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Original Article

Multicenter Randomized Controlled (Comparative) Open Prospective Study to Evaluate The Efficacy of The R-DA-EPOCH-21 And R-mNHL-BFM-90 ± Autologous Hematopoietic Stem Cell Transplantation Programs in Untreated Patients With De Novo Diffuse B-Cell Large Cell Lymphoma With Signs of Poor Prognosis - DLBCL-2015 Protocol

Aminat Magomedova[1], Sergey Kravchenko[1], Anna Misyurina[1], Yana Mangasarova[1], Oleg Margolin[1], Ekaterina Fastova[1], Fatima Babaeva[1], Lilia Gorenkova[1], Madina Bagova[1], Ekaterina Nesterova[1], Ksenia Sychevskaya[1], Tatyana Moiseeva[1], Alla Kovrigina[1], Tatyana Obukhova[1], Valentina Dvirnyk[1], Salia Maryina[1], Irina Galtseva[1], Vladimir Galuzyak[1], Karen Danishyan[1], Irina Kostina[1], Mikhail Gitis[1], Andrey Sudarikov[1], Elena Nikulina[1], Bella Biderman[1], Galina Klyasova[1], Gennady Galstyan[1], Mikhail Spirin[1], Sergey Kulikov[1], Yulia Chabaeva[1], Elena Zinina[2], Irina Kryuchkova[3], Svetlana Sizikova[3], Vera Sergeyevicheva[3], Tatyana Ksenzova[4], Ekaterina Anikina[4], Tatyana Shelekhova[5], Olga Arzhanukhina[5], Kamil Kaplanov[6], Tatyana Konstantinova[7], Olga Serdyuk[8], Tatyana Sychyova[9], Tatyana Chagorova[10], Irina Nec hunayeva[11], Lyudmila Anchukova[12], Oksana Dzarasova[13], Valery Savchenko[1], Elena Parovichnikova[1]

[1]National Medical Research Center for Hematology, Moscow, Russian Federation (Russia)

[2]Regional Clinical Hospital, Hematology Department, Surgut, Russia

[3]Research Institute of Fundamental Clinical Immunology, Hematology Department, Novosibirsk, Russia

[4]Regional Clinical Hospital No. 1, Hematology Department, Tyumen, Russia

[5]Clinic of Occupational Pathology and Hematology, Hematology Department, Saratov, Russia

[6]Regional Oncological Clinic No. 1, Hematology Department, Volgograd, Russia

[7]Regional Hematology Centre, Yekaterinburg, Russia

[8]Regional Oncological Clinic. Hematology Department, Krasnodar, Russia

[9]Regional Clinical Hospital, Hematology Department, Astrakhan, Russia

[10]Regional Oncological Clinic, Hematology Department, Penza, Russia

[11]City Hematology Centre, Novosibirsk, Russia

[12]Regional Clinical Hospital, Hematology Department, Vologda, Russia

[13]Republican Clinical Hospital, Hematology Department, Vladikavkaz, Russia

Correspondence

Aminat Magomedova

National Medical Research Center for Hematology, Moscow, Russian Federation (Russia)

E-mail: maminat@mail.ru

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Abstract

Background: NHL-BFM-90 chemotherapy is highly effective in pediatric aggressive B-cell lymphomas.
Purpose: To evaluate the efficacy and toxicity of the R-mNHL-BFM-90 and R-DAEPOCH-21 programs in adult patients with *de novo* DLBCL.
Patients and methods: Inclusion criteria: newly diagnosed DLBCL (NOS), no previous chemotherapy, 2 or more signs of poor prognosis, age 18-60. The protocol included 140 patients from 13 medical centers in Russia: R-DA-EPOCH-21 – 33; R-DAEPOCH-21+auto-HSCT - 29; R-mNHL-BFM-90 - 33; R-mNHL-BFM-90+ auto-HSCT -35 patients.
R-DA-EPOCH-21 branch: 6 courses were performed. If CR was not achieved, 2 courses of R-DHAP were performed ± auto-HSCT. Branch R-mNHL-BFM-90 included 6 cycles: RA-RB-RA-RB-RA-RB. If CR was not achieved, 2 courses of R-DHAP ± auto-HSCT.

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Results: Of 62 patients on R-DA-EPOCH-21±auto-HSCT, CR was achieved in 36 (58.1%) patients, PR was achieved in 14 (22.6%) patients, progression was reported in 6 (9.7%) patients, 3 (4.8%) patients had died, and treatment continued in 3 (4.8%) patients. Of 68 patients on R-mNHL-BFM-90±auto-HSCT CR was achieved in 63 (92.7%) patients, PR was achieved in 2 (2.9%) patients, progression was not reported, 2 (2.9%) patients had died, and treatment continued in 1 (1.5%) patient. The 4-year OS of patients in the high-risk group 94% on R-mNHL-BFM-90 therapy, 81% on R-DA-EPOCH-21 therapy;. the 4-year EFS of patients in the high-risk group was 78% and 43%, respectively (p = 0.0004).
Conclusion: R-mNHL-BFM-90 program is highly effective in de novo DLBCL NOS adult patients; toxicity is acceptable.

Introduction

Over the past 20 years, a large number of randomized studies have been conducted in patients with diffuse large B-cell lymphoma (DLBCL). The induction program of all studies was CHOP/R-CHOP in various modifications: CHOP with and without etoposide, CHOP-14 and CHOP-21, 6 courses of CHOP-14 versus 8 courses, R-CHOP versus CHOP with obinutuzumab, R-CHOP versus R-DA-EPOCH. All these studies have shown that the 3-year overall (OS) and event-free (EFS) survival of patients with DLBCL range from 40.6% to 78.1% and from 32.5% to 70%, respectively, and the rates are even lower in the high-risk group [1-7].

According to the international study SCHOLAR-1, the efficacy of chemotherapy in patients with refractory DLBCL defined as no response to the last chemotherapy or relapse ≤12 months after autologous hematopoietic stem cell transplantation (auto-HSCT), is very low; the complete remission (CR) rate was 7% and the median overall survival was 6.3 months [8].

Attempts to improve the results of DLBCL therapy by maintaining remission using the BEAM program with auto-HSCT did not yield positive results [9-11].

We have long assumed that the effect of treatment depends on the intensity of induction, and not on consolidating therapy.

NHL-BFM-90 short-pulse induction therapy has been shown to be highly effective in children with aggressive B-cell lymphomas [12]. Therefore, we decided to use this therapy (R3 branch) in adult patients under 60 years of age at moderate to high risk of de novo DLBCL progression. Given the poor tolerability of chemotherapy in adults compared to children, the protocol was initially modified: the dose of methotrexate (MTX) was reduced to 1.5 g/m^2 and the administration time was reduced to 12 hours. However, after treating 6 patients (3 from the high-risk group and 3 from the moderate-risk group), we observed a low efficacy in the high progression risk group. Therefore, we once again modified the NHL-BFM-90 program by adding doxorubicin at a dose of 25 mg/m^2 to the AA course on days 1 and 2; we also added MTX at a dose of 1.5 g/m^2 for 12 hours in the CC course. We called it the modified NHL-BFM-90 program (mNHL-BFM-90). Subsequently, between 2002 and 2007, this program was used in the treatment of 86 high-intermediate- and high-risk DLBCL patients in a pilot, prospective, single-center study. The efficacy of the mNHL-BFM-90 program was found to be superior compared to the historical data of the CHOP/R-CHOP program [13-16]. Five to ten years later, 40 of 86 patients (who consented) were screened for late toxicity. The study showed the absence of clinically significant hematological, cardio-, nephro- and hepatotoxicity [17,18].

We then conducted a retrospective analysis of the pilot study, which resulted in the exclusion of the CC course. We conducted another study investigating mesenchymal hematopoietic bone marrow stem cells in patients with DLBCL [19]. Finally, we conducted a randomized study and present the results in this article.

Based on our many years of experience in treating patients with lymphomas and the knowledge we possessed, we formulated a hypothesis that *de novo* DLBCL does not recur if CR is achieved, regardless of its clinical forms (nodal, extranodal), molecular types (GC- type, non-GC-type) and therapy, provided that the therapy is adequate. This hypothesis was tested in this study.

Purpose

To evaluate the efficacy and toxicity of the R-mNHL-BFM-90 and R-DA-EPOCH-21 programs in adult patients with de novo DLBCL with 2 or more signs of poor prognosis, and to determine the role of auto-HSCT.

Patients and methods

Patients

The study was conducted in accordance with the Helsinki Declaration. The protocol was approved by the ethics committee of each participating center. All patients signed an informed consent form.

Inclusion criteria: newly diagnosed DLBCL (NOS), no previous chemotherapy and/or radiation therapy, 2 or more signs of poor prognosis according to aaIPI, age 18-60 [19]. 11 patients older than 60 years were included at the start of the protocol.

Exclusion criteria: transformation of low-grade lymphomas to DLBCL, unclassifiable B-cell lymphoma with features intermediate between DLBCL and Hodgkin lymphoma (HL), high-grade B-cell lymphoma (NOS, double/triple-hit), DLBCL of the central nervous system (CNS), testicular DLBCL, primary mediastinal large B-cell lymphoma (PMBCL), HIV-associated DLBCL, and pregnancy.

The diagnosis was established in accordance with the 2008 and 2017 WHO criteria [20, 21].

Randomization

T164 patients were evaluated for randomization from February 2015 to June 30, 2021. The protocol included 140 patients from 13 medical centers in Russia. Randomization was carried out at the start of therapy in a ratio of 1:1:1:1: R-DA-EPOCH-21 - 33 patients; R-DA-EPOCH-21+auto-HSCT - 29 patients; R-mNHL-BFM-90 - 33 patients; R-mNHL-BFM-90+ auto-HSCT - 35 patients.

Information about patients from other medical centers was transmitted via WhatsApp and email. Patients underwent mandatory routine examinations, which included: a physical

examination, laboratory tests, ECG, echocardiography, computed tomography (CT) of the chest, abdomen, pelvis, head and neck (if indicated) or positron emission tomography (PET/CT), diagnostic lumbar puncture and bone marrow trephine biopsy. In the case of bone marrow damage, we also performed immunophenotyping by flow cytofluorometry or immunohistochemistry, as well as molecular testing for B-cell clonality of the bone marrow by polymerase chain reaction (PCR).

Cytogenetic study of tumor tissue by FISH for rearrangement of the Bcl-2, Bcl-6, C-myc genes was carried out in 72 patients, the study of TP53 gene mutation was conducted in 12 patients.

The disease was staged according to the Lugano classification [22].

Control examination was carried out after every 2 cycles of treatment and 1, 3, 6, 12, 24, 36, 48 months after completion of treatment.

Treatment response was defined as CR, partial remission (PR), or disease progression according to the Lugano 2014 criteria [22].

Adverse events were described in accordance with the Common Terminology Criteria for Adverse Events (CTCAE) 4.0 [23].

The effect of therapy was evaluated using PET/CT data. In the case of bone marrow damage, we also used trephine biopsy, immunophenotyping by flow cytofluorometry, and molecular testing for B-cell clonality of the bone marrow by PCR.

Of the 140 randomized patients, 10 (7.14%) were excluded from the analysis for various reasons: the diagnosis of DLBCL in 5 patients in the prephase changed to: Burkitt's lymphoma in 1 patient, HIV+ DLBCL in another 1, high-grade B-cell lymphoma malignancy in 2 patients, follicular lymphoma (FL) morphological type 3 in 1 patient; 2 patients did not meet the inclusion criteria, 1 patient refused treatment. Data for 2 patients were entered into the database twice by mistake.

Thus, 130 patients were included in the final analysis (Table 1).

Patients were included according to “intention to treat”. Therefore, when a diagnosis was not revised in the reference laboratory before the start of treatment, a blind revision of the diagnosis was carried out. In cases of PR after 6 courses, progression at any stage of treatment or relapse in 14 (10.8%) patients, we performed a second tumor biopsy. The diagnosis changed to transformation from indolent lymphoma to DLBCL or other forms of lymphoma in all patients (Table 2).

Given the above, therapy efficacy analysis was carried out in 2 stages.

At the first stage, all 130 patients presented in Table 1 were analyzed.

At the second stage, the efficacy of therapy was analyzed in the de novo DLBCL group with characteristics presented in Table 3. The groups are comparable in all parameters.

Table 1. *Characteristics of DLBCL patients*

	R + DA-EPOCH ± auto-HSCT n = 62 (48%)	**R + mNHL-BFM-90 ± auto-HSCT n = 68 (52%)**	**P**	**Total n = 130 (100%)**
Age, years **Median (range)** ≤60 >60	 54 (87.1%) 8 (12.9%)	 65 (95.6%) 3 (4.4%)	 0.2	 119 (91.5%) 11 (8.5%)
Sex, n (%) M F	 30 (48.4%) 32 (50.6%)	 41 (60.3%) 27 (39.7%)	0.21 ODR=0.61 (0.31–1.24)	 71 (54.6%) 59 (45.4%)
Nodal Extranodal	53 (85.5%) 9 (14.5%)	58 (85.3%) 10 (14.7%)	1.0 ODR=0.98 (0.37–2.61)	111 (85.4%) 19 (14.6%)
Stage II (bulky diseases) III IV	 2 (3.2%) 12 (19.4%) 48 (77.4%)	 5 (7.3%) 18 (26.5%) 45 (66.2%)		 7 (5.4%) 30 (23.1%) 93 (71.5%)
ECOG >2	19 (31%)	17 (25%)	ODR = 0.75 (0.34–1.62)	36 (28%)
Bone marrow involvement	11 (17.7%)	11 (16.2%)	0.76 ODR = 0.72 (0.22–2.29)	22 (16.9%)
TP53 rearrangement (n=12)	2 (16.6%)	2 (16.6%)		4 (33.2%)
Neuroleukemia Intratumor CNS	1 (1.6%) 0	0 0		1 (0.76%) 0
aaIPI 1 2 3	 0 21 (33.9%) 41 (66.2%)	 1 (1.5%) 19 (27.9%) 48 (70.6%)	 0.5	 1 (0.8%) 40 (30.8%) 89 (68.4)

Table 2. *Distribution of patients by nosological forms of lymphomas.*

Diagnosis	**R + DA-EPOCH ± auto-HSCT n = 62 (48%)**	**"R + mNHL-BFM-90 ± auto-HSCT n = 68 (52%) "**	**P 0.63**	**Total n = 130 (100%)**
DLBCL	55 (89%)	62 (91%)		116 (89.23%)
FL grade 2	1 (1.5%)	0		1 (0.76%)
FL grade 3 (A/B)	4 (6.5%)	3 (4.41%)		7 (5.4%)
NLPHL	0	1 (1.47%)		1 (0.76%)
PMBL	0	1 (1.47%)		1 (0.76%)
AITL	1 (1.5%)	0		1 (0.76%)
NMZL	2 (3%)	0		2 (1.53%)
HGBL double-hit: MYC and BCL2 rearrangements	0	1 (1.47%)		1 (0.76%)

Note: FL, follicular lymphoma; NLPHL, nodular lymphocyte-predominant Hodgkin lymphoma; PMBL, primary mediastinal (thymus) large B-cell lymphoma; AITL, angioimmunoblastic T-cell lymphoma; NMZL, nodal marginal zone lymphoma.

Table 3. *Characteristics of patients with de novo DLBCL*

	R + DA-EPOCH ± auto-HSCT n = 62 (48%)	**R + mNHL-BFM-90 ± auto-HSCT n = 68 (52%)**	**P**	**Total n = 130 (100%)**
Age, years **Median (range)** ≤60 >60	 48 (88.9%) 6 (11.1%)	 59 (95.2%) 3 (4.8%)	0.44	 107 (92.2%) 9 (7.8%)
Sex, n (%) M F	 26 (48%) 28 (52%)	 39 (63%) 23 (37%)	0.13 ODR=0.54 (0.26–1.15)	 65 (56%) 51 (44%)
Nodal Extranodal	45 (83%) 9 (17%)	52 (84%) 10 (16%)	1.0 ODR =1.04 (0.39–2.78)	97 (84%) 19 (16%)
Stage II (bulky diseases) III IV	 2 (3.70%) 11 (20.37%) 41 (75.92%)	 5 (8.06%) 16 (25.80%) 41 (66.12%)	0.4	 7 (6.03%) 27 (23.27%) 82 (70.68%)
ECOG >2	17 (31.48%)	16 (25.80%)	0.54 (0.33–1.69)	33 (28.44%)
Bone marrow involvement	7 (13%)	11 (17.7%)	0.28 ODR=2.58 (0.43–15.31) "	18 (15.5%)
TP53 rearrangement (n=12)	2	2		4
Neuroleukemia Intratumor CNS	1 (1.85%) 0	0 0	0	1 (0.86) 0
aaIPI 1 2 3	0 19 (35.2%) 35 (64.8%)	1 (1.6%) 18 (29%) 43 (69.4%)	0.5215	1 (0.9%) 37 (31.9%) 78 (67.2%)

Table 4. *Modified protocol R-mNHL-BFM-90*

			Days					
	Drugs	Doses	0	1	2	3	4	5
Pre-phase	Dexamethasone (IV, 30 min.)	10 mg/m^2		x	x	x	x	x
	Cyclophosphamide (IV, 1 h)	200 mg/m^2		x	x	x	x	x
Course A	Rituximab (IV, 4–6 h)	375 mg/m^2	x					
	Vincristine (IV, bolus)	2 mg/m^2		x				
	Methotrexate (IV, 12 h)	1000 mg/m^2		x				
	Doxorubicin (IV, 30 min.)	25 mg/m^2		x	x			
	Cytarabine (IV, 1 h)	100 mg/m^2					x	x
	Etoposide (IV, 1 h)	100 mg/m^2					x	x
	Dexamethasone (IV, 30 min.)	10 mg/m^2		x	x	x	x	x
	Ifosfamide (IV, 1 h)	800 mg/m^2		x	x	x	x	x
Course B	Rituximab (IV, 4–6 h)	375 mg/m^2	x					
	Methotrexate (IV, 12 h)	1000 mg/m^2		x				
	Vincristine (IV, bolus)	2 mg		x				
	Doxorubicin (IV, 30 min.)	25 mg/m^2					x	x
	Cyclophosphamide (IV, 1 h)	200 mg/m^2		x	x	x	x	x
	Dexamethasone (IV, 30 min)	10 mg/m^2		x	x	x	x	x

Treatment protocol

R-DA-EPOCH-21 branch: 6 courses were performed as previously described [24]. If CR was not achieved, 2 courses of R-DHAP were performed.

Branch R-DA-EPOCH-21+auto-HSCT: 6 courses were performed. If CR was achieved, R-BEAM and auto-HSCT on Day 7 as previously described [25] + rituximab 375 mg/m2 on Day 0 were used; if CR was not achieved, 2 courses of R-DHAP and then R-BEAM+auto-HSCT were performed.

Mobilization of hematopoietic stem cells was performed after any course at the discretion of the attending physician, and in the case of bone marrow damage, after elimination of the B-cell clone in the bone marrow.

Branch R-mNHL-BFM-90 included 6 cycles: RA-RB-RA-RB-RA-RB. The start of the next course was on Day 22. Administration of G-CSF after course A was carried out according to the general rules, after course B at the discretion of the attending physician.

The R-mNHL-BFM-90 + auto-HSCT branch includes 6 cycles of R-mNHL-BFM-90: RA-RB-RA-RB-RA-RB+ R-BEAM-auto-HSCT on Day 7; if there was no CR, 2 courses of R-DHAP were performed and R-BEAM + auto-HSCT after that.

The R-mNHL-BFM-90 protocol is presented in Table 4.

The concentration of methotrexate was determined as described previously [12].

None of the patients received preventive treatment of neuroleukemia or radiation therapy.

Treatment was discontinued if the lymphoma progressed, the patient refused to continue treatment, or at the discretion of the attending physician in the event of intercurrent illness or side effects.

The primary endpoints were CR, PR, progression, and death during therapy.

The secondary endpoints were OS and EFS.

Statistical analysis

We used standard methods of descriptive statistics, frequency and event analysis for statistical processing. Contingency table analysis was used to test for categorical variables in the compared groups. Fisher's exact test (for tables 2*2) and $\chi 2$ test (for tables of higher dimensions) were used to check the difference. The odds ratio (ODR) with an appropriate 95% confidence interval (CI) was interpreted as a measure of association. The nonparametric Mann-Whitney rank test was used to test differences in the distributions of numerical variables.

Estimated overall and event-free survival, as well as the probability of achieving CR, were calculated using Kaplan-Meier methods, and a logarithmic rank test was used to compare groups.

For overall survival, time was defined as the interval from the date of diagnosis to the date of death; date of last contact.

For event-free survival, time was defined as the interval from the date of diagnosis to the date of the first adverse event (death, progression, and relapse), taking the date of last contact into account.

To assess the probability of achieving CR, time was defined as the interval from the date of diagnosis to the date of CR according to PET results, the date of censorship of the last contact, or the date of death.

Cox proportional hazards regression model was used to assess the influence of factors on the distribution of the target trait; the relative risk value and the corresponding 95% CI indicate the measure of the relationship. Statistical analysis was carried out using the procedures of the SAS 9.4 package.

Results

Efficacy

Table 5 shows the results of treatment in all 4 branches.

Since we used only 2 treatment programs, 4 groups were combined into 2 groups to evaluate efficacy and toxicity: R-DA-EPOCH-21±auto-HSCT and R-mNHL-BFM-90±auto-HSCT, respectively

First stage of analysis

At the end of 6 cycles, of 62 patients treated with R-DA-EPOCH-21±auto-HSCT, CR was achieved in 36 (58.1%) patients, PR was achieved in 14 (22.6%) patients, progression was reported in 6 (9.7%) patients, 3 (4.8%) patients had died, and treatment continued in 3 (4.8%) patients.

Of 68 patients treated with R-mNHL-BFM-90±auto-HSCT, by the end of 6 cycles, CR was achieved in 63 (92.7%) patients, CR was achieved in 2 (2.9%) patients, progression was not reported, 2 (2.9%) patients had died, and treatment continued in 1 (1.5%) patient.

The probability of achieving CR is shown in Figure 1.

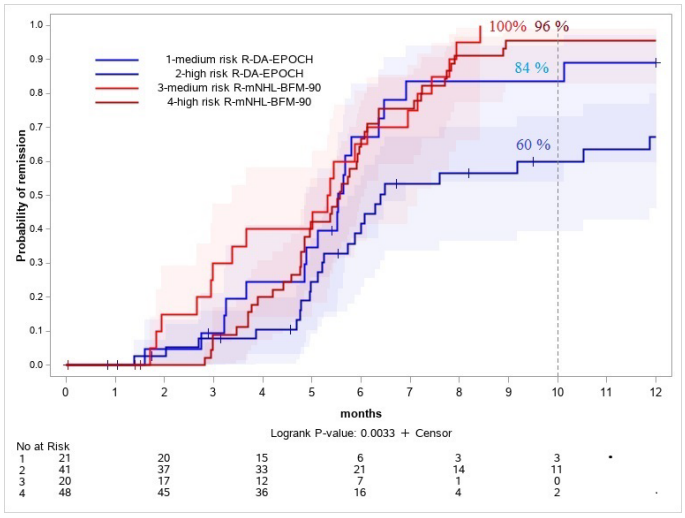


Figure 1. *Probability of achieving CR*

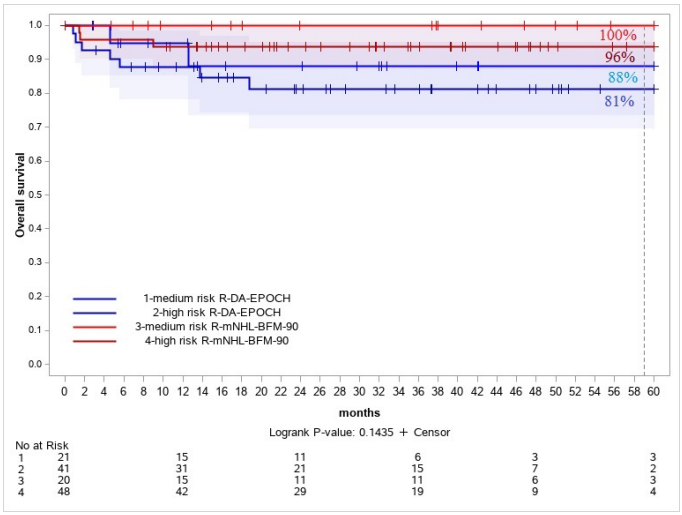


Figure 2. *Overall survival*

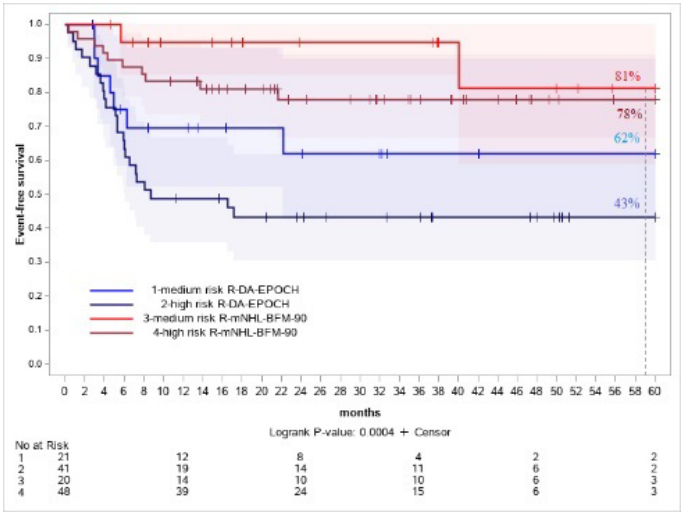


Figure 3. *Event-free survival*

In the moderate-risk group, the compared treatment programs did not show any statistically significant differences, but in the high-risk group they accounted for 96% and 60%, respectively (p=0.0033), which is significantly superior to intensive therapy.

Additional therapy after 6 courses of therapy (R-DHAP, auto-HSCT, rescue therapy, ibrutinib, lenalidomide, polatuzumab vedotin, glofitamab, etc.) was used in 20 (32.1%) patients according to the R-DA-EPOCH-21 protocol and only 2 (2.9%) patients according to the R-mNHL-BFM-90 protocol.

The four-year overall survival of patients in the moderate-risk group was 100% on R-mNHL-BFM-90 therapy, 88% on R-DA-EPOCH-21 therapy, and 94% and 81% in the high-risk group, respectively (p = 0.14) (Figure 2).

The four-year event-free survival of patients in the moderate-risk group was 81% on R-mNHL-BFM-90 therapy, 62% on R-DA-EPOCH-21 therapy, and 78% and 43% in the high-risk group, respectively (p = 0.0004) (Figure 3).

Thus, overall survival in the compared programs did not differ significantly due to additional therapy in 20 (32.1%) patients treated with R-DA-EPOCH-21. However, the frequency and probability of achieving CR, as well as event-free survival, were significantly higher with R-mNHL-BFM therapy (Figures 2 and 3).

Second stage of analysis

The second stage of analysis of the efficacy of therapy was carried out in 116 patients. The characteristics of the patients are presented in Table 3.

Of 54 patients who received R-DA-EPOCH-21±auto-HSCT, CR was achieved in 35 (64.8%) patients, PR was achieved in 8 (14.8%) patients, progression was reported in 5 (9.2%) patients, 3 (5.5%) patients had died, and treatment continued in 3 (5.5%) patients.

Of 62 patients who received R-mNHL-BFM-90±auto-HSCT, CR was achieved in 59(95.2%) patients, PR and progression were not reported, 2 (3.2%) patients had died, and treatment continued in 1 (1.6%) patient.

The probability of achieving CR is shown in Figure 4.

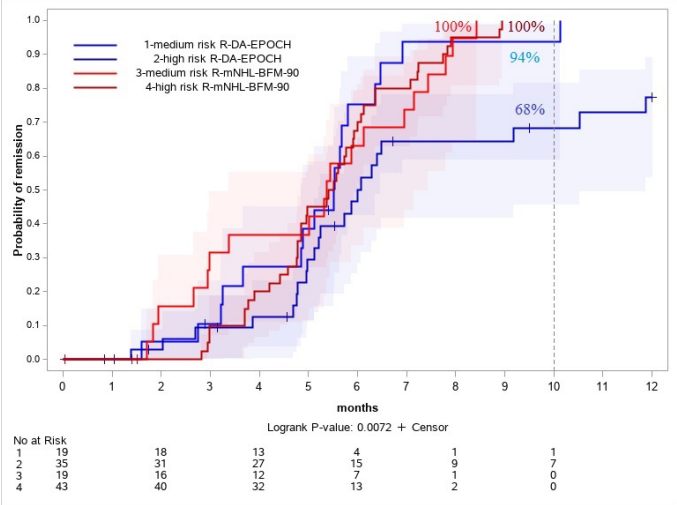


Figure 4. *Probability of achieving CR.*

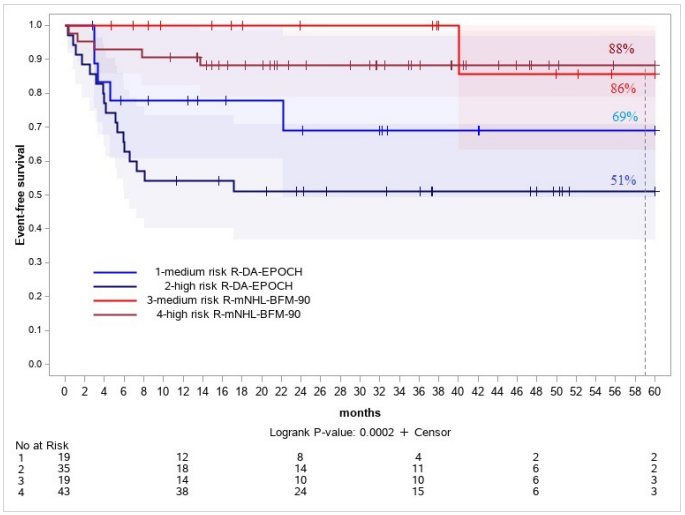


Figure 6. *Event-free survival*

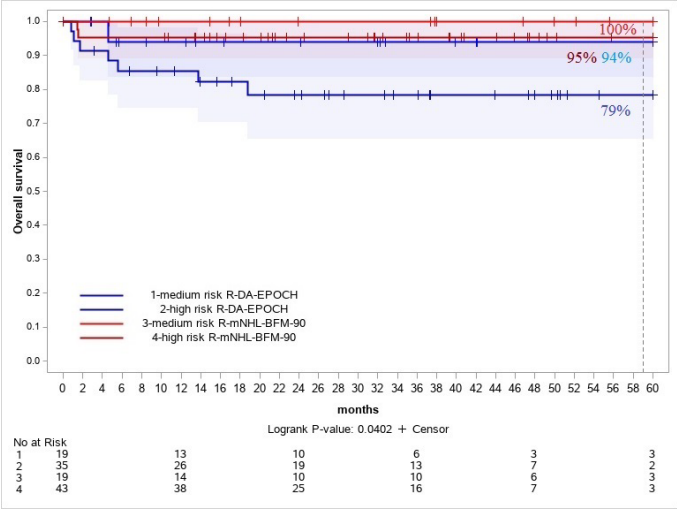


Figure 5. *Overall survival*

In the moderate-risk group, the compared treatment programs did not show any statistically significant differences, but in the high-risk group the rates were 94% and 68%, respectively (p=0.0072).

Additional therapy (R-DHAP, auto-HSCT, ibrutinib, lenalidomide, polatuzumab vedotin, glofitamab, etc.) was administered in 20 (32%) patients according to protocol R-DA-EPOCH-21±auto-HSCT and only 2 (2.9%) patients according to protocol R-mNHL-BFM-90±auto-HSCT.

The four-year overall survival of patients in the moderate-risk group was 100% with R-mNHL-BFM-90±auto-HSCT, 94% with R-DA-EPOCH-21±auto-HSCT, and 95% and 79% in the high-risk group, respectively (p = 0.0402) (Figure 5).

Event-free survival in the moderate-risk group was 86% with R-mNHL-BFM-90±auto-HSCT and 69% with R-DA-EPOCH-21±auto-HSCT, and 88% and 51% in the high-risk group, respectively (p=0.0002) (Figure 6).

Thus, the second stage of the analysis allowed us to identify significant benefits of R-mNHL-BFM-90 therapy.

Toxicity of the DLBCL–2015 protocol

Toxicity (Table 5) was evaluated for 198 courses of R-DA-EPOCH-21 and 201 courses of R-mNHL-BFM-90. There were no data for other courses.

Hematological and non-hematological toxicities were acceptable. However, neutropenic fever and grade 3–4 thrombocytopenia were significantly different.

The role of auto-HSCT will be discussed in another article.

Discussion

Considerable knowledge has been accumulated to date about the mechanisms of resistance of tumor cells, but the ways to eliminate them are unknown.

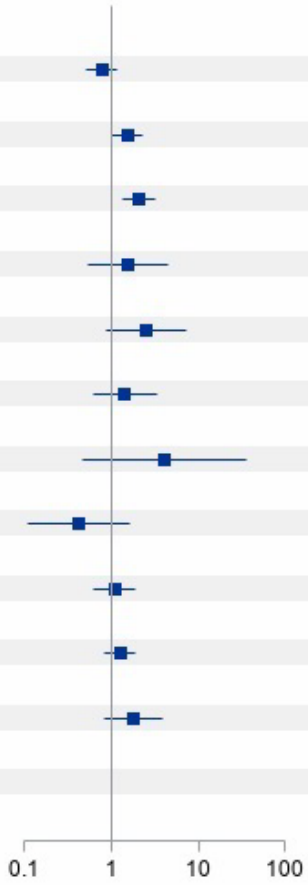
So far, patients with DLBCL have only been cured with immunochemotherapy. Moreover, as shown by numerous randomized studies over the past 10 years, R-CHOP in any modification is ineffective in the treatment of high-risk patients.

Our work was based on the theoretical concepts of tumor progression, formulated in the late 70–80s of the last century, when the idea of primary multiple cases of hematological malignant neoplasms was replaced by the concept of their clonality. Changes in the signs of the tumor during its growth, the appearance of resistance to previously effective antineoplastic agents were explained by repeated mutations of tumor cells, the appearance of subclones and the isolation of more stable forms among them. These theoretical foundations are essential for understanding tumor growth as well as for finding effective treatments.

For many years, the development of treatment programs has been directed, on the one hand, to achieve long-term complete remission, and on the other hand, to maintain a reserve of antineoplastic agents in case of relapse. Therefore, a positive effect was usually achieved by sequential administration of different drugs [26]. However, if we consider tumor progression a selection phenomenon, the phenomenon of surviving tumor subclones remaining outside the control of specific antineoplastic agents, then this approach to the treatment of DLBCL seems to be erroneous. Antitumor therapy should be aimed at eliminating the tumor clone with all subclones during induction therapy. We used this concept in our work by applying and modifying the

***Table 5**. Toxicity of the DLBCL–2015 protocol*

	% R-Da-EPOCH	% R-mNHL-BFM-90	ODR	Pvalue
Neutropenia grades 3 - 4	62	56	0.76 (0.51-1.16)	0.2125
Neutropenic fever	34	44	1.52 (1.01- 2.30)	0.0463
Thrombocytopenia grades 3-4	28	44	2.04 (1.33- 3.13)	0.0009
Pneumonia	3	5	1.52 (0.53- 4.37)	0.4293
Sepsis	3	6	2.49 (0.86- 7.22)	0.0824
Viral infection	4	2	1.43 (0.62- 3.31)	0.3999
Acute renal failure	0.5	2	4.04 (0.45- 36.51)	0.1787
Thrombosis	4	2	0.42 (0.11- 1.65)	0.1999
Enteropathy	16	18	1.08 (0.63- 1.83)	0.7866
Mucositis/stomatitis	59	64	1.24 (0.83- 1.89)	0.2924
Haemorrhage	6	10	1.81 (0.84- 3.91)	0.1281
Paroproctitis	0	0		



NHL-BFM-90 pediatric program, which proved to be highly effective in adult patients with DLBCL. We have demonstrated that the survival rates of patients at high risk of progression can be significantly improved with intensive induction therapy [27].

No disease progression was observed with R-mNHL-BFM-90 therapy. However, 2 patients developed early relapses. In one case, a mutation in the TP53 gene was found (it was not studied at the time of diagnosis). The second case had interesting clinical manifestations: at the time of diagnosis, only the right breast was affected; at the first relapse, only the pleura was affected; at the second relapse, only the left breast was affected. It should be noted that the disease has been progressing slowly (from February 2017 to the present). The patient was treated with rescue therapy: nivolumab, polatuzumab vedotin, lenalidamide, glofitamab, idelolisib, ibrutinib. A partial response was achieved only with mini-CHOP therapy, and to date the patient has undergone allo-HSC. According to biopsy results at the second relapse, B-cell lymphoma of high severity was diagnosed, DE (c-myc+, BCL-2+), del17p were detected; rearrangement of *BCL-2, BCL-6, C-myc* genes was not detected. All this leads us to the idea that transformation of MALT-lymphoma may occurred affecting the breast and pleura. In this regard, I would like to point out that the problem of diagnosing *de novo* DLBCL remains a cornerstone. Morphological, biological, and clinical studies have divided DLBCL into morphological variants, molecular subtypes, and individual diseases. However, there are many cases that may be biologically heterogeneous but do not have clear and generally accepted criteria for separation. These cases are classified as DLBCL, NOS, which is also heterogeneous: in some cases, it manifests itself aggressively; in other cases, it has a short history, a variable immunophenotype, clinical manifestations, has various cytogenetic abnormalities, a different profile of genetic changes (MYD88, BCL2, SOCS1/SGK1, TET2/SGK1 and NOTCH2 and unclassified group) and variable response to therapy [21, 28].

Our hypothesis that *de novo* DLBCL does not recur is confirmed in this study, despite the small number of patients included in the study. In the same study, we were able to isolate clinical and laboratory features that are uncharacteristic of *de novo* DLBCL and point to other forms of large cell lymphomas or to the transformation of mature cell lymphomas into DLBCL. These include: exclusive or predominant retroperitoneal localization of the tumor with compression of the ureters, as well as the development of hydronephrosis, asymmetric lymphostasis of the lower extremities caused by compression of enlarged lymph nodes by a conglomerate. This can be explained by fibrosis, which is characteristic of mature cell (indolent) and other types of lymphomas, in contrast to *de novo* DLBCL. In

addition, *de novo* DLBCL is not characterized by paraprotein secretion, discordant damage to the bone marrow and peripheral blood, intratumor in the CNS at the time of diagnosis, progression or relapse [29]. These differences may be based on different pathogenesis and different signaling pathways, as well as the molecular mechanisms involved. We have conducted a study that suggested changes in the properties of multipotent mesenchymal stem cells (MMSCs) under the influence of cytokines produced by tumor cells [30, 31]. However, further studies are needed to confirm the above.

All patients with relapses showed transformation of mature cell lymphomas to DLBCL. We failed to detect histological signs of transformation only in 2 cases of relapse (both with R-mNHL-BFM-90 therapy): in one case described above, there was progression for 5 years and damage to the breasts and pleura, and paraprotein secretion in the second case.

In addition, within the same study, we prospectively performed a pharmacoeconomic analysis of R-DA-EPOCH and R-mNHL-BFM-90 immunochemotherapy. According to the results, the total cost of treatment under the R-DA-EPOCH regimen (including second-line and subsequent anticancer therapies and targeted, immunomodulatory, epigenetic drugs, and concomitant support) exceeded the cost of R-mNHL-BFM-90. Due to its greater efficacy, R-mNHL-BFM-90 immunochemotherapy eliminates the additional cost of second- and subsequent-line antitumor therapies, as well as concomitant treatments [32].

Another benefit of R-mNHL-BFM-90 was that there was no need for neuroleukemia prevention in adult patients with *de novo* DLBCL, as no CNS relapse or progression was reported in any program. Prevention of neuroleukemia in other B-cell lymphomas does not prevent the development of neuroleukemia, nor does it prevent intratumoral progression and relapse [33].

Moreover, radiotherapy was not performed for residual lesions or as remission consolidation.

Thus, *de novo* DLBCL is a curable disease which does not recur. The R-mNHL-BFM-90 program is highly effective, while the efficacy of R-DA-EPOCH does not exceed 60% in patients with *de novo* DLBCL, both in terms of CR frequency and OS, EFS. The toxicity of R-mNHL-BFM-90 therapy is acceptable. The estimated probability of achieving CR within 10 months in the high-risk group was 100% compared to 57% on R-DA-EPOCH therapy (p=0.0047). Achievement of CR serves as an efficacy criterion in patients with *de novo* DLBCL.

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