ISSN: 2832-2584

Research Article

Journal of Clinical Pediatrics and Child Care Research

Pediatric Acute Lymphoblastic Leukemia: Russian Experience with the ALL-IC BFM 2002 Protocol

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Submitted: 20 Nov 2022; **Accepted**: 24 Nov 2022; **Published**: 02 Dec 2022

Citation: *Valiev, T., Korkina, Y., Shervashidze, M., Kirgizov, K., & Varfolomeeva, S. (2022). Pediatric acute lymphoblastic leukemia: Russian experience with the ALL-IC BFM 2002 protocol. J Cli Ped Chi Res, 3(1): 99-109.*

Abstract

Background: *Treatment protocols for pediatric acute lymphoblastic leukemia (ALL) developed by the BFM (Berlin-Frankfurt-Munster) group are among the most effective in the world. The longstanding overall survival rate of children with ALL is more than 90%. The highly successful treatment results obtained for ALL are the reason that the ALL-IC BFM 2002 protocol is widely used in Russia.*

Aim: *This study presents the results of the Russian multicenter study for pediatric ALL treatment by the ALL ICBFM 2002 rotocol.*

Materials and Methods: *In total, 433 patients with primary ALL from 10 Russian pediatric hematology/oncology clinics were included in retrospective and prospective studies from 01.11.2003 to 12.10.2021. The ages of the patients ranged from 3 months to 21 years. All patients were treated according to the ALL IC-BFM 2002 protocol. The overall survival (OS), relapse-free survival (RFS), and event-free survival (EFS) were assessed on 11.12.2021.*

Results: *An overwhelming majority of patients, 97.9% (n=424), achieved clinical and laboratory remission by 33 days of treatment based on the ALL IC-BFM 2002 protocol. The 10-year OS was 91.8+/-1.5%, the RFS was 87.4+/-1.8%, and the EFS was 84.1+/-1.9%. The results of the 10-year OS in the standard-risk and intermediate-risk groups were 92+/-1.7%, and 93.1+/-3.0%, respectively, and the percentage of relapse in the high-risk group was 71.1+/-11.1%.*

Conclusion: *The ALL-IC BFM 2002 protocol for pediatric ALL could be performed in Russian federal and regional clinics. The treatment results for ALL using the ALL-IC BFM 2002 protocol are dramatic and comparable to those of leading clinics in Europe and the United States. To improve the survival rate in high-risk groups of patients, it is necessary to use additional risk-stratifying factors such as minimal residual disease (MRD).*

Keywords: Acute Lymphoblastic Leukemia, Treatment, ALL-IC BFM 2002, Children

Introduction

The successful treatment of pediatric acute lymphoblastic leukemia (ALL) was one of the most significant achievements of clinical oncohematology in the 20th century. The field has come a long way from methotrexate monotherapy at doses of 20–50 mg/m2 to the multicomponent risk-adapted intensive programs that became the modern antitumor treatment.

ALL was known as a fatal disease for a long time. The first unstable remissions were reported more than 70 years ago with the use of methotrexate. At the same time, there were reports of the antileukemic effects of 6-mercaptopurine (J.H. Burchenal, 1952). An opportunity to combine several cytostatic agents with antileukemic effects (prednisone, vincristine, 6-mercaptopurine, and methotrexate) and the necessity for a maintenance therapy of pediatric ALL patients were demonstrated by D. Pinkel in 1962 for the first time. That approach made it possible to obtain a 3-5 years relapse free-survival in 50% of patients [1,2].

While studying the special clinical aspects, it became clear ALL presented as a systemic disease, and it was necessary to treat not only the bone marrow but also the extramedullary manifestations. In the 1970s, a combination therapy arose out of the development of the principles of intrathecal treatment and the determination of

the radiation therapy possibilities. One of the first treatment programs with the intrathecal administration of cytostatic drugs and radiation therapy was the so-called Berlin Protocol. The strategy of remission induction, re-induction, prevention, and treatment of CNS disease as well as maintenance therapy were included in this Berlin Protocol for the first time. With the birth of the ideology of ALL treatment, the rules for the accompanying therapy were simultaneously formed. The aim was to reduce the rate of induction mortality and the number of complications from anticancer treatment. As a result, by the mid-1970s, a 5-year event free-survival had become a 55+/-6% chance for pediatric ALL patients in leading German clinics [3]. However, the protocol carried out in single clinics did not allow conclusions to be drawn based on representative results in a short time. It was clear that there was a need to form a multicenter group, not only to obtain reliable data but also to gain experience and to jointly discuss the clinical and diagnostic issues of ALL. As a result, in 1974–1975, a number of clinics in Berlin, Frankfurt, and Munster implemented the Berlin Protocol and organized one of the first multicenter groups for the treatment of pediatric ALL in the world. It was called the BFM (Berlin–Frankfurt–Munster) group [4].

The first programs of the BFM group (ALL-BFM 70/76) did not stratify patients into prognostic risk groups according to the clinical and laboratory characteristics of ALL. The treatment included Protocol I (methotrexate, cyclophosphamide, and 6-mercaptopurine) and maintenance therapy (prednisone and vincristine), but 60% of patients with initial hyperleukocytosis who received that variant of therapy had relapses within 1 year after starting their treatments. In addition to the leukocytosis patient's age (under 2 and over 10 years), CNS and mediastinal involvements, hepato/splenomegaly, acid phosphatase, and PAS-positive cytochemical blasts were associated with lower survival rates. Therefore, these factors became the risk-stratifying criteria for ALL. Later, the immunological features of blast cells (T- or B-linear immunophenotype) were added to these prognostic factors [5,6].

To increase the effectiveness of therapy for patients with unfavorable prognosis factors (high-risk of relapse), repeated intensification was added to the ALL-BFM 76/79 program. This was Protocol II, a set of antitumor drugs similar to Protocol I. The early intensification in the ALL-BFM 79 protocol was effective, and the survival of high-risk patients increased by 30% compared to what was achieved by the previous protocol. These data made it possible to include Protocol II in the treatment program for patients of all risk groups. As a result, the 5-year overall-survival rate increased to 70% [6].

In the 1980s, there was a comparison between the effectiveness of drug and radiation methods in the prevention of neuroleukemia in the BFM group protocols (ALL-BFM 81/83). Intermediate-risk patients (as the most numerous) received methotrexate at a dose of 500 mg/m2/24 h (four doses) intravenously in combination with intrathecal administration, or preventive CNS irradiation at a total basic dose of 18 Gy. It turned out that both ways were equally effective [7]. In the 1980s, complete clinical and hematological remission for 5–10 years was achieved in patients for the first time. An understanding of the potential possibility of curing children from ALL was formed during those years.

In 1986, the BFM group developed the ALL-BFM 86 protocol. For the first time, risk-stratifying criteria took into account important prognostic factors such as response to the eighth day of therapy. The survival results in groups of patients with an absolute number of blast cells of more than 1000/mics in blood on the 8th day of therapy were almost two times worse than those in the group with a number of blasts fewer than 1000/mics. Another significant modification of this protocol was the high dosage of methotrexate (5 g/m2/24 h, four injections in combination with intrathecal administration of methotrexate at age-specific dosages), which was used regardless of prognostic risk group. Such an approach made it possible to effectively prevent neuroleukemia and to reduce the total basic dose of radiation therapy to 12 Gy [8].

As the number of children recovering from ALL was increasing, a lot of attention was paid to the long-term side effects (mineral metabolism disturbances, growth, heart failure, infertility, second tumors, cognitive dysfunctions, etc.) in the development of treatment programs. Thus, in the ALL-BFM 90 protocol, standard-risk and intermediate risk patients had less-intensive therapy. This was not accompanied by a decrease in survival rates in those groups; however, the results of the treatment of high-risk patients were unsatisfactory—the 5-year event-free survival did not exceed 37%. To in-crease this parameter to thus intensify remission induction, one more administration of L-asparaginase was added during consolidation and the common idea of treating high-risk patients was changed. Short, high-intensity "blocks" such as those in the anti-relapse protocol ALL-REZ BFM 90 were included [9].

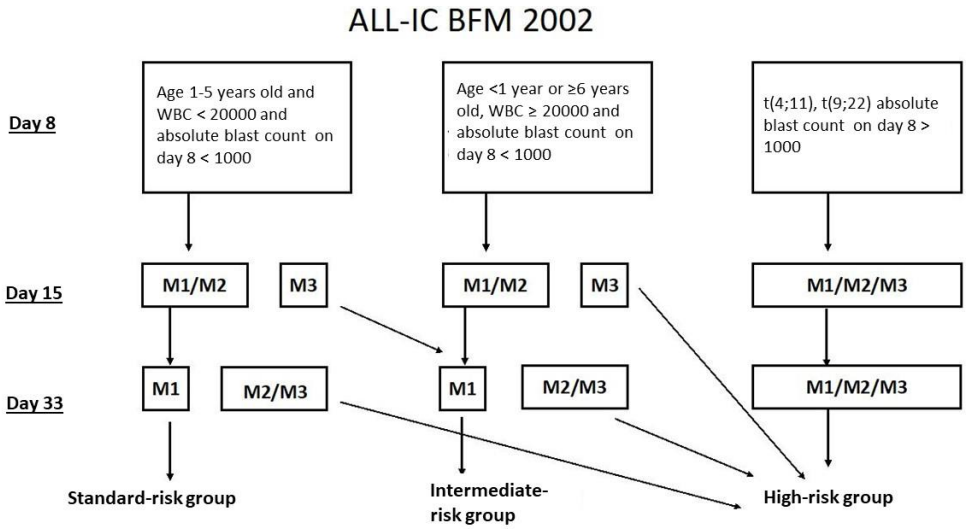
In the ALL-BFM 95 protocol, there was a reduction in the dose of anthracyclines by 50% in the groups of standard-risk and intermediate-risk patients. The duration of maintenance therapy was determined to be 12 months. The 6-year EFS in the standard-risk group was 89,5+/-1,1%, in intermediate-risk group was 79,7+/-1,2% and in the high-risk group was 49,2+/-3,2% [10].

The ALL-IC BFM 2002 protocol is one of the latest versions of the ALL treatment protocol developed by the BFM group. Nowadays beside the BFM other scientific groups all over the world have developed different ALL treatment protocols. Its effectiveness based on the results of event-free survival is shown in table 1.

Table 1: EFS of different modern protocols for ALL/

Protocol	EFS, %
CCSG L95-14	78,5
DFCI ALL 95-01	79,0
AIEOP-2000	75,9
POG 2001	73,0
ALL-MB-2002	78,3
CCG 2002	76,0
ALL-IC BFM 2002	82,5
UKALL 2003	87,3
COALL 07	83,5
NOPHO ALL 2008	85,1
DCLSG	82,6
NOPHO ALL—2008	89
TCCSG L04-16	78,1
CMCP ALL2008	78,5

*the observation period was 5-10 years



Note: WBC-white blood cells

Figure 1: Criteria for prognostic risk groups in the ALL-IC BFM 2002 protocol [11].

Patient stratification into prognostic risk groups is based on the clinical, immunological, and cytogenetic characteristics of the leukemic clone. This makes it possible to determine the need for an intensification in the treatment and to prevent an elaboration of cancer cell population resistance in the shortest possible time. The 8-year Overall survival in ALL, according to the ALL-IC BFM 2002 protocol, in European clinics was 91.4-92%. These results are among the best in the world. Taking into account the efficiency of the pediatric ALL therapy, according to the ALL-IC BFM 2002 protocol, the Ministry of Health of the Russian Federation approved this program as a clinical recommendation in 2020 (ID: 529).

The goal of this work is to study the effectiveness of pediatric ALL treatment as a retrospective-prospective trial in 10 united clinics.

Materials and Methods

Patients

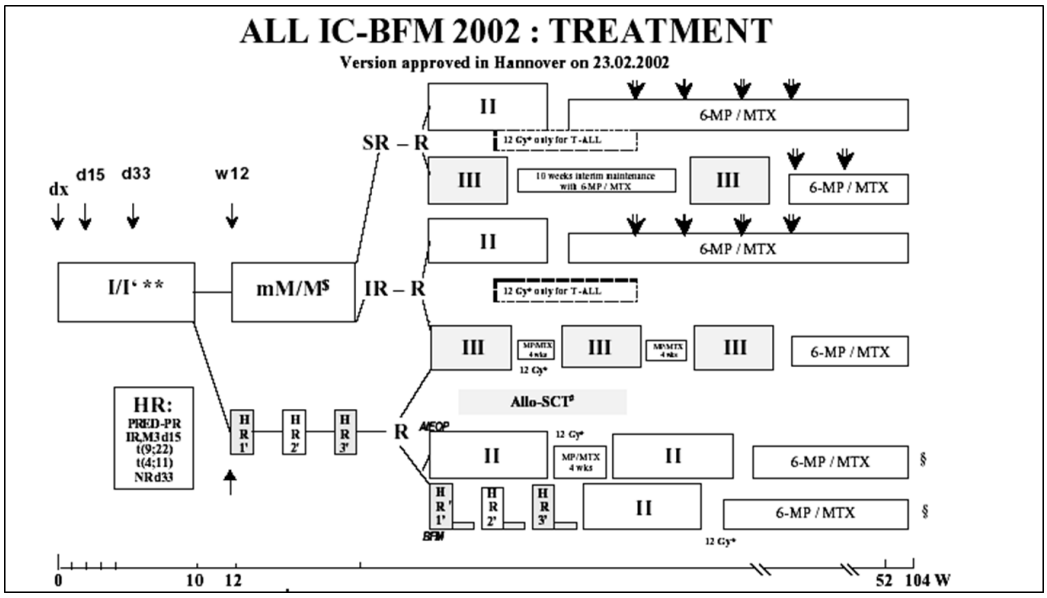
The multicenter retrospective-prospective study included 433 patients aged 3 months to 21 years with newly diagnosed ALL. They were treated according to the ALL-IC BFM 2002 protocol from 01.11.2003 to 12.10.2021. Overall survival, relapse-free (RFS), and event-free survival parameters were counted on 11.12.2021

Diagnosis

Diagnosis of ALL was determined from the results of cytological, cytochemical, immunological and cytogenetic bone marrow examinations in the local clinic laboratories. All patients' legal representatives signed informed consents for the treatment, in accordance with the ALL-IC BFM 2002 protocol. The design of the study is shown in Fig. 2

Stratification

The stratification into prognostic risk groups is shown at Figure 1. It is based both on the initial characteristics of ALL and the response to treatment at days 8, 15, and 33 (Fig. 1).



Note: Treatment outline and randomized questions in ALL IC-BFM 2002 (Acute Lymphoblastic Leukemia Intercontinental Berlin-Frankfurt-Munster [BFM] 2002) study. Protocol I: standard-risk (SR) T-cell acute lymphoblastic leukemia (T-ALL), all intermediate-risk (IR) and high-risk (HR) patients; protocol I: SR B-cell precursor (BCP) –ALL only; protocol M: only T-ALL, SR/IR; protocol mM: only BCP-ALL, SR/IR. (*) Presymptomatic cranial irradiation. (†) Protocol I daunorubicin 30 mg/m2 2 only for SR patients with BCP-ALL. (‡) For BCP-ALL: methotrexate (MTX) 2 g/m2 per day for 4 days; for T-ALL: MTX 5 g/m2 per day for 4 days. (§) Selected indications for allogeneic stem-cell transplantation (allo-SCT) in all strata of HR. (¶) No randomization of Associazione Italiana Ematologia Oncologia Pediatrica (AIEOP) versus BFM, but choice by group according to previous experience with one of the two HR strategies in trials AIEOP-ALL 95 and ALL-BFM 95. Shaded boxes depict experimental arms of delayed intensification. 6-MP, mercaptopurine; BM, bone marrow; Dx, diagnosis; d, day; HR-1, HR experimental group; HR-1, consolidation block HR-1; HR-2, consolidation block HR-2; HR-3, consolidation block HR-3; HR-2A, HR control arm (AIEOP option); HR-2B, HR control arm (BFM option); II, III, protocol designations; IR-1, IR control group; IR-2, IR experimental group; IT, intrathecal; NR, nonresponder; PRED-PR, prednisone poor response; R, randomization; SR-1, SR control group; SR-2, SR experimental group; wk, week; wks, weeks

Figure 2: ALL IC-BFM 2002 design protocol [11].

Criteria for response to treatment

Due to the criteria of the ALL-IC BFM 2002 protocol, the bone marrow cytological response is based on the number of blast cells on days 15 and 33 of therapy:

- M-1: less than 5% of blasts in bone marrow;
- M-2: the number of blasts in bone marrow is ≥5–<25%;
- M-3: the number of blasts in bone marrow is ≥25%.

An assessment of complete clinical and hematological remission was carried out on the 33rd day of therapy based on the following criteria:

- An absence of extra medullary manifestations of ALL during clinical and instrumental examination;
- In the case of an initial involvement of the mediastinal lymph nodes and thymus (usually in T-precursor ALL), the volume reduction must be 70% or more;
- An absence of blast cells in the blood;
- An absence of blast cells in the spinal fluid; and
- Cytological response M-1 in the bone marrow.

Treatment

Design of the ALL treatment due to protocol ALL-IC BFM 2002 is shown at Figure 2.

A statistical analysis of the data was carried out by constructing contingency tables according to Pearson's $\chi 2$ test. The survival rates were assessed using the construction of curve lines as per the Kaplan–Meier method. Overall survival was counted from the beginning of treatment until the death of the patient (or until last contact with the patient). Relapse-free survival was counted from the moment remission was re-ported until a relapse developed. Event-free survival was reported starting from the beginning of the treatment to the occurrence of an event, regardless of cause (progression of ALL, death during induction of remission or in complete clinical and hematological remission from any other cause, or relapse). Survivorship curves were compared between groups using the Logrank method. The statistical significance for all analyzed parameters was set at $p<0.05$.

Results

There were 433 patients in the study. The sex distribution was 1:1. The average age was 7.08 years old (from 3 months to 21 years). The distribution of ALL patients by age is presented in Fig. 3

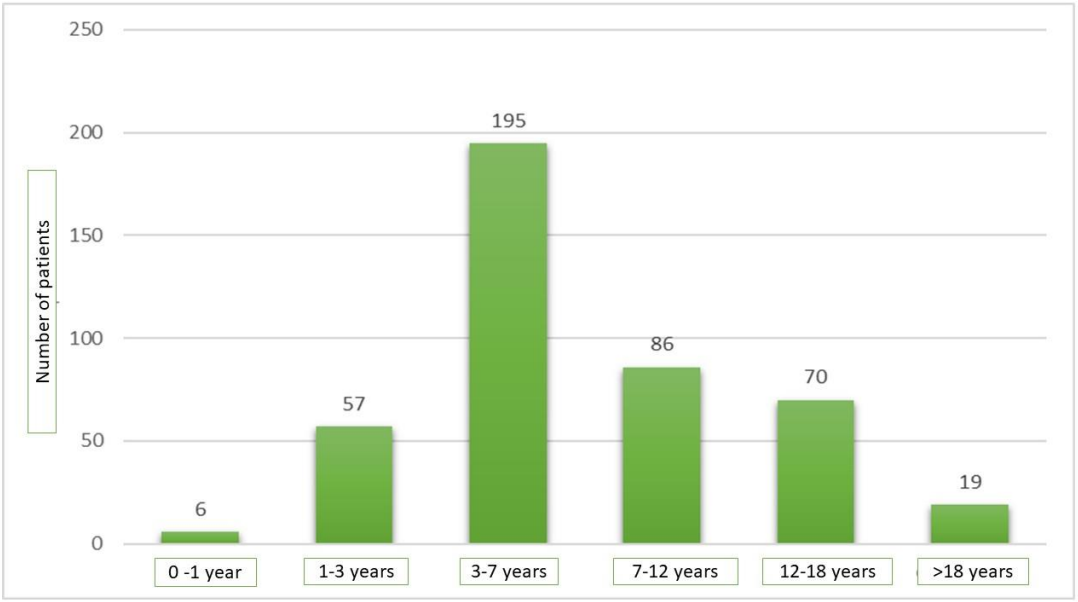
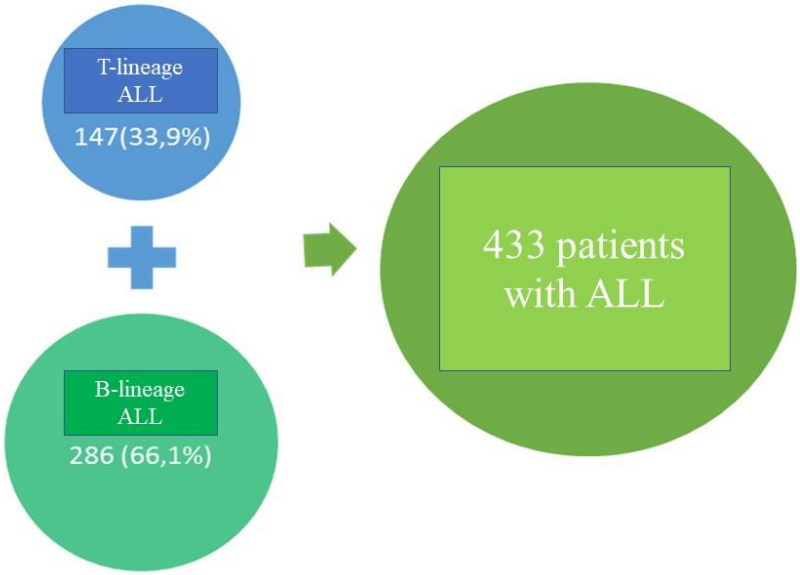


Figure 3: Distribution of ALL patients by age.

The most populous group was in the age range of 3–7 years: 195 patients (45%). Adolescents made up 16% (n=70), young adults (18–21 years) made up 4.4% (n=19), and patients under the age of 1 year made up 1.4% (n=6).

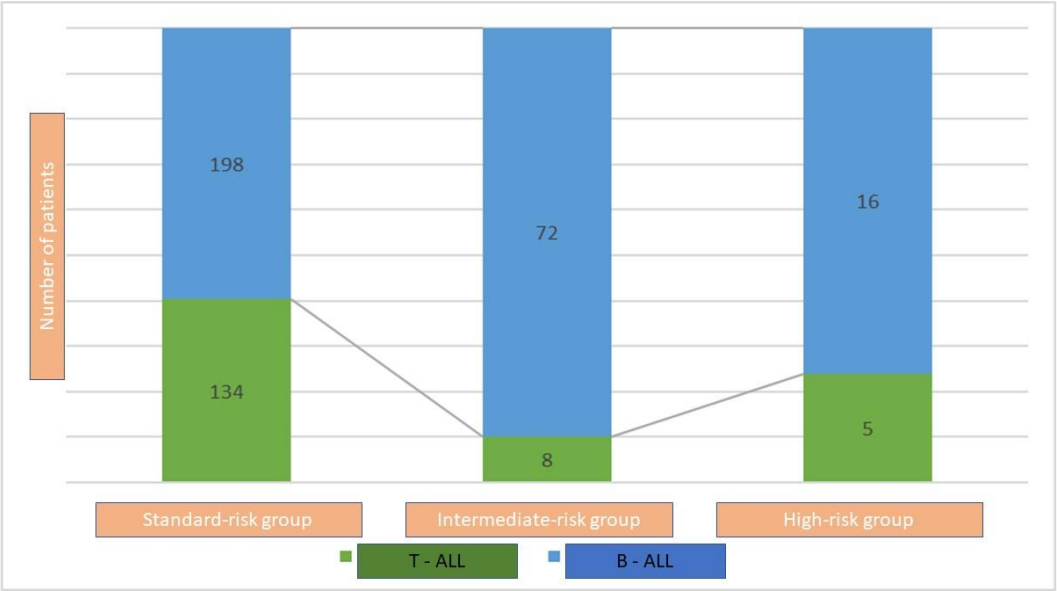
Among the patients' ALL immunological variants, those with B-lineage ALL numbered 286 (66.1%). The distribution of ALL patients by age and immunological variants corresponds to published literature data (Fig. 4).



Note: ALL-acute lymphoblastic leukemia

Figure 4: Distribution of ALL patients by immunological variant.

According to the stratification of patients into prognostic risk groups by age, cytogenetic aberrations, and therapy response on days 8, 15 and 33, the most numerous was the standard-risk group, with 332 patients (76.7%), followed by the intermediate-risk group, with 80 patients (18.5%), and the high-risk group, with 21 patients (4.8%) (Fig. 5).



Note: T-ALL- T-lineage acute lymphoblastic leukemia, B-ALL – B-lineage acute lymphoblastic leukemia

Figure 5: Distribution of ALL patients by immunophenotype and prognostic risk group.

Complete clinical and hematological remission by the 33rd day of therapy was achieved in 97.9% (n=424) of patients and not achieved in 1.8% (n=8). In one patient (0.2%), the remission status on day 33 could not be assessed because of the patient's death during induction therapy.

Mortality during the rest of treatment was 3.46% (15 patients out of 433 died before the end of the therapy program), which is in accordance with the data found in the literature.

The 10-year OS was 91,8+/-1,5%, RFS was 87,4+/-1,8%, and EFS was 84,1+/-1.9% (Fig. 6-8).

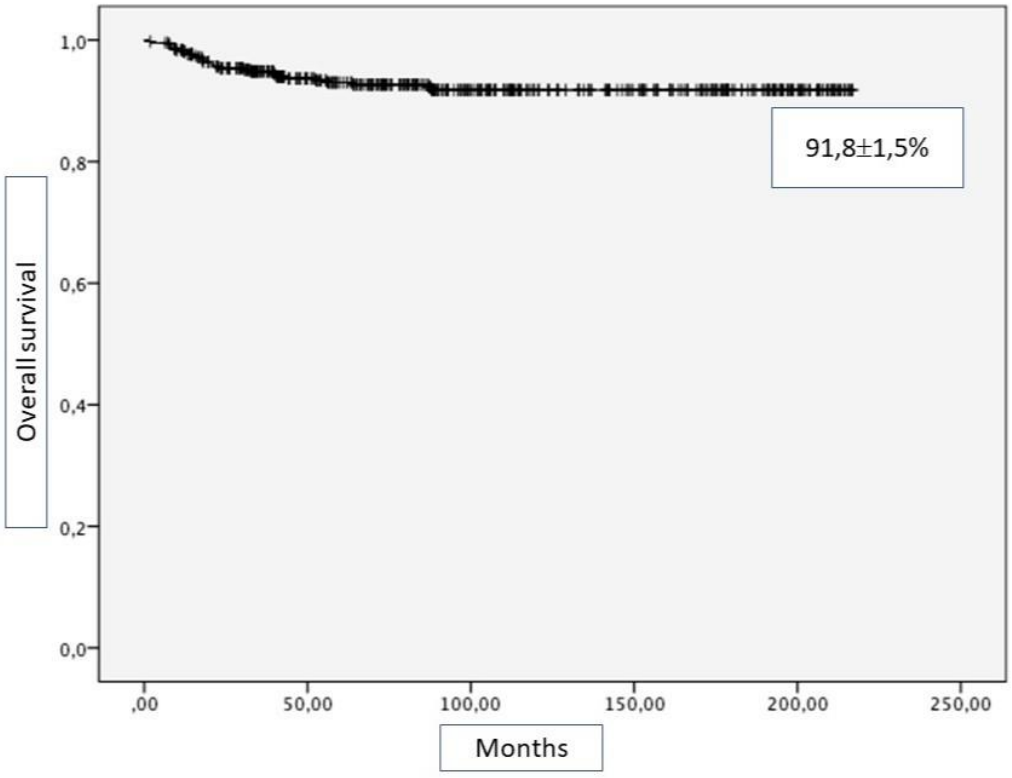


Figure 6: Overall survival of patients with ALL during therapy performed according to the ALL-IC BFM 2002 protocol.

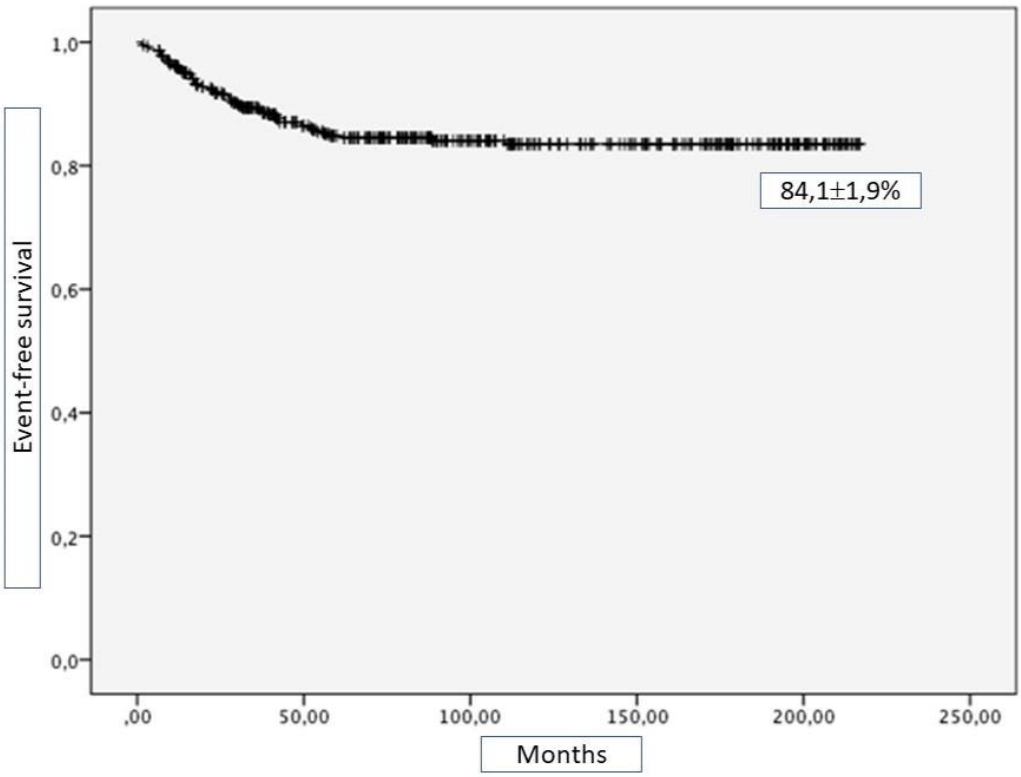


Figure 7: Event-free survival of patients with ALL during therapy performed according to the ALL-IC BFM 2002 protocol.

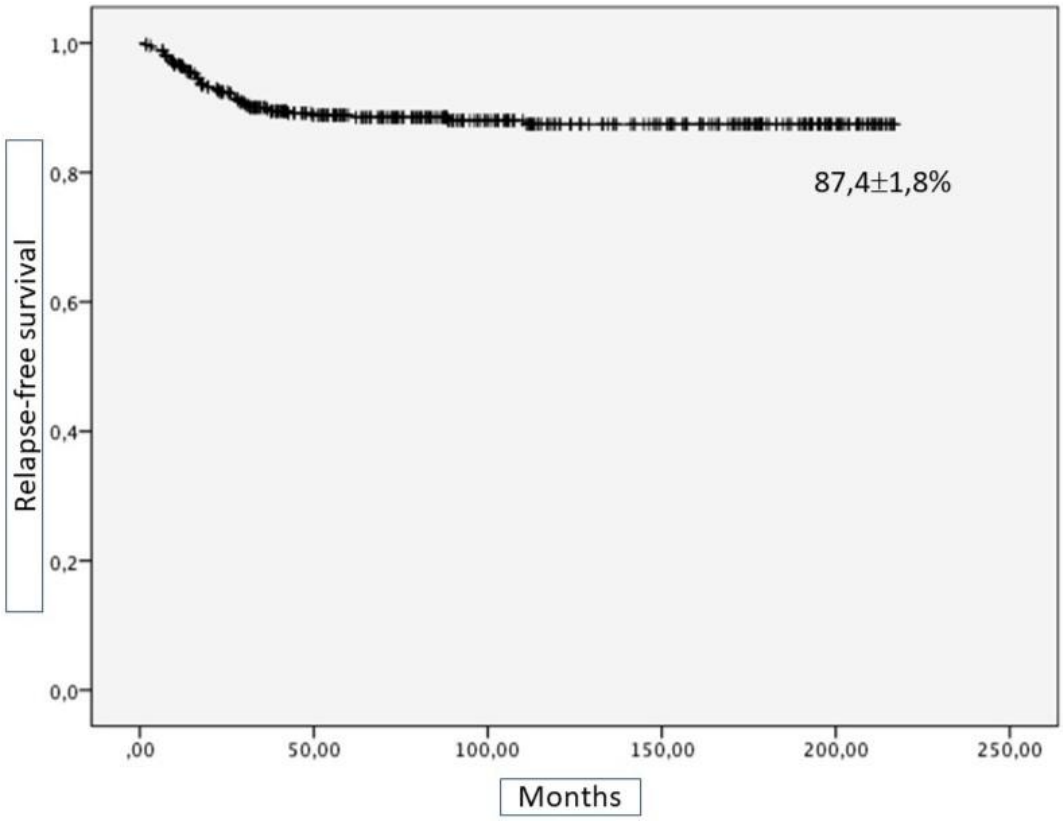
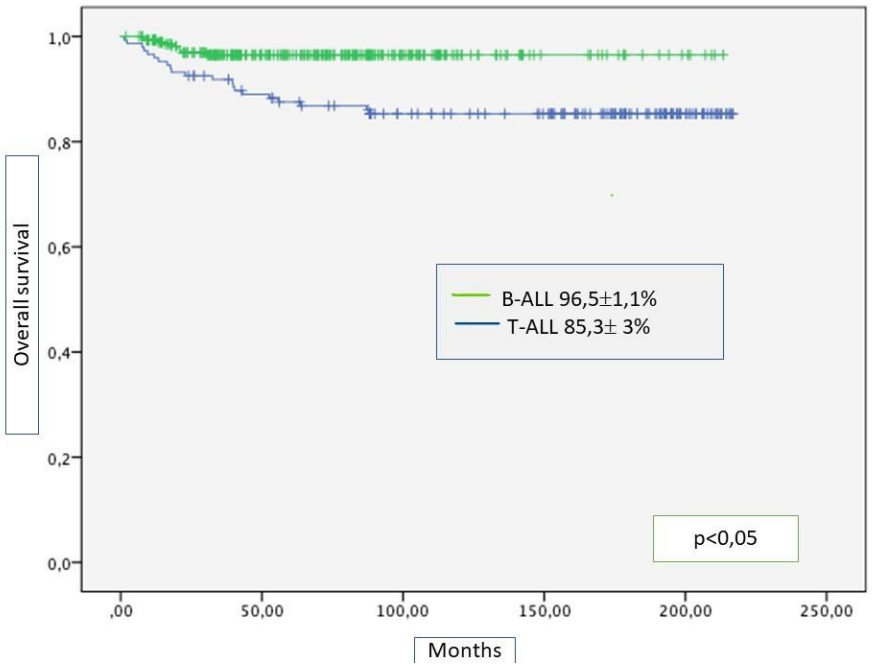


Figure 8: Relapse-free survival of patients with ALL during therapy performed according to the ALL-IC BFM 2002 protocol.

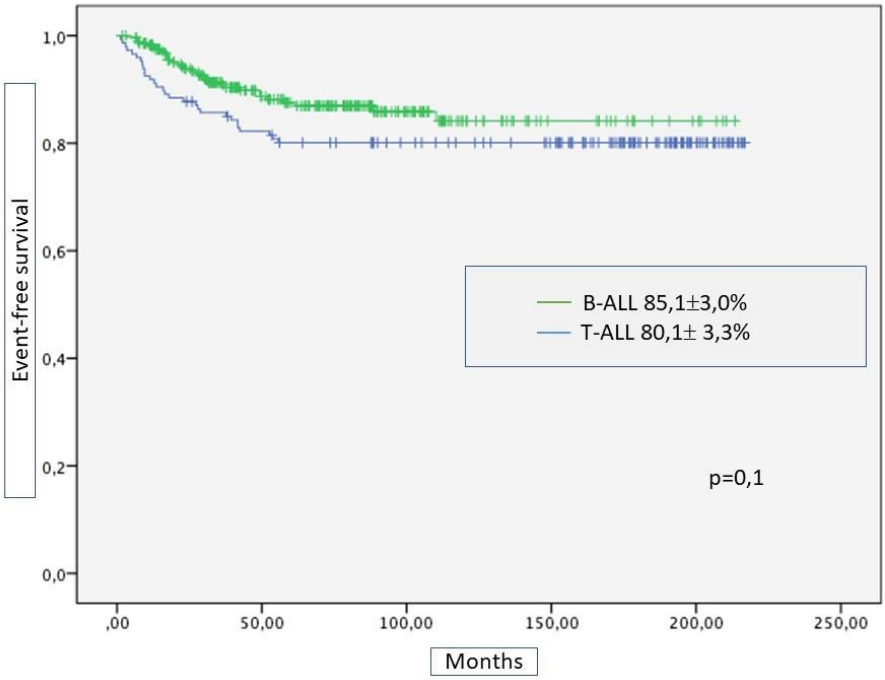
According to the study of the influence of the ALL immunophenotype on patients' survival, regardless of other prognostic factors, we obtained the following data: 10-year OS in the group of patients with B-ALL was 96,5+/-1,1%, and T-ALL was 85,3+/-3% (Fig. 9).



Note: T-ALL- T-lineage acute lymphoblastic leukemia, B-ALL – B-lineage acute lymphoblastic leukemia

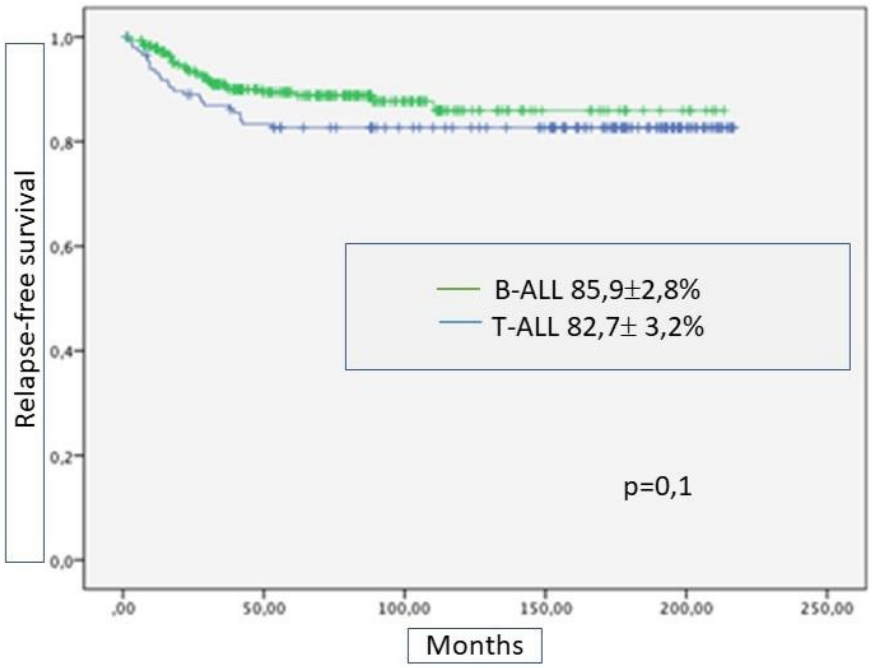
Figure 9: Overall survival of patients with ALL according to immunophenotype.

Despite the differentiated ALL therapies based on the immunophenotype of the tumor cell (the dose of methotrexate for patients with T-ALL was 5000 mg/m2, and for patients with B-ALL, it was 2000 mg/m2), T-cells turned out to be a significant factor of poor prognosis in OS. The EFS and RFS parameters did not depend on the immunological nature of ALL. Thus, the EFS of B-precursor ALL turned out to be 85,1+/-3%, and that of T-precursor was 80,1+/-3,3% (p=0.1). RFS was 85,9+/-2,8% and 82,7+/-3,2%, respectively (Fig. 10, 11).



Note: T-ALL- T-lineage acute lymphoblastic leukemia, B-ALL – B-lineage acute lymphoblastic leukemia

Figure 10: Event-free survival of patients with ALL according to immunophenotype



Note: T-ALL- T-lineage acute lymphoblastic leukemia, B-ALL – B-lineage acute lymphoblastic leukemia

Figure 11: Relapse-free survival of patients with ALL according to immunophenotype

All included patient survival rates were assessed according to their prognostic risk groups. As a result, in the standard-risk group, EFS was 84±2.2%, RFS was 88.9±1.9%, and OS was 92.8±1.7%. In the intermediate-risk group, EFS was 84.4±5%, RFS was 85.4±4.9%, and OS was 94.6±2.6%. Among the high-risk group, EFS was 63.5±12.7%, RFS was 63.5±12.7%, and OS was 71.1±11.1%. The data were statistically significant and reflect a general pattern of lower survival rates in the high-risk group of patients with ALL ($p<0.05$) (Fig. 12, 13, 14).

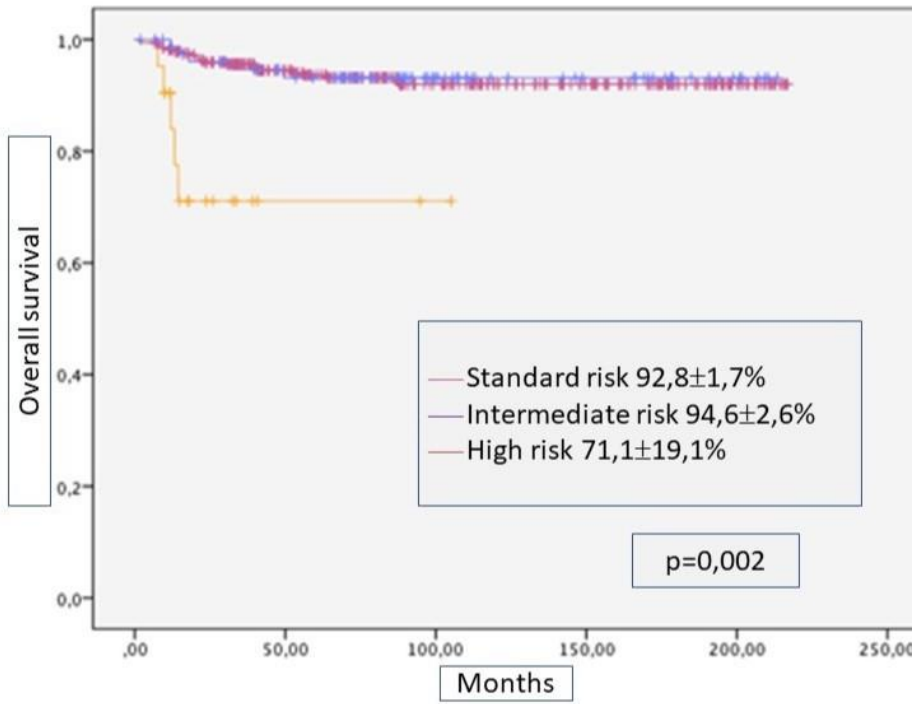


Figure 12: Overall survival of patients with ALL according to prognostic risk group.

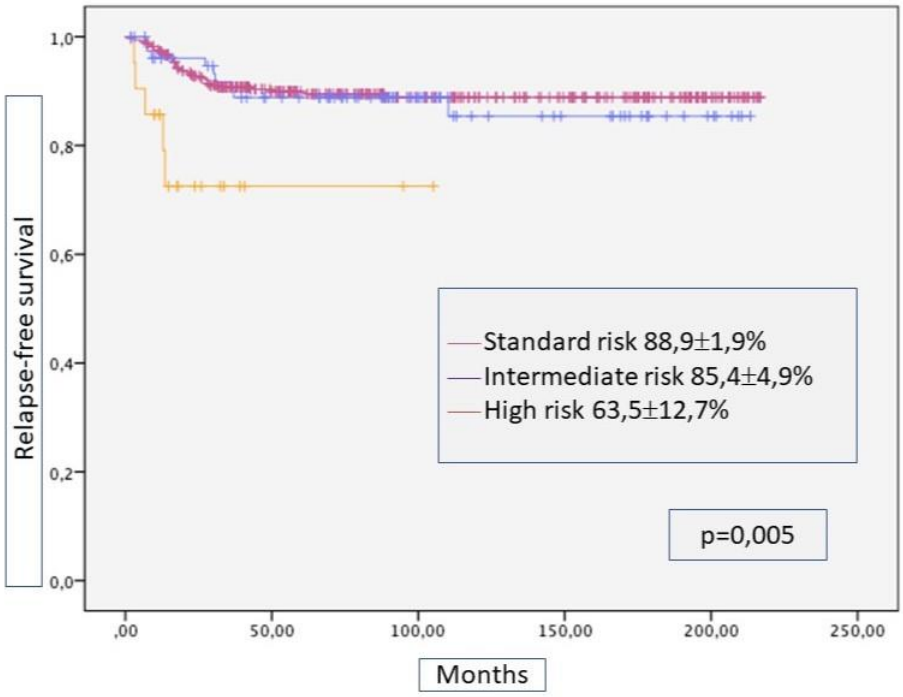


Figure 13: Relapse-free survival of patients with ALL according to prognostic risk group.

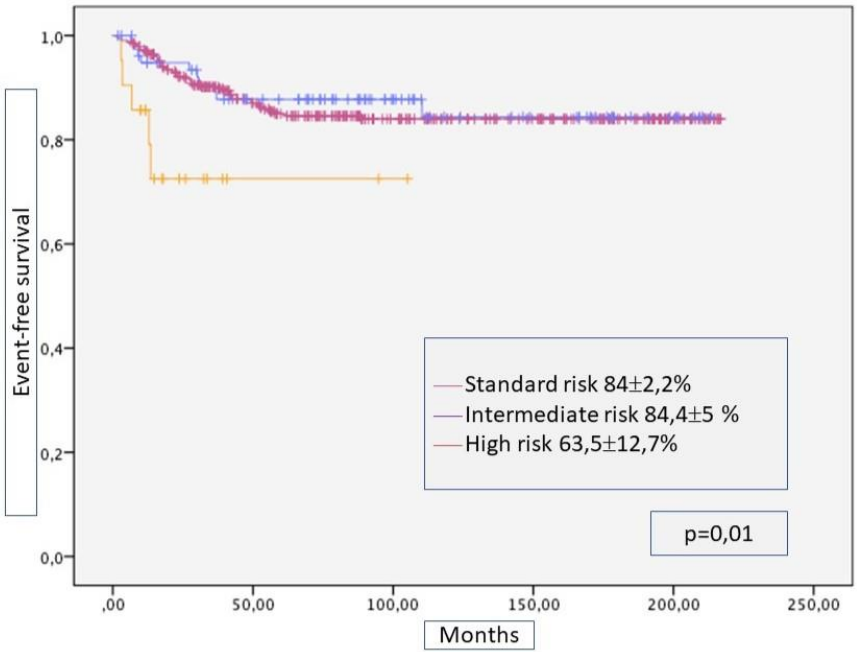


Figure 14: Event-free survival of patients with ALL according to prognostic risk group.

Discussion

Progress in the treatment of pediatric ALL is associated with exploring leukemogenesis and understanding the clinical, immunological, and biological heterogeneity of ALL. The data made it possible to determine the prognostic value of the clinical (age, initial leukocytosis, response to therapy on days 8, 15, and 33 of treatment), immuno-logical (T- or B-linear immunophenotype), and genetic (translocations t (9; 22), t (4; 11), formation of a chimeric transcript of MLL-AF4) factors in pediatric ALL. Special aspects of ALL significantly correlated with patient survival rates. They have become the basis for identifying the prognostic risk groups [1,2].

One of the most recognized international scientific groups specialized in the treatment of pediatric ALL is the BFM group. The ALL-BFM therapy protocols allow for the achievement of the highest results. This explains the local scientific and practical groups formed for the treatment of pediatric ALL using the BFM-orient-

ed protocols. As a result, multicenter studies are being successfully developed to estimate the effectiveness of the ALL- IC BFM 2002 protocol in Germany, the Czech Republic, Poland, Greece, Austria, Latin America, etc. This article presents the experiences of 10 clinics for a period of almost 20 years (from 2003 to 2021) for the treatment of pediatric ALL according to the ALL- IC BFM 2002 protocol.

The 10-year overall survival of the 433 patients with ALL was 91.8±1.5%; the RFS was 87.4±1.8%, and the EFS was 84.1±1.9%. The data for the 10-year OS in T-ALL turned out to be significantly lower than that in B-ALL: 85.3±3% vs. 96.5±1.1%. EFS and RFS were not statistically different in T- and B-linear ALL.

Differentiated therapy according to the prognostic factors made it possible to obtain the highest survival rates in the standard-risk and intermediate-risk groups of patients. Thus, in the standard-risk group, the 10-year EFS was 84±2.2%, the RFS was 88.9±1.9%, and the OS was 92.8±1.7%. Among patients of the intermediate-risk group, EFS was 84.4±5%, RFS was 85.4±4.9% and OS was 94.6±2.6% In the high-risk group, EFS was 63.5±12.7%, RFS was 63.5±12.7%. In addition, OS was 71.1±11.1%.

Table 2: Survival rates for each risk group

Group	OS, %	EFS, %	RFS,%
Standard risk	92.8	84.0	88.9
Intermediate risk	94.6	84.4	85.4
High risk	71.1	63.5	63.5

Possible ways to improve the effectiveness of therapy in the high-risk group include the addition of stratification criteria with data on minimal residual disease, expansion of the indications for the transplantation of allogeneic hematopoietic stem cells, and the inclusion of mono/biclonal antibodies (epratuzumab and blinatumomab) in antitumor treatment programs.

Conclusion

Thus, the results of the treatment of pediatric ALL in Russia according to the ALL IC-BFM 2002 protocol were comparable to those in European and U.S. clinics. The indisputable advantages of the ALL IC -BFM 2002 protocol include both efficiency and reproducibility in federal and regional clinics. Intensity-differentiated therapy for prognostic risk groups can reduce the toxicity of treatment in groups of patients with standard risk and intermediate risk. Among patients with high-risk ALL, a further search for additional antitumor approaches involving cellular and targeted methods is required.

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