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. www.clinicaltrials.gov NCT02842931

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].

National Medical Research Center for Hematology, Moscow, Russian Federation et al (n=12).

Abstract

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. 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 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

Background

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. 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. According to the international study SCHOLAR-1, the efficacy of chemotherapy in patients with refractory DLBCL is very is low. Short-pulse NHL-BFM-90 chemotherapy is highly effective in pediatric aggressive B-cell lymphomas. We modified R3 arm of NHL-BFM-90 program (named R-mNHL-BFM-90) for adults under 60 years with high-risk de novo DLBCL and conducted the randomized study compared to well-known R-DA-EPOCH-21 chemotherapy.

Objective

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

Materials & Methods

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. 164 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. Of the 140 randomized patients, 10 (7.14%) were excluded from the analysis for various reasons. Therapy efficacy analysis was carried out in 2 stages.

Treatment protocol.

R-DA-EPOCH-21 branch: 6 courses. If CR was not achieved, 2 courses of R-DHAP were performed.

Branch R-DA-EPOCH-21+auto-HSCT: 6 courses were performed, R-BEAM and auto-HSCT on Day 7; if CR was not achieved, 2 courses of R-DHAP and then R-BEAM+auto-HSCT were performed.

Branch R-mNHL-BFM-90 included 6 cycles: RA-RB-RA-RB-RA-RB. 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.

At the first stage, all 130 patients.

At the second stage, the efficacy of therapy was analyzed in the *de novo* DLBCL group

Table 1. Modified protocol R-mNHL-BFM-90

			Days				
	Drugs	Doses	01	2	3	4	5
	Dexamethasone (IV, 30 min.)	10 mg/m^2	x	x	x	x	x
Pre-phase	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
	Ifosfamide (IV, 1 h)	800 mg/m^2		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
	Dexamethasone (IV, 30 min)	10 mg/m^2		x	x	x	x

Results

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 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 1).

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 2).

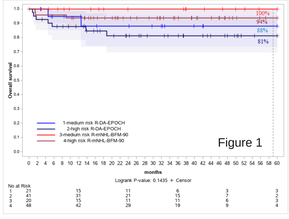


Figure 1

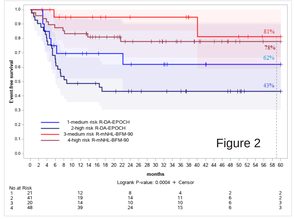


Figure 2

Second stage of analysis. The second stage of analysis of the efficacy of therapy was carried out in 116 patients.

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 four-year 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 3).

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 4).

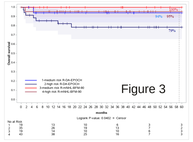


Figure 3

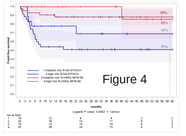


Figure 4

Toxicity of the DLBCL–2015 protocol.

Toxicity 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.

Summary

Thus, *de novo* DLBCL is a curable disease which does not recur. The R-mNHL-BFM-90 program is highly effective. The probability of achieving CR is shown in Figure 5 (*First stage of analysis)*. 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.

The probability of achieving CR is shown in Figure 6 (*Second stage of analysis)*. 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).

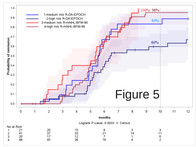


Figure 5

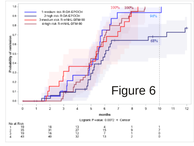


Figure 6

Discussion

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. 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 NHL-BFM-90 pediatric program, which proved to be highly effective in adult patients with DLBCL. 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). 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. Our hypothesis that de novo DLBCL does not recur is confirmed in this study, despite the small number of patients included in the study. 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. 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.

References

1. Improved treatment results in childhood B-cell neoplasms with tailored intensification of therapy: A report of the Berlin-Frankfurt-Münster Group Trial NHL-BFM 90. Blood 1999;
2. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood. 2017;
3. Nine years of experience in the treatment of patients with diffuse large B-cell lymphosarcoma. Therapeutic archive. 2011.