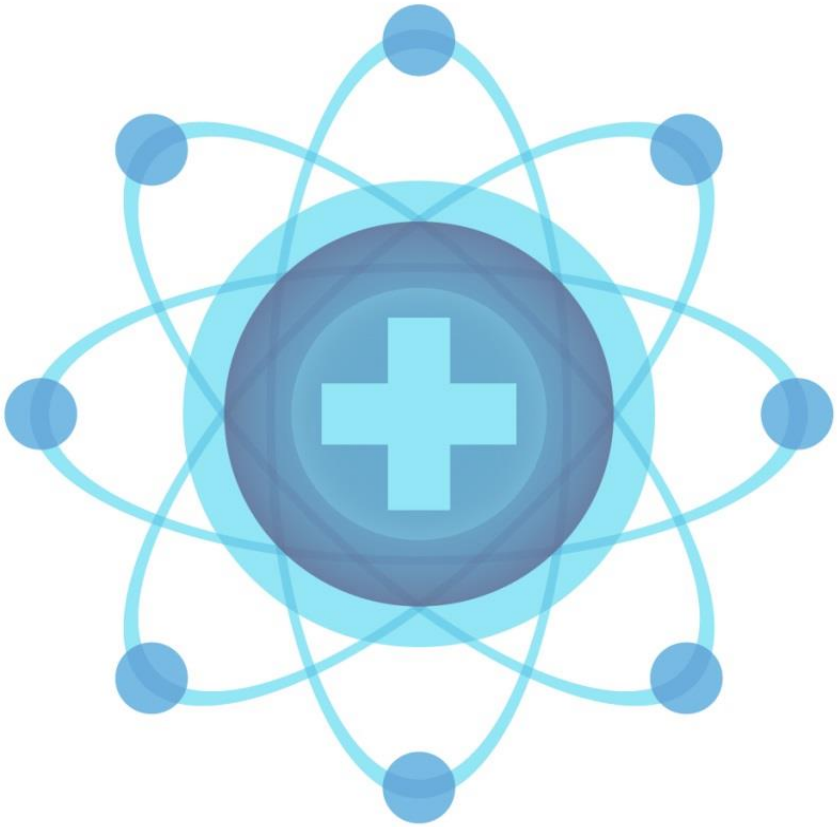

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Comparative analysis of the results of therapy according to the protocols all-bfm-95m and all-mb-2008 in Uzbekistan

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Abstract. The results of treatment of 368 primary patients with ALL (aged from 1 to 18 years) were analyzed. Of these, 145 received treatment according to the ALL-BFM -95m protocol and 223 children according to the ALL-MB-2008 protocol in the children's department of the Republican Specialized Scientific and Practical Medical Center of Hematology. Clinical, morphological, immunological, molecular genetic research studies of bone marrow and statistical methods for processing the results. The results of therapy of 145 patients according to the ALL-BFM-95m protocol were analyzed. Overall survival (OS) was 48% ± 4% (67 patients). The 10-year disease-free survival (EFS) was 48% ± 4% (67 patients). The cumulative recurrence risk (CIR) was 38% ± 4.1% (53 patients). There were 11.2% ± 2.6% of cases of deaths associated with therapy (TRD) - 16 patients. According to the results of therapy, 223 patients who received treatment according to the ALL_MB-2008 protocol: overall survival (OS) was 75% ± 3% (162 patients). The 10-year relapse-free survival (EFS) was 71% ± 3% (152 patients), the cumulative recurrence risk (CIR) was 16.4% ± 2.5% (36 patients). There were 8.8% ± 1.9% of cases of deaths associated with therapy (TRD) - 19 patients. In a comparative analysis of the results of treatment programs with different intensities of chemotherapy, 10-year relapse-free survival (EFS) according to the All-BFM-95m protocol was 48% ± 4% versus 71% ± 3% according to the ALL-MB-2008 protocol. The percentage of achieving remissions was higher in patients under the ALL-MB-2008 protocol, 95.1% (n = 213) compared to 90.3% under the All-BFM-95m protocol (n = 131, p = 0.0765).

Thus, it is possible to reduce the intensity and toxicity of the chemotherapy performed without reducing the final results of treatment. At the same time, the high intensity of chemotherapy according to the All-BFM-95m protocol was the reason for the high induction mortality.

Keywords: children, acute lymphoblastic leukemia, chemotherapy, risk groups, survival, relapse

Introduction. Acute lymphoblastic leukemia (ALL) occupies a leading place in the structure of oncohematological pathology in childhood and adolescence. It accounts for up to 20% of all malignant diseases (Fiel R.J. et al., 1988) and up to 75% of all leukemias (Stiller C.A. et at., 1990) [1,2,9]. The high efficiency of ALL treatment in children is one of the most impressive achievements of modern medicine. The programs of chemotherapy, developed over the last period, ALL in children can achieve a cure in 80% of patients with ALL [3,4,6]. Currently, there are opportunities for organizing effective measures for early diagnosis, treatment and

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prevention of complications [11,12]. In particular, the successful experience of introducing in Russia the original Moscow-Berlin protocol, created in cooperation with the Charite Clinic (Berlin, Germany), has shown the effectiveness of multicenter research technology in hematology/oncology to optimize the therapy of hematological malignancies in children [4,13].

Earlier in Uzbekistan, non-programmed treatment of ALL was carried out with a very low disease-free survival rate close to zero, then in 1999 it was started according to the ALL-BFM-95m protocol without immunophenotyping and molecular genetic analyzes, without stratification into risk groups. Since 2008, the implementation of the new ALL-MB-2008 protocol began, which involves risk-adapted therapy using new diagnostic technologies [3,8]. Advances in ALL treatment have demonstrated the potential of modern high-dose chemotherapy, the role of concomitant therapy, and the important role of multicenter randomized clinical trials. In this ALL-MB-2008 protocol, stratification was carried out into 3 risk groups, which was carried out taking into account the size of the spleen, initial leukocytosis, the results of immunophenotyping and molecular genetic research [4, 2]. Isolation of such prognostic factors as the age and sex of patients, initial leukocytosis, lesions of the central nervous system and mediastinum, the immunological phenotype of the tumor substrate, served as a rationale for modifying therapy programs, reducing the toxic effects of therapy for patients with a good prognosis and, conversely, for intensifying treatment protocols for patients. high risk, which significantly increased their chances of survival [4,5,6]. Of all the known prognostic factors, only the factors associated with the ongoing therapy can be modified and improved as the treatment protocols are optimized [4,10,13].

Material and research methods. The results of treatment of 368 primary patients with ALL (aged from 1 to 18 years) were analyzed. Of these, 145 received treatment according to the ALL-BFM -95m protocol and 223 children according to the ALL-MB-2008 protocol in the children's department of the Republican Specialized Scientific and Practical Medical Center of Hematology.

The analysis included 368 patients, including 226 boys (61.4%) and 142 girls (38.5%) aged 1 to 18 years (median age - 5.1 years).

The number of boys (63.4% and 60.1%) and girls (36.6% and 39.9%), depending on the treatment protocol, is approximately the same ($p = 0.5178$). According to age groups, patients were distributed as follows: up to 10 years - 300 (81.5%); from 10 to 18 years old - 68 (18.5%). The age composition of the patients of both groups is approximately the same: <10 years - 76.6% and 84.3%, >10 years - 23.4% and 15.2%, respectively ($p = 0.0476$).

There were 198 (53.8%) patients with initial leukocytosis in peripheral blood (PC) less than 10,000 / μl; more than 100,000 / μl - 54 (14.7%). Depending on the initial leukocytosis, the distribution of patients also does not differ: <10 thousand - 51.7% and 55.2 ($p = 0.5186$), >10 thousand<30 thousand. - 17.7% and 9.5% ($p = 0.6837$), >30 thousand<100 thousand. - 16.6% and 13% ($p = 0.3436$), >100 thousand - 15.9% and 13.9% ($p = 0.6034$).

The proportion of patients with an initial increase in the size of the spleen (more than 4 cm) was 38.3% (n = 141), did not depend on gender and was the same in different age groups. According to the size of the spleen, the distribution of patients is also the same: spleen <4 cm - 56.6% and 64.6%, spleen >4 cm - 43.4% and 35% (p = 0.1024).

Initial CNS damage was registered in 5 (3.2% of patients), 2.8% and 0.4% in patients of two groups, respectively (p = 0.0614) (See Table 1.).

Table 1.

Initial characteristics of patients

	BFM-95		MB-2008		p
	n	%	n	%	
Total	145	100	223	100	
Sex					
Boys	92	63.4	134	60.1	0.5178
Girls	53	36.6	89	39.9	
Age					
<10	111	76.6	189	84.3	0.0476
>=10	34	23.4	34	15.2	
Leukocytosis					
<10	75	51.7	123	55.2	0.5186
>=10 <30	23	15.9	39	17.5	0.6837
>=30 <100	24	16.6	29	13	0.3436
>=100	23	15.9	31	13.9	0.6034
Spleen					
<4	82	56.6	145	64.6	0.1024
>=4	63	43.4	78	35	
Answer 8 day					
<1000	142	100.0	108	86.4	<0.0001
>=1000	0	0	17	13.6	
неизвестно	3		98		
Answer 15 day					
<10	108	76.6	89	70.6	0.2689
>=10 <30	25	17.7	12	9.5	0.0526
>=30	7	5.0	25	19.8	0.0002
неизвестно	5		97		
CNS defeat	4	2.8	1	0.4	0.0614
Immunophenotyping					
B-ALL	3	2.1	123	55.2	
non B-ALL	0	0	15	6.7	
Unknown	142	97.9	85	38.1	
Cytogenetics					
t(4;11)	0	0	0	0	
t(9;22)	0	0	4	1.8	
t(12;21)	0	0	8	3.6	
Unknow	145	100	154	69.1	
Risk group					
SRG	57	39.3	83	37.2	0.6864

ImRG	68	46.9	121	54.3	0.1672
HRG	20	13.8	19	8.5	0.1083

Research methods: clinical, morphological, immunological studies of bone marrow by flow cytofluorimetry in the Russian Children's Clinical Hospital (Moscow), molecular genetic research of bone marrow in the laboratory of biochip diagnostics of the Federal Scientific Clinical Center for Pediatric Hematology, Oncology and Immunology named after V.I. Dmitry Rogachev "Ministry of Health and Social Development of Russia (Moscow) and statistical methods for processing the results.

Results and discussion.

The results of therapy of 145 patients according to the ALL-BFM-95m protocol were analyzed. Overall survival (OS) was 48% ± 4% (67 patients). The 10-year disease-free survival (EFS) was 48% ± 4% (67 patients). The cumulative incidence of relapse (CIR) was 38% ± 4.1% (53 patients). There were 11.2% ± 2.6% of cases of deaths associated with therapy (TRD) - 16 patients. (See Figure 1).

The results of therapy of 223 patients who received treatment according to the ALL-MB-2008 protocol were analyzed. Overall survival (OS) was 75% ± 3% (162 patients). The 10-year disease-free survival (EFS) was 71% ± 3% (152 patients). The cumulative incidence of relapse (CIR) was 16.4% ± 2.5% (36 patients). There were 8.8% ± 1.9% of cases of treatment-related death (TRD) - 19 patients. The results are presented in Figure 1 and Table 2.

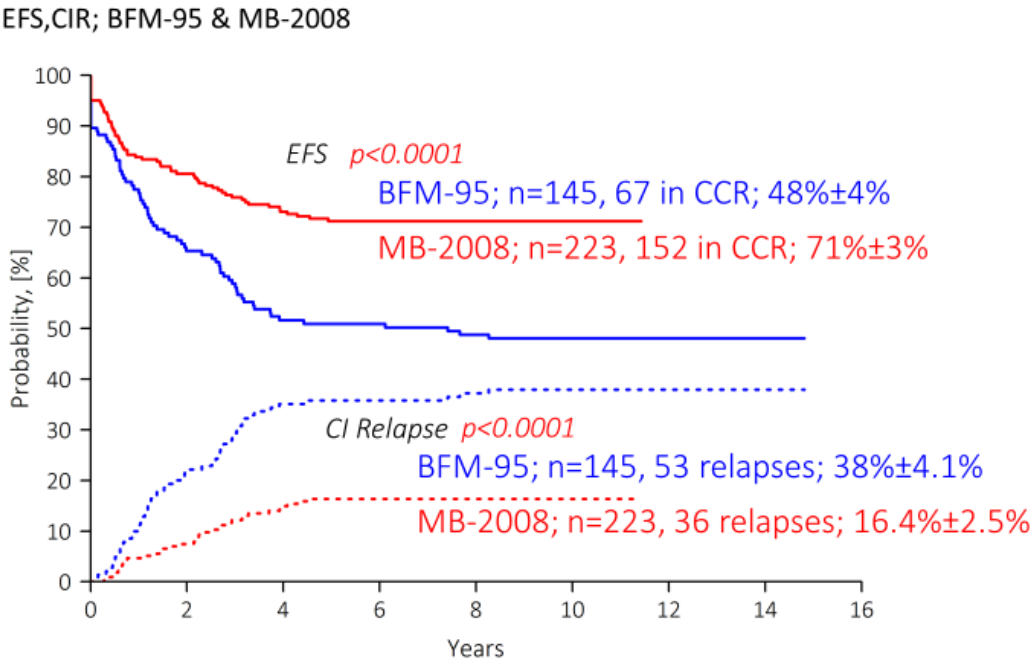

Fig. 1. Treatment results according to the protocols ALL-BFM-95m and ALL-MB-2008

Table 2.

Result treatment; BFM-95 & MB-2008

	BFM-95		MB-2008		p
	n	%	n	%	
Total	145	100.0	224	100.0	
Early death	10	6.9	4	1.8	0.0121
Not responder	4	2.8	7	3.1	0.8398
CR	131	90.3	213	95.1	0.0765
Remission death	6	4.1	15	6.7	0.3001
Second tumour	0	0.0	1	0.4	0.4204
Relapse	53	36.6	36	16.1	<0.0001
LFU	5	3.4	9	4.0	0.7797
CCR	67	46.2	152	67.9	<0.0001

Results of therapy by risk groups according to the ALL-BFM-95m protocol

The distribution of patients by risk groups was SRG - 57 patients, 30 of them in CCR, EFS was 56%. 68 patients were assigned to the ImRg group, 30 in PPR, EFS was 46%. HRG was 20 patients, 7 in PR, EFS was 35%. There is also a high relapse rate in HRG of 40%. In the SRG group, 37.1% (20), in the ImRg group, 38% (25), the relapse rate is also high. A high percentage of relapses is possibly associated with an unknown immunophenotype and cytogenetics, the lack of the possibility of stratification into risk groups and, as a consequence, of adequate therapy, when all patients, regardless of the risk group, received the same therapy. (See Figure 2.)

EFS,CIR; BFM-95; Группы риска

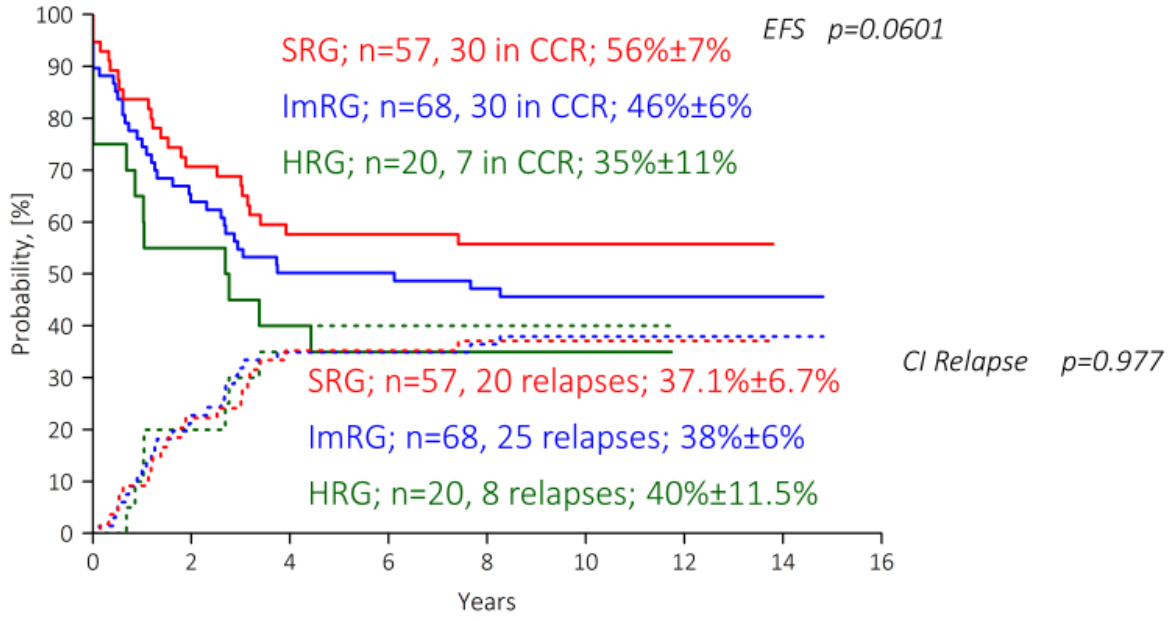

Fig. 2. Results of treatment by risk groups according to the ALL-BFM-95m protocol

It is noteworthy that the frequency of induction deaths is quite high and amounts to 6.9% for all patients, and 9.18% in the HRG group. Induction mortality rates did not differ in SRG and ImRG - 6.9%. Mortality in remission was 4.1%; it did not differ in the standard and intermediate risk groups. In 2.8% of patients were resistance (non-responder) to chemotherapy. There were no secondary tumors in the study group. In 53 patients (36.6%), the development of a relapse of ALL was recorded, while among SRG patients more than 70% of relapses developed 6 months after the end of therapy and later, then in ImRG and HRG patients, very early and early relapses prevailed. In general, and among individual risk groups, isolated bone marrow relapses prevailed. The incidence of relapses with CNS involvement was 18.8% among all patients, 5.6% in SRG and 11.3% in ImRG. The incidence of combined BM+CNS relapses is higher in ImRG –3.7% (2); 5 patients lost to follow-up 3.4% (LFU). Relapses with lesions of the testicles were registered in 2 (3.7%) patients, in 2 more patients with combined bone marrow and testicular.

Results of therapy by risk groups according to the ALL-MB-2008 protocol

The distribution of patients by risk groups was SRG - 83 patients, 68 of them in CCR, EFS was 83%. 121 patients were assigned to the ImRg group, 79 in PPR, EFS was 69%. HRG was 19 patients, 5 in CCR, EFS was 30%, it should be noted that due to the lack of the possibility of high-dose chemotherapy according to the ALL-MB-2008 protocol and the possibility of performing allogeneic BMT, patients in this group received treatment at an intermediate risk group. There is also a high relapse rate in HRG of 42.5%. In the SRG group, 8.5% (7) relapses, in the ImRg group, 18.2% (21) relapses were recorded. (See Figure 3) The high relapse rate in the intermediate risk group is possibly associated with a large number of patients with unknown immunophenotype and cytogenetics.

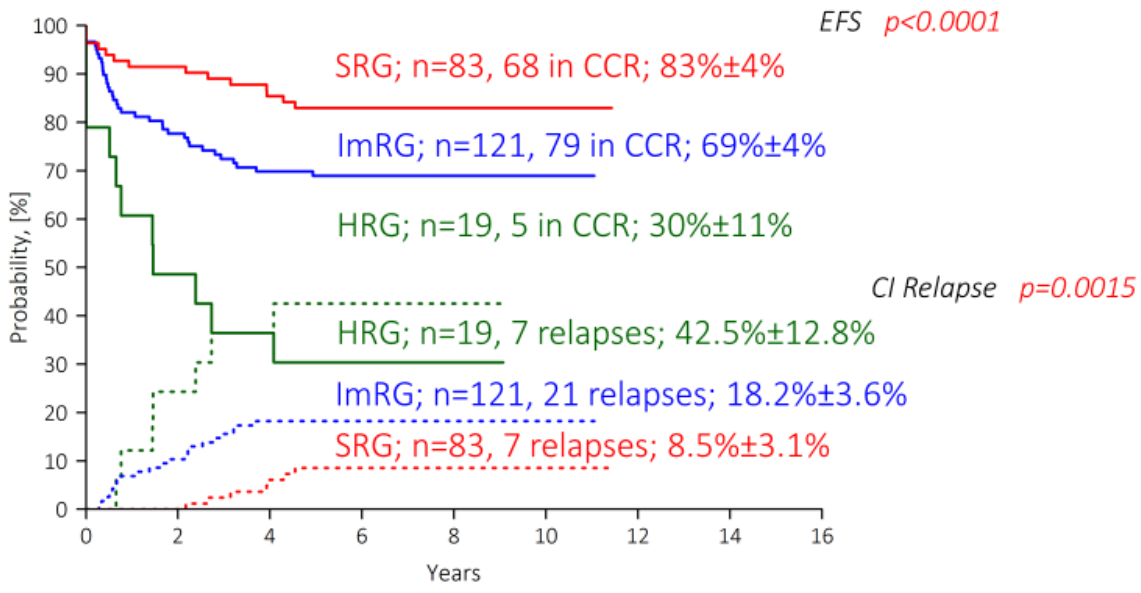

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Figure 3. Results of treatment by risk groups according to the ALL-MB-2008 protocol

The incidence of induction deaths was 1.8% for all patients, 6.18% in the HRG group. Induction mortality rates did not differ in SRG and ImRG. Mortality in remission was 6.7%, did not differ in the groups of standard and intermediate risk and was about 5%.

In 1 patient, the development of a secondary tumor was registered 15.2 months after the end of ALL therapy in the form of bladder cancer.

In 36 patients (16.1%), the development of a relapse of ALL was recorded, while more than 50% of relapses were late among SRG patients, more early relapses were observed in ImRG and HRG patients. Isolated bone marrow relapses prevailed in all risk groups. There were 5 (13.8%) isolated CNS relapses among all patients, most of them were in ImRG, combined (BM+CNS) relapses were 2. There were only 1 relapses with testicular lesions, and 1 Extramedullary relapse (EMR) in the form of unilateral damage to the cervical lymph node.

Table 3.

The number and location of relapses

Localization of relapse	All-BFM-95	ALL-MB-2008	P
Bone marrow	37 (69,8%)	27 (75%)	0.2689
CNS	10 (18,8%)	5 (13,8%)	<0.0001
Testicular	2 (3,7%)	1 (2,7%)	0.0002
Combined (BM + CNS)	2 (3,7%)	2 (5,5%)	0.0614
Combined (BM + testicular)	2 (3,7%)	_	
Extramedullary relapse (EMR) (cervical lymph node involvement)	_	1 (2,7%)	
Total	53 (36,6% of the total 145)	36 (16,1% of the total 223)	<0.0001

In a comparative analysis of the results of treatment programs with different intensities of chemotherapy, 10-year relapse-free survival (EFS) according to the All-BFM-95m protocol was 48% ± 4% versus 71% ± 3% according to the ALL-MB-2008 protocol. The percentage of achieving remissions was higher in patients in the ALL-MB-2008 protocol, 95.1% (n = 213) compared to 90.3% in the All-BFM-95m protocol (n = 131, p = 0.0765). It should be noted that induction mortality was high in patients of the first group (6.9%) compared with the second group (1.8%, p = 0.0121). There is also a high TRD of 11.2% ± 2.6% versus 8.8% ± 1.9%. There were no significant differences in the number of non-responder patients.

In a comparative analysis of the risk groups of the two protocols in the standard risk group (SRG), EFS in the All-BFM-95m group was 56% compared to EFS in the ALL-MB-2008 group of 83%, which is significantly higher.

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In the All-BFM-95m group, the result of therapy in the intermediate risk group (ImRg) was 46% EFS, compared with a similar risk group in the ALL-MB-2008 group of 69%, which is also significantly higher. In the HRG group under the All-BFM-95m protocol, EFS was 35%, which is higher than under the ALL-MB-2008 protocol, here EFS was 30%. But given the small number of patients, the comparison is unreliable. The relapse rate was significantly higher in SRG and ImRg risk groups when treated with the All-BFM-95m protocol.

Conclusions.

Thus, it is possible to reduce the intensity and toxicity of the chemotherapy performed without reducing the final results of treatment. At the same time, the high intensity of chemotherapy according to the All-BFM-95m protocol was the reason for the high induction lethality. The rate of death in remission in patients under the ALL-MB-2008 protocol was somewhat high, 6.7% compared to 4.1% ($p = 0.3010$), but the difference was not statistically significant. About 90% of deaths are due to infectious complications. The number of relapses is significantly higher in the first group, 36.6% (53) compared to 16.1% (36), and the difference is statistically significant ($p < 0.0001$). Perhaps this is due to the fact that patients of the first group underwent the same chemotherapy regardless of the risk group, since it was not possible to carry out a full diagnosis (lack of immunophenotyping, cytogenetic studies) and stratification into risk groups, as well as non-compliance with the timing of treatment, in more than 50% of patients with this In a group of patients, post-induction chemotherapy was performed with a delay of 10 days to 20 days, although the intensity of post-induction therapy was much higher. CCR in the first group of patients was 46.2% compared to 67.9% in the second group, that is, significantly higher ($p < 0.0001$).

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