REPUBLIC OF AZERBAIJAN

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ABSTRACT

of the dissertation for the degree of Doctor of Sciences

EPIDEMIOLOGY AND PRINCIPLES OF TREATMENT OF ACUTE LYMPHOBLAST LEUCOSIS IN AZERBAIJAN

Speciality: 3232.01 – hematology and blood transfusion

Field of science: Medicine

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INTRODUCTION

The actuality of the subject. Acute lymphoblastic leukaemia (ALL) is a form of malignant tumor characterized by transformation of lymphoblast from lymphoid cells of bone marrow, and its medical, social and economical difficulty and complexity of its treatment is connected with the fact that it is extremely expensive and not effective enough, more than withthe probability of spreading the disease. The etiopathogenesis of ALL have been deeply studied, the objective criteria of diagnosis were substantiated, many treatment options were developed and standardized. Adopted versions of international standards in different countries have been scientifically substantiated. In Kazakhstan clinical protocols ALL-2013 Kz, ph+ALL-2013Kz, Hyper-CVAD/HD-M+xAra-C, GMALL 03/87, 04/89, 05/93; 06/99, 07/2003, 02/84 and 07/2003 have been approved at the level of the Ministry of Health based on best world practice (Clinical protocol of diagnosis and treatment of acute lymphoblastic leukemia in adults). In the Russian Federation it is recommended to carry out treatment according to the protocol ALLJC-BFM 2002 in different programs depending on the probable prognosis[1;2;3;4].

There are many criteria for the effectiveness of treatment of ALL in accordance with clinical protocols, the most relevant of them is the probability of survival, which characterizes the longevity of patients and scientific research on this sphere is being conducted intensively[5;6;]. In developed countries (Germany and the United States) the survival

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probability of patients differs sharply from each other. In recent yearslarge-scale scientific research works are carried out to substantiate the effectiveness of treatment of ALL taking into consideration different groups of patients[7;8;·] Research on new drugs and the effectiveness of treatment are going on[9]. Different results of treatment on different ages and substantiating of national protocols taking into account age factors are on the center of attention[;10]

Due to insufficient achievements and high financial costs of treatment of ALL scientists search ways to prevent the disease by identifying risk factors. One of the noteworthy aspects of the work carried out in this direction is the evidence of sharp differences in the spread of the disease by country and region within the country.[11;12] Modern concepts of risk factors (atmospheric air pollution, environ mental degradation, electromagnetic field intensity, family social status, prenatal drug treatment, antenatal infections, exposure to toxic substances in the workplace, radiation, etc.) of the disease suggest that its initial prevention is possible[13;14;15].

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The role of external factors in ALL probabilitycreates the basis for the seasonality of the disease. Although research in this sphere has been conducted for many yearshas not lost its relevance at the moment. Especially the role of climate changes, observed and deepen in recent years, in the subject-dependent dynamics of the disease has been identified.

Modern scientific research on the treatment and prevention of ALL shows that, one of the important conditions for solution of this problem is to identify proven waysin correspondence with socio-economic, medical-demographic, socio-ecological environment of the country. As the Azerbaijan Republic has different demographical (the prevalence of children and youth in the population), social and economic (accessibility of medical care) and climatic (numerous climatic zones) condition the model of organization of treatment and prevention of ALL is more relevant here.

The object of study: Azerbaijan citizen up to 30 years old with a diagnosis of ALL.

The subject of study: Physiological indicators of the organism, lethality and survival.

The purpose of the study: To substantiate the model of application of effective treatment protocols by revealing the regularities of the epidemiological characteristics of ALLamong the socially promising population (children and youth)of the Azerbaijan Republic.

Methods of the study: clinical, laboratory and instrumental examination methods; epidemiological analysis and the Kaplan-Mayer method; descriptive and analytical statistical methods.

Objectives of the study:

- To determine the morbidity rate, long-term dynamics and regional characteristics of ALL among children and young population of the Azerbaijan Republic;
- Complex characterization of ALL morbidity among children and young population in administrative and economic territorial units of the Azerbaijan Republic;
- Optimization of methodology for assessing the seasonal morbidity of ALL and identifying its long term characteristics in Azerbaijan;

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- To determine the status and causes of death and lethality, the probability of survival of patients with ALL diagnosis;
- Substantiate the application model of the international protocol ALL-MB2002 and comprehensively evaluate its effectiveness in treatment of children with ALL;
- Substantiate the application model of the international protocol ALL-MB2002 and GMALL 05/93m ALL-MB2002 and comprehensively evaluate its effectiveness in treatment of young persons with ALL (15-29 years old);
- Substantiate the optimal model of treatment and prevention of ALL for the Republic of Azerbaijan.

Scientific innovations of results of the study:

- Mathematical model of long term dynamics of ALL morbidity among children in the Azerbaijan Republic was substantiated, the country's rate among the countries of the world due to this feature has been determined;
- Characteristics of morbidity rate of ALL depending on age, gender and regions was determined;
- For the first time a long-term trend in the spread of ALL among 0-4, 5-9, 10-14, 15-29, 0-14 and 0-29 years oldpopulation has been identified, its features characteristic for big cities, economic regions, administrative regions has been determined, classification of regions and cities depending on morbidity rate wasjustified;
- For the first time was found conformity of dependence of morbidity of children and young people with ALL in the eco-climatic conditions of the Republic of Azerbaijan on months and seasons of the year and its age depending characteristics was determined;
- At the current condition of the healthcare system of the Azerbaijan Republic mortality risk dynamics, level of cumulative lethality 0-29 years old of people with ALL diagnosis, the probability of 1,2,3,4,5,6 years survival of patients was determined, their dependence on age and the integrated nature of health care has been proven;
- For the first time initial complex characteristics (age, sex, leukocytes, immune phenotypes, central nervous system damage, mediastinal area, liver enlargement, spleen enlargement, risk groups, hemoglobin, platelets, blast cells in the blood and bone marrow, key indicators of

peripheral blood) of the children with ALL diagnosis treated with the ALL-MB 2002 protocol was determined, the results of induction therapy, treatment in the stages of consolidation and reduction, the level and probability of survival of patients, their sensitivity, specificity, prognostic significance were assessed.

– For the first time initial complex characteristics (age, sex, leukocytes, immune phenotypes, central nervous system damage, mediastinal area, liver enlargement, spleen enlargement, risk groups, hemoglobin, platelets, blast cells in the blood and bone marrow, key indicators of peripheral blood) of the 15-29 years old patients with ALL diagnosis treated with ALL-MB2002, GMALL 05/93m programs and without any program, treatment outcomes, characteristics and predictors of efficacy, and factors affecting the likelihood of survival were identified.

Scientific and practical significance of the study results

– to develop substantiated regression models to determine the prognosis of the disease on the long-term trend of morbidity in children and young people with ALLand to develop action plans for national and regional health care systems in this regard;
– regression models of spreading of ALL among population give the basis forpredicting the number of patients in the country, regions, cities and districts and correspondingly to determine the volume and structure ofrequired resources;
– allows to direct medical activity during periods of increased risk for early detection of the disease on the basis of dependence of morbidity rate of ALL on calendar months and seasons;
– Tactics and strategies, criteria, predictors of treatment of children with ALL diagnosis with ALL-MB2002 protocol can be used in practical health care system.
– Tactics and strategies of treatment of 15-29 years old people with ALL-MB2002, GMALL 05 / 93m protocols, options, efficiency criteria are suitable for practical use.

The activity of health care organizations and systems in treatment of people with ALL diagnosis can be assessed according to the criteria of survival, taking into account the initial condition of patients.

The main provisions submitted for defence:

- ALL morbidity rate depends on age and gender of population in different years and separate regions of the country, it is expressed by well-approximated regression models in its dynamics, regression models allow to substantiate predictions.
- ALL morbidity rate among children and young peoplehas statistically accurate age, gender, regional characteristics.
- ALL morbidity risk changes depending on calendar month and seasons of a year and there are regional characteristics of change.
- Effectiveness of treatment of children with diagnosis of ALL using ALL-MB 2002 protocol is satisfactory, it has no alternatives for the modern period;
- Treatment of 15-29 years old people with ALL diagnosis using ALL-MB 2002 and GMALL 05/93m protocols is effective, it is necessary to use them widely in the country.

Approbation of the dissertation. The dissertation has been discussed at the meeting of the Scientific Council of the Scientific and Research Institute of Hematology and Transfusiology named after B.Eyvazov dated on 03.07.2018 (protocol №5). The dissertation was discussed at the meeting of the Scientific Council of the National Center of Hematology and Blood Transfusion held on 10.12.21. (protocol №5). According to the statement of the scientific seminar held on 05.04.24 at the scientific seminar of the dissertation council of the BED 2.27 AMU (protocol №1).The main provisions of the dissertation also was discussed at theIV Congress of Oncologists and Radiologists held in Baku in 2006 year, topical issues of children's oncology, hematology and immunology of the XII international scientific and practical conference (Minsk, 2012), at the materials of the scientific and practical conference devoted to 90^{th} anniversary of the national leader H.Aliyev (Baku, 2013), brochure of the scientific-practical conference on "Actual issues of hematology and transfusiology" devoted to 90^{th} anniversary of H.Abdullayev (Baku, 2013), International Association of Cancer Registries 35th conference (22-24 October 2013. Buenos Aires, Argentina) and IV Congress of Hematologists of Russia (Moscow, 2018).

Publication of the results of the dissertation. Articles on the basis of dissertation materials have been published in 20 scientific

journals included to the list of Higher Attestation Commission. 10 fragments of the research were presented at international conferences and symposiums held in foreign countries, at national conferences in the country and relevant theses were published.

Practical implementation of results of the research work. Epidemiological results of the reseach work is being used for planning of hematological and oncological care in the regions. Treatment protocols the efficiency of which has been approved, is being used for treatment of patients with ALL diagnosis. The achieved results are used in the training process of hematologists and oncologists, therapists and family doctors in the residency and postgraduate education stages.

The name of the organization where the dissertation work was performed: National Center of Hematology and Blood Transfusion

The structure and volume of the dissertation work. The dissertation consists of introduction, literature review (Chapter I- 83704 sings), description of research materials and methods (Chapter II – 29378 sings), personal information (Chapters III- 29242 sings, Chapters IV- 29642 sings, Chapters V- 22679 sings, Chapters VI- 21248 sings, Chapters VII – 54298 sings, Chapters VIII- 49236 sings, Chapters IX – 4081 sings, Chapters X - 33017 sings), conclusions – 2633 sings, practical advices – 840 sings, the list of literature. The total volume of the dissertation is 275 pages, 39 of which are tables, 15 - figures. The list of used literature consists of 303 sources, 276 of which are in English, 20 – in Russian and 4 – in Azerbaijan languages. The total volume of the dissertation with a mark is 370916 symbols (excluding the title, pages, table of contents, tables, diagrams, references, abbreviations and spaces).

MATERIALS AND METHODS OF THE STUDY

As an initial observation document for assessment of morbidity rate of ALL among population of regions and cities of the Azerbaijan Republic (i.e. morbidity case for the first time) "Stat coupon" of the last confirmed diagnoses has been used. According to the accepted rules approving of ALL diagnosis, treatment and examination of patients is being implemented in a centralized manner and this function was entrusted to Scientific and Research Institute of

Hematology and Transfusiology named after B. Eyvazov. That is why all initial documents are in the archive of the institute.

The morbidity rate of ALL among population during 1998-2014 years has been studied and indicators average annual cases per 100 000 population was calculated. As observation in 0-4, 5-9, 10-14, 15-19 and 20-29 age groups was planned in our research work morbidity cases also covered these age groups. The quantity of population in these age groups was taken from a database published annually by the State Statistics Committee of Azerbaijan and posted on its website in electronic version.

Correlation between calendar years and intensity of morbidity caes was found, the coefficients of the regression equations were substantiated and equations that provide optimal approximation were derived. The calendar years (x) as freely variable, (y) the morbidity rate of ALL was taken as the dependent variable in calculations. A linear relationship between y and x, its expression is as following:

$$y=a + bx$$

The morbidity rate in 0-4, 5-9, 10-24, 15-29, 0-14 and 0-19 age groups was determined in cities, economic regions and districts of the country in republican subordination and the accuracy of the difference between cities was assessed. All indicators of descriptive statistics were used for this purpose.

One of problems solved within the frames of our research work is approving of the concept of the presence or absence of seasonal factors in the development of ALL. We used the following criteria to characterize seasonality:

I. Distribution of diseases by calendar months by calendar years;
II. Calculation of the average monthly number of morbidity cases (the days of the calendar months are standardized).

The probability of survival of patients was calculated by the Kaplan-Meyer method.

Another problem covered in our research work is to apply andto prove the advantages of ALL-MB2002 and GMALL 05/93m protocols inthe clinical experience over non-programmed treatment. 179 residents of the Azerbaijan Republic aged 1-29 years with ALL diagnosis were

observed for this purpose. Patients received programmed treatment at Scientific and Research Institute of Hematology and Transfusiology named after B.Eyvazov and Children's Scientific-Practical Oncology and Hematology Center of the Republic of Belarus on basis of contract from November, 2002 till November, 2008 year.

Information about 159 patients treated in Children's Scientific-Practical Oncology and Hematology Center of the Republic of Belarus-during 2002-2008 years was used for the control group. So, clinical observation was conducted over 338 patients with initial ALL diagnosis.

159 of these patients were aged 1-9 years, 54 - 10-14 years, 34 - 15-17 and 91 - 18-25 years. 24 of 1-9 years old patients were Azerbaijan residents treated in Children's Scientific-Practical Oncology and Hematology Center of the Republic of Belarus, 122 were residents of Belarus, 13 were Azerbaijan residents treated in Scientific and Research Institute of Hematology and Transfusiology named after B.Eyvazov. 8 of 10-14 years old patients were Azerbaijan residents treated in Children's Scientific-Practical Oncology and Hematology Center of the Republic of Belarus, 37 patients were residents of Belarus, and 9 patients were treated in Scientific and Research Institute of Hematology and Transfusiology named after B.Eyvazov. All of 15-17 years old patients (34 persons) were the Azerbaijan residents, 6 of which were treated in Belarus Republic and 28 were treated in above mentioned scientific research center. Only 1 of 91 18-25 years old patients was treated in Belarus Republic, 90 patients were treated in Baku.

213 patentsaged 1-14 years were treated with ALL MB-2002 protocol (22 of them were treated in Baku, 32 residents of Azerbaijan and 159 residents of Belarus were treated in Minsk). 27 of 34 15-39 years old patients treated according this protocol are residents of Azerbaijan and treated in Minsk, 7 patients are residents of Azerbaijan and treated in Baku. Modified version of GMALL – 05/93m protocol GMALL – 05/93m was used for treatment of 53 patients in Baku. Not program treatment was applied to 38 Azerbaijan residents treated in Baku.

Therapeutic plan of ALL - MB -2002 protocol.

In order to organize the treatment of all patients, 3 strategic groups were identified from them on the basis of the protocol of the Russian-Belarusian cooperative group:

- SRG (standard risk group): 124 residents of Belarus, 30 residents of Azerbaijan (12 in Baku, 18 Minsk);
- ImRG (intermediate risk group): 28 residents of Belarus, 23 residents of Azerbaijan (10 in Baku, 13 in Minsk);
- HRG (high risk group) 7 residents of Belarus, 1 residents of Azerbaijan.

Induction and 1, 2, 3 consolidation, preservative radiation therapy and protective therapy were used in SRG.

Minor changes have been made to the GMALL 05/93m protocol: etoposide was used instead of teniposide because of the lack of teniposide in Azerbaijan. All patients received prednisolone, vincristine, daunorubomicin, L-asparaginase, methotrexate in the first induction phase of remission.

The result of the treatment was determined by the level of blast cells in the bone marrow at the end of the 1st and 2nd inductions.

GMALL 05/93m protocol treatment scheme for adolescents and young adult patients:

In the first phase of remission induction:

Prednisone (1 - 28 days), vincristine (days 1, 8, 15 and 22), rubomycin (days 1, 8, 15 and 22), L-asparaginase (days 15 - 28), methotrexate (1- in the day);

In the 2nd phase of remission induction:

Cyclophosphamide (days 29, 43, 57), sitarabin (days 31-34, 38-41, 45-48, 52-55) days), mercaptopurine (days 29-57), methotrexate (days 31, 38, 45, 52), irradiation of the head.

Early consolidation of remission:

I course (13 weeks): methotrexate (day 1), L-asparaginase (day 2), cytarabin (day 1), dexamethasone (day 1);

II course (15 weeks): methotrexate (day 1), L-asparaginase (day 2);

III course (17 weeks): etoposide (days 1-5), citarabin (days 1-5), methotrexate (day 1), citarabin (day 1), dexamethasone (day 1).

Remission of remission (21 – 26 weeks)

I phase: prednisone (days 1-28), vincristine (days 1, 8, 15, 22), doxorbusin (days 1, 8, 15, 22), methotrexate (day 1), citarabin (1- day), dexamethasone (day 1).

II phase: cyclophosphamide (day 29), sitarabin (days 31-34, 38-41), 6-thioquanine (days 29-42), methotrexate (day 29), cytarabin (day 29), dexamethasone (day 29) 29th day).

Late consolidation of remission.
I phase (33,35,45,47 weeks): methotrexate (day 1), L-asparaginase (day 2);
Phase II (39, 51 weeks): etoposide (1-5 days), cytarabin (1-5 days).
Prevention of neuroleukemia in late consolidation (33,39,45,51 weeks):
Methotrexate (day 1), sitarabin (day 1), dexamethasone (day 1).
Remission maintenance therapy (Up to 31 weeks, after diagnosis):
6-mercaptopurine (daily), methotrexate (once a week).

Clinical-laboratory methods used in the study are followings

Clinical-laboratory (peripheral blood analysis, bone marrow puncture analysis, cerebrospinal fluid analysis) and instrumental (chest X-ray, abdominal ultrasound, echocardiography, computed tomography) methods have been used for verification of ALL diagnosis. The most common of the clinical symptoms were general weakness (72,4%), pale skin (75,5%), enlargement of lymph nodes and parenchymal organs (95,5%), hemorrhage syndromes (88,7%).

Blast cell identification was performed by smearing the peripheral blood and bone marrow puncture stained by the Romanovsky-Gimza method. Verification of ALL diagnosis provided with ≥30% blast cells at the bone marrow puncture. Cytochemical verification of the diagnosis was conducted according Grechma-Knol method for myeloperoxidase reaction, Davis phospholipids, Shabadash glycogen. The reaction to myeloperoxidase and phospholipids is negative, but the reaction to glycogen is positive in case of ALL.

ALL – L1:blast cells are small, have a narrow cytoplasm, the nucleus is in the correct shape, has a thin nuclear chromatin, nucleoli are not visible;

ALL – L2:blast cells are large, heterogeneous, the cytoplasm is noticeable, the nucleus is not in the correct shape, the nuclear chromatin is heterogeneous, one or more nucleoli appear;

ALL – L3: blast cells are large, basaphil cytoplasm is noticeable, nucleus is large, nuclear chromatin is homogeneous and dense, vacuolation is present in the cytoplasm and nucleus.

Immunologicalphenotypes of ALL were determined according to the flow cytometry method using labelled fluorochrome monoclonal antibodies (MKB, firm DAKO and Beckton Dickinson).

Determining the diagnostic variations of ALL by the immunological phenotypes. The recommendations of the European Group (EGIL) on the immunological classification of leukemias were used. This classification determines 4 subtypes of type B, 5 subtypes of type T.

Short-term culture of bone marrow tissue was used for cytogenetic analyses.Chromosome aberrations according to the international nomenclature were described. The results of at least 20 metaphase analyses were used to determine the anomalous clone.

Meaning of main terms used during the study:

Full remission: blast cells in bone marrow <5%, normal peripheral blood, absence of extra medullary damage on 36^{th} day of ALL MB-2002 protocol;

Death during induction (early death): Lethality up to the 29th day of treatment with GMALL 05 / 93m protocol, up to the 36th day of treatment with ALL MB-2002 protocol;

Death in remission: lethality for any reason after achieving remission.

Recurrences of ALL: blast cells in the bone marrow ≥25%; blast cells in the cerebrospinal fluid against the background of damage to the central nervous system >5%, cytosis ≥5 cells /mkl.

Recurrences are classified by onset time:

- Too early recurrences (up to 6 months after diagnosis);
- Early recurrences (12 months after diagnosis until 6 months after the end of therapy);
- Later recurrences (24 or after the end of treatment).

Treatment efficiency (TE) – the years of prolonged life are calculated by the following formula:

TE =AFSP×Y, where

AFSP – accident-free survival period (period);

Y – observation years.

The calculations were performed on a personal computer in Excell using the "data analysis" package, and their methodology is based on biostatistics.

While planning the treatment of patients with ALL using ALL MB-2002 protocol the characteristics (initial characteristics)

manifested at the beginning of treatment were studied.The following signs and degrees of symptoms have been distinguished:

Gender: male (80 patients, citizen of Belarus and 37 patients citizen of Azerbaijan -14 of the were treated in Baku, 23 were treated in Minsk); female (79 patients, citizen of Belarus, 17 patients,citizen of Azerbaijan - 8 of them were treated in Baku, 9 of them were treated in Minsk;

Age (years): 0-4 years old (81 patients, citizen of Belarus, 28 patients, residents of Azerbaijan – 9 of the were treated in Baku, 19 were treated in Minsk);

5-9 years old (41 patients, citizen of Belarus, 9 patients,citizen of Azerbaijan - 4 of them were treated in Baku, 5 of them were treated in Minsk);

10-14 years old (37 patients, citizen of Belarus, 17 patients, citizen of Azerbaijan - 9 of them were treated in Baku, 8 of them were treated in Minsk;

The number of leukocytes (10^9/l) <50 (137 patients, citizen of Belarus, 41 patients,citizen of Azerbaijan - 16 of them were treated in Baku, 25 of them were treated in Minsk),

≥50 (22 patients, citizen of Belarus, 13 patients, citizen of Azerbaijan - 6 of them were treated in Baku, 7 of them were treated in Minsk).

Immunologic phenotype: B-type (143 patients, citizens of Belarus, 43 patients, citizens of Azerbaijan - 14 of them were treated in Baku, 29 of them were treated in Minsk),

T-type (16 patients, citizens of Belarus, 6 patients, citizens of Azerbaijan - 3 of them were treated in Baku, 3 of them were treated in Minsk),

Phenotype not determined (5 patientswere treated in Baku);

Damage to the central nervous system: (7 patients, citizens of Belarus, 1 patient, citizen of Azerbaijan - treated in Minsk);

The recommendations of the European Group (EGIL) on the immunological classification of leukemias were used for diagnostic variations of ALL according to immunological phenotypes.

Short-term cultivation of bone marrow tissue was used for cytogenetic research. Chromosome aberrations according to the international

nomenclature are described. For detecting the abnornal clone the results of the analysis of at least 20 metaphases were taken as a basis.

Criteria for the effectiveness of treatment in subgroups (lethality, remission, toxic complications, etc.) were assessed according to degree of all above mentioned initial characteristics. Four-area tables have been compiled for assessing of significance of initial characteristics as aprognostic sign.

MORBIDITY RATE, DYNAMICS AND REGIONAL FEATURES OF ACUTE LYMPHOBLASTIC LEUKEMIA AMONG CHILDREN IN AZERBAIJAN

The relative quantity of initial ALL cases per 100 000 0-14 years old children in Azerbaijan during 1998-2014 years is given in Table.

As it is seen, the lowest morbidity rate was noted in 1998. In 1999 the morbidity rate increased ($1,5^0/_{0000}$), remained practically stable in 1999-2002 (respectively 1,5; 1,45; 1,57 and $1,41^0/_{0000}$), in 2003 has reduced to the rate of 1998 year ($1,33^0/_{0000}$). In 2004 the morbidity rate ($1,68^0/_{0000}$) was more than in previous years, in 2005 year this indicator decreased ($1,45^0/_{0000}$) and in 2006 year increased again ($1,81^0/_{0000}$). In 2006 and 2007 (1,81 & $1,75^0/_{0000}$), in 2008 and 2009 (2,68 & $2,58^0/_{0000}$), in 2010 and 2011 (3,15 & $3,64^0/_{0000}$) years the morbidity rate was close between two years in pair and was more in each pair compared to previous years. In 2011-2014 years the morbidity rate dynamically decreased and respectively was: 3,64; 2,73; 2,01 & $2,02^0/_{0000}$. The morbidity ratechanged chaotically in calendar year, it was possible to determine the main direction of the dynamics by applying the smoothing method to detect the trend of change of the general regularity. As it is seen in Table the smoothed morbidity rates in 1998 – 2004 years were nearly similar (the highest rate was 1,51; the lowest rate was $1,42^0/_{0000}$).

The level of the indicator has increased in 2005 – 2006 years (1,65 & $1,67^0/_{0000}$),the morbidity rates increased dynamically during next 5 years (2,08; 2,33; 2,80; 3,12 & $3,17^0/_{0000}$) and reached the pick in 2011. Although the morbidity rate decreased slightly after 2012 year,it was much higher than in 1998-2006.

Table.

Child population in Azerbaijan with ALL

Years	ALL 100 thous. by population	The regression equation	ALL 100 thous. by population	The regression equation	Rate of change (%)
1998	1,32	$y = -0,0006x^4+0,0179x^3-,1591x^2+0,5124x+0,9686$ $R^2 = 0,8591$	-	$y= -0,0042x^3 + 0,1018x^2 – 0,5688x + 2,165$ $R^2 =0,8918$	100
1999	1,50		1,42		113
2000	1,45		1,51		97
2001	1,57		1,48		108
2002	1,41		1,44		90
2003	1,33		1,47		94
2004	1,68		1,49		126
2005	1,45		1,65		86
2006	1,81		1,67		124
2007	1,75		2,08		96
2008	2,68		2,33		153
2009	2,58		2,80		96
2010	3,15		3,12		122
2011	3,64		3,17		115
2012	2,73		2,79		75
2013	2,01		2,25		73
2014	2,02		-		100

For detecting the main trend of the morbidity rate a mathematical model of the dynamics was obtained by applying the method of least squares.

A polynomial mathematical model of the dynamics of the incidence rate over the calendar years is as following:

$y = -0,0006x^4+0,0179x^3-0,1591x^2+0,5124x+0,9686;$ $R^2 = 0,8591$

Where, y – morbidity rate; x – the number of consecutive calendar years (1998 – 1; 1999 – 2 etc.)

R^2 - determination coefficient (shows the strong correlation between calendar years and morbidity rate in these years - r>0,9).

A mathematical model of the level of morbidity is as following:

$y = -0{,}0042x^3 + 0{,}1018x^2 - 0{,}5688x + 2{,}165; \quad R^2 = 0{,}8918.$

The lowest morbidity rate among 0-4 years old children was noted in 1998 year ($2{,}5\pm{}^0/_{0000}$; 95% reliability interval 1,36 – $3{,}64^0/_{0000}$). In next year the morbidity rate was different, but only in 2008 year the morbidity rate was higher in statistically accurate manner ($5{,}3\pm0{,}92\ ^0/_{0000}$; 95% reliability interval 3,46 – $7{,}14^0/_{0000}$). In 2008 – 2011 years the morbidity rate was more in comparison with previous years, during next years this indicator decreased till level of 1998 year. Thus, the morbidity rate of ALL among 0-4 years old children chaotically changed between 1998-2014 years, and the morbidity rate ($2{,}5\pm0{,}57$ – $3{,}8\pm0{,}81^0/_{0000}$) in the first 8-year phase (1998-2005 years) changed narrowly, in comparison with the second 8-year phase (2007-2014) ($2{,}9\pm0{,}58$ – $6{,}2\pm0{,}93^0/_{0000}$). The accuracy of the mathematical model of dynamics is more than 78%:

$y = -0{,}0008x^4+0{,}0224x^3-0{,}1942x^2+0{,}7179x+2{,}669; \quad R^2 = 0{,}7596$

The morbidity rate of ALL among 5-9 years old children changed between $1{,}1\pm0{,}35^0/_{0000}$ (1998 year) – $3{,}5\pm0{,}74^0/_{0000}$ (2011 year), the difference between the maximum and minimum values is statistically significant. This confirms that the morbidity rate is not stable, but variable over the calendar years. The main trend is dynamic growth and it is expressed with 60% accuracy by linear regression equation ($y=0{,}1139x+0{,}8171$; $R^2=0{,}6085$).

The morbidity rate of ALL in group of 10-14 years old children changed between $0{,}4\pm0{,}21^0/_{0000}$ (2003 year) – $1{,}2\pm0{,}40^0/_{0000}$ (2011 year), the difference between the maximum and minimum values is not statistically significant. The trend of dynamics can be expressed by the following mathematical equation:

$y = -0{,}0013x^3+0{,}0362x^2-0{,}2409x+0{,}8531; \quad R^2 = 0{,}8028.$

Comparison of morbidity rate in different age groups due to calendar years shows that the difference between them in all years is statistically accurate. The morbidity rate is high among 0-4 years old children ($\geq2{,}5\pm0{,}57^0/_{0000}$), moderate among 5-9 years old children ($\geq1{,}1\pm0{,}25$ – $3{,}5\pm0{,}74^0/_{0000}$), and low among 10-14 years old children ($\leq1{,}2\pm0{,}40^0/_{0000}$).

The age-related relative risk of ALL (old ratio) was 5 in 0-4 age group in comparison with 10-14 age group (control group) in 1998, and the attributive risk was $2^0/_{0000}$. The relative morbidity risk and attributive risk for 0-4 age grouphas not changed proportionslly. Thus, the highest level of relative risk was recorded in 2004 (9.5), and the highest level of attributive risk was recorded in 2011 ($5^0/_{0000}$).

The ALL-morbidity rate among 0-4 years old children was relatively small in Shirvan ($2.4\pm2.4^0/_{0000}$) and relatively high in Baku (7.8 ± 2.1 0/0000) and differed from each otherstatistically accurately (χ^2=3,9; υ=1,0; P<0,05). The ALL morbidity rates among 0-4 years old children in Sumgayit and Ganja cities were close to each other (respectively 6,0±4,6 & 6,6±5,4 $^0/_{0000}$) and did not differ statistically significantly from Baku (P>0,05). Morbidity rate in Mingachevir city is close to indicators in Shirvan town 3,2±3,1 $^0/_{0000}$). In general the ALL morbidity rate among 0-47 years old urban children was 7,3±1,74 $^0/_{0000}$ (95% reliability interval 13,82– $10,78^0/_{0000}$), did not differ statistically from the corresponding indicator for the country (in 2009-2014 years - 3,00 – 6,20 $^0/_{0000}$).

The morbidity rate of ALL among 5-9 years old children has changed within the interval of 2,2 -7,9 $^0/_{0000}$, the low morbidity rate was registered in Ganja and Mingachevir cities, high level – in Shirvan town. The difference between cities is not statistically accurate (χ^2=3,0; υ=1,0; P>0,05). General indicator for urban population was 3,9±1,45 $^0/_{0000}$ (95% reliability interval 1,0 – $6,8^0/_{0000}$) and did not differ statistically significantly from the republic indicators (2.1 - $3.5^0/_{0000}$).

The ALL morbidity rate among 10-14 years old children was relatively low in all cities, in Baku it was 1,8±1,2 $^0/_{0000}$, in Sumgayit - $3,3\pm3,3^0/_{0000}$, in Ganja - 2,1±2,1 $^0/_{0000}$, in Mingachevir - $1,8\pm1,7^0/_{0000}$, in Shirvan - $3,4\pm3,4^0/_{0000}$. General morbidity rate for cities was $2,1\pm1,11^0/_{0000}$ (95% reliability interval 0 – $4,3^0/_{0000}$) and statistically differed from indicator for whole republic (0,8 – 1,2 $^0/_{0000}$).

The morbidity rate of ALL among 15-29 years old population in Baku city was $0,8\pm0,4^0/_{0000}$, in Sumgayit - $1,8\pm1,5^0/_{0000}$, in Ganja - $1,2\pm1,2^0/_{0000}$, in Mingachevir - $0,9\pm0,9^0/_{0000}$ and in Shirvan - 1,2± $1,2^0/_{0000}$, the $0,9\pm0,35^0/_{0000}$ common indicator for all cities was (95%

reliability interval 0,2 – 1,6$^{0}/_{0000}$) close to morbidity rate for whole republic.

The ALL morbidity rate among children (0-14 years old) was relatively high in Baku (5,0±1,1 $^{0}/_{0000}$; 95% reliability interval 2,8 – 7,2$^{0}/_{0000}$), and relatively low in Mingachevir (2,6±2,6 $^{0}/_{0000}$; 95% reliability interval 0 – 5,2$^{0}/_{0000}$), but there was not registered statistically significant difference between them (P>0,05). Morbidity rate of the urban population as a whole was 4,8±0,84 $^{0}/_{0000}$ (95% reliability interval 3,16 – 6,48$^{0}/_{0000}$) and close to morbidity rate in whole republic (2,0 – 3,64 $^{0}/_{0000}$).

Difference on ALL morbidity rate among 0-29 years old patients between cities is not statistically significant: 2,6±0,5 $^{0}/_{0000}$ in Baku, 3,1±1,4 $^{0}/_{0000}$ in Sumgayit, 2,3±1,2 $^{0}/_{0000}$in Ganja, 2,1±2,1 $^{0}/_{0000}$ in Mingachevir, 2,3±2,3 $^{0}/_{0000}$ in Shirvan, 2,7±0,44 $^{0}/_{0000}$ in all cities.

The quantity of children in all districts allows achieving the correct average annual data on ALL morbidity rate. That is why the comparison was made mainly by applying the conformity criterion. The general morbidity rate of ALL for all districts of Ganja-Gazakh region was 3,2 $^{0}/_{0000\ in}$ 0-4 age group, 1,2 $^{0}/_{0000}$in 5-9 age group, 2,0 $^{0}/_{0000}$ in 10-14 age group, 1,0 $^{0}/_{0000}$in 15-29 age group, 2,5 $^{0}/_{0000}$ in 0-14 age group and 1,7 $^{0}/_{0000}$ in 0-29 age group. As it is noted, the ALL morbidity rate among 0-29 years old population in Ganja city was 2,3±1,2$^{0}/_{0000}$, in districts of the region this indicatorwas 1,7±0,61 $^{0}/_{0000}$ and there was no statistically significant difference in comparison with Ganja city (P>0,05). Comparison of morbidity rates by districts of the region also showed that the inter-district difference is not statistically accurate. Thus, in Gazakh, Agstafa, Tovuz, Shamkir, Gedebey, Samukh, Goygol and Goranboy districts the morbidity rate in 0-4 (respectively, 2,2; 2,3; 4,2; 3,3; 2,1; 3,8; 3,0 and 3,6 $^{0}/_{0000}$), 0-14 (respectively, 1,7; 0,9; 3,4; 2,6; 1,6; 2,9; 5,1; 2,2 $^{0}/_{0000}$) and 0-29 (respectively, 0,7; 0,8; 2,5; 2,2; 0,7;1,2; 2,6 və 1,6 $^{0}/_{0000}$) age groups do not differ statistically from each other, situation on morbidity rates in 5-9, 10-14 and 15-29 age groups is the same.

The morbidity rate among 0-4 years old children in Sheki-Zagatala economic region was 3,6±2,63 $^{0}/_{0000}$ and do not differ statistically form Ganja–Gazakh region (3,2±2,01 $^{0}/_{0000}$) and morbi-

dity rate in whole republic (2,9 – 6,2 $^{0}/_{0000}$). The morbidity rate among 0-4 years old children is relatively high in Sheki district (6,3 $^{0}/_{0000}$), relatively low in Zagatala (1,7 $^{0}/_{0000}$) and indicators in these districts didn't differ from each other significantly (χ^2= 2,4; υ=1,0; P>0,05). In districts of this region the incidence of ALL among children aged 5-9, 10-14 years was episodic, in some districts (Gakh, Sheki, Oguz and Gabala) no new cases were registered during the observation period.The morbidity rate among the population aged 15-29 is low and differences between districts is not significant (0,4$^{0}/_{0000}$in Zagatala, 1,6$^{0}/_{0000}$ in Balaken).

The morbidity rate among 0-29 years old population in districts of Sheki-Zagatala region changed within the interval of 0,6 – 2,7$^{0}/_{0000}$, relatively small indicator was observed in Gabala and relatively high indicator – in Sheki. Their comparison also allows to reject the null hypothesis (χ^2= 3,9; υ=1,0; P<0,05).

The morbidity rate during 1998-2014 years changed within the 1,32 – 3,64$^{0}/_{0000}$interval, with dynamics expressed by a regression equation that provides good approximation with the main trend increasing ($y= -0,0042x^3+0,1018x^2 – 0,5688x + 2,165$; R^2 =0,8918) and in comparison with the world countriesAzerbaijan is in the middle position due to morbidity rate of ALL among children.

ALL morbidity rate depends on age, during 1998-2014 years it changed between 2,5±0,57 – 6,2±0,93 $^{0}/_{0000}$0-4 years old population, between 1,1±0,35 – 3,6±0,74 $^{0}/_{0000}$ in 5-9 years old children, between 0,4±0,21 – 1,2±0,40 $^{0}/_{0000}$ in 10-14 years old children, the morbidity rate in 0-4 years is higher than in 10-14 yearsfor 5-9 times.

Due to the low morbidity rate of ALL, it is not statistically significant to assess its regional characteristics by calendar years, therefore, multiple observations are required. We used 6 years interval for our observations (2009-2014 years) and chronological averages were calculated.

In the cities of Azerbaijan of republican subordination (Baku, Sumgayit, Ganja, Mingechevir and Shirvan) the ALL morbidity rate differs from morbidity rate in whole republic and changes within the ,3±1,74 and 4,3±0,3 $^{0}/_{0000}$ interval among 0-4 years old children, within the 3,9±1,45 və 2,6±0,3 $^{0}/_{0000}$ among 5-9 years old children, within the 2,1±1,1 və 1,0±0,2 $^{0}/_{0000}$ interval among 10-14 years old children and

within the 1,0±0,2 $^{0}/_{0000}$ interval among 15-29 years old patients. The morbidity risk is high among urban population, it is especially high among population of Baku, Sumgayit and Ganja cities.

In the economic regions of Azerbaijan (Ganja-Gazakh, Lankoran, Aran, Sheki-Zagatala, Guba-Khachmaz) and administrative districts of regions the ALL-morbidity risks are different: the morbidity risk is high in Guba-Khachmazregion, and relatively low in Aran and Lankoran regions.

The ALL-morbidity risk depends on gender, girls have less risk than boys.

PREVALENCE OF ACUTE LYMPHOBLAST LEUKOSIS AMONG CHILDREN POPULATION IN THE AZERBAIJAN REPUBLIC

The ALL-morbidity rate in 1998 year was 7,26±0,97$^{0}/_{0000}$, and was statistically accurately more than the relevant indicators of 5-9 (3,25±0,60$^{0}/_{0000}$), 10-14 (1,41±0,41$^{0}/_{0000}$), 15-29 (1,15±0,23$^{0}/_{0000}$), 0-14 (3,87$^{0}/_{0000}$) and 0-29 (2,64$^{0}/_{0000}$) years old population. Considering the morbidity rate among 0-29 years old population as conventional normalization measure, then the relative intensity indicator, ie the level of relative risk (relative to the population under 30 years of age) would be2,75 (0-4 years old), 1,23(5-9 years old), 0,53 (10-14 years old), 0,44 (15-29 years old), 1,47 (0-14 years old).

The ALL morbidity rate among 0-4 years old children changes depending on calendar years. Comparing indicators by yearsthere is no statistically significant increase ($P \leq 0.05$) than in the previous years, because the average error of the indicator is relatively large. But if we compare the indicators of calendar years with a 4-year interval statistically significant differences and increases are not unequivocally confirmed.

The ALL morbidity rate among 5-9years old children in 1998 and 1999 years was relatively low and close to each-other (respectively 3,250,60 and 3,12±0,58$^{0}/_{0000}$). In the following years till 2004 year the morbidity rate of disease increased, statistical signify-cance of increasing is being observed after 2001 year (3,12±0,58 $^{0}/_{0000}$ in 1999, 5,19±0,77 $^{0}/_{0000}$ in 2001; $P<0,05$).

The ALL morbidity rate among 5-9years old children increased sharply in 2010year (this can be associated with effective results in the treatment of the disease) and was 12,03±1,37 $^{0}/_{0000}$, statistically significantly more than morbidity rate in all previous calendar years (≤8,67±1,15 $^{0}/_{0000}$ in 2008). In comparison with indicators of 2010 year statistically significant morbidity rate of ALL was registered in 2012 year 2012 (16,51±1,2$^{0}/_{0000}$), 2013 (18,02±1,70 $^{0}/_{0000}$) and 2014 year (17,95±1,70 $^{0}/_{0000}$).

The morbidity rate of ALL among 10-1 years old children in 1998 year (1,41±0,41$^{0}/_{0000}$) was statistically significant (P <0.05) and respectively 5.15 and 2.31 times lower than the prevalence rate among children aged 0-4 and 5-9 years. The morbidity rate of disease in these age groupshas little changed over the years, but characterized by a general trend of growth, only in 2007 and following years there was a statistically significant increase in comparison with 1998 year.

The morbidityrate of ALL in 2007-2011 years among 10-14 years old children changed, but this change was not statistically significant. In comparison with the relevant indicator of 2007 the statistically significant increase was registered in 2012 (6,39± 0,98$^{0}/_{0000}$) and 2014- (6,56±1,0$^{0}/_{0000}$) years. As it is seen, the morbidity rate of ALL among 10-14 years old children is periodically increasing.

The prevalence rate of ALL among 15-29 years old population was 1,15±0,23 $^{0}/_{0000}$in 1998 which is 2 times less than among 0-14 years old children (387 $^{0}/_{0000}$). The prevalence rate of ALL mong population aged 15-29 years statistically significantly increased. In 1999-2006 yearsthe level of the indicator was not statistically accurate against the background of variability in the prevalence of ALL among the population aged 15-29 years. However, it was statistically accurately more than in 1998.

The ALL morbidity rate among 0-4 years old children in Baku city was 36,5±4,47$^{0}/_{0000}$ (95% reliability interval 27,6 – 45,4 $^{0}/_{0000}$) and a characteristic feature for this age group is that, it is statistically more (1,7 times)than the national average (20.46± 1.78 and 24.86 ± 1.69 0/0000 in 2009 and 2014). In cities of republican subordination the ALL morbidity rate among 0-4 years old children changed within the

interval of 11,4±11,4 $^{0}/_{0000}$ - 36,5±4,47 $^{0}/_{0000}$. The morbidity rates in Baku, Ganja and Sumgayit cities were close to each other (respectively 36,5±4,47; 31,1±11,69 & 28,1±10,0 $^{0}/_{0000}$), but were different in Mingechevir and Shirvan. In comparison with Baku the morbidity rate among 0-4 years old children in Mingechevir and Shirvan was statistically low ($\chi^2 \geq 3,9; \vartheta = 1,0; P \leq 0,05$)

ALL morbidity rate among 5-9 years old children in Baku, Ganja and Sumgayit cities was statistically low in comparison with 0-4 years old children ($\chi^2 \geq 4,2; \vartheta = 1,0; P<0,05$), in in Mingechevir was similar, but in Shirvan was statistically more ($\chi^2=3,9; P<0,05$). For this age group the morbidity rate in whole republic changed within the interval of 9,79±1,22$^{0}/_{0000}$ and 17,95±1,70$^{0}/_{0000}$. ALL morbidity rate among 5-9 years old children in Baku, Sumgayit, Ganja and Mingechevir cities was statistically significantly different from morbidity rate for whole republic ($\chi^2 \leq 2,1; \vartheta = 1,0; P>0,05$), but in Shirvan the morbidity rate was significantly higher ($\chi^2= 4,2; \vartheta = 1,0; P<0,05$).

ALL morbidity rate among 10-14 years old children changed between 8,6±2,69$^{0}/_{0000}$ and 16,0±16,0$^{0}/_{0000}$, relatively high rate was registered in Sumgayit and Shirvan, and relatively low rate - in Baku, Ganja and Mingechevir. The difference between the morbidity rate in cities for this age group is not statistically accurate. A similar result on ALL morbidity rate is also observed among individuals aged 15-29 years, and changes within the narrow interval: relatively low rate is registered in Baku (3,5±0,81$^{0}/_{0000}$), relatively high rate – in Sumgayit cities.

ALL morbidity rate among 5-9 years old children is the lowest in Nakhchivan (2,4±0,48$^{0}/_{0000}$) and the highest 13,7±6,39$^{0}/_{0000}$) in Guba-Khachmaz region (but did not differ statistically from each other). In comparison qith Nakhchivanstatistically correct high figure was recorded in Aran (12.01 ± 2,72$^{0}/_{0000}$).

ALL morbidity rate among 0-14 years old children in the republic changed between 2,9±0,94$^{0}/_{0000}$ (Nakhchivan) and 12,8± 3,75$^{0}/_{0000}$ (Guba-Khachmaz) and were statistically significantly different from each other. Statistically significant high indicator (P<0,05) was recorded in Aran (9,2±1,48$^{0}/_{0000}$), Lenkaran (8,3± 1,51$^{0}/_{0000}$), Ganja-Gazakh (11,9±2,13$^{0}/_{0000}$), Sheki-Zagatala (11,1±

2,77$^{0}/_{0000}$) and Mountainous Shirvan (7,8±1,31$^{0}/_{0000}$) regions. Indicators of these regions didn't statistically significantly differ from Guba-Khachmaz region (P>0,05).

The ALL morbidity rate among 0-29 years old population changed within the interval of 1,4±0,54$^{0}/_{0000}$ (Nakhchivan) and 11,2±1,95$^{0}/_{0000}$ (Guba-Khachmaz) and the difference between them was not statistically significant (P<0,01). In all other regions this indicator was statistically significant in comparison with Nakhchivan (4,9±0,78$^{0}/_{0000}$ in Aran, 6,2±0,91$^{0}/_{0000}$ in Lenkaran, 7,3±1,38$^{0}/_{0000}$ in Ganja-Gazakh, 7,6±1,65$^{0}/_{0000}$ in Sheki-Zagatala, 6,0±0,78$^{0}/_{0000}$ in Mountainous Shirvan). In comparison with Guba-Khachmaz region statistically low morbidity rate of ALL was recorded in Aran (P<0,01), Lenkaran (P<0,01), Ganja-Gazakh (P<0,05), Sheki-Zagatala (P<0,05) and Mountaimous Shirvan (P<0,01) regions.

Classification of cities and districts of the republican subordination of Azerbaijan due to ALL morbidity rate among 0-29 years old population:

- With high morbidity rate of ALL (>90th sentil, >12,4 $^{0}/_{0000}$): Baku (12,4$^{0}/_{0000}$), Sumgayit (14,6$^{0}/_{0000}$) cities, Sheki (13,6$^{0}/_{0000}$), Khachmaz (14,4$^{0}/_{0000}$), Guba (16,7$^{0}/_{0000}$), Goygol (12,5$^{0}/_{0000}$) districts;
- With very high morbidity rate of ALL (>75th sentil, <90th sentil, >10,3 - <12,4$^{0}/_{0000}$): Ganja (10,7$^{0}/_{0000}$), Mingechevir (10,4$^{0}/_{0000}$) and Shirvan (10,9$^{0}/_{0000}$) cities, Balaken (11,3$^{0}/_{0000}$), Shabran (10,7$^{0}/_{0000}$), Astara (10,3$^{0}/_{0000}$), Shemkir (11,8$^{0}/_{0000}$) districts;
- With moderate morbidity rate of ALL (>25 <75th sentils, 3,1 – 10,3$^{0}/_{0000}$): Zagatala (4,9$^{0}/_{0000}$), Gakh (5,6$^{0}/_{0000}$), Oghuz (5,6$^{0}/_{0000}$), Gusar (6,6$^{0}/_{0000}$), Siyezen (7,4$^{0}/_{0000}$), Lenkaran (6,7$^{0}/_{0000}$), Masalli (6,3$^{0}/_{0000}$), Jalilabad (5,6$^{0}/_{0000}$), Lerik (3,8$^{0}/_{0000}$), Yardimli (4,8$^{0}/_{0000}$), Gazakh (3,3$^{0}/_{0000}$), Agstafa (3,6$^{0}/_{0000}$), Gedebey (3,1$^{0}/_{0000}$), Samukh (5,5$^{0}/_{0000}$), Goranboy (7,7$^{0}/_{0000}$), Salyan (5,0$^{0}/_{0000}$), Yevlakh (5,0$^{0}/_{0000}$), Ujar (7,2$^{0}/_{0000}$), Zardab (5,3$^{0}/_{0000}$), İmishli (7,3$^{0}/_{0000}$), Hajıgabul (4,2$^{0}/_{0000}$), Goychay (5,2$^{0}/_{0000}$) and Absheron (9,9$^{0}/_{0000}$).
- With low morbidity rate of ALL (<10th sentil, <3,1$^{0}/_{0000}$): Gabala (3,0$^{0}/_{0000}$), Saatli (3,0$^{0}/_{0000}$), Sabirabad (1,8$^{0}/_{0000}$), Kurdemir (2,7$^{0}/_{0000}$) and Beylagan (3,2$^{0}/_{0000}$).

THE SEASONAL FACTORS IN THE FORMATION OF ACUTE LYMPHOBLAST LEUCOSIS

There are seasonal factors in diagnosing of ALL, butwe have no reason to attribute this to the seasonal nature of the disease. The probability of seasonality in the manifestation of symptoms and in the application for medical care can be considered as proven (this is confirmed by both our observations and the results achieved by other scientists).

The followings are from main data base proving dependence of ALL morbidity from seasons:

During 17 years the quantity of ALL cases was statistically significant on the 12nd of May, 12nd of July, 10th of October, 8th of June, 6th of August, 7th of September, 8th of April in comparison with other months.

As the result of observation held during 17 years it was registered that in July (10,5±1,0), December (10,3±1,0%), May (9,9±1,0%) and October (9,5±0,9%) ALL morbidity rate was the higher-than-average monthly rate (8,3%).

In 15 winters of 17 years and 17 winters the quantity of ALL incidents due to seasons was the smallest, and in 5 summers, 17 springs and 4 autumns of 17 years was the biggest. The average quantity of ALL incidents in spring, summer and autumn months is close to each other (respectively, 15,49±1,13; 15,89±1,08 and 15,71±1,24) and statistically more than indicators registered in winter months (11,07±0,76).

During the 14 May-October months (summer season), 3 November-December month of 17 years of observation period the quantity of ALL incidents was relatively more.

In months May (12,2 ±1,6%), July (9,2 ±1,4%), October (16,4 ±1,8%), December (15,0 ±1,7%) the ALL morbidity rate among 0-4 years old children was higher than average monthly morbidity rate (8,3%), the highest seasonal morbidity rate (50%) was observed in summer months (May – October).

The ALL morbidity rate among 5-9 years old children was more than average monthly rate on March (12,7±2,2%), June (9,1±1,9%), September (11,8 ±2,2%) and December (13,6 ±2,3%), was more than

seasonal average rate (25%) in winter (29,5 ±3,1%) and summer (29,1 ±3,1%), in winter months (November-April) was more than average seasonal rate (54,6 ±3,36%).

The ALL morbidity rate among 10-14 years old children was more than average monthly rate (8,3%) on April (14,1±3,6%), May (14,1±3,6%), July (14,1±3,6%), August (9,8±3,1%), September (14,1±3,6%) and November (13,0±3,5%) months, the prevalence of morbidity rate over average seasonal rate (25%) was observed in spring (31,5 ±4,8%) and summer (35,9±5,0%) months, and was more than average seasonal level in summer months (59,8±5,11%).

The ALL morbidity rate among 15-29 years old people was more than average monthly rate (8,3%) on April (16,3±2,4%), May (10,2±1,9%), June (15,5±2,3%), July (13,9±2,2%), August (15,9 ±2,3%) months, more than average seasonal rate (25%) in spring (35,1±3,0%) and summer (42,4 ±3,2%), more than average seasonal rate (50%) in spring (62,0±3,08%).

Taking into account the clinical manifestations and course of ALL the monthly and seasonal multi-season (6-month) division is considered more reliable for assessment of seasonality of disease.

The total quantity of patients with diagnosis of ALL in 1998 – 2014 years dynamically increases (from 120 to 452 people) and, consequently, the mortality rate among the population increases: was 0,6±0,11 per 100 000 population younger than 30 years old in 1998; and 0,9±0,14 in 2014;

As a positive sign of treatment of patients annual mortality rates among observed patients tend to decrease: was 20,8±3,7% in 1998, and 8,6±1,3% in 2014;

During the period past after diagnosing the ALL the probability of lethality increases every 6 months for the first 2 years, decreases in the 6-month periods of subsequent years: during I 6 months was respectively 2,8; 3,6; 5,4 and 5,7% for 0-4, 5-9, 10-14 and 15-29 years old patients and was respectively 4,8; 5,5; 7,6 and 8,6% in IV 6 months, 3,9; 9,6; 6,5; 7,8% in V 6 months and 1,1; 0,5; 2,2 and 1,6% XIII 6 months;

The cumulative lethality of patients increases proportionally in the period after the diagnosis of ALL: in 0-4, 5-9, 10-14 and 15-29 years old patients was respectively 5,5; 7,3; 9,8 and 10,6% during 1

year, 11,5; 13,2; 22,8 and 24,9% during 2 years, 18,2; 25,0; 33,7 and 37,5% during 3 years, 22,4; 30,0; 39,1 and 42,0% during 4 years, 24,0; 32,7; 43,5 and 47,4% during 5 years, 25,3; 34,5; 48,9 and 50,2% during 6 years, 26,5; 35,0; 51,1 and 51,8% during 7 years;

The risk of mortality in patients with a diagnosis of ALL depends on age, the probability of death increases with age. The lethality risk among 15-29 years old patients is more than in 0-4 years old patients: 2,0 times in 0-6 months, 1,9 times in 0-12 months, 2,16 times in 0-24 months, 1,88 times in 0-48 months, 1,95 times in 0-78 months;

The quantity of 1-year survival varies in 1 year (94.5; 92,6; 90,2 & 89,8%), 2 years (86,7; 79,1; 79,0 & 77,5%), 3 years (81,0; 75,0; 76,6; 67,8%), 4 years (77,7; 72,7; 67,4 & 64,8%), 5 years (76,5; 71,8; 65,2 & 63,2%), 6 years (75,4; 70,8; 61,9 & 61,6%) and 7 years (73,4; 69,5; 59,8 & 60,0%) patients with ALL diagnosis on age 0-4, 5-9, 10-14 and 15-29 years differ from each other: the initial age of the patient is inversely proportional to the probability of survival;

Surviving chance of patients in Baku, where health opportunities are different (relatively better) and other regions of the republic (relatively less satisfactory) is different: on ages 0-4, 5-9, 10-14, 15-29 years the probability of 1-year survival varies little (99; 98; 96 & 96% in Baku, 95; 94; 92 & 90% in regions), but the probability of 6-year survival is large (80; 66; 60,0 & 56,0% in Baku, 64; 60; 44 & 43% in regions);

Increasing the opportunities of healthcare in Azerbaijan are associated with an increased likelihood of survival of patients with a diagnosis of ALL: in 1998, 2000, 2004 and 2008 years survival indicators for 1 year (92,6; 95,8; 97,9; 94,7%), 2 years (85,4; 91,6; 95,8 & 90,8%), 3 years (75,6; 81,3; 89,6 & 88,2%), 4 years (63,4; 72,9; 83,3 & 84,2%), 5 years (51,2; 66,6; 75,0 & 77,6%), 6 years (39,0; 56,3; 64,6; 71,1%) approves this thesis.

APPLICATION AND EFFICIENCY OF THE ALL-MB-2002 PROTOCOL IN THE TREATMENT OF ACUTE LYMFOBLAST LEUKOSIS IN CHILDREN

This part of our study is based on our application of the ALL MB-2002 protocol for treatment of 54 patients form Azerbaijan and

159 patients from Belarus in the Belarusian Scientific-Practical Center for Pediatric Oncology and Hematology on basis of Agreement with the Azerbaijan Scientific Research Institute of Hematology and Transfusiology named after B. Eyvazov.

There is a difference in the initial characteristics of patients depending on nationality of patients (citizens of Belarus or Azerbaijan), implementation of the treatment in Baku or in Minsk: the share of 10-14 years old children among patients treated in Baku (40,9%) is more than citizens of Azerbaijan (25,0%) and Belarus (23,3%) treated in Minsk.

The share of female among patients from Belarus (49,7%) is more than the similar indicator among Azerbaijan population (31,5%).

The initial risk signs and children patients among Azerbaijan population prevails in comparison with Belarus population: the share patients amount of leukocytes in which is $\geq 50\times10^9$/l respectively is 24,1 & 13,8%; with liver enlargement ≥4 cm - is 55,6 & 28,3%; with enlargement of the spleen ≥4 cm is 48,2 & 20,8%, İmRG 42,6 & 17,6%; with the amount of hemoglobin <50q/l is 29,6 & 5,7%, with platelet count $<50\times10^9$/l is 27,7 & 6,3%; with the amount of blast cells in the peripheral blood >50% is 29.6 & 10.6%.

General level of lethality in the induction phase was 2,4±1,1%, in Minsk was 2,1±1,0%, in Baku was 4,6±4,6%, in boys was 4,3±1,9%, in girls was "0".

The amount of leukocytes - $\geq 50\times10^9$/l (8.6%), enlargement of the mediastinal area - (20.0%), enlargement of the spleen ≥4 cm (8.5%), ImRG group (8.5%), the amount of erythrocytes - $<30\times10^{12}$/l (5,6%), erythrocyte sedimentation rate (ESR) ≥30 mm/hour (5.3%), segment nucleated lymphocytes <5% (5,9%) and lymphocytes >60% (9,1%) are associated with an increased risk of lethality. The sensitivity of these symptoms as a predictor of lethality is weak (≤20%), specificity is high (≥94,3%), prognostic significance of presence of symptoms is in high (≥60%), prognostic significance of absence of symptoms is in medium (50 – 96,6%) level.

Possibility of patients not reaching remission (due to lethality and other reasons) was observed in 3.3% of patients, including 6,0% of boys (5,8% in Minsk and 7.1% in Baku), 1.8% at age 0-4 years, 4,8% at age ≥5 years. The risk factors in this situation are: leukocytes

are ≥50×10^9/l, enlargement of the liver, spleen for ≥4 cm, ImRG and other evaluated initial signs. The sensitivity of these symptoms is weak (≤14,3%), specificity is high (≥98,2%), prognostic significance of positivity is (71,4 – 100%), is greater than the prognostic value of negativity (13,1 – 85,4%).

Mortality of patients in the stages of induction and remission is 4,2%, in Minsk is 3,1%, in Baku is 13,6%, in boys is 5,3%, in girls is 3,1%, is in 0-4 years old children 3,7%, is 4,8% in children ≥5 years. The risk of lethality associated with initial characteristics has increased. The sensitivity of the initial characteristics is weak (≤14,3%), specificity is high (≥96,9%), the prognostic value of positivity (44,4 – 100%) is greater than the prognostic value of negativity (13,6 – 83,6%).

Presence of relapses in remission period was 9,9%, is similar in Minsk and in Baku (9,9 and 9,1%), in boys was (14,6%) more than in girls (5,2%), 7,5% in 0–4-year-old children, 13,1% in children of ≥5 years. The role of initial characteristics as a predictor was observed, their sensitivity was weak (≤26,9%), specificity was high (≥92%), the prognostic value of positivity (33,3 – 90,5%) is similar to the prognostic value of negativity (13,6 – 87,6%).

The overall survival probability of treatment with the ALL-MB 2002 protocol was 89% in Belarus, 89% for Azerbaijan citizens treated in Minsk, in Baku wass 75%, respectively, the probability of accident-free survival was 83; 89 and 66%, probability of survival without recurrence was 88; 92 and 85%. As the initial characteristics age, leukocyte amount, immunophenotype, damage to the central nervous system, medastenal zone, enlargement of the spleen and liver (≥4 cm), ImRG and HRG, treatment clinic, nationality had a statistically significant effect on survival.

RESULTS OF TREATMENT OF 15-29 YEARS OLD PATIENTS WITH ALL-MB2002 AND GMALL 05 / 93m PROGRAMS AND WITHOUT ANY PROGRAM

34 patients had been treated with ALL-MB2002 program, 53 patients – with GMALL 05/93m and 38 patients have been treated without any program (Not program).

Important characteristics of patients treated with ALL-MB2002 and GMALL 05/93m protocols: 35,3 & 32,1% were women, 47,1 & 28,3% were teenagers, 52,9 & 71,7% were 20-29 years old patients; amount of leukocytes >50 $\times$ $10^{9/l}$ 23,5 & 28,3%, damage of the central nervous system 8,8 & 7,5%, damage of the mediastinal area 11,8 & 15,1%, enlargement of the spleen ≥4 cm 35,3 & 47,2%, hemoglobin <80 g/l 35,3 &60,4%, platelet amount <100 $\times$ $10^{9/l}$ 47,1 & 52,8%, the amount of blast cells in the peripheral blood <30% 70,6 & 64,2%.

In the stages of induction and remission in the treatment of 15-29 years old patients with the ALL-MB2002 protocol the lethality rate was 11,8±5,5%, did not change significantly depending on age and gender, statistically significant increase depending on the initial amount of leukocytes (>50 $\times$ $10^{9/}$l), on ≥4 cm growth of the spleen, hemoglobin <80 g / l, platelet count <100 × 109 / l, peripheral blood blast cells >30%. Sensitivity of these predicates was between 8,7 – 50%, specificity was between 81,8 – 96,2%, prognostic significance of positivity was between 50 – 25%, prognostic significance of negativity was between 30 – 81,3%.

The frequency of relapses in treatment 15-29 years old patients with ALL-MB 2002 protocol was 20,6±6,9 %, changed within the interval of 10,0 – 66,7% depending initial characteristics, sensitivity of initial symptoms changed within the interval of 21,7–66,7%, specificity changed within the interval of 76,9 – 90,9%, prognostic significance of positivity changed within the interval of 57,1–85,7%, prognostic significance of negativity changed within the interval of 33,3 – 90,9%.

During treatment of patients aged 15-29 years with the protocol ALL-MB2002 there was observed diabetes steroids in 8,85% of patients, infection in 5,9% of patients, neutropenia in 32,4% of patients, thrombocytopenia in 29,4% of patients, lack of early reactionin 23,5% of patients, (M2 & M3). The frequency of these toxic complications varied statistically depending on the initial characteristics.

The lethality rate during treatment of 15 – 29 years old patients with GMALL 05/93m protocol was 20,8% (7,6% in induction, 13,2% in remission), changed within the interval of 5,3 – 33,3% depending

on the initial characteristics. Sensitivity of initial characteristics regarding the risk of general lethality changed within the interval of 22,2 – 33,3%, regarding the specificity changed within the interval of 82,4 – 94,7%, prognostic significance of positivity changed within the interval of 45,6 – 90,9%, prognostic significance of negativity changed within the interval of 25,0 – 81,8%.

Relapses were registered in 41.5% of cases treatment of 15-29 years old patients with GMALL 05/93m protocol, statistically accurate depending of the risk of recurrence on the initial characteristics changed within the interval of 21,1 – 66,7%. Sensitivity to initial symptoms due to the risk of recurrence was high (50 – 66,7%), specificity was very high (67,4 – 80,0%), prognostic significance of positivity changed within the interval of 36,4 – 86,4%, prognostic significance of negativity changed within the interval of 38,7 – 87,9%.

At the treatment of 15-29 years old patients with GMALL 05/93m protocol inadequate response was seen in 34,0 ±6,5% of patients on the 15th day of the treatment (M2 & M3), diabetes steroids in 5,7% of patients, localized infectious complications in 22,6% of patients, neutropenia in 60,4% of patients, thrombocytopenia in 52,8% of patients. The frequency of these complications changed statistically correctly depending on the initial symptoms.

There was no response of the treatment of 15-29 years old patients with GMALL 05/93m protocol in 34,5±7,9% of patients. The specific gravity of such patients changed within the interval of 25 – 77,8% depending on initial characteristics. Sensitivity of initial symptoms due to lack of response was between 40,0 – 77,8%, specificity was between 60,9 – 75,0%, prognostic significance of positivity was between 40 – 73,3%, prognostic significance of negativity was between 52,2 – 91,3%.

The frequency of recurrences after treatment of 15-29 years old patients without any program was seen in 44,7±8,1% cases, lack of responce (M3≥25) on 15th and 29th days of the treatment was respectively 31,6±7,5% və 26,3±7,1%. Frequency of these results chnaged statistically correctly depending on initial characteristics, as predictors of those characteristics sensitivity was between 30 – 88,9%,

specificity was between 66,7 – 84,2%, prognostic significance of positivity was between 41,2 – 76,5%, prognostic significance of negativity was between 23,8 – 84,6%.

CONCLUSION

From a medical and social point of view ALLhas been studied on the basis of deep scientific methodology as a pathology that causes serious problems for mankind for a long time. Currently Cyto-morphological, cytochemical immunological and important molecular-genetic features of the pathogenesis of this disease are known, but there is noserious achievements for prevention of the disease. Scientifically based algorithm for diagnosis and treatment of the disease has been documented at both international and national-regional levels. Such documents are improved from year to year. Documents adopted in recent years attracts attention with higher scientific potential:

- Acute lymphoblastic leukemia. Effective date: July, 2016. Clinical practice guideline;
- Evidence – based guidelines for the use of tyrosine kinase inhibitors in adults with Philadelphia chromosome-positive or BCR ABL positive lymphoblastic leukemia: a Canadian consensus;
- Clinical recommendations on diagnosis and treatment of children with acute leukemia;
- Clinical protocol of diagnosis and treatment. Acute lymphoblastic leukemia in adults;
- World Health Organization classification the role of the hematopatology laboratory in the diagnosis and managements of acute lymphoblastic leukemia;
- NCCN clinical practice Guidelines in oncology (NCCN Guidelines)/ acute lymphoblastic leukemia;
- Scottish intercollegiate Guidelines Network.

Unfortunately there is no national clinical recommendations, protocols and standards as a result of international experience in Azerbaijan and it complicates the observation of patients in a single centralized manner.

There are many programs on treatment of ALL and researches for updating them are going on. A lot of money is required forimplementation of treatment protocols.

A single center that identifies ways of solution of the scientific and practical problems of ALL in Azerbaijan is Scientific-Research Institute of Hematology and Blood Transfusion of the Republic of Azerbaijan named after B.Eyvazov.

Several large-scale trends in the study of ALL can be identified:

- Deepening and improving the etio-pathogenesis and early diagnosis of the disease;
- Identifying of the likelihood of disease and the risk factors that increase this likelihood;
- Improving treatment protocols of disease, evaluation of their application by objective criteria.

As the modern stage of studying the etio-pathogenesis of the disease is carried out at the cellular and gene level in the study of rich centers serious innovations are possible in this sphere.

For assessment of epidemiological character of ALL, especially the morbidity rate, the number of observed contingents must be at least 100 thousand. Therefore, such studies are traditionally conducted in big countries. The annual birth of 150,000 children and the big quantity of children population in Azerbaijan (more than 25% of the population) make the study this problem possible at the national level and in large regions of the country and we have conducted this study in our research work.

The main criterion for the risk of disease, including ALL, is its morbidity intensity among population. Incidence characterizes the morbidity cases that took place for the first time. Information about this is given in the literature periodically.

Our study on researching of ALL incidences in the territory of the Azerbaijan Republic has several specific moments:

- Our study covers long time period (1998 – 2014) and the reliability of presented information is high;
- We divided the territory of Azerbaijan to big clusters: ALL morbidity rate was studied in its cities and towns of republican subordination (with different ecological conditions), economic

regions (with different economies, economic activities, geographical conditions) and in all administrative-districts of republican;

The followings are some most important results achieved by us:

- The morbidity rate per 100 thousand children population (0-14 years old) in Azerbaijan during 1998 – 2014 years changed within the interval of 1,32 – 3,64%. This morbidity rate is close to morbidity rate in Israel ($3,5^0/_{0000}$), given by the Wold Health Organization, but is too low in comparison with morbidity rate registered in USA ($17,3^0/_{0000}$). As a European country the Azerbaijan Republic has a low ALL morbidity rate in this region;
- Though the ALL morbidity rate among children population in big cities of Azerbaijan (accurate statistically results can be obtained only in big cities) ($5,0\pm1,1^0/_{0000}$ in Baku, 95% reliability interval 2,8 – $7,24^0/_{0000}$; $4,8\pm0,84^0/_{0000}$ in all cities of republican subordination; 95% reliability interval 3,2 – $7,4^0/_{0000}$) is statistically correctly high in comparison with general morbidity rate in whole country (2,7±0,2; 95% reliability interval 2,3 – $3,1^0/_{0000}$) does not exceed the high morbidity rate in the European region (6.00 / 0000 - in Italy and Malta). This also confirms that the ALL morbidity rate among children population is within the frames of morbidity rate in European countries. In cities with unsatisfactory ecological condition the ALL morbidity rate among children is relatively low (i.e., the known low level in Europe - $3,5^0/_{0000}$): Gəncə-Qazax regionunda $2,5\pm1,1^0/_{0000}$ in Ganja-Gazakh region, $9,7\pm1,46^0/_{0000}$ in Sheki-Zagatala region, $2,0\pm0,93^0/_{0000}$ in Lenkaran region, $3,5\pm1,64^0/_{0000}$ in Guba-Khachmaz region, $1,6\pm0,93^0/_{0000}$ in Aran region. Thus, due to morbidity rate among children characteristic difference for European countries (minimum $3,5^0/_{0000}$, maximum $6,0^0/_{0000}$) is expressed in Azerbaijan – in cities and regions with different ecological conditions (minimum $1,6\pm0,63^0/_{0000}$, maximum $5,0\pm1,1^0/_{0000}$). These information let us tosubstantiate the following scientific provisions:
- Against the background of ecological, economic, geographical and urbanization differences in the settlements of the

population in the Republic of Azerbaijan the ALL morbidity rate among children in the territory of Azerbaijan is changeable, regional difference is 1:5, high level is observed in Baku, Guba-Khachmaz regions and low level is observed in Aran.

- In the world practice, the most important risk factor for ALL is age. As in the development of the disease there are differences between countries and regions, intensive indicators for assessment of its dependence on age are less adequate (per 100 thousand population), it is advisable to use relatively intensive indicators to increase its adequacy (the ratio of the intensity of one age group to the intensity of another age group).
- There is no unambiguous opinion on dependence of ALL morbidity risk on age. The prevalence of morbidity rate among boys more than girls in Mexico was observed among 1-4 and 5-9 years old children, but among 10-14 years old children the morbidity rate is higher in girls than in boys. The ALL morbidity rate in El-Salvadore was high among 5- years old boys, girls aged <1 and 10-14 years. Our study absolutely confirms that the morbidity rate among boys is higher than among girls.
- In 1998-2014, the growth dynamics prevailed in ALL morbidity rate among children population of Azerbaijan. The approximation of the regression equation, which gives a linear description of the dynamics, is weak. Approximation of the polynomial regression equation describing the trend of dynamics is 85%: $y= - 0,0006x^4 + 0,0179x^3 – 0,1591x^2 + 0,5124x + 0,9686$ ($R^2=0,8591$).
- One stage of our research (1998-2008 years) was studied in Azerbaijan and Belarus. The ALL morbidity rate in 1998 in Azerbaijan was lower for 1,7 times, in 1999 - for 1,4 times, in 2000 - for 1,2 times, in 2001 - for 1,9 times, in 2002 - for 1,8 times, in 2003 - for 1,8 times, in 2004 - for 1,9 times, in 2005 - for 1,5 times, in 2006 - for 1,5 times, in 2007 - for 1,7 times, in 2008 - for 1,3 times.

The increasing dynamics of ALL morbidity rate in Azerbaijancan be considered as dangerous. If the current dynamics remains or intensifies Azerbaijan can come to higher levels among European countries due to ALL morbidity rate. Azerbaijan, which is currently close tocountries with low morbidity rates (Israel) can be closer to countries with high morbidity rate (Italy).

The morbidity rate characterizes new incidents of ALL, but doesn't directly attract medical and social importance of ALL. Thereliable criterion for this reason is the prevalence of disease among population. As the prevalence of diseasecharacterizes the information on the quantity of all patients in the country determines demands for medical services for treatment and prediction of the disease.

Results of analysis of achieved results on ALL morbidity rate, are presented in Chapter IV.The most interesting provisions from this information are as followings:

- In different age groups of the child population (0-4, 5-9, 10-14 years old) , in adolescents and young adults (15-29 years old) dynamics of ALL morbidity rateis similar, in 1998-2014 years increased respectively for 3,42; 5,52; 4,65; 3,96 times.
- The lowest ALL morbidity rate was registered in 0-4, 5-9, 10-14, 15-29 age groups, in 0-4, 5-9 and 10-14 age groups the morbidity rate of the disease in 1998 years increased respectively for 6,31; 2,83 and 1,23 times, in 2014 year – for 5,45; 3,94 and 1,44 times in comparison with the last age group.
- There is a significant regional difference in the prevalence of ALL among the population, as well as in the incidence of ALL. The morbidity rate of the disease is relatively high in Baku (0-4, 5-9, 10-14, 15-29 age groups - 36,5±4,47; 18,8± 3,81; 8,6±2,69 and 3,5±0,81 $^{0}/_{0000}$), Sumgayit (respectively 28,1±10,0; 18,8±8,67; 15,4±8,65; 8,6±3,24$^{0}/_{0000}$), in Ganja (respectively 31,1±11,69; 10,2±6,66; 10,0±6,52; 5,6±2,57 $^{0}/_{0000}$), and is relatively low in regions of the country such as Aran (12,2±1,98; 12,0±2,72; 2,1±1,1 and 1,4±0,5 $^{0}/_{0000}$), Lenkaran (10,4±1,77; 8,7±3,03; 5,1±1,82; 4,3±1,01 $^{0}/_{0000}$), Ganja-Gazakh (14,4±1,31; 11,0±4,67; 9,8±3,21; 3,8±1,27

$^{0}/_{0000}$), Sheki-Zagatala 15,9±3,52; 11,7±6,02; 4,3±2,75 and 5,1±0,95 $^{0}/_{0000}$), Guba-Khachmaz (19,7±3,97; 13,7±6,39; 2,6±1,59 and 9,7±1,90 $^{0}/_{0000}$), Mountainous Shirvan (8,8± 1,12; 7,9±2,24; 4,2±1,71 and 4,1±0,95 $^{0}/_{0000}$) and Nakhchivan (5,0±1,01; 2,4±0,48; 1,2±0,24 and 0,9±0,18 $^{0}/_{0000}$).

The indicator on the epidemiological features of chronic diseases, including ALL, attracting attention is the ratio of the prevalence of ALL to the incidence of ALL - an indicator of patient survival, constant observation. Assuming that patients do not die and are constantly observed, then the prevalence of the disease (xy) is equal to the sum of the incidence of the disease in previous years (Σxh). Using the ration of the morbidity rate to the incidence of disease for to characterizing of the duration of patients' observation periodrecommended in evidence-based medicine and clinical epidemiology.

Thus, due to the lack of opportunities for primary prevention of ALL, the morbidity rate increasesalthough at a slow dynamics andearly diagnosis, treatment and adequate monitoring of patients are provided due to the expansion of health care opportunities, the mortality as the result of the disease decreases, its accumulation increases. Our evidences for proving of this last conception are given in Chapters VI and IX.

The average annual quantity of patients in 1998 year was 120 persons and this figure increased till 452 persons in 2014 year. Taking into account the fact that drug costs only for treatment of ALL patients with ALL MB 2002 GMALL 05/93m protocol are between 14 000 – 17 000 US $, it is clear thatthe socio-economic burden of ALL for health care system is enough heavy. The society should accept this heaviness and expect its increasing in future.

Numerous studies have been devoted to the risk factors of ALL. Risk factors are mainly formed under the influence of the external environment; there are many observations about radiation, toxic chemicals, infectious agents and so on. One of the factors justifying the provisions on the external environment is the probability of seasonal reproduction of ALL, which attracted attention of all scientists. This idea is being sounded time by time during 40

years.Even if seasonal increasing of ALL incidences is considered proven long time ago,it is not clear to what factor (increasing of infectious diseases, exposure to sunlight, etc.)it is directly related.

Seasonal character of diseases is being studied during many years, but there are approaches, which methodologically differ from each-other. Manifestations of the ALL mainly with non-specific symptoms, its gradual development, makes serious problems for assessment of its seasonal character. Expecting of immediate response to the effects of seasonal factorssimplifies the onset of the disease. Undoubtedly, a seasonal factor can playmotivating role. Tking into account all these moments, we studied seasonality of the diseases on different directions. First of all it is very difficult to identify annual increasing of ALL incidents and its pick period (reaching the highest level).

The second methodological approach tested in our study was the comparison of ALL incidents due to seasons of a year: winter December 20– March 20, spring March 20– June 20, summer June 20– September 20, autumn September 20– December 20.

Characteristics of ALL incidents in spring, summer, autumn and winter seasons of 1998-2014 years:

- Average seasonal ALL incidents: 15,4±1,13; 15,89±1,08; 15,71±1,24; 11,07±0,76;
- Mode of seasonal ALL incidents: 13; 19,3; 12.7; 8,0;
- Median of seasonal ALL incidents: 13,3; 15,4; 13,7 and 10,0.
- All these information shows that unlike the spring, summer and autumn seasons in winter the quantity of ALL incidents is statistically less, and average quantity of ALL incidents in spring, summer and autumn seasons is close to each-other.
- So, the model which we applied shows that from December 20 till March 20 the quantity of ALL incidents is little, but within the intervals of March 20-June 20, June 20-September 20, September 20- December 20 the quantity of ALL incidents is more. Difference is statistically correct.

The methodology we apply for assessment of ALL incidents is based on a comparison of morbidity in the summer (May, June, July, August, September, October) and winter (November, December, January, February, March, April) seasons covering 6-month periods.

The probability of survival is considered more reliable for assessment of results of treatment of patients. This indicator is being calculated by means of Kaplan-Meier method all over the world. The advantage of this method is that, it allows you to calculate both lethality and survival rates at the same time. When we presented this methodology in our study we achieved new results conducting calculation in two variations:

- The lethality recorded after the onset of the disease at 1, 2, 3, 4 and moresix-month intervals. The lethality during 0-6 (1^{st} six months), 6-12 (2^{nd} six months), 12-18 (3^{rd} six months), 18-24 (4^{th} six months). It shows that if a patient doesn't die during the first 2 years of sickness he has more chances of surviving next years.
- Calculation of the cumulative level of lethality on one, two, three, four years periodwithout dividing the intervals after the onset of the disease shows that the lethality increases dynamically. If the annual mortality rate among 10-14 years old children was 9,8% (after onset of disease) the mortality rate during 2 or 3 years was respectively 22,8; 33,7%, and 48,9% during 6 years.

Beləliklə, letallığın səviyyəsi onun qiymətləndirmə So, the mortality rate differs depending on its assessment methodology. From this point of view the surviving probability calculated byKaplan-Meier method is more informative.

The results which we have achieved show that the probability of surviving first of all depends on age when a patient get sick. The probability of surviving during 1,2,3,4,5,6 and 7 years in children withALL diagnosis which got sick at ages 0-4 years (respectively 94,5±1,1; 86,7±1,1; 81,0±2,1; 77,7±2,3; 76,5±2,4; 75,4±2,4; 73,4±2,5%) is more than children which got ALL diagnosis when they were 5-9 years old (respectively 92,6±1,8; 79,1±2,3; 75,0±3,2; 72,7±3,5; 71,8±3,7; 70,8±3,8; 69,5±3,9). In its term the surviving probability of children which got sick at age 5-9 years (90,2±3,2; 79,0±4,1; 70,6±5,6; 67,4±6,2; 65,2±6,5; 61,9±6,4; 59,8±7,3%) is higher than children which got sick at age 10-14 years. Also, the surviving probability of children which got sick at age 10-14 years is higher than patients which got sick at age 15-29 years.

Thus, the onset of the disease at an early age is positive from the prognostic point of view. The survival prognosis of adults with ALL diagnosis is more negative than prognosis of 0-4 years old patients.

The chances of survival of patients living in Baku and the regions who fall ill at the same age range are different.Relatively accessible and good quality medical services in Baku makes the chances of survival of patients living in Baku higher than patients living in regions. It also should be taking into consideration that the basic treatment of patients living both in Baku and in regions was conducted in the same center. It also approves that the adequate examination and treatment of patients increases their chance to survive.

Results of our study show that one year (92,6; 95,8; 97,9 & 94,7%), two years (85,4; 91,6; 95,8 & 90,8%), three years (75,6; 81,3; 89,6 & 88,2%), four years (63,4; 72,94 83,3 & 84,2%), five years (51,2; 66,6; 75,0; 77,6%), six years (39; 56,3; 64,6; 71,1%) and seven years (26,8; 47,9; 54,5 & 61,8%) survival chances of patients diagnosed ALL in 1998, 2000, 2004 and 2008 years are different. It can be related with the fact that materials provisison of health care system in the republic dynamically improved since 2000 year, the supply of medicines to patients has increased, in particular, the possibility of treatment in accordance with international standards has expanded.

Comparing the achieved results with literature we concluded that, the probability of survival of patients with a diagnosis of ALL in our country is moderate, and in some cases, is close to results of developed countries. [146] In California the survival chance of 0-39 years old patients with ALL diagnosis was studied in 1996-2005 years and it became clear that the five years survival probability depending on age has changed within the interval of 30-805, the highest result was observed among 4-8 years old patients. The five year survival chance in our study among 0-4 years old patients was 76,5%, in 15-29 years old patients was 63,2%. The closeness of the indicators is obvious.

The positive results achieved in treatment of patients with ALL first of all depends on the expansion of the use of standardized clinical protocols.

We used ALL MB-2002 and GMALL protocols in our study, according agreement between Belarus Scientific-Practical Oncology and Transfusiology Center and Azerbaijan Scientific Research Institute of Hematology and Blood Transfusion named after B.Eyvazov on bilateral scientific activity, because they are more reliable. Algorithm for applying these protocols, information on their structure and duration are presented on Chapter II, and results are given on Chapters VII and VIII.

Main objective of application of treatment protocols is to prolong the life, reduce suffering, improve quality of life of patients. The most reliable criteria of these protocols along with the probability of general survival are survival probabilities without complication and relapses. Application of these criteria in different stages (induction, remission) of the treatment makes necessary to study the risk of lethality, relapses, toxic complications. We assessed and compared application of protocols ALL-MB-2002 and GMALL 05/93m among Belarus and Azerbaijan citizens in Minsk, and only Azerbaijan residents in Baku within the frames of our study. Such a comparison gives grounds to determine the effectiveness of the protocols on the one hand, and the probability that they have features related to their application in different conditions, in different ethnic groups on the other hand.

We should note that, it is difficult to adequately compare the results of not only different protocols (in our example, the treatment of Belarus and Azerbaijan children in Minsk, Azerbaijan children in Baku and Minsk), but also the application of the same protocol in different groups in the treatment of ALL. This happens because ALL manifests itself in different forms and weights in each individual, affecting of phenotypes of the disease, immunological status of the organism, lifestyle, living conditions of patients the outcome of treatment. Therefore, there should be a comprehensive approach in the selection of treatment programs.

During the treatment of the adult population under the age of 30 in Russia with the ALL-MB 2002 protocol [20] lethality in induction was 2,9%, in our study was 5,95% (3 of 105 patients in Russia, 2 of 34 patients in our study died in induction). We assessed the difference

between these indicators by χ^2 criteria (χ^2=0,64; P>0,05). The difference was statistically incorrect. Lethality in the induction phase in our study was similar with observation of. Full remission in these studies was respectively 94,4% and 94,3%. Lethality during the remission period 5,9% and 2%, and the difference was not statistically correct. Frequency of relapses during treatment in Russia was 18%, in our study was 20,6% and they were nearly similar.

Treatment results of all disease, including ALL, depend on initial condition of patients at the beginning of the treatment. The distribution of patients involved to our study and contingent of is basically similar due to age (<10 years - 75.0 and 75.3%), sex (28.1% girls and 46.9% girls), standard risk (56.3 and 63.2%), B-cell KLL- to specific weight (90.6 and 93.3%).

Thus, although the treatment results of children treated with ALL-MB 2002 protocol and adolescents and young adults treated with ALL-MB 2002 and GMALL 05/93m protocols within the frames of our study, and initial characteristics of patients involved in treatment are different from similar features in the treatment of ALL written in literature, similar and common aspects between them also exist. The most important point is that patients' survival, reduction of relapses and other positive results are close to the achievements of the world practice.

There are new approaches not applicable to other research in our study. In our study we applied the methodology for using the patient's initial characteristics as a predictor of treatment outcomes and achieved reliable results.

In-depth and complex study of initial characteristics is necessary in treatment planning. Studying of these characteristics is included to patient examination standards. In addition to traditional signs (sex, age, risk groups, immunophenotype, amount of leukocytes, platelets and hemoglobin, number of blast cells in the blood and bone marrow, enlargement of the liver and spleen, damage to the central nervous system and mediastinal areas, etc.) immunegrams and key indicators of peripheral blood were used in our study. Standard approaches were used to distinguish subgroups due to levels of these symptoms. In distinguished subgroups the incidences of lethality, relapses,

remission, and toxic complications at all stages of treatment were compared. Existing of statistically correct differrence during the comparison lets us to study specificity, sensitivity, prognostic significance of these symptoms as risk factors.

Sensitivity of initial symptoms (the probability of lethality, relapses and complications against the background of the initial sign) changed within the interval of 1% and 26,9% (treatment with ALL-MB 2002 protocol).

Specificity of initial symptoms (the possibility of lethality, relapses, complications during treatment in the absence of initial symptoms) was high (92,0 – 100%).

The prognostic significance of the positivity of the initial signs (the probability of initial symptoms in patients with lethality, relapse and complications) changed within the large interval (20 – 100%).

Prognostic significance of negativity of initial signs (Probability of negativity of the initial sign in a group of patients who survived, without recurrence and complications) was within the frames of 13,0%– 87,6%.

These characteristics are very important for the doctor treating patients.

ACHIEVED RESULTS

1. Morbidity of children population of the Azerbaijan Republic with acute lymphoblastic leukaemia (ALL) in 1998-2004 years was within the interval of 1,32% – $3,64^{0}/_{0000}$, the main trend is growth and aproximation is highly expressed by regression equation ($y=-0,0042x^3+0,1018x^2-0,5688x+2,165$) (with determination coefficient 0,8918). The morbidity rate among 0-4 years old children was $2,5\pm0,57$ – $6,2\pm0,93^{0}/_{0000}$, among 5 – 9 years old children was $1,1\pm0,35$ – $3,5\pm 0,74^{0}/_{0000}$, among 10 – 14 years old children was $0,4\pm0,21^{0}/_{0000}$. The morbidity rate in Baku, Sumgayit and Ganja cities was higher than republican level, in Aran region was relatively low, and is on intermediate level in Guba-Khachmaz region [19;26].

2. The morbidity rate of acute lymphoblastic leukaemia in the Republic of Azerbaijan among 0 – 4, 5 – 9, 10 – 14, 15 – 29 years old population increased more than three times from 1998 year (respectively 7,2±0,97; 3,25±0,60; 1,41±0,41; 1,15± $0,23^{0/}{}_{0000)}$ till 2014 year (respectively 24,86±1,69; 17,95±1,70; 6,56±1,00 and $4,56±0,41^{0/}{}_{0000)}$. The morbidity rate of the disease in Baku, Sumgayit and Ganja cities (on corresponding ages ≥28,1; ≥10,2; ≥8,6 and $≥3,5^{0/}{}_{0000)}$, differs from regions (on corresponding ages 5,0 – 19,7; 2,4 – 13,7; 1,2 – 9,8; 0,9 – $9,7^{0/}{}_{0000)}$ [20;22].
3. Seasonality of acute lymphoblastic leukaemia exists as an objective factor, the average quantity of ALL incidence is similar in spring (15,49±1,13), summer (15,89±1,08) and autumn (15,71±1,24) and statistically higher than in winter (11,07±0,71). In summer season (May – October) ALL incidences are 1.2 times more than in winter (November – April) (respectively 5,4±0,21 and 4,6±0,23) [24;25].
4. Results of treatment of acute lymphoblastic leukaemia without any protocol are not satisfactory: there is no response to treatment in 39,5±7,2% of cases, relapses are recorded in 44,7±8,1%of cases, the probability of ten-year survival is zero. Therefore, it is necessary to provide mandatory protocol treatment of patients in the country [2].
5. Through adequate treatment of acute lymphoblastic leukaemia with ALL-MB 2002 protocol in childhood it is possible to increase the general, accident-free and relapse-free survival probabilities till 89,83 and 88% level. The general survival probability depends on age (<10 years old 91%, ≥10 years old 78%), on the initial level of leukocytes (in patients with $<50×10^9$/l is 91%; in patients with $≥ 50×10^9$/l is 69%), from initial damage to the central nervous system (undamaged 89%, damaged 63%), on the growth rate of the spleen (<4s – 90%; ≥4cm – 82%), on risk group (SRG – 91%; İmRG – 80%; HRG – 63%), reaction on the 15^{th} day of treatment (M1<5 – 92%; M2≥5 <25 – 81%; M3≥25 – 80%), on clinical base (Minsk – 89%; Baku – 75%) [4;23].
6. The ten-year total (65 and 45%), accident-free (65 and 36%), and relapse-free (74 and 50%) survival rates of adolescents treated

with ALL-MB2002 and GMALL protocols are different. The ten-year total (65 and 45%), accident-free (65 and 36%), and relapse-free (74 and 50%) survival rates of adolescents treated with 05/93m protocol are different. The difference is also existed in the treatment results of young adults aged 20-29 years, total survival is 55 and 31%, accidental survival is 51 and 28%, and recurrence-free survival is 63 and 38%. Treatment results in these protocols depend on the initial characteristics of the patients [6;7].

PRACTICAL RECOMMENDATIONS

1. As the prevalence of initial characteristics of patients with diagnosis of acute lymphoblastic leukaemia with high risk among Azerbaijan population is connected with late diagnosing of the disease, to strengthen the awareness of doctors about this disease in outpatient clinics;
2. Taking into consideration the seasonality of ALL incidences increase attention to non-specific symptoms of the disease (Pallor in 75.5% of cases, enlarged lymph nodes in 25.5% of cases, weakness in 72.4% of cases, hemorrhagic syndromes in 88.7% of cases) in the preventive examination of children in summer;
3. To prefer ALL-MB2002 or GMALL 05 / 93m protocols than non-program treatment of patients;
4. Fully and comprehensively assess the initial characteristics of patients for implementation of protocol treatment of patients;
5. To use initial characteristics as predictors of risks of lethality, recurrence and complication.

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