lethargy, hypodynamia, asthenia, fever from subfebrile to febrile values, sweating, and weight loss. The disease manifestation was due to the multiplication and accumulation of blast cells. Exceeding the conditional threshold limit (more than 1000 billion) of blast cells leads to the depletion of the body's compensatory capabilities depending on the degree of hematopoiesis suppression and the intensity of manifestations outside the bone marrow [10, 11]. This was confirmed by the length of the period from the onset of the first symptoms to the diagnosis (Figure 1).

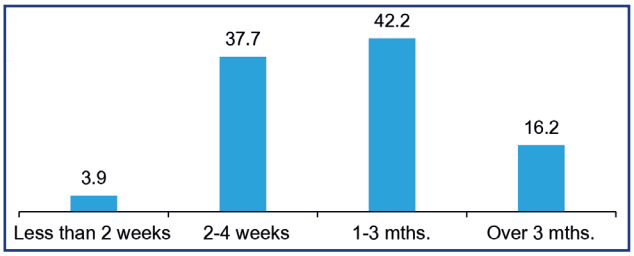


Figure 1 - Duration of the disease before diagnosis in children with B-ALL (%)

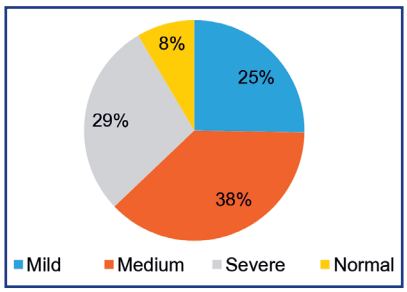


Figure 2 - Anemia levels in children with B-ALL (%)

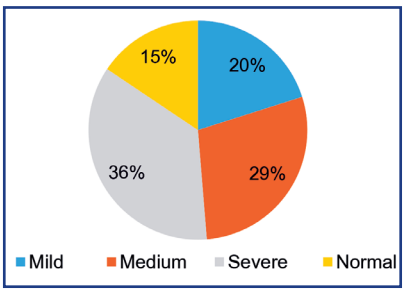


Figure 3 - Thrombocytopenia levels in children with B-ALL (%)

The severity of the anemic syndrome is shown in Figure 2. In 75% of cases, hemorrhagic syndrome of varying severity was observed due to thrombocytopenia (Figure 3).

The level of leukocytes in the blood was normal in 30 (5%) cases; =14), leukocytosis over 100x10$^9$/l – in 4.5% (n=7), leukopenia – in 26.6% (n=41) of patients. Blastemia, regardless of the total number of leukocytes, was observed in 87% of patients.

The analysis of EFS and OS in all five groups (Figures 4-8) showed high survival rates in children in groups with leukocytosis up to 50 thousand cells per µl (OS – 85.6±5.5, EFS – 83.3±5.8), as well as with normal (OS – 74.5±6.3, EFS – 74.5±6.3) and low levels of leukocytes (OS – 85.4±5.5, EFS – 82.1±6.2), and a significantly lower survival rate, especially EFS, in children with initial hyperleukocytosis (OS – 42.9±18.7, EFS – 28.6±17.1). At the same time, this statistically unreliable indicator difference was most likely due to a statistically unrepresentative sample of patient groups.

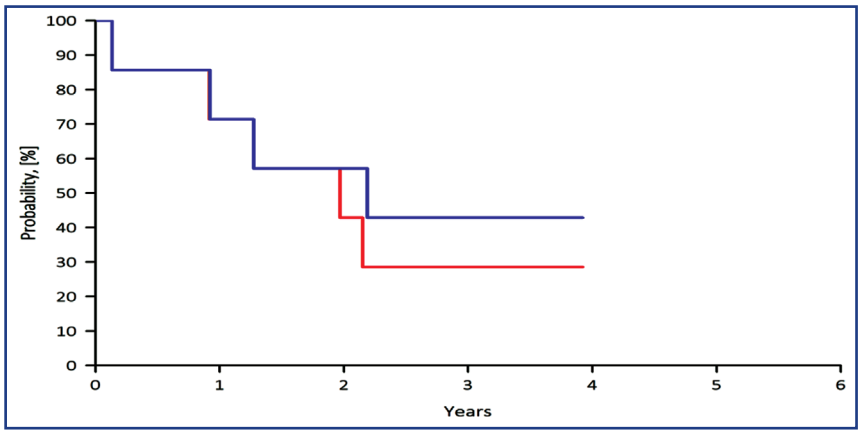


Figure 4 – EFS and OS of children with hyperleukocytosis (over 100,000/L)
(n=7, OS – 42.9±18.7%, EFS – 28.6±17.1%)

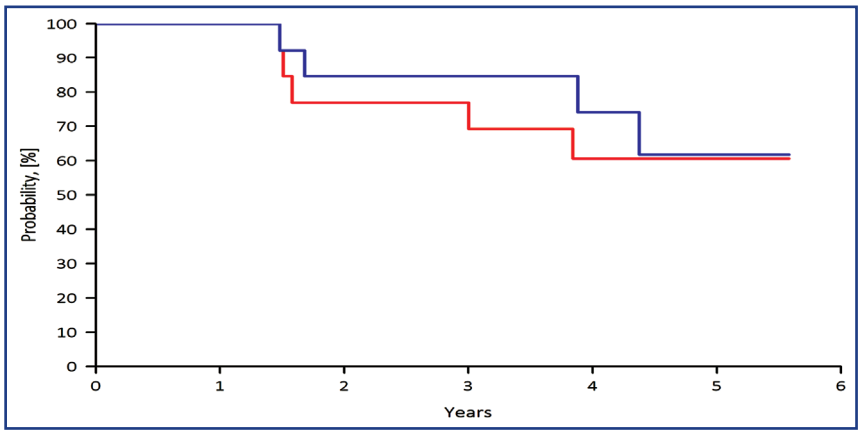


Figure 5 - EFS and OS of children with hyperleukocytosis (50-99,900/L)
(n=13, OS – 61.7±15.7%, EFS – 60.6±13.8%)

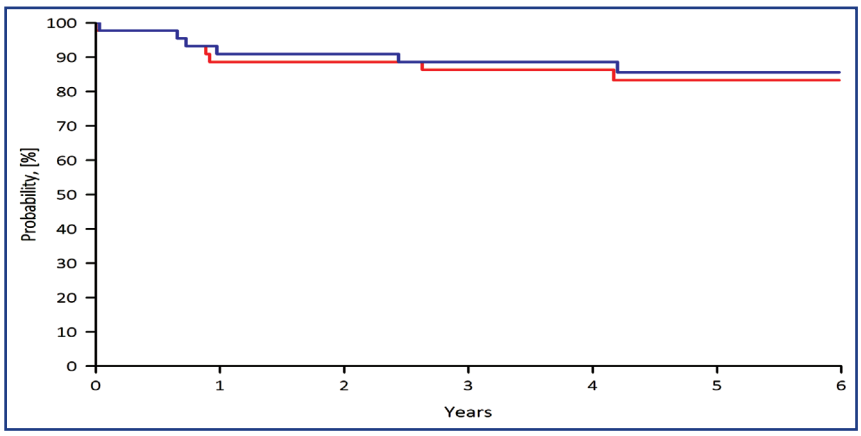


Figure 6 – EFS and OS of children with leukocytosis (up to 49,9000/L)
(n=45, OS – 85.6±5.5%, EFS – 83.3±5.8%)

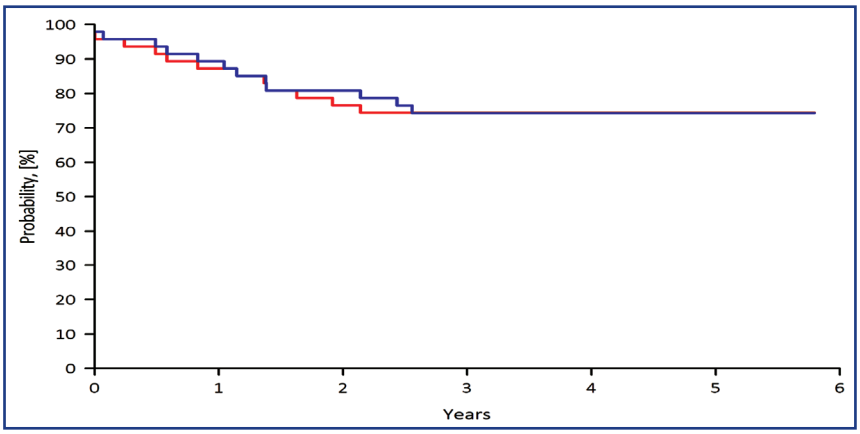


Figure 7 - EFS and OS in children with normal leukocyte levels
(n=47, OS – 74.5±6.3%, EFS – 74.5±6.3%)

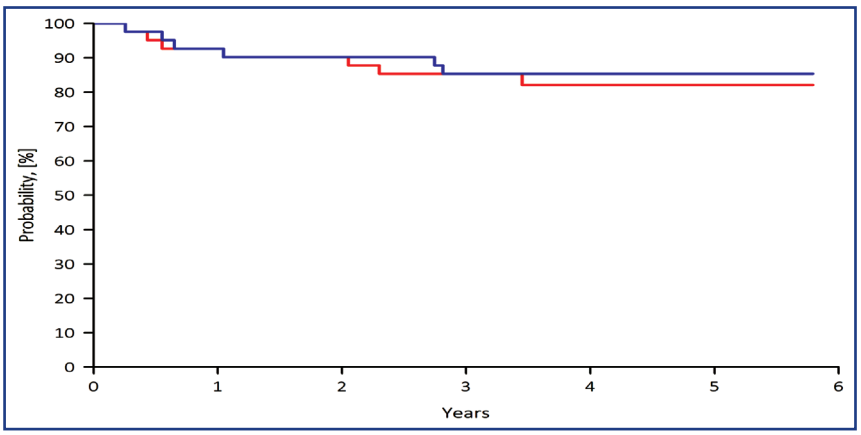


Figure 8 - EFS and OS in children with leukopenia
(n=41, OS – 85.4±5.5%, EFS – 82.1±6.2%)

LPS, one of the typical symptoms of this disease in children, was determined in 75.3% of cases. A comparison of survival rates showed a relatively worse survival prognosis in children with various manifestations of hyperplastic syndrome (Fig. 9 & 10).

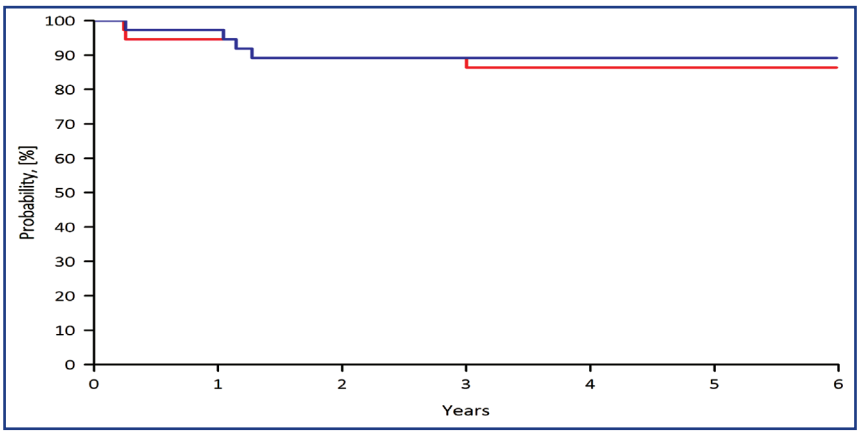


Figure 9 – EFS and OS in children without LPS
(n=37, OS – 89.2±5.1%, EFS – 86.4±5.6%)

Various mask diagnoses manifested clinically in the debut period (such as SARS, pneumonia, tonsillitis, otitis media, infectious mononucleosis, arthritis, mumps, lymphadenitis, stomatitis, hepatitis, and cholecystitis) challenged the diagnosis.

The cytomorphological study revealed the following B-ALL variants: L1 – 41 (26.7%), L1-L2 – two cases (1.3%), L2 – 107 (69.5%), and L3 – four cases (2.6%).

In our study, in all cases of B-linear leukemia, blast cells expressed CD19 and/or CD79a and/or cytoplasmic

CD22 and stem cell marker CD34, as well as differentiation clusters CD33 and CD41. In total, the B-ALL immunological variants determined by a set of line-associated markers of the differentiation stage included B1 in nine cases (5.8%), B2 – 123 (79.8%), B3 – 18 (11.7%), and B4 – in 3 cases (1.9%). Leukemization of B-cell lymphoma was noted in one (0.6%) patient.

At present, cytogenetic and molecular genetic studies are widely used to diagnose blood cancers. The cytometric DNA index is a quantitative indicator of chromosomal anomalies in tumor cells. Chromosomal translocations that determine ALL subvariants usually occur first, followed by point mutations and deletions acquired due to clonal evolution. A cytogenetic study of bone marrow blast cells revealed chromosomal anomalies in 58 (37.6%) patients. See Table 1 for cytogenetic test results and the most common chromosomal anomalies detected in the study participants.

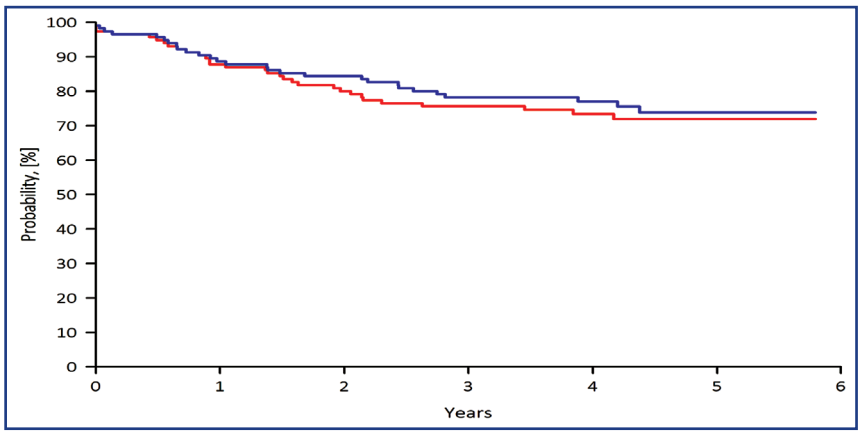


Figure 10 – EFS and OS in children with HFRS
(n=116, OS – 73.9±4.4%, EFS – 72.0±4.3%)

**Table 1 – Chromosomal anomalies in patients with B-ALL**

| Anomalies | Number of patients (abs. /%) | Concomitant anomalies |
|---|---|---|
| Translocation t(12; 21)(p13; q22) | 6/3.9% | + ETV / RUNX 1 - 4, + RTV / RUNX ! - 1 |
| Hyperploid karyotype | 12/7.8% | |
| C - MYC | 2/1.3% | +t(8;14)(q24;q32) – 1 |
| MLL | 5/3.2% | |
| Translocation t(1;19)(q23;p13) | 9/5.8% | |
| Translocation t(9;22)(q34;q11) | 2/1.3% | (+ t (7;12)(q36;p13), chromosome 12 monosomy – 1) |
| Trisomy of 21st chromosome | 3/1.9% | (+ additional isochromosome 7, |
| Deletion of chromosome 9 | 5/3.2% | (+ t(4;11)(q21;q23) t(5;12) (q33; p13) – 1, + monosomy of chromosome 20 – 1, + monosomy of chromosome 7 – 1, + t (9;22) ( q34 ;q11) – 1) |
| Single cases of anomalies | + concomitant anomalies | |
| Translocation t(14;15)(q32;q11) | | |
| Translocation t(9;17)(p13;p12) | | |
| Translocation t(1;19)(q23;p13) | isochromosome 9 | |
| Translocation t(2;11)(p21;q23)MDS | trisomy 8 | |
| Trisomy of 7th chromosome | isochromosome 7 | |
| Karyotype 45, xx | monosomy on chromosome 20 | |
| Translocation t(4;11)(q21;q23) | extra X chromosome | 48 XY, + der (4) |
| Karyotype 45, XY | Translocation t(12;13) (p13;q12) | |
| Karyotype 46, XY | Translocation t(12;20) (q13;p11.2) | add (22 q ) ETV 6/ RUNX 1 |
| The (1;18)(q10;q10) translocation in 60% of cells | Translocation t(1;18;22) was detected in 10% of cells | |
| Translocation t(3;6)(p21;q15). | | |
| Translocation t(8;11)(p11;p15) | | |
| Translocation (t(8;14), t(8;22), | Duplication of the q-arm of the 1st chromosome | |
| Rob (14;14) (q10:q10) | | |

Among quantitative anomalies, hyperploidy (additional chromosomes 4,10,17) was detected in 12 (7.8%) cases. All these patients showed an early response to therapy and preserved remission to date; no relapses were recorded.

Translocations mean the exchange of genetic material between chromosomes [4, 10]. The most common examples of such translocations are t(12;21)(p13; q22) with the TEL-AML hybrid gene and t(9;22) translocation with the BCR-ABL chimeric gene. In B-ALL, chromosomal rearrangements t(8;14)(q24.1;q32) transfer the MYC oncogene under the control of regulatory elements in the IGH locus [10].

The identified translocations from the group of qualitative anomalies were distributed among patients inhomogeneously (Table 1). Thus, in our study, t(12;21) translocation detected in 6 (3.9%) patients was a favorable prognostic factor. All six patients were in remission during treatment.

Three (1.9%) patients with a hereditary burden (Down's syndrome) had a trisomy of 21st chromosome with concomitant anomalies including an additional isochromosome 7 and trisomy 4, 6, 15, and 17.

The Philadelphia chromosome t(9;22)(q34;q11) was found in two (1.3%) patients.

In our study, nine (5.8%) patients had a t(1;19)(q23;p13.3) translocation. In children with ALL, this cytogenetic marker is associated with a high risk of recurrence with CNS damage. This group of patients achieved remission and preserved it to the present. One patient died during consolidating therapy from infectious complications.

A deletion of chromosome 9 was registered in 5 (3.2%) cases. One patient died from a relapse; another was continuing polychemotherapy at the time of the study. The group of single random rearrangements, also presented in Table 1, includes changes with no diagnostic value and those requiring further study of their significance for treatment and prognosis.

In recent decades, the introduction of chemotherapy protocols for ALL in children resulted in a significantly higher curability of many patients. Traditional chemotherapy consists of four important phases: remission induction, consolidation, reinduction (delayed intensification), and continuation (maintenance). Steroids, vincristine, L-asparaginase, cytarabine, methotrexate, and 6-mercaptopurine are prescribed based on stratified risk classification. Multidrug pediatric chemotherapy for ALL is performed in various combinations and sequences depending on the treatment protocol. An analysis of the association between the initial clinical and laboratory data and long-term treatment outcomes brought the researchers to the idea of biological heterogeneity of the disease and possible identification of initial characteristics of the so-called risk groups of patients characterized by different probabilities of remission against similar therapy. This induced the concept of risk-adapted therapy when the therapy intensity and toxicity should correspond to the risk group. In other words, patients with a favorable prognostic baseline should receive the least toxic therapy and not be at risk of developing severe complications due to high doses or a combination of chemotherapy drugs. In contrast, patients with initially unfavorable forms of the disease should receive high-dose therapy, increasing the chances for recovery [2, 6].

The risk profiling of patients for different therapy protocols takes into account such initial parameters as initial leukocytosis, blast cell immunophenotype, and early response to therapy. This grouping is also used to assess complex parameters such as the specific genotype of leukemic cells and the kinetics of the disappearance of the residual tumor population. Therefore, modern diagnostics shall include cyto- and molecular-genetic testing [14].

In our study, the following risk groups were identified according to the BFM group protocols [15]: standard risk – 140 (90.9%) children and high risk – 14 (9%) patients. Early response to therapy was assessed on Day 8 of prednisolone monotherapy by reducing blast cells in the peripheral blood. The absolute number of blast cells was below 1,000 in 136 (88.3%), over 1,000 – in 12 (7.8%) patients, and unknown in 6 (3.9%) children. Patients with less than 1,000 blasts/1 μL formed a group of good response (prednisone good response, PGR) (Figure 11), with more than 1,000 blasts/1 μL – a group of poor response ( prednisone poor response, PPR) (Figure 12).

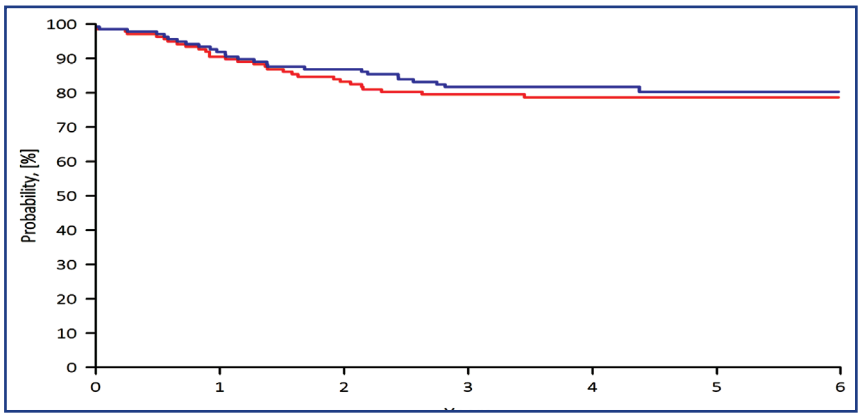


Figure 11 – EFS and OS in patients with a good response to prednisolone (n=136, OS – 80.3±3.5%, EFS – 78.7±3.5%)

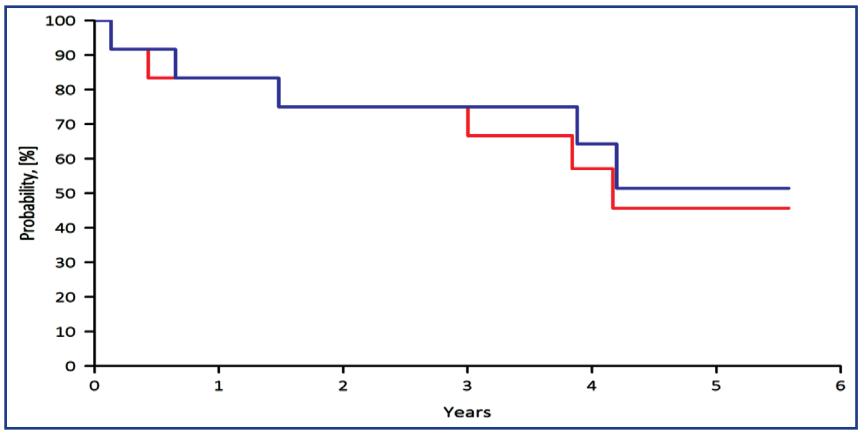


Figure 12 – EFS and OS in patients with poor response to prednisone (n=12, OS – 51.4±16.3%, EFS – 45.7±15.5%)

In the protocols used, early response is assessed by the number of blasts in the bone marrow on Days 15 and 33 of induction. On Day 15 of the protocol, 46 (29.9%) patients had an "empty" bone marrow on the myelogram, 69 (44.8%) had a remission, 32 (20.8%) did not achieve remission, and the result was unknown in 7 (4.5%) patients. On Day 33 of the protocol, remission was achieved in 140 (90.9%) patients, not achieved in 11 (7.1%), and the result was unknown in 3 (1.9%) patients. Regardless of the evaluation criteria, a good early response (PGR or M1 status at Day 15) allows distinguishing a group with a 5-year EFS >80% (Figure 13), while a poor early response (PPR or M3 status at Day 15) defines a group with a 5-year EFS around 40%.

Remission status after 4-6 weeks of therapy is also a major prognostic factor. The probability of long-term EFS in patients who have not achieved remission by this time does not exceed 30% [6].

The analysis of treatment outcomes under the BFM program in 154 patients showed death in induction in 2 (1.3%) patients and death from complications in remission in 15 (9.7%) patients. Relapses were the main cause of therapy failure in 4 (2.6%) patients. Remission continues in 133 (86.4%) patients.

***Discussion:*** In our study, as in other research [10, 11], the age peak incidence of B-ALL was at 3 to 7 years.

The debut in most children has an acute onset and is characterized by heterogeneous clinical symptoms [10]. Diagnosing is often difficult at the initial stages of the disease since the disease is manifested by blast infiltration into internal organs and systems, with no characteristic changes in blood tests [12].

In most children, B-ALL is manifested by vivid clinical symptoms ahead of hemogram data, and this is one of the most important reasons for the late diagnosis of this malignant disease. Many sources emphasize the absence of a single clinical sign characteristic of acute leukemia and its subvariants [11, 12]. Consequently, this disease's polymorphic clinical picture requires oncological awareness of the doctors of all specialties. They should study the anamnestic and clinical data and the appropriate laboratory tests and refer such patients to a pediatric hematologist.

Immunophenotyping of lymphoblasts revealed the prognostic significance of certain markers' expression in various ALL types. Thus, according to published data [8], the CD34 expression on leukemic cells in the B variant had a favorable prognostic value. In contrast, in the T variant, it was associated with a poor prognosis.

The described bone marrow cytogenetic and molecular genetic tests are necessary to classify pediatric hematological malignancies. All children with leukemia shall undergo a cytogenetic test before protocol treatment, which reveals clonal chromosomal anomalies in 80-90% of cases. Most common molecular genetic changes in ALL include quantitative and structural anomalies, such as translocations, inversions, deletions, duplications, and point mutations [2, 10]. The most justified was the targeted identification of quantitative anomalies represented by hyperploidy (7.8% of cases). Among the structural chromosomal anomalies, the t(12; 21)(p13; q22) translocation, a favorable prognostic factor, was the most frequent. The detection of the Philadelphia chromosome and trisomy of the 21st chromosome, as well as the t(1; 19)(q23; p13.3) translocation, is associated with an extremely unfavorable course of ALL. This study's results align with the general trends [13, 14].

Modern pediatric polychemotherapy programs resulted in the successful treatment of childhood B-ALL [15]. In this study, remission was observed in 93.2% of B-ALL patients.

The identification of new biomarkers, and therefore a better understanding of the molecular basis of ALL, may improve the monitoring of the course of this disease. An in-depth identification of genetic aberrations in this neoplasm is crucial for assessing the prognosis of the disease and introducing molecular targeted therapy to improve response to treatment and better survival. A more accurate prognosis calculation will allow more effective treatment of all types with fewer side effects. A deep under-

standing of the full spectrum of genetic defects opens the door to the potential targeting of therapy and precision medicine in childhood.

***Conclusion:*** This study confirmed the high efficiency of modern program therapy for ALL children. An analysis of the results of program therapy for B-ALL in 154 patients showed remission in 93.2% of patients and five-year event-free survival in 86.4% of patients.

At the same time, the response to therapy and long-term prognosis is largely determined by such biological factors as the cytogenetic features of the tumor, as well as the degree of aggressiveness manifested in the form of symptoms of lymphoproliferation and hyperleukocytosis.

Research continues to develop new monoclonal antibodies and cellular immunotherapy, but at the moment, they are effective only in some patients. New research is needed using targeted therapies to treat first-line disease.

***References:***


*1. Rumyancev A.G. Prioritety fundamental'noj pediatrii v kontrole mladencheskoj i detskoj smertnosti // Pediatriya im. G.N. Speranskogo. – 2019. – T. 98 (2). – S. 8-13 [Rumyantsev A.G. Priorities of fundamental pediatrics in the control of infant and child mortality // Pediatrics named after G.N. Speransky. – 2019. – Vol. 98(2). – P. 8-13 (in Russ.)]. https://pediatriajournal.ru/archive?show=369&section=5478*

*2. Turabov I.A., Kudryavcev A.V., Rykov M.Yu., Karpunov A.A., Ulanova A.S. Onkologicheskaya zabolevaemost' detej Arxangel'skoj oblasti i Neneckogo avtonomnogo okruga: e'kologicheskoe issledovanie // Onkopediatriya. – 2019. – Vyp. 6(2). – S. 70–77 [Turabov I.A., Kudryavtsev A.V., Rykov M.Yu., Karpunov A.A., Ulanova A.S. Oncological incidence of children in the Arkhangelsk region and the Nenets Autonomous Okrug: an ecological study // Oncopediatrics. – 2019. – Vol. 6(2). – P. 70–77 (in Russ.)]. https://znanium.com/read?id=348300*

*3. Gematologiya: nacional'noe rukovodstvo / pod red. O.A. Rukavicyna. – M.: GE'OTAR-Media, 2017. – 784 s. [Hematology: national guide / ed. O.A. Rukavitsyn. - M.: GEOTAR-Media, 2017. - 784 p. (in Russ.)] – ISBN 978-5-9704-4199-2*

*4. Rumyancev A.G. E'volyuciya lecheniya ostrogo limfoblastnogo lejkoza u detej // Pediatriya im. G.N. Speranskogo. – 2016. – №95 (4). – S. 11-22 [Rumyantsev A.G. Evolution of acute lymphoblastic leukemia treatment in children. Pediatrics named after G.N. Speransky. – 2016. – Vol. 95 (4). – P. 11-22 (in Russ.)]. https://cyberleninka.ru/article/n/evolyutsiya-lecheniya-ostrogo-limfoblastnogo-leykoza-u-detey*

*5. Zlokachestvennye novoobrazovaniya v Rossii v 2018 godu (zabolevaemost' i smertnost') / pod red. A.D. Kaprina, V.V. Starinskogo, G.V. Petrovoj. – Moskva: MNIOI im. P. A. Gercena. – Filial FGBU «NMIC radiologii» Minzdrava Rossii, 2019. – 250 s. [Malignant neoplasms in Russia in 2018 (morbidity and mortality) / ed. HELL. Kaprina, V.V. Starinsky, G.V. Petrova. - Moscow: MNIOI named after P.A. Herzen. – Branch of the Federal State Budgetary Institution "NMITs Radiology" of the Ministry of Health of Russia, 2019. – 250 p. (in Russ.)]. – ISBN 978-5-85502-251-3. https://glavonco.ru/cancer_register/Забол_2018_Элекmр.pdf*

*6. Maschan M.A., Myakova N.V. Ostryj limfoblastnyj lejkoz u detej // Onkogematologiya. – 2006. – №1-2. – S. 50-63 [Maschan M.A., Myakova N.V. Acute lymphoblastic leukemia in children // Oncohematology. – 2006. – Vol. 1-2. – P. 50-63 (in Russ.)]. https://elibrary.ru/item.asp?id=15185938*

*7. Cheng S., Pole J.D., Sung L. Early deaths in pediatric acute leukemia: a population-based study // Leuk. Lymphoma. – 2014. – Vol. 55(7). – P. 1518-1522. https://doi.org/10.3109/10428194.2013.850685*

*8. Krivcova L.A., Osmul'skaya N.S., Kockaya N.N. Ostryj limfoblastnyj lejkoz u detej Omskoj oblasti: klinika i isxod v zavisimosti ot ego immunologicheskogo fenotipa // Mat' i ditya v Kuzbasse. – 2010. – № 3 (42). – S. 22-25 [Krivtsova L.A., Osmulskaya N.S., Kotskaya N.N. Acute lymphoblastic leukemia in children of the Omsk region: clinic and outcome depending on its immunological phenotype // Mother and Child in Kuzbass. – 2010. – Vol. 3 (42). – P. 22-25 (in Russ.)]. https://cyberleninka.ru/article/n/ostryy-limfoblastnyy-leykoz-u-detey-omskoy-oblasti-klinika-i-ishod-v-zavisimosti-ot-ego-immunologicheskogo-fenotipa*

*9. Ulanova A.S., Kudryavcev A.V., Turabova A.L., Grigor'eva N.A., Turabov I.A., Rykov M.Yu. Immunofenotipicheskie i citogeneticheskie osobennosti ostrogo lejkoza u detej Arxangel'skoj oblasti: retrospektivnoe issledovanie // Sib. Onkol. Zh. – 2021. – №20(2). – S. 13-21 [Ulanova A.S., Kudryavtsev A.V., Turabova A.L., Grigorieva N.A., Turabov I.A., Rykov M.Yu. Immunophenotypic and cytogenetic features of acute leukemia in children of the Arkhangelsk region: a retrospective study // Sib. Oncol. J. – 2021. – Vol. 20 (2). – P. 13-21 (in Russ.)]. https://doi.org/10.21294/1814-4861-2021-20-2-13-21*

*10. Rumyancev A.G., Borodina I.D., Zhukovskaya E.V., Chechel'nickaya S.M., Karelin A.F., Baerbax A.V., Nikulin V.A., Kasatkin V.N. Osobennosti fizicheskogo statusa detej 4-18 let, lechivshixsya ot gemoblastozov i opuxolej CNS // Pediatriya im. G.N. Speranskogo. – 2019. - T. 98 (2). – S. 227-234 [Rumyantsev A.G., Borodina I.D., Zhukovskaya E.V., Chechelnitskaya S.M., Karelin A.F., Baerbakh A.V., Nikulin V.A., Kasatkin V.N. Features of the physical status of children aged 4-18 years, treated for hemoblastoses and tumors of the central nervous system // Pediatrics named after G.N. Speransky. – 2019. – Vol. 98 (2). – P. 227-234 (in Russ.)]. https://pediatriajournal.ru/archive?show=369&section=5526&returnurl*

*11. Yudickij A.D., Ozhegov A.M. Polimorfizm kliniko-gematologicheskix proyavlenij ostrogo limfoblastnogo lejkoza u detej // Prakt. med. (Pediatriya) – 2015. – №7(92). – S. 22-25 [Yuditsky A.D., Ozhegov A.M. Polymorphism of clinical and hematological manifestations of acute lymphoblastic leukemia in children // Prakt. honey. (Pediatrics) – 2015. – Vol. 7 (92). – P. 22-25 [ (in Russ.)]. https://cyberleninka.ru/article/n/polimorfizm-kliniko-gematologicheskih-proyavleniy-ostrogo-limfoblastnogo-leykoza-u-detey*

*12. Zarubina K.I., Parovichnikova E.N., Gavrilina O.A., Sokolov A.N., Troickaya V.V., Kuz'mina L.A., Mamonov V.E., Galstyan G.M., Savchenko V.G. Toksichnost' i e'ffektivnost' tirozinkinaznyx ingibitorov v sochetanii s ximioterapiej pri rezistentnom techenii ostrogo Ph-pozitivnogo limfoblastnogo lejkoza (obzor literatury i klinicheskij sluchaj) // Onkogematologiya. – 2017. – №12(3). – S. 41-49 [Zarubina K.I., Parovichnikova E.N., Gavrilina O.A., Sokolov A.N., Troitskaya V.V., Kuzmina L.A., Mamonov V.E., Galstyan G.M., Savchenko V. .G. Toxicity and efficacy of tyrosine kinase inhibitors in combination with chemotherapy in resistant course of acute Ph-positive lymphoblastic leukemia (literature review and clinical case) // Oncohematology. – 2017. – Vol. 12(3). – P. 41-49 (in Russ.)]. https://doi.org/10.17650/1818-8346-2017-12-3-41-49*

*13. Zarubina K.I., Parovichnikova E.N., Surin V.L., Pshenichnikova O.S., Gavrilina O.A., Isinova G.A., Troickaya V.V., Sokolov A.N., Gal'ceva I.V., Kapranov N.M., Davydova Yu.O., Obuxova T.N., Sudarikov A.B., Savchenko V.G. Issledovanie aktiviruyushhix mutacij genov signal'nyx kaskadov RAS/RAF/MEK/ERK i JAK/STAT pri V-kletochnyx ostryx limfoblastnyx lejkozax vzroslyx // Terap. Arxiv. – 2020. – №92 (7). – S. 31-42 [Zarubina K.I., Parovichnikova E.N., Surin V.L., Pshenichnikova O.S., Gavrilina O.A., Isinova G.A., Troitskaya V.V., Sokolov A.N., Galtseva I. .V., Kapranov N.M., Davydova Yu.O., Obukhova T.N., Sudarikov A.B., Savchenko V.G. Study of activating mutations in the RAS/RAF/MEK/ERK and JAK/STAT signaling cascade genes in adult B-cell acute*

*lymphoblastic leukemias. Therap. Archive. – 2020. – Vol. 92 (7). – P. 31-42 (in Russ.)]. https://cyberleninka.ru/article/n/issledovanie-aktiviruyuschih-mutatsiy-genov-signalnyh-kaskadov-ras-raf-mek-erk-i-jak-stat-pri-v-kletochnyh-ostryh-limfoblastnyh*

*14. Maxonova L.A., Myakova S.A., Popa A.V., Tupicyn N.N., Morozova O.V., Bozh'eva M.G., Slugin A.I., Valiev T.T., Gavrilova I.E., Kurdyukov B.V., Serebryakova I.N., Belyaeva E.S., Mentkevich G.L. Sovremennye podxody k diagnostike i terapii limfoidnyx opuxolej u detej // Pediatriya. – 2019. – T. 87(4). – S. 15-19 [Makhonova L.A., Myakova S.A., Popa A.V., Tupitsyn N.N., Morozova O.V., Bozheva M.G., Slugin A.I., Valiev T.T., Gavrilova I. .E., Kurdyukov B.V., Serebryakova I.N., Belyaeva E.S., Mentkevich G.L. Modern approaches to the diagnosis and therapy of lymphoid tumors in children // Pediatrics. – 2019. – Vol. 87(4). – P. 15-19 [ (in Russ.)]. https://cyberleninka.ru/article/n/sovremennye-podhody-k-diagnostike-i-terapii-limfoidnyh-opuholey-u-detey*

*15. Valiev T.T., Shervashidze M.A., Osipova I.V., Burluckaya T.I., Popova N.A., Osmul'skaya N.S., Aleskerova G.A., Sabancev S.L., Gordeeva Z.S., Smirnov V.Yu., Poberezhnaya O.A., Yuldasheva S.N., Babich I.A., Batmanova N.A., Varfolomeeva S.R. Protokol ALL-IC BFM 2002: rezul'taty lecheniya ostrogo limfoblastnogo lejkoza u detej v ramkax mnogocentrovogo klinicheskogo issledovaniya // Klin. onkogematol. – 2022. – №15(2). – S. 119-129 [Valiev T.T., Shervashidze M.A., Osipova I.V., Burlutskaya T.I., Popova N.A., Osmulskaya N.S., Aleskerova G.A., Sabantsev S.L., Gordeeva Z S., Smirnov V.Yu., Poberezhnaya O.A., Yuldasheva S.N., Babich I.A., Batmanova N.A., Varfolomeeva S.R. Protocol ALL-IC BFM 2002: results of treatment of acute lymphoblastic leukemia in children in a multicenter clinical trial // Klin. oncohematol. – 2022. – Vol. 15(2). – P. 119-129 (in Russ.)]. https://cyberleninka.ru/article/n/protokol-all-ic-bfm-2002-rezultaty-lecheniya-ostrogo-limfoblastnogo-leykoza-u-detey-v-ramkah-mnogotsentrovogo-klinicheskogo*

## АҢДАТПА

# ҚАЗАҚСТАН РЕСПУБЛИКАСЫНДАҒЫ БАЛАЛАРДАҒЫ В-ЖАСУШАЛЫҚ ЛЕЙКОЗДАРДЫҢ БАҒДАРЛАМАЛЫҚ ТЕРАПИЯСЫНДАҒЫ КЛИНИКАЛЫҚ-ГЕМАТОЛОГИЯЛЫҚ ЖӘНЕ ЦИТОГЕНЕТИКАЛЫҚ СИПАТТАМАЛАРДЫҢ РӨЛІ

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***Өзектілігі:*** *Балалардағы лейкоздардың иммунологиялық және молекулалық-генетикалық сипаттамаларын және жедел в-сызықты лимфобластикалық лейкоздың (в-ОЛЛ) ісік популяциясының биологиялық ерекшеліктерінің терапияның нәтижелілігіне әсерін зерттеу Қазақстан Республикасы үшін аса өзекті болып табылады.*

***Зерттеудің мақсаты*** *– В-жасушалы жедел лейкоздардың биологиялық сипаттамасына байланысты балалардағы заманауи бағдарламалық химиотерапияның тиімділігін бағалау.*

***Әдістері:*** *Зерттеу барысында 2016-2018 жылдары "Педиатрия және балалар хирургиясы ғылыми орталығы" АҚ (Алматы, Қазақстан Республикасы) стационарлық емдеуде болған 6 айдан 15 жасқа дейінгі бастапқы В-ОЛЛ бар 154 баланың деректері талданды.*

***Нәтижелері:*** *Ең көп зардап шеккен жас топтары 3-7 жаста (43,5%) болды, бұл нәресте шыңы деп аталады. Барлық типтегі клиникалық көріністе манифестация кезеңімен бірге жүретін интоксикация синдромы пациенттердің 75,3% - ында болды. Дебюттік кезеңнің клиникалық полиморфизмі "маскалар"диагноздарының әртүрлі тізімін анықтады. Бауыр жеткіліксіздігі түріндегі органдар мен жүйелердің зақымдануы 41 (26,6%) балада, тыныс алу жеткіліксіздігінің дамуымен 12 (7,8%), 5 науқаста жүрек-қантамыр жеткіліксіздігімен (3,2%), 3 науқаста ОПП (1,9%), 5 (3,2%) науқаста ОЖЖ зақымдануы анықталды.*

*Барлық иммунологиялық нұсқалардың таралуы анықталды мынадай түрде: В1 – 9 (5,8%), В2 – 123 (79,8%), В3-18 (11,7%), В4-3 (1,9%). Сүйек кемігін цитогенетикалық зерттеу кезінде 12(7,8%) жағдайда гиперплоидия анықталды, 6(3,9%) пациенттерде t (12;21) (p13;q22) транслокациясы анықталды және қолайлы болжамдық фактор болды (ремиссия тіркелген).Трисомия 21 хромосома 3 (1,9%) науқастарда байқалды, балалардың 1,3% - Кост сүйек кемігін зерттеу кезінде біріктірілген ауытқулар анықталды(изохромосома 7, трисомия 4, 6, 15, 17, транслокация t(9; 22) (q34;q11), t(1;19)(q23;p13.3) транслокациялары 5,8%, del 9p – 3,2% жағдайда болды.*

***Қорытынды:*** *Терапияға жауап және ұзақ мерзімді болжам көбінесе ісіктің цитогенетикалық ерекшеліктері, преднизолонға сезімталдық, сондай-ақ лимфопролиферация мен гиперлейкоцитоздың айқын белгілері ретінде көрінетін агрессивтілік дәрежесі сияқты биологиялық факторлармен анықталады. Зерттеу балалардағы заманауи ALL-BFM бағдарламалық терапиясының жоғары тиімділігін көрсетті.*

***Түйінді сөздер:*** *балалар, жедел в-жасушалық лимфобластикалық лейкемия, бласт жасушалары, иммунофенотиптеу, цитогенетикалық зерттеу.*

## АННОТАЦИЯ

# РОЛЬ КЛИНИКО-ГЕМАТОЛОГИЧЕСКИХ И ЦИТОГЕНЕТИЧЕСКИХ ХАРАКТЕРИСТИК В ПРОГРАММНОЙ ТЕРАПИИ В-КЛЕТОЧНЫХ ЛЕЙКОЗОВ У ДЕТЕЙ В РЕСПУБЛИКЕ КАЗАХСТАН

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***Актуальность:*** *Изучение иммунологических и молекулярно-генетических характеристик лейкозов у детей и влияния биологических особенностей опухолевой популяции острого В-линейного лимфобластного лейкоза (В-ОЛЛ) на результатив-ность терапии представляется особо актуальным для Республики Казахстан.*

***Цель исследования*** *– оценить эффективность современной программной химиотерапии у детей в зависимости от био-логической характеристики В-линейных лейкозов.*

***Методы:*** *В ходе исследования были проанализированы данные 154 детей в возрасте от 6 месяцев до 15 лет с первич-ными В-ОЛЛ, находившихся на стационарном лечении в АО «Научный центр педиатрии и детской хирургии» (Алматы, Республика Казахстан) в 2016-2018 гг. При определении событий руководствовались критериями протоколов группы ALL-BFM.*

***Результаты:*** *Большинство пациентов с В-ОЛЛ относились к возрастной группе 3-7 лет (43,5%), что отражает "мла-денческий пик" согласно протоколам BFM. Интоксикационный синдром, сопутствовавший периоду манифестации, при-сутствовал у 75,3% больных. Клинический полиморфизм дебютного периода определял самый разнообразный перечень диа-гнозов-«масок». Поражение органов и систем в виде печеночной недостаточности выявлено у 41 (26,6%) ребенка, дыха-тельной недостаточности – у 12 (7,8%) детей, сердечно-сосудистой недостаточности – у 5 больных (3,2%), ОПП – у 3 (1,9%), поражение ЦНС – у 5 (3,2%) больных. При иммунофе-нотипировании бластных клеток определялись следующие варианты: В1 – 9 (5,8%), В2 – 123 (79,9%), В3 – 18 (11,7%), В4 – 4 (2,6%). При цитогенетическом исследовании костного мозга в 12 (7,8%) случаях была выявлена гиперпло-идия, транслокация t(12;21)(p13;q22) определена у 6 (3,9%) пациентов и являлась благоприятным прогностическим факто-ром (зафиксирована ремиссия). Трисомия 21 хромосомы наблюдалась у 3 (1,9%) больных, у 1,3% детей при исследовании костного мозга выявлены сочетанные аномалии (изохромосома 7, трисомия 4, 6, 15, 17, транслокация t(9; 22)(q34;q11). Транслокации t(1;19)(q23;p13.3) имелись в 5,8%, del 9p – в 3,2% случаев.*

***Заключение:*** *Ответ на терапию и долгосрочный прогноз во многом определяются такими биологическими факторами, как цито-генетические особенности опухоли, чувствительность к преднизолону, а также степень агрессивности, которая проявляется в виде выраженных симптомов лимфопролиферации и гиперлейкоцитоза. Проведенное исследование показало высокую эффективность совре-менной программной ALL-BFM терапии у детей.*

***Ключевые слова:*** *дети, острый В-клеточный лимфобластный лейкоз (В-ОЛЛ), бластные клетки, иммунофенотипирование, цитоге-нетическое исследование.*

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