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Comparative Analysis of Treatment Standards for Acute Lymphoblastic Leukaemia

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ABSTRACT

Background: Acute lymphoblastic leukemia (ALL) is a critical hematologic malignancy, particularly affecting children. Treatment outcomes depend significantly on adherence to standardized, evidence-based protocols. While international guidelines exist, understanding regional variations in clinical standards within the Commonwealth of Independent States (CIS) is essential for optimizing care. This study specifically examines the current national treatment standards for ALL in Uzbekistan, Russia, and Kazakhstan.

Methods: A cross-national comparative analysis was conducted. Official national clinical guidelines, protocols, and formularies for ALL diagnosis and treatment from Uzbekistan, Russia, and Kazakhstan were systematically reviewed and compared. Key areas of comparison included diagnostic criteria and required tests, recommended treatment phases, specific therapeutic regimens, and the list of approved and accessible pharmaceuticals, including cytotoxic agents, targeted therapies, and supportive care drugs.

Results: Significant variations were identified across the three countries in all examined domains. Differences existed in the specificity of diagnostic requirements, the intensity and structure of treatment protocols, and crucially, in the formularies of accessible drugs. Disparities in the availability of newer targeted therapies and certain supportive care medications were particularly noted compared to international standards.

Conclusion: This comparative analysis highlights substantial heterogeneity in the national standards for ALL management across Uzbekistan, Russia, and Kazakhstan, especially concerning accessible therapeutics. These findings provide a crucial foundation for subsequent in-depth pharmacoeconomic evaluations and targeted market access strategies. The ultimate goal is to utilize this evidence to advocate for improved alignment with international best practices and to enhance the availability of effective, innovative treatments for ALL patients within the CIS region.

Keywords: Acute Lymphoblastic Leukaemia, Treatment Standards, Diagnostics, Treatment Methods, Antitumor Drugs, Targeted Therapy

Introduction

Acute lymphoblastic leukemia is the most common cancer in children, accounting for 1 in 3 cancer cases. Approximately 3 out of 4 acute leukemia cases in children and adolescents are acute lymphoblastic leukemia (ALL), whereas the remainder are acute myeloid leukemia (AML). Approximately 2,500–3,500 new ALL cases are diagnosed annually worldwide, or approximately 3.4 cases per 100,000 children [1].

ALL commonly occurs during early childhood. The incidence peaks between 2 and 5 years of age, is slightly more common in Hispanic and white children than in African American and Asian children, and is more common in boys than in girls [1].

Currently, overall survival and 5-year disease-free survival (DFS) in children with ALL can reach 90%, indicating that 9 out of 10 children with ALL recover. The poverty rate is worse in countries with lower living standards [1].

A review of treatment standards will help compare diagnostic and treatment methods for ALL in different countries, revealing their advantages and differences. This review will also consider the list of drugs used for treating ALL, making it possible to select drug groups for further research in the fields of pharmacoeconomics and marketing.

Experimental

To review treatment standards in the Republic of Uzbekistan, Russia, and Kazakhstan and compare diagnostic and treatment methods for ALL, as well as to consider the drugs used in different countries for further pharmacoeconomic analysis to provide the population with clinically and cost-effective drugs.

The study was conducted using comparative analysis and expert assessment of treatment standards. The study materials are the standards of treatment of ALL of the Republic of Uzbekistan (Order of the Ministry of Health of the Republic of Uzbekistan dated November 30, 2021 No. 273), Russia (All-Russian National Union "Association of Oncologists of Russia" Minutes dated February 01, 2020 No. 1/3П/2020), Kazakhstan (Ministry of Health of the Republic of Kazakhstan from "18" August 2023 Protocol No. 187) and also the Helzer protocols I, II phase, ALL – 2009 and Hyper CVAD Block A, B [2,3,4,5,6,7].

Discussion and Result

First, when choosing diagnostics and treatments for any disease, it is necessary to know the characteristics and classification of the disease and then make a further decision on this issue.

In acute lymphoblastic leukemia, precursors of lymphoid neoplasms are classified based on their origin as follows:

B-lymphoblastic leukemia/lymphoblastic lymphoma (B-ALL/LBL)

T-lymphoblastic leukemia/lymphoblastic lymphoma (T-ALL/LBL)

The disease can manifest as leukemia if tumor cells (lymphoblasts) penetrate the blood and bone marrow (detected in quantities of > 20% of blast cells in the bone marrow) or as lymphoma when blasts penetrate predominantly into extramedullary tissues.

The World Health Organization Classification of Lymphosarcomas of lymphoid neoplasms (World Health Organization [WHO]) for the period 2016 includes genetic data, clinical features, cell morphology, and immunophenotype, which are important for the prognosis and monitoring of the disease.

In all standards of diagnosis and treatment of ALL, medical measures begin with the collection of anamnesis and complaints; a thorough collection of complaints and anamnesis is recommended for all patients to identify factors that may influence the verification of the diagnosis and the choice of treatment tactics.

The symptoms of acute lymphoblastic leukemia usually appear several days or weeks before diagnosis.

The most common symptoms are associated with impaired hematopoiesis and subsequent development.

- Anemia
- Thrombocytopenia
- Granulocytopenia

Anemia is characterized by fatigue, weakness, pallor, malaise, shortness of breath with exertion, tachycardia, and chest pain.

Thrombocytopenia may result in mucous membrane bleeding, easy bruising, petechial hemorrhage/hemorrhagic rash, nosebleeds, bleeding gums, and heavy menstrual bleeding. Hematuria and gastrointestinal bleeding are rare. Patients with intracranial or intra-abdominal hematomas may experience spontaneous bleeding.

Granulocytopenia or neutropenia increases the risk of developing bacterial, fungal, and viral infections. Patients may experience fever and severe and/or recurrent infection.

Infiltration of organs by leukemic cells leads to enlargement of the liver, spleen, and lymph nodes. Infiltration of the bone marrow and periosteum can cause bone and joint pain, especially in children with ALL.

As a rule, the diagnosis of ALL can be assumed based on the data of physical examination, initial blood test, and coagulogram study and determination of fibrinogen (sharply reduced).

All treatment standards for ALL use the same **physical examination**, which may reveal varying degrees of pallor, petechial rash, bruising, bleeding gums, fever, lymphadenopathy, including enlarged tonsils, splenomegaly, hepatomegaly, enlarged kidneys, and tenderness to bone percussion. Skin involvement in ALL is rare and is associated with a pre-B immunophenotype [5,6,7,8].

Laboratory diagnostic tests for ALL.

The following laboratory diagnostic studies were conducted:

1. Morphological cytochemistry is the initial method for examining bone marrow, and it allows for the visual assessment of blast cells and counting their number.
2. FLO cytometry was used to determine the subtype of ALL and AML. This test can be used to determine the type of leukemia based on the presence of certain substances inside the cell. The procedure involves adding certain chemicals to bone marrow (BM) samples. After they interact with enzymes and other substances in the blast cells, it is possible to confirm what type of cells the blasts are developing into, as well as their degree of maturity.
3. Cytogenetics and FISH. These methods allow us to determine whether specific abnormalities exist in tumor cell chromosomes.
4. Molecular genetics is the final stage of the diagnostics of acute leukemia, allowing the evaluation of “breakdowns” in the cell DNA.

All treatment standards recommend that patients undergo a general (clinical) blood test with a white blood cell count and platelet count 2–3 times a week to verify diagnosis or during treatment to assess the dynamics of the therapy.

According to the treatment standards of Uzbekistan and Russia, cytochemical blood tests are performed to determine the volume of tumor lesions. This type of analysis and endolumbar puncture with the study of cerebrospinal fluid are not performed according to the treatment standards of ALL in Kazakhstan.

Myelograms are performed in all standards, this is an analysis (cytological) of bone marrow cells, which is performed using aspiration and/or biopsy of the bone marrow.

Urinalysis is recommended to prevent kidney damage.

In addition, according to the standards of Uzbekistan and Russia, blood tests for hepatitis B, C, and AIDS are performed to exclude concomitant pathology.

Standard cytogenetic testing is a necessary component of diagnostic procedures in a patient with suspected ALL. Karyotype abnormalities can also be identified by examining peripheral blood cells. Chromosomal abnormalities in ALL can be divided into quantitative or structural, associated with quantitative abnormalities, or isolated. Hyperploidy is the acquisition of additional chromosomes such that the total number of chromosomes in a single cell exceeds 46. In ALL, this process does not appear to be random. For this reason, this analysis was performed for the standards (Table 1).

Table 1. Diagnostic procedures for laboratory diagnosis of acute lymphoblastic leukemia in adults

Types of diagnostics	Uzbekistan USD		Kazakhstan USD		Russia USD	
General (clinical) blood test	+	2.4	+	3.3	+	8.51
Myelogram	+	5.28	+	22.2	+	196.42
Trephine biopsy	+	5.28	-		+	196.42
Cytochemical study	+	17.6	-		+	157.14
Endolumbar puncture with cerebrospinal fluid examination	+	14.24	-		+	109.12
Blood chemistry analysis	+	8	+	54.0	+	1.86
Oagulogram	+	3.28	-		+	17.24
And urine analysis	+	2.48	-		+	5.89
Blood culture reservoir	+	8	-		+	0,00
Determination of blood group and Rh factor, study of autoantibodies in erythrocytes	+	3.76	-		+	5.11
Blood test for hepatitis B	+	3.28	-		+	5.11
Blood test for hepatitis C	+	3.28			+	5.70
Blood test for AIDS	+	3.2			+	2.70
Immunophenotyping of bone marrow cells	-		+	52.9	-	
Spinal tap	-		+	332.3	-	
Cytogenetic studies	+	72	+	8.9	+	42.56
Total cost		195.9		473.6		753.78

Table 1 presents diagnostic procedures for the laboratory diagnosis of acute lymphoblastic leukemia in adults and the average cost of these tests. The average diagnostic test costs presented in the standard were also calculated. The results showed that the average cost of diagnostic procedures in the Republic of Uzbekistan was US$195.9, in the Republic of Kazakhstan was US$473.6, and in the Russian Federation was US$753.78 [9,10,11].

In addition, functional diagnostic procedures were performed for ALL. Unlike the standard of Kazakhstan, the standards of Uzbekistan and Russia recommend that all patients undergo an electrocardiographic examination (hereinafter referred to as ECG) and echocardiography (hereinafter referred to as EchoCG) to identify concomitant cardiac pathology and prevent or treat possible cardiac complications (Table 2).

Table 2. procedures for diagnosis of acute lymphoblastic leukemia in adults

Types of diagnostics	Uzbekistan		Kazakhstan		Russia	
ECG,	+	2.72	-		+	13.7
EchoCG	+	5.6	-		+	40.4
Ultrasound examination of peripheral and intra-abdominal lymph nodes	+	4.48	+	3.7	+	18.6
Ultrasound examination of abdominal organs	+	4.48	+	26.6	+	37.3
Ultrasound examination of the pelvic organs in women	+	4.48	+	15.5	+	32.3
Ultrasound examination of the prostate gland in men	+	6.16	+	15.5	+	32.1
Chest X-ray	+	10	-		+	45.5
Computed tomography of the chest segment	-		+	56.5	+	86.9
FGDS	-		+	26.6	-	
Total cost		29.6		144.4		306.8

Table 2 shows that all standards recommend performing an ultrasound examination (hereinafter referred to as ultrasound) of the peripheral and intra-abdominal lymph nodes, abdominal organs, pelvic organs in women, and prostate gland in men to identify concomitant pathology.

The treatment standard in Kazakhstan and Russia includes computed tomography of the chest segment to detect infiltrative changes in the lung tissue and an increase in the size of the intrathoracic lymph nodes. The standard procedure in Kazakhstan is fibroesophagogastroduodenoscopy (FGDS) to determine signs of esophagitis, gastritis, bulbitis, and duodenitis (Table 2). The average cost of functional diagnostic procedures is $ 29.6 in the Republic of Uzbekistan, $144.4 in the Republic of Kazakhstan, and $306.8 in the Russian Federation [12,13,14,15].

After the above procedures for diagnosing suspected ALL, the patient is referred to a specialist for consultation. It is necessary to identify concomitant diseases that may cause contraindications for treatment or risk of complications. In all cases, the patient is referred to a neurologist, ophthalmologist, otolaryngologist, gynecologist (women), or nephrologist for consultation. In Kazakhstan, patients are also referred for consultation with a boracic surgeon to determine indications for lung/mediastinal biopsy (table 3).

Table 3. Consultation with specialists in a narrow field

Specialists in the field	Uzbekistan		Kazakhstan		Russia	
Gynaecologist consultation	+	7.11	+	22.4	+	24.2
Cardiologist consultation	+	3.9	+	22.4	+	36.3
Consultation with a nephrologist	+	5.8	+	22.4	+	24.2
Consultation with a neurologist	+	4.7	+	22.4	+	33.0
Ophthalmologist consultation	+	4.7	+	22.4	+	18.7
Consultation with an otolaryngologist	+	6.9	+	22.4	+	18.7
Consultation with a surgeon	+	4.7	+	22.4	+	27.5
Consultation with a thoracic surgeon	-		+	22.4	-	
Phthisiatrician consultation	+	15.9	+	4.5	+	29.6
Total cost		54.18		183.63		212.8

Table 3 presents the average prices for consultations with specialists in a narrow field. The average cost of specialists in the Republic of Uzbekistan is 54.18 US dollars, in the Republic of Kazakhstan 183.63 US dollars, and in the Russian Federation 212.08 US dollars.

With any principle of chemotherapeutic action for treating ALL, there are several main stages of therapy: induction of remission, consolidation of remission, maintenance therapy, and prevention (treatment) of neuroleukemia.

The initial treatment period, which significantly reduces tumor mass and achieves CR, is called the remission induction period. In ALL therapy, two induction phases are used, each lasting 4 weeks, with no break between them. It is during this period that, against the background of the use of cytostatic agents, the number of leukemic cells in the BM decreases by approximately 100 times; i.e., at the time of CR detection, less than 5% of tumor cells are morphologically determined in the BM.

The second stage of OL therapy is consolidation of remission (reinforcement achieved antitumor effect). Currently, in most cases, consolidation is the most aggressive and high-dose stage of ALL treatment. The goal of this period was to further reduce the number of leukemic cells remaining after induction. Most often, 1–2 such courses are provided. Then, before maintenance treatment, reinduction programs (longer, similar to IT) can be used. In the protocol of Uzbekistan and Russia, the consolidation period is referred to as five long consecutive (3–4-week) stages, between which there are no breaks (!), but only the set of drugs used during this period changes, and the dosages of several cytostatic agents are modified (Table 4).

Table 4. Chemotherapeutic therapy

Protocol			ALL-MB 2009		
Phase	Dose	Path	Weeks	Day (Days)	Dose
Induction I -phase					
Prednisolone				2-28	60mg/ m^2
Dexamethasone	6 mg / **m2**	RO	1-4	1-28	10 mg/ m^2
Vincristine	**1.5** mg/ **m2**	**vv**	1-6	8,15,22,	2 mg/ m^2
Daunorubicin	45 mg/ m^2	**vv**	1(3)	8,15,22	45 mg/ m^2
L - asparaginase	10000 mg/ m^2	**vm**	5.6	29.36	10000 U/ m^2
Induction II - phase					
Mercaptopurine				43-70	25 mg/ m^2
Cyclophosphamide				43	1000 mg/ m^2
Cytarabine				45-48, 59-62	75 mg/ m^2
L - asparaginase	10000 mg/ m^2	**vm**	5.6	50,57,64	10000 U / m^2
Intensification			**Consolidation 1 (MB)**		
Doxorubicin				71.85	30 mg/ m^2
Dexamethasone	6 mg/ m^2	RO	14-15	71-84	10 mg/ m^2
Vincristine	1.5mg / **m^2**	**vv**	14-15	71.85	2 mg/ m^2

After completion of the consolidation stage, a period of maintenance treatment follows, i.e. continuation of cytostatic action in lower doses than during the period of remission induction, on the possible remaining tumor clone (Table 5).

Table 5. Chemotherapy therapy (Phase 4 and maintenance therapy)

Consolidation II				
Mercaptopurine	50 mg/ **m2**	RO	16-21	92-105
L - asparaginase	10000 U/ m2	VM	6-21	92.99
Consolidation III				
Mercaptopurine *	25 mg/ m2	RO	24-29	106-133
L - asparaginase	10000 units / m2	VM	24-29	163, 170, 177, 184, 191, 198
Cytarabine	75 mg/ m2			108-111,127
Cyclophosphamide	1000 mg/ m2			113,127
Consolidation IV				
Methotrexate	1.5 g / m2	VM	24-29	134
Dexamethasone	30 mg/m2	RO	30-31	134-136
L - asparaginase	10000 units / m2	VM	24-29	136
Consolidation V				
Cytarabine	2 g/m2 (2 times a day)			148
Dexamethasone	30 mg/m2	RO	30-31	148-150
L - asparaginase	10000 units / m2	VM	24-29	150
Supportive therapy				
Mercaptopurine	50 mg/ m2	RO	32-37,40-45, 48-53,56-61, 64-65,72-77, 80-85,88-93, 96-105	4-28
Methotrexate	30 mg/ m2	VM		2,9,16,23
Dexamethasone	10 mg/ m2	RO	38-39,46-47, 54-55,62-63, 70-77, 78-78, 86-87, 94-95	1-3
Vincristine	2 mg/ m2	**vv**		1
Daunorubicin	45 mg/ m2			1
L - asparaginase	10000 units / m2	VM	24-29	3.10

The drugs used for the treatment of ALL are presented in comparison in Table 6.

Table 6. Drugs used to treat ALL

Drug group	International nonproprietary name of the drug	Uzbekistan	Kazakhstan	Russia
Antineoplastic drugs	Daunorubicin	1	1	1
	Methotrexate	1	1	1
	Mercaptopurine	1	1	1
	Rituximab		1	1
	PEG - asparaginase		1	1
	L- asparaginase	1	1	1
	Etoposide		1	1
	Cyclophosphamide	1	1	1
	Cytarabine	1	1	1
Targeted therapy	Blinatumomab		1	
	Venetoclax		1	
	Dasatinib	1	1	
	Imatinib	1	1	1
	Nilotinib		1	
	Ponatinib		1	

Basically, for ALL without concomitant diseases, antineoplastic drugs are used (Daunorubicin, Methotrexate, Mercaptopurine, Rituximab, PEG-asparaginase, L- asparaginase, Etoposide, Cyclophosphamide, Cytarabine) and targeted therapy (Blinatumomab, Venetoclax, Dasatinib, Imatinib, Nilotinib, Ponatinib). In the treatment standards of Uzbekistan and Russia, only Imatinib is used for targeted therapy.

Conclusion

As a result of the review and comparison of standards in the treatment of ALL, the following was revealed:

1.In the standards of Uzbekistan and Russia, the following tests are not used in diagnostic procedures for laboratory diagnosis of acute lymphoblastic leukaemia in adults: Immunophenotyping of bone marrow cells, and spinal puncture.

2.In the treatment standards of Uzbekistan, consultation with a thoracic surgeon is not used for functional diagnostics to diagnose acute lymphoblastic leukaemia in adults.

3.A comparative analysis of the cost of procedures for diagnosis revealed that the total cost in the Republic of Uzbekistan is 279.68 US dollars, the Republic of Kazakhstan 801.63 US dollars, and the Russian Federation 1272.66 US dollars.

4.Based on the results of recalculation of the total cost of procedures, it was revealed that the cost of diagnostic procedures in the Republic of Uzbekistan is approximately 3 times cheaper than in Kazakhstan and 4 times cheaper than in Russia.

5.In the treatment standards of Uzbekistan, drugs such as Blinatumomab, Venetoclax, Dasatinib, Nilotinib, and Ponatinib are not used in the treatment of ALL.

In conclusion, following the comparison of treatment standards for ALL, it was noted that for further and more accurate conclusions, marketing pharmacoeconomic studies of drugs used for this disease will be conducted.

References

[1] https://wiki.nenaprasno.ru/nosologies/detskaia-onkologiia/leikozy-u-detei/675

[2] Order of the Ministry of Health of the Republic of Uzbekistan dated November 30, 2021 No. 273

[3] All-Russian National Union "Association of Oncologists of Russia" Protocol dated "01" February 2020 No. 1/3П/2020

[4] Ministry of Health of the Republic of Kazakhstan dated August 18, 2023, Protocol No. 187, Helzer I , II phase, ALL – 2009

[5] Hyper CVAD Block A, B., With classification of lymphoid neoplasms (WHO) (World Health Organization [WHO])

[6] Hematology: The latest reference book / Under the general editorship of K.M. Abdulkadyrov. - M.: Eksmo Publishing House; St. Petersburg: Sova Publishing House, 2004.-928 p., ill.

[7] Clinical oncohematology: A guide for doctors / Edited by M.A. Volklj. - 2nd edition, revised and enlarged. - M .: OJSC "Izdatelstvo" Medicine ", 2007. - 1120 p.

[8] International Classification of Diseases Tenth revision (ICD-10) Russian-Uzbek edition. - T., 2004 - 742 p.

[9] National standards of the Russian Federation. Protocols for patient management: Von Willebrand disease (GOST R 52600.1-2008). Hemophilia (GOST R 52600.3-2008). Moscow: NEWDIAMED, 2009.197 p.

[10] Programmatic treatment of leukaemia / edited by prof., MD, Corresponding Member of the Russian Academy of Medical Sciences V.G.Savchenko. - 2008, M., 1 v.
[11] Handbook of hematology: in 3 volumes/Ed. By A.I. Vorobyov. 3rd ed., revised and enlarged.M.: Newdiamed; 2003. 280 p.
[12] Rukavitsyn O.A., Skvortsov S.V., Zenina M.N. Hematology. Atlas-directory. St. Petersburg: publishing house "DETSTVO-PRESS", 2009.-256 p., ill.
[13] Collection of protocols and algorithms for chemotherapy and accompanying treatment of leukaemia, myelodysplasia and hematopoietic aplasia (1 volume). - 2008. - 487 p.
[14] Serov V.N., Barkagan Z.S., Vorobyov P.A. Protocol for patient management. Iron deficiency anaemia. - Moscow, 2005.
[15] Standards for providing specialized care to children and adolescents with haematological and oncological diseases. – M.: MEDPRAKTIKA-M publishing house, 2009.-576 p.