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АССОЦИАЦИЯ КЛИНИКО-ДИАГНОСТИЧЕСКИХ ПОКАЗАТЕЛЕЙ КАРДИОВАСКУЛЯРНОЙ ТОКСИЧНОСТИ У ПАЦИЕНТОВ С НЕХОДЖКИНСКИМИ ЛИМФОМАМИ В ПРОЦЕССЕ ПРОГРАММНОЙ ПРОТИВООПУХОЛЕВОЙ ТЕРАПИИ

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Assessment of Clinical and Diagnostic Indicators of Cardiovascular Toxicity in Patients with Non-Hodgkin's Lymphomas in the Course of Programmatic Antitumor Therapy

Резюме

Цель исследования. Изучить ассоциацию клинико-диагностических показателей кардиоваскулярной токсичности у пациентов с неходжкинскими лимфомами, находящихся в процессе программной противоопухолевой иммунохимиотерапии. **Материалы и методы.** Проспективно было отобрано 72 пациента с подтвержденным диагнозом «индолентная неходжкинская лимфома», которым показано проведение противоопухолевого лечения по схеме R-CHOP. Пациенты были обследованы в два визита: V1 — на старте и V2 — после 6 курсов терапии. В процессе наблюдения пациенты были поделены на 2 группы: основную — с признаками сердечно-сосудистой токсичности (21 пациент, 16 (76,2 %) мужчин, средний возраст 55,2 (9,8) лет) и контрольную — без нее (51 пациент, 21 (41,2 %) мужчин, средний возраст 53,7(13,6) лет. Кардиоваскулярная токсичность верифицировалась на основании сочетания жалоб с изменениями в сократительной способности миокарда: снижения фракции выброса левого желудочка >10 % от исходного уровня или в абсолютном выражении менее, чем 53 % и/или снижения продольной систолической деформации левого желудочка >12 % от исходного уровня. **Результаты.** По окончанию основного лечения в обеих группах наблюдения отмечено статистически значимое увеличение QTc. Значимо менялось значение глобальной продольной систолической деформации левого желудочка у пациентов основной группы при одномоментном отсутствии ключевых сдвигов в отношении фракции выброса левого желудочка. Наиболее чувствительным лабораторным показателем кардиоваскулярной токсичности оказался NT-proBNP, концентрация которого статистически значимо увеличивалась у основной группы пациентов. **Заключение.** Расширение минимальной диагностической панели и комплексный подход к верификации кардиоваскулярной токсичности у пациентов онкогематологического профиля, получающих потенциально токсичную для сердечно-сосудистой системы терапию, позволит существенно улучшить показатели эффективности работы ключевых служб здравоохранения, снизить финансовые расходы на нивелирование осложнений и повысить качество жизни пациентов.

Ключевые слова: *кардиоваскулярная токсичность, кардиотоксичность, кардиоонкология, онкогематология, НХЛ*

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Конфликт интересов
Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

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Abstract

Introduction. Standard antitumor immunochemotherapy used in the treatment of non-Hodgkin's lymphomas has clinically significant cardiovascular toxicity for patients. Modern medicine of the XXI century dictates the need for oncological specialists to closely monitor the state of the cardiovascular system of patients with malignant neoplasms, expanding the diagnostic panel with regard to early verification at the stage of subclinical changes. **The purpose of the study.** To study the association of clinical and diagnostic indicators of cardiovascular toxicity in patients with non-Hodgkin's lymphomas undergoing programmatic antitumor therapy. **Materials and methods.** 72 patients with a confirmed diagnosis of indolent non-Hodgkin's lymphoma were prospectively selected, who were shown to undergo antitumor treatment according to the R-CHOP scheme. The patients were examined in two visits: at the start and after 6 courses of therapy. During the follow-up, patients were divided into 2 groups: the main group with signs of cardiovascular toxicity (21 patients, 16 (76.2 %) men, average age 55.2 (9.8) years) and the control group without it (51 patients, 21 (41.2 %) men, average age 53.7 (13.6) years. Cardiovascular toxicity was verified based on a combination of complaints with changes in myocardial contractility: a decrease in the left ventricular ejection fraction >10 % from baseline or in absolute terms less than 53 % and/or a decrease in longitudinal systolic deformation of the left ventricle >12 % from baseline. **Results.** At the end of the main treatment, a statistically significant increase in QTc was noted in both follow-up groups. The value of global longitudinal systolic deformity of the left ventricle significantly changed in patients of the main group with the simultaneous absence of key shifts in relation to the ejection fraction of the left ventricle. The most sensitive laboratory indicator of cardiovascular toxicity was NT-proBNP, the concentration of which increased statistically significantly in the main group of patients. **Conclusion.** The expansion of the minimum diagnostic panel and an integrated approach to verifying cardiovascular toxicity in patients with oncohematological profile receiving potentially toxic therapy for the cardiovascular system will significantly improve the performance of key health services, reduce financial costs for leveling complications and improve the quality of life of patients.

Key words: *cardiovascular toxicity, cardiotoxicity, cardioncology, hematology, NHL*

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The authors declare no conflict of interests

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CT — cardiovascular toxicity, ECG — electrocardiogram, TEE — transthoracic echocardiographic examination, NHL — non-Hodgkin lymphomas, stress-echoCG — echocardiographic stress test, LV EF — left ventricle ejection fraction, LV LD — longitudinal systolic deformity of left ventricle, NT-proBNP — N-terminal pro brain natriuretic peptide, type B, BMI — body mass index, ESD — end-systolic dimension, EDD — end-diastolic dimension, EDV — end-diastolic volume, ESV — end-systolic volume, LVMMI — left ventricle myocardium mass index, LA — left atrium volume, OT — outflow tract distal diameter, RA — right atrium volume

Introduction

In modern healthcare, full attention is given to the development of new drugs, which significantly improve overall survival of patients with malignancies. Despite better cancer therapies, some compounds used in the treatment of the target group have toxic effects on cell structures and the body in general. The most common adverse event associated with all antineoplastic drugs is cardiovascular toxicity (CT) [1]. Some chemotherapies have just limited cardiovascular effects, while others have broad effects and involve ion channels, receptors and neurotransmitters. Currently, various CT predictors have been studied: laboratory, instrumental, genetic. Patients undergoing anticancer therapy have a basic assessment of their cardiovascular function: electrocardiogram (ECG) recording, transthoracic echocardiographic examination (TTE), laboratory tests of some markers (highly-sensitive troponins, natriuretic peptides, etc.).[1]

In 2022, the number of newly diagnosed malignancies in the Russian Federation was 624,835, where 5.7 % accounted for lymphatic and blood-forming tissue conditions [2]. Among all hematologic malignancies, non-Hodgkin lymphomas (NHL) play a significant part; according to statistical records, NHLs were

[1] 2022 European Heart Journal, Volume 43, Issue 41, 1 November 2022, Pages 4229–4361, https://doi.org/10.1093/eurheartj/ehac244

verified in 544,000 patients worldwide [3]. Patients with confirmed NHL have several treatment options: standard chemotherapy, targeted radiation therapy, target drugs, haematopoietic stem cell transplantation or (a more common case) a combination of several options.[2] Obviously, due to some limitations (drug-related and/or professional), in regions of the Russian Federation, a commonly used option is standard antitumour immunochemotherapy, which combines several drugs, each of which affects the cardiovascular function ~~in its own way~~.

Study objective: To study the association between clinical and diagnostic parameters of cardiovascular toxicity in patients with non-Hodgkin lymphomas undergoing programmed antitumour immunochemotherapy.

Materials and Methods

Study design

A study was conducted over the period from January 2022 to September 2023, which assessed the association between clinical and diagnostic parameters of cardiovascular toxicity in patients with non-Hodgkin lymphomas undergoing programmed antitumour immunochemotherapy. The Federal State Budgetary Institution of Higher Education Samara State Medical University of the Ministry of Health of Russia and the State Budgetary Healthcare Institution Samara Regional Oncology Dispensary hosted an observational case-control study of 72 patients with confirmed non-Hodgkin B-cell lymphoma, cytologic type 1–2, who were prescribed 6 rounds of R-CHOP immunochemotherapy: Rituximab 375 mg/m^2 IV infusion (day 0 or 1), Doxorubicin 50 mg/m^2 IV infusion (day 1), Cyclophosphamide 750 mg/m^2 IV infusion (day 1), Vincristine 1.4 mg/m^2, no more than 2 mg in total (day 1), Prednisolone 100 mg per os (days 1–5); therapy was resumed on day 22. Inclusion criteria: patients over 18 years of age; confirmed target diagnosis and indications for therapy; no prior history of cardiovascular conditions; negative echocardiographic stress test (stress-echoCG); signed informed consent form. Non-inclusion criteria: patients less than 18 years of age; decompensated comorbidities; a history of cardiotoxic therapy; positive stress-echoCG. Exclusion criteria: complications which make it impossible to use scheduled therapy; emergence of conditions and/or diseases which are among non-inclusion criteria; patient refusal to undergo further assessments. The sample size was pre-calculated using MedCalc (version 20.104, MedCalc Software Ltd). With type I error of 0.05 and type II error of 0.2 (80 % power of the study) taking into account 30 % incidence of cardiac toxicity in the population and the ratio between both groups of 1 : 2, the sample size was 72 patients.

During the study, all patients were divided into two groups: study group included patients with CT manifestations (21 patients, mean age: 55.2 (9.8) (M (SD)) years old, including 16 males (76.2 %)), and controls, i.e. patients without cardiovascular complications (51 patients, mean age: 53.7 (13.6) years old, including 21 males (41.2 %)). According to Russian experts specialising in prevention, diagnosis and therapy of cardiovascular toxicity (2021), CT is verified if left ventricle ejection fraction (LV EF) is > 10 % of the baseline value, or, in absolute terms, less than 53 %, and/or reduction in longitudinal systolic deformity of left ventricle (LV LD) > 12 % of the baseline value [4]. Patients with these parametritic values of myocardial contractility combined with clinical signs were included in the study group. The study did not involve a detailed description of baseline clinical characterisation of patient groups (including analysis of arterial blood pressure) due to demonstration of a limited part of the work within the scope of clinical testing. The total duration of follow-up of each patient was 6 months. The primary end point was CT development.

Test methods

All patients had: complaint questionnaire; medical examination; 12-lead electrocardiogram (ECG) using Fukuda FX-7102 device (Japan, Fukuda Denshi Co.); TTE with LV LD assessment while lying on one side via left-sided parasternal and apical access using Mindray Resona I9 (China, Mindray)[3]; assessment of supposed laboratory markers of CT (troponin T, creatine phosphokinase, myoglobin, C-reactive protein, total cholesterol, N-terminal pro brain natriuretic peptide, type B (NT-proBNP)), in two stages: before therapy and after 6 rounds of therapy. Given the lack of patients from the moderate, high and extremely high CT risk groups at enrolment, changes in target parameters were assessed after completion of the main treatment. Obtained information was recorded in the case record form.

Ethics

This study presents a limited amount of information obtained during the clinical testing approved by the Ministry of Health of the Russian Federation in 2022, The Method of Early Diagnosis of Cardiac Toxicity in Patients with Indolent Non-Hodgkin Lymphoma. All enrolled patients signed voluntary informed consent in accordance with good clinical practice. Possible risks from participation in the study are similar to those in patients who were not included in the study. There are no additional risks from participation in the study.

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[2] 2020 Clinical Guidelines for Follicular Lymphoma https://cr.minzdrav.gov.ru/recomend/151_1

[3] Otto K. M. Textbook of Clinical Echocardiography, translated from English/ K. M. Otto; ed. M. M. Galaguza, T. M. Domnitskaya, M. M. Zelenikina, T. Yu. Kulagina, V. S. Nikiforova, V. A. Sandrikova. Moscow: Logosfera. 2019; 1352 p. ISBN 978-5-98657-064-8. EDN BUAHUQ.

Statistical analysis

Statistical processing of obtained results was performed using IBM Statistics SPSS, version 26 (USA). Data were assessed under parametric and non-parametric statistic methods. Quantitative variables were presented as arithmetic mean and standard deviation with normal distribution (M (SD), median (Me), 25th percentile and 75th percentile if an attribute was other than normal distribution; qualitative parameters — as an absolute number of patients and percentage (%). Among non-parametric statistic methods for two unrelated populations, Student t-test was used for normal distribution of an attribute, Mann–Whitney U test was used for non-normal distribution, while Wilcoxon rank sum test was used for related variables in two groups. The significance of differences in qualitative variables was assessed using cross tables. If the number of observations in any cell of these tables was at least 10, chi-square was used; for the number of observations from 5 to 9 — Yates' correction was applied; and where the number of observations was below 5 in any cell, then Fisher's ratio test was used.

The model was generated with the help of binary logistic regression. In order to evaluate the predictive value of the model, Nagelkerke coefficient of determination, sensitivity, specificity, prognostic value of a positive and negative result were calculated, and ROC analysis was performed with the calculation of AUC value. An analysis of the relationship between predictors included in the model and the probability of CT outcome is presented as odds ratio and their 95 % confidence interval; both unadjusted OR (determined using one-factor logistic regression) and adjusted OR (on the basis of a multifactor model) were calculated.

Differences were statistically significant at $p < 0.05$.

Results and Discussion

This was a study to analyse the association between clinical and diagnostic parameters of cardiovascular toxicity in patients with non-Hodgkin lymphomas undergoing R-CHOP antitumour therapy. All patients had their disease verified, met inclusion criteria, and did not present with any signs from the list of non-inclusion criteria. Table 1 contains results of a comparative analysis of the CT group and controls in terms of main clinical parameters.

Table 1. *Key characteristics of the patients included in the study*

Indicator	Main group, n=21	Control group, n=51	p — value
Age, full years*	55,2 (9,8)	53,7 (13,6)	0,597
BMI, kg/m^2	24,2 (22,1;27,4)	22,1 (20,9;24,4)	0,015
Gender, m/w, n (%)	16 (76,2) / 5 (23,8)	21 (41,2) / 30 (58,8)	0,007
Smoking, n (%)	10 (47,6) / 11 (52,4)	13 (25,5) / 38 (74,5)	0,095

Notes. * — quantitative features are presented in the form of an arithmetic mean and standard deviation M (SD)
Abbreviations: BMI — body mass index

Table 2. *The results of electrocardiographic examination in the study groups*

Indicator	Main group, n=21	Control group, n=51	p — value
HR before treatment, /min	75,0 (69,0;84,0)	70,0 (59,0;75,0)	0,033
HR after 6 courses of treatment, /min	74,0 (68,0;90,0)	75,0 (62,0;81,0)	0,413
	p=0,0709	p=0,043	
PQ before treatment, msec	120,0 (100,0;150,0)	147,0 (110,0;190,0)	0,087
PQ after 6 months of treatment, msec	110,0 (100,0;200,0)	160,0 (120,0;178,0)	0,232
	p=0,481	p=0,847	
QRS before treatment, msec	96,0 (90,0;100,0)	90,0 (80,5;100,0)	0,288
QRS after 6 months of treatment, msec	90,0 (80,0;100,0)	90,0 (80,0;100,0)	0,775
	p=0,460	p=0,809	
QTc before treatment, msec	360,0 (245,0;411,0)	333,0 (218,0;384,5)	0,193
QTc after 6 months of treatment, msec	411,0 (210,0;455,0)	345,0 (278,0;409,5)	0,139
	p=0,020	p=0,014	

Notes. * — quantitative features are presented in the form of an arithmetic mean and standard deviation M (SD)
Abbreviations: HR — heart rate; PQ — PQ interval; QRS — QRS complex; QTc — corrected QT interval

Table 3. *Echocardiographic parameters of the studied patients*

Indicator	Main group, n=21	Control group, n=51	p — value)
LVESD before treatment, mm	32,1 (32,0;39,0)	30,0 (27,0;32,8)	0,001
LVESD after 6 months of treatment, mm	34,0 (31,0;39,0)	30,0 (27,0;33,0)	<0,001
	p=0,686	p=0,886	
LVEDD before treatment, mm	49,0 (41,0;52,0)	45,0 (37,5;48,0)	0,03
LVEDD after 6 months of treatment, mm	46,0 (41,0;51,0)	44,0 (40,0;47,0)	0,135
	p=0,270	p=0,229	
LVMMI before treatment, g/m^2	89,0 (77,0;100,0)	74,0 (66,0;79,0)	<0,001
LVMMI after 6 months of treatment, g/m^2	87,0 (75,0;102,0)	72,0 (64,0;79,5)	0,002
	p=0,431	p=0,321	
LVEDV before treatment, ml	98,0 (90,0;114,0)	86,0 (71,0;97,0)	0,013
LVEDV after 6 months of treatment, ml	94,0 (77,0;110,0)	87,0 (73,5;94,5)	0,077
	p=0,244	p=0,118	
LVESV before treatment, ml	59,0 (47,0;71,0)	44,0 (31,5;49,0)	0,001
LVESV after 6 months of treatment, ml	52,0 (38,0;70,0)	41,0 (35,0;50,5)	0,019
	p=0,211	p=0,846	
LVEF before treatment, %	55,0 (52,0;63,0)	58,0 (53,0;63,0)	0,49
LVEF after 6 months of treatment, %	54,0 (45,0;61,0)	57,0 (52,0;61,0)	0,368
	p=0,217	p=0,079	
LA volume before treatment, ml/m^2	32,0 (31,0;35,0)	29,0 (27,0;32,0)	0,002
LA volume after 6 months of treatment, ml/m^2	32,0 (30,0;33,0)	27,0 (24,0;32,0)	0,015
	p=0,039	p=0,041	
VROT2 before treatment, mm	30,0 (29,0;33,0)	29,0 (27,0;32,0)	0,146
	31,0 (28,0;34,0)	29,0 (27,0;32,0)	0,136
VROT2 after 6 months of treatment, mm	p=0,835	p=0,732	
VROT1 before treatment, mm	25,0 (22,0;28,0)	22,0 (20,0;23,5)	0,002
VROT1 after 6 months of treatment, mm	24,0 (22,0;28,0)	22,0 (21,0;24,5)	0,037
	p=0,875	p=0,106	
RA volume before treatment, ml/m^2	29,0(25,0;32,0)	24,0(21,0;27,0)	0,002
RA volume after 6 months of treatment, ml/m^2	28,0(24,0;32,0)	24,0(21,0;27,5)	0,016
	p=0,888	p=0,041	
PA before treatment, mmHg	25,0 (22,0;28,0)	22,0 (17,0;27,0)	0,166
PA after 6 months of treatment, mmHg	24,0 (21,0;31,0)	22,0 (15,5;25,5)	0,108
	p=0,590	p=0,152	
GLS LV before treatment, %	|21,1 (19,7;22,4)|	|21,0 (20,5;22,0)|	0,921
GLS LV after 6 months of treatment, %	|17,0 (14,0;21,0)|	|20,7 (19,0;21,5)|	0,001
	p=0,003	p=0,080	

Notes. * — quantitative features are presented in the form of an arithmetic mean and standard deviation M (SD)
Abbreviations: LVESD — left ventricular end- systolic diameter; LVEDD — left ventricular end- diastolic diameter; LVMMI — left ventricular mass index of the myocardium; LVEDV — left ventricular end- diastolic volume, LVESV — left ventricular end- systolic volume; LVEF — the ejection fraction of the left ventricle; LA — the left atrium; VROT1 — distal right ventricular outflow tract; VROT2 — proximal right ventricular outflow tract; RA — the right atrium; PA — pulmonary artery; GLS LV — global longitudinal strain, longitudinal systolic deformity of the left ventricle

Table 4. *Laboratory indicators of the cardiovascular system*

Indicator	Main group, n=21	Control group, n=51	p — value
Total cholesterol before treatment, mmol/l	4,7(4,14;5,2)	4,1(3,41;4,45)	0,003
Total cholesterol after 6 months of treatment, mmol/l	5,2(4,4;7,9)	4,13(3,35;5,0)	0,002
	p=0,0110	p=0,030	
CPK before treatment, Units/l	110,0(97,0;114,0)	84,0(69,0;107,0)	0,033
CPK after 6 months of treatment, Units/l	91,0(57,0;109,0)	75,0(59,5;92,5)	0,321
	p=0,022	p=0,008	
CPK (MB) before treatment, Units/l	22,0(21,0;25,0)	16,0(12,0;21,0)	<0,001
CPK (MB) after 6 months of treatment, Units/l	22.0(21,0;31,0)	16,5(12,5;21,0)	0,002
	p=0,375	p=0,605	
Myoglobin before treatment, mcg/l	47,0(37,0;51,0)	39,0(27,0;50,5)	0,152
Myoglobin after 6 months of treatment, mcg/l	50,0(34,0;67,0)	41,0(22,5;52,5)	0,107
	p=0,422	p=0,521	
Troponin before treatment, pg/ml	10,1(8,7;12,4)	10,9(7,07;14,9)	0,771
Troponin after 6 months of treatment, pg/ml	10,5(7,18;31,2)	11,1(8,85;52,5)	0,724
	p=0,131	p=0,503	
CRP before treatment, mg/l	2,2(0,5;4,3)	3,1(1,06;5,35)	0,111
CRP after 6 months of treatment, mg/l	2,5(1,1;5,2)	3,2(2,05;5,25)	0,581
	p=0,204	p=0,564	
NT-proBNP before treatment, mg/ml	77,0(67,0;109,0)	74,0(46,5;100,5)	0,301
NT-proBNP after 6 months of treatment, mg/ml	154,0(73,0;765,0)	55,0(39,0;88,0)	<0,001
	p=0,008	p=0,237	

Notes. * — quantitative features are presented in the form of an arithmetic mean and standard deviation M (SD). Abbreviations: CPK — creatine phosphokinase; CPK (MV) — a form of creatine kinase found in the heart muscle; CRP — C-reactive protein; NT-proBNP — N-terminal propeptide of the B-type natriuretic hormone.

An assessment of the key comparative attributes in the groups demonstrated that patients were comparable in terms of potentially cardiotoxic therapy, age and smoking status ($p > 0.05$). Patients from the study group, who developed cardiovascular complications during therapy, had a higher baseline body mass index ($p = 0.015$), and males prevailed ($p = 0.007$).

An analysis of two-stage electrocardiographic parameters (Table 2) showed a lower pre-therapy heart rate (HR) combined with its relative increase in the control group, with single-point normal values. More prominent changes were observed in corrected QT interval (QTc): it was higher in both groups after antitumour therapy completion ($p = 0.020$ and $p = 0.014$, respectively). No statistically significant shifts were observed during the analysis of other parameters.

Table 3 shows echocardiographic data obtained during TTE.

A pre-therapy comparative analysis demonstrated that patients with CT had higher ($p < 0.05$) end-systolic dimension (ESD), end-diastolic dimension (EDD), end-diastolic volume (EDV), end-systolic volume (ESV), left ventricle myocardium mass index (LVMMI), left atrium volume (LA), outflow tract (OT) distal diameter, right atrium volume (RA) vs. controls, and studied parameters are within the normal population range[4]. After antitumour therapy completion and 6 months of follow-up, significant hemodynamic parameters ($p < 0.05$) still were ESD, ESV, LVMMI, LA volume, OT distal diameter, RA volume. It is also worth mentioning that LV LD was statistically lower ($p = 0.003$ and $p = 0.080$, respectively) in both groups as a result of the therapy with cardiotoxic compounds.

Myocardial contractility parameters were supplemented with results of a direct correlation analysis with potential laboratory markers of CT (Table 4).

According to study results, at the start of antitumour therapy, patients from the study group had higher total cholesterol, creatine phosphokinase (CPK) and CPK (MB) as compared to controls; however, values were within the normal range. Similar changes in total

[4] https://scardio.ru/content/Guidelines/recommendations_structure_heart_2012.pdf

cholesterol and CPK (MB) persisted in the study group after 6 rounds of antitumour therapy. Also, after 6 rounds of antitumour therapy, statistically significant increase in NT-proBNP level (p = 0.008) was observed in the study group.

One method to assess CT manifestations in all participating patients was collection of complaints about cardiovascular disorders (Table 5).

Since the primary division of patients was based on presence/absence of signs of CT, key clinical manifestations which were statistically significant were recorded mostly in the study group (p < 0.05). No statistically significant differences in thrombotic events were recorded between the groups.

We have developed a prognostic model for CT arising during 6 months after the therapy, depending on clinical and diagnostic factors, assessed before the therapy, under the binary logistic regression method. The resulting regression model is statistically significant (p < 0.001). Taking into account the Nagelkerke coefficient of determination, 70.7 % of CT dispersion is due to the factors included into the model. Characteristics of each factor are presented in Table 6.

The threshold value of logistic function P was 50 %. If P > 50 %, the risk of CT is high. If P < 50 %, the risk of CT is low. The sensitivity and specificity of the model with the mentioned threshold value were 66.7 % and 94.1 %, respectively. The positive and negative prognostic

Table 5. *Clinical manifestations of cardiovascular toxicity*

Indicator	Main group, n=21	Control group, n=51	P — value
Heart failure, n (%)	13 (61,9 %)	1 (2,0 %)	<0,001
Arterial hypertension, n (%)	17 (81,0 %)	2 (3,9 %)	<0,001
Edema, n (%)	8 (38,1 %)	1 (2,0 %)	<0,001
Thrombotic events, n (%)	3 (14,3 %)	1 (2,0 %)	0,072
Cardialgia, n (%)	11 (52,4 %)	1 (2,0 %)	<0,001
Hypotension, n (%)	4 (19,0 %)	0 (0,0 %)	0,006

Table 6. *Characteristics of the relationship of predictors with the probability of CT*

Predictors	Single-factor regression analysis		Multivariate regression analysis	
	COR; 95 % confidence interval	p-value	AOR; 95 % confidence interval	p-value
Gender	4,570; 1,450-14,40	0,01		
BMI, kg/m^2	1,140; 1,010-1,290	0,034	1,314; 1,074-1,609	0,007
Smoking	2,660; 0,920-7,690	0,072		
TC, mmol/l	2,770; 1,380-5,560	0,004	4,763; 1,427-15,90	0,011
KPC, Units/l	1,017; 1,001-1,034	0,041		
GLS LV, %	0,937; 0,727-1,208	0,616		
LVESV, ml	1,088; 1,039-1,140	0,001	1,126; 1,044-1,213	0,002
LVEDV, ml	1,028; 1,006-1,051	0,012		
LVESD, mm	1,203; 1,067-1,357	0,003	1,296; 1,081-1,553	0,005
LVESD, mm	1,087; 1,003-1,177	0,043		
LVMMI, g/m^2	1,084; 1,036-1,135	0,001		
NT-proBNP, mg/ml	1,003; 0,991-1,014	0,657		
Troponin, pg/ml	0,996; 0,899-1,037	0,34		
KPK(MB)	1,160; 1,040-1,280	0,005		
HR, /min	1,047; 1,009-1,088	0,016		

Notes. Abbreviations: BMI — body mass index; TC — total cholesterol; KPC — creatine phosphokinase; GLS LV — global longitudinal strain, longitudinal systolic deformity of the left ventricle; LVESV — left ventricular end- systolic volume; LVEDV — left ventricular end- diastolic volume, LVESD — left ventricular end- systolic diameter; LVEDD — left ventricular end- diastolic diameter; LVMMI — left ventricular mass index of the myocardium; NT-proBNP — N-terminal propeptide of natriuretic hormone B-type; heart rate — heart rate

values were 82.4 % and 87.3 %, respectively. The diagnostic value was 86.1 %.

The area under ROC curve, which corresponded to the relationship between CT prognosis and the value of the logistic regression function, was 0.948 (0.024) with 95 % CI of 0.900–0.995. The resulting model was statistically significant ($p < 0.001$).

Usually, the standard programmed antitumour therapy used for patients with non-Hodgkin lymphomas has the highest negative effect for the cardiovascular system. In a 2022 systematic review by Maria Adriely Cunha Lima et al., who analysed 32,009 patients with malignancies, just 2,255 cases (8.3 %) did not have CT [5]. Bin Lu et al. (2022), who evaluated the efficacy of the therapy of oncohaematological tumours and the impact of (R)-CDOP therapy on cardiovascular system in patients with non-Hodgkin lymphomas, established that the incidence of CT was 7.45 % (confidence interval (CI) = 4.86–10.44 %) [6].

Since such adverse events cause the need to reduce a drug dose and very often result in loss of response to the therapy, detection of subclinical changes to justify a cardioprotective strategy is important than ever. Currently, there are numerous Russian and foreign articles dedicated to attempted search for prognostic value of laboratory, instrumental and genetic predictors of CT.

One of the most common and widely used methods to detect cardiovascular changes in oncohaematological patients is ECG recording. Starting from 1990s, it was found out that some chemotherapy agents had considerable impact on QTc and cause fatal rhythm disturbances, including sudden cardiac arrest. In a 2017 systematic review of ECG changes in patients with malignancies who underwent a target therapy, prolonged QTc of > 500 ms was recorded in 5.4 % of patients with CT [7]. In this study including 72 patients with NHL, significantly prolonged QTc was recorded with an increase in the cumulative antitumour dose (from 360.0 (245.0; 411.0) to 411.0 (210.0; 455.0), with $p = 0.020$ in the study group, and from 333.0 (218.0; 384.5) to 345.0 (278.0; 409.5), with $p = 0.014$ in controls).

In all currently published textbooks in oncology and cardiology, standard TTE with LV EF assessment is recommended as a first-line method in CT screening. According to a large-scale work by Ainsley Ryan Yan Bin Lee et. al. (2023), the number of cases of an absolute reduction in LV EF by 10 % of the baseline value, or LV EF reduction below 50 % in patients undergoing therapy, including antracyclic antibiotics, was 17 % (CI: 11–24; 71 %) [8]. In a study by A. T. Teplyakov et al. (2019) of 176 women with breast cancer who were treated with antracyclic antibiotics as a component of antitumour therapy, no significant changes in LV EF (TTE results) vs. baseline data were recorded [9]. Normal LV EF

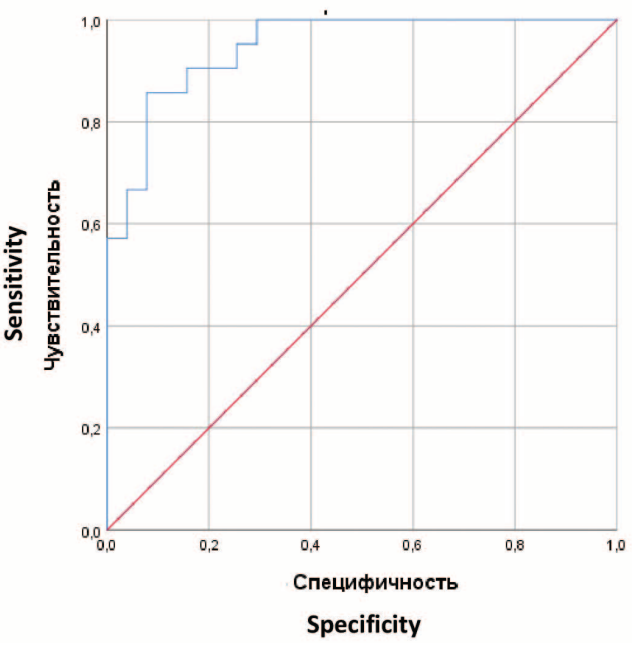

Figure 1. *Sensitivity and specificity of the model*

values were recorded in 40 breast cancer patients over a 6-month follow-up period in a paper by scientists from the Scientific Research Institute of Comprehensive Cardiovascular Issues [10]. In this study, patients with NHL treated with doxorubicin did not demonstrate statistically significant changes in LV EF over the entire follow-up period.

Given the variability of LV EF values in cancer patients, as well as parameter intactness before the myocardium is irreversibly damaged, modern medical literature recommends using more sensitive methods for CT diagnosis[5]. Currently, LV LD analysis is a very promising tool for verification of subclinical signs of cardiovascular toxicity. A study of myocardial contractility in 1,504 patients undergoing antitumour therapy demonstrated that reduction in LV LD value by 10–15 % during therapy is a more informative parameter in CT prognosis than a standard LV EF assessment [11]. This hypothesis is proven by a systematic review of 21 studies analysing 1,782 patients with malignancies, including breast cancer, haematological malignancies or sarcomas, who were treated with anthracyclines with or without trastuzumab [12]. Results of this study do not demonstrate any critical inconsistencies with global medical literature: patients with NHL demonstrated statistically significant reduction in LV LD values during antitumour immunochemotherapy (from |21.1 (19.7;22.4)| to |17.0 (14.0;21.0)|, with $p = 0.003$ in the study group, and from |21.0 (20.5;22.0)| to |20.7 (19.0;21.5)|, with $p = 0.080$ in controls).

[5] Eurasian clinical guidelines for cardiovascular complications of cancer treatments: diagnosis, prevention and treatment (2022)/ Chazova I. E., Ageev F. T., Aksenova A. V. [et al.] // European Heart Journal. — 2022. — No. 1(38). — P. 6-79. — DOI 10.38109/2225-1685-2022-1-6-79. — EDN SIVDQT.

As far as CT diagnosis on the basis of laboratory predictors is concerned, there is no consensus. A study by Russian scientists of patients treated with antracyclines, including 74 patients with non-Hodgkin lymphomas, demonstrated a significant increase in troponin I and NT-proBNP concentrations ($p < 0.0001$) [13]. According to foreign literature, NTproBNP values of > 900 pg/mL are a marker of severe cardiovascular events in patients with non-Hodgkin lymphomas [14]. At the same time, some studies confirm high sensitivity of NT-proBNP in CT; however, there are evidences of other causes of increased values of this parameter, including atrial fibrillation and valvular heart disease [15]. In this article analysing laboratory parameters in patients with NHL and verified CT, the most sensitive marker of cardiovascular dysfunction is NT-proBNP: a statistically significant increase of the value from 77.0(67.0;109.0) mg/mL to 154.0(73.0;765.0) mg/mL, with $p = 0.008$ in the study group (patients with CT), who had 6 rounds of antitumour immunochemotherapy, was recorded.

A limiting factor of this study is the lack of direct correlation analysis of a cardioprotective strategy and changes in laboratory and instrumental parameters; a relatively small sample size of patients (resulting from a limited cohort of patients without a history of cardiovascular disorders).

Conclusions

In this paper, a multifactor regression analysis of patients with indolent non-Hodgkin lymphomas demonstrated that some common risk factors of cardiovascular events before therapy with potentially cardiotoxic agents remain unchanged (sex, smoking status, total cholesterol, BMI). Also, larger values of ESV, LV ESD on TTE, which represent myocardial remodelling, at the start of antitumour therapy supplement information on the cardiovascular system functioning, allowing a healthcare professional to implement a timely cardioprotective strategy, even in low-risk patients. Currently, the matter of early verification of CT in oncohaematological patients appears relevant due to the need to improve the quality of life of patients, especially during relapse-free periods. The results for the target group show the need for extending the diagnosis protocol for cardiovascular complications by adding LV LD and NT-proBNP. Besides, a comprehensive approach to the assessment of cardiovascular system functioning will allow identifying subclinical changes, implementing a timely cardioprotective strategy in patients with malignancies, and reducing cancer-unrelated mortality.

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