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Assessment of the dynamics of markers for direct damage and myocardial dysfunction, indicators of endothelial dysfunction in patients with indolent lymphomas before and after anticancer therapy

Aim To study changes in markers for myocardial direct injury and dysfunction and endothelial dysfunction (ED) indexes in patients with indolent lymphoma during the antitumor treatment.

Material and methods Current antitumor therapy for lymphoma is often associated with cardio- and vasculotoxicity, studying of which is a relevant scientific direction. Markers for myocardial direct injury and dysfunction and ED indexes were studied in patients with indolent lymphomas receiving polychemotherapy (PCT). The study included 77 patients with newly diagnosed indolent type lymphoma. The main group (n=52): mean age, 63.4±2.8 years, 15 (28.8%) men who had received one course of PCT. The comparison group (n=25): mean age, 61.8±3.7 years, 8 (32%) men who had not received PCT. Troponin I (TnI), high-sensitivity troponin I (hs-cTnI), heart-type fatty acid binding protein (h-FABP), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were measured in patients of both groups. ED was evaluated by measuring the level of vascular cell adhesion molecule (VCAM) and by assessing the structure and function condition of small blood vessels using photoplethysmography. In both groups, the study parameters were determined at the start of the study (T1) and following the PCT course in the main group; if the PCT schedule included anthracycline antibiotics, the second point (T2) was assessed at 6 h following the drug administration.

Results In both groups, the level of NT-proBNP was increased. This increase was significantly more pronounced in the comparison group (49.896±23.228 vs 20.877±8.534 pmol/l, respectively, p=0.011) whereas a tendency to its increase was observed after the PCT course. Before the start of the treatment, laboratory and instrumental signs of ED were noticed: the level of VCAM was 4951±1297 and 3225±757 ng/ml in the comparison group and the main group, respectively (p=0.246); reflection index was <1.8 in 23 (44.2%) patients of the main group and in 16 (64%) patients of the comparison group (p=0.098). During the PTC course, the endothelial function significantly improved; the level of VCAM decreased by 748 ng/ml (p=0.016), which was associated with significant decreases in erythrocyte sedimentation rate by 2.71 mm/h (p=0.027) and lactate dehydrogenase level by 62.38 U/l (p=0.026). Statistically significant decreases in other inflammatory markers (alpha-2-globulin, fibrinogen, C-reactive protein, neutrophil count) were not observed.

Conclusion The level of NT-proBNP showed the highest sensitivity in assessing the cardiotoxic effect of PCT. The dynamics of VCAM level suggested a possible role of the disease itself in the development of ED in this patient group.

Keywords Endothelial dysfunction; cardiotoxicity; treatment of indolent lymphomas; troponin I; high-sensitivity troponin I; heart-type fatty acid binding protein; brain natriuretic peptide; vascular cell adhesion molecule; photoplethysmography

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Introduction

Recent pharmacotherapeutic achievements have enabled the prognosis of lymphoproliferative diseases to be evaluated in a new light. The use of modern antitumor drugs has helped to increase life expectancy in patients with lymphoma. However, the development of cardiovascular diseases (CVDs) has been observed more often during follow-up in patients who have

recovered from hemoblastosis. This is to a great extent due to the cardiotoxic effects of antitumor drugs, but the mechanisms of these complications are not completely clear. Endothelial dysfunction (ED) is an essential pathogenic factor in the development of a cardiac pathology [1–3]. Thus, ED development associated with multi-agent chemotherapy (MAC) may also contribute to increased cardiovascular risk in patients with lymphoma receiving antitumor treatment. Therefore, we studied the changes in the markers of direct myocardial damage and ED indicators in patients with indolent lymphomas during MAC.

Material and methods

The study was carried out in the hematology unit of University Clinical Hospital No. 1 of the First Moscow State University n.a. I.M. Sechenov (Sechenov University). The study included 77 patients with newly detected indolent lymphoma. All patients were divided into two groups: the main group (n=52; the course of indolent lymphoma required the initiation of MAC); and the comparison group (n=25; MAC had not yet been administered). Lymphoproliferative disease was diagnosed using the criteria established in the WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues 2017 (including clinical pattern, computed tomography, or positron emission tomography, histological and immunohistochemical assays of bone marrow trepanobioptate and/or lymph node). Patients with the following nosologies were included in the study: marginal zone lymphoma (n=14; 18%); small cell lymphoma/B-cell chronic lymphocytic leukemia (n=18; 23%); follicular lymphoma of cytologic type 1–2 (n=13; 17%); follicular lymphoma of cytologic type 3 (n=22; 29%); and Waldenström's macroglobulinemia (n=10; 13%, macroglobulinemia). Table 1 shows the detailed clinical characteristics of patients in the study groups. Patients in the main group received various courses of MAC: R-CHOP; R-COP; R-FC,; RB; and RL (R – rituximab, C – cyclophosphane, H – doxorubicin, O – vincristine, B – bendamustine, L – chlorambucil, P – prednisolone, F – fludarabine).

In accordance with the study design, endothelial function, markers of direct myocardial damage, and N-terminal pro-brain natriuretic propeptide (NT-proBNP) were determined in the main group before (T1), and after (T3) one course of MAC, which averaged about 7 days. If anthracycline antibiotics were included in the therapy, the levels of myocardial damage markers and NT-proBNP were additionally determined at 6–8 hours after administration of cytostatics (T2). In the comparison group, the levels of the biomarkers studied were determined once (T1) after verification of the indolent lymphoma diagnosis. The following laboratory plasma parameters were studied: troponin I (TnI); high-sensitivity troponin I (hs-cTnI); heart-type fatty acid-binding protein (h-FABP); NT-proBNP; and DE marker vascular cell adhesion molecule (VCAM). Enzyme-linked immunoassay and immunochemiluminescence were applied to determine the levels of these markers by means of: Human VCAM-1 Platinum ELISA reagents; NT-proBNP BIOMEDICA; Troponin I (Human cardiac-specific) Enzyme immunoassay test kit; TnI-Biotech test system; and Human h-FABP HK402 Hycult test system. In order to assess structural and functional changes to the microcirculatory bed, all patients underwent non-invasive photoplethysmography using an Angioskan-01 device (Russia).

Table 1. Main demographics and medical history of the patients included in the study

Indicator	Main group (n=52)	Comparison group (n=25)	Statistical significance
Age (M±m), years	63.4±2.8	61.8±3.7	p(WW)=0.827
Sex (M/F), n	15/37	8/17	p(F)=0.999
Diabetes mellitus type 2, n (%)	13 (25)	3 (12)	p(F)=0.140
Smoking, n (%)	14 (27.3)	5 (20)	p(F)=0.572
BMI >25 kg/m^2, n (%)	23 (43.9)	11 (44)	P(U)=0.547
No history of increased BP, n (%)	31 (59.1)	10 (40)	p(χ^2)=0.348
AH grade 1, n (%)	8 (15.9)	8 (32)	
AH grade 2, n (%)	6 (11.4)	4 (16)	
AH grade 3, n (%)	7 (13.6)	3 (12)	
Antiplatelet drugs, n (%)	6 (11.36)	2 (8)	p(χ^2)=0.55
Anticoagulants, n (%)	17 (33.09)	6 (24)	
Beta blockers, n (%)	16 (30.61)	13 (52)	p(F)=0.126
ACE inhibitors, n (%)	6 (12.02)	6 (24)	p(F)=0.152
Angiotensin II receptor antagonists, n (%)	6 (12.02)	3 (12)	p(F)=1.00
Thiazide diuretics, n (%)	5 (8.82)	4 (16)	p(F)=0.245
Slow calcium channel blockers (dihydropyridine derivatives), n (%)	7 (13)	3 (12)	p(F)=1.00

p(U), the significance by the Mann–Whitney U-test; p(WW), the significance by the Wald–Wolfowitz test; p(χ^2), the significance by the chi-squared test; p(F), the significance by the Fisher's exact test. BMI, body mass index; BP, blood pressure; AH, arterial hypertension; ACE, angiotensin-converting enzyme.

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The parametric and non-parametric methods were used for the statistical processing of the data obtained. Statistical processing was performed using Spearman correlation analysis, comparison of means, and statistical observation. The differences between the comparison indicators were statistically significant at $p<0.05$.

Results

Study of changes to the indicators of direct myocardial damage and NT-proBNP

In both groups, the baseline levels of the markers of direct myocardial damage were within the reference values. Tables 2 and 3 show the results of primary measurements and changes to the laboratory parameters

Table 2. Baseline values of the markers of direct myocardial damage and dysfunction, the marker of endothelial dysfunction in the studied groups

Indicator	Reference	Comparison group (n=25)	Main group (n=52)	p(U)
Troponin I (TnI), ng/mL	0.03–50	1.043±0.15	0.924±0.095	0.119
High-sensitivity troponin I (Hs-cTnI) ng/mL	0.006–50	0.054±0.04	0.035±0.016	0.057
Heart-type fatty acid binding protein (h-FABP), ng/mL	Up to 15	1.833±0.26	1.818±0.171	0.94
N-terminal pro-brain natriuretic peptide (NT-proBNP), pmol/L	0–14.29	49.896±23.228	20.877±8.534	0.011
Vascular cell adhesion molecule (VCAM) , ng/mL	400.6–1340.8	4951±1297	3225±757	0.246

The data are presented as the mean and standard error of the mean (m); p(U), the significance by the Mann–Whitney U-test.

Table 3. Changes to the study markers of myocardial damage, NT-proBNP, acute-phase indicators in the main group during anti-tumor therapy

Test	Changes between measurement points	n	Mean					Rank values
			mean	m	SD	t	p (t)	p (T)
TnI, ng/mL	T2–T1	18	–0.185	0.185	0.453	–0.70	0.492	0.584
	T3–T2	18	–0.025	0.031	0.140	–0.80	0.440	0.475
	T3–T1	20	–0.076	0.080	0.367	–0.95	0.353	0.893
hs-cTnI, ng/mL	T2–T1	18	–0.008	0.000	0.001	–0.62	0.539	0.48
	T3–T2	18	+0.001	0.001	0.004	1.05	0.305	0.48
	T3–T1	25	–0.002	0.000	0.003	0.003	0.550	1.00
h-FABP, ng/mL	T2–T1	18	–0.514	0.158	0.418	–3.25	0.017	0.043
	T3–T2	18	+0.083	0.239	0.585	0.35	0.741	0.753
	T3–T1	37	–0.290	0.169	0.757	–1.71	0.103	0.061
NT-proBNP, pmol/L	T2–T1	18	–12.688	8.148	8.737	0.38	0.705	0.950
	T3–T2	18	+24.366	21.258	95.070	0.98	0.338	0.064
	T3–T1	32	+11.677	10.146	67.304	1.15	0.256	0.076
VCAM, ng/mL	T2–T1	50	–748	395	1769	–1.89	0.074	0.035
ESR, mm/h	T2–T1	50	–2.71	3.10	14.19	–0.88	0.391	0.027
LDH, U/L	T2 – T1	50	–62.38	21.7	99.43	–2.88	0.009	0.026
Alpha-2 globulin, %	T2 – T1	50	–0.44	0.3	1.39	–1.46	0.159	0.399
Fibrinogen, g/L	T2 – T1	50	–0.48	1.54	0.33	–1.45	0.16	0.29
CRP, mg/dL	T2 – T1	50	–0.24	0.21	0.97	–1.14	0.268	0.149

n, number of observations; m, standard error of the mean; SD, standard deviation; t, Student's t-test; p(t), the significance by the Student's t-test; p(T), the significance by the Wilcoxon test; ESR, erythrocyte sedimentation rate; LDH, lactate dehydrogenase; CRP, C-reactive protein.

studied during specific therapy. It was found that mean levels of TnI, hs-cTnI, h-FABP, and NT-proBNP were higher in the comparison group than in the main group. This difference was insignificant in the case of the markers of direct myocardial damage: (p (TnI)=0.119; p (hs-cTnI)=0.057; and p (h-FABP)=0.94). Mean NT-proBNP was statistically significantly higher in the comparison group than in the main group (p (NT-proBNP)=0.011), while both groups were comparable in all terms of patient selection criteria. Since the effects of kidney function on NT-proBNP is well known, the glomerular filtration rate (GFR) was analyzed in both groups. The mean estimated GFR (MDRD) was 58.18 mL/min in the comparison group and 70.98 mL/min in the main group (p (t)=0.06). This is the most likely factor in explaining the results obtained.

During treatment, no statistically significant changes in the markers of direct myocardial damage were detected, as the values obtained were still not higher than the reference ones: p (TnI)=0.893; p (hs-cTnI) =1.000; and p (h-FABP)=0.061. The excursion of the study markers was multidirectional. The baseline levels of TnI increased during treatment in 3 (5.8%) patients, while hs-cTnI increased in 4 (8.6%) patients, and h-FABP increased in 12 (23%) patients. Despite the normal levels of TnI, hs-cTnI, h-FABP, a correlation analysis was performed between the increased levels of the markers of direct myocardial damage, and patient sex, age, presence of type 2 diabetes mellitus, arterial hypertension, administration of anthracycline antibiotics. The analysis established a strong direct correlation between increased TnI and the MAC courses including anthracyclines (Spearman's rank correlation coefficient R=0.7; p (t)=0.046).

An assessment of the effects of one course of MAC on the levels of NT-proBNP showed a trend towards an increase in the group mean levels from 20.877±8.534 pmol/L to 32.555±13.978 pmol/L (p=0.076) (normal 0–14.29 pmol/L). However, a detailed analysis showed that the excursion of NT-proBNP was multidirectional during MAC. The difference in marker levels after completion of the MAC course and the baseline value of the indicator ranged from 36.8 to 439.8 pmol/L, i.e., treatment resulted in decreased levels of NTproBNP in some patients and increased levels in others.

Study of the changes to laboratory and clinical indicators of ED

Baseline VCAM assessment established ED in both groups, as confirmed by higher mean values than the references for healthy donors (400.6–1340.8 ng/mL). It was 4951±1297 ng/mL in the comparison group and 3225±757 ng/mL in the main group (p=0.246). During the course of MAC, there was a statistically significant decrease in mean VCAM by 748±15 ng/mL (p (T)=0.016). Assessment of the effects of MAC on ED showed a moderate negative correlation (r (S)= –0.497) between the treatment effect and baseline VCAM. Thus, the larger the baseline VCAM level, the greater the decrease after treatment. It should be noted that with decreased VCAM in the main group, the activity of acute inflammation test tests also decreased: ESR during MAC decreased from 15.71±3.27 to 13.00±3.80 mm/h (p=0.027); lactate dehydrogenase (LDH) from 421.86±46.40 to 359.48±31.82 U/L (p=0.026); alpha-2 globulin from 11.02±0.43 to 10.58±0.26% (p=0.399); fibrinogen from 4.15±0.39 to 3.67±0.24 g/L (p=0.29); and C-reactive protein from 1.14±0.26 to 0.89±0.21 g/dL (p=0.149). Moreover, the neutrophil count decreased from (4.2±0.46) ×103 cells/μL to (3.8±0.48) ×103 cells/μL (p=0.36). A moderate correlation (r (S)=0.3; p=0.11) was detected between the levels of LDH and VCAM. It should be noted that the levels of VCAM changed in 9 (18%) patients during one course of treatment. This was expressed in terms of increased levels with a negative trend in the acute inflammation tests. Retrospective analysis showed an adverse course of an underlying condition in this group. However, a more detailed additional examination should confirm this.

The reflection index (RI, normal <30%) was analyzed in photoplethysmography (PPG), in order to examine the structures of arterioles. RI>30% was detected in 34 (66%) patients in the main group, and 17 (68%) in the comparison group (p=0.267). The mean value was 37.7±3.86% in the main group, and 40.55±5.27% in the comparison group. The analysis of RI means showed that arteriole elasticity decreased in the patients included, i.e., ED at the level of small resistive vessels. During treatment, this indicator decreased by 6.3±4.13% in the main group (p=0.095).

RI (normal<1.8) was analyzed, in order to assess the functional state of the microcirculatory bed (MCB). The baseline analysis of both groups revealed MCB injuries in 23 (44.2%) patients in the main group, and 16 (64%) patients in the comparison group (p (F)=0.098). The course of MAC was accompanied by some improvement in the functional state of the arterioles: a mean increase in RI of 0.17±0.14; and statistically insignificant (p (t)=0.24, p (T)=0.313).

Discussion

Analysis of the results obtained showed that one course of MAC did not cause statistically significant

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changes to the markers of direct myocardial damage. The data obtained corresponded to the reference values. However, cases of elevated TnI in the main patient group clearly correlate with the use of anthracycline antibiotics, even in small doses. Elevated NT-proBNP was detected not only at the very first stages of therapy but also in untreated patients in the comparison group. Patients with indolent lymphoma presented signs of ED before therapy, established using laboratory methods (VCAM), and clinical examination (PPG). Endothelial function improved during MAC. This was confirmed by decreased levels of VCAM. It should be noted that improved endothelial function correlated with decreased activity during acute inflammation and neutrophil levels. There were no significant changes to the PPG indicators. This is most probably explained by the brief observation period.

Thus, NT-proBNP is a key indicator for assessing cardiotoxic effects in patients with indolent lymphomas during MAC. It is useful in determining its levels both before the initiation of cytostatics and during treatment, since increased NT-proBNP levels were observed in both groups. The changes to its levels were statistically significant after one course. When comparing our findings with the available literature, it was noted that changes to the NT-proBNP levels for predicting MAC cardiotoxicity have been studied in several trials, although the findings are controversial. Prognostic approaches such as baseline increase and changes to the levels of this neurohumoral modulator during therapy were estimated. For example, Ferraro et al. [4] confirmed that the baseline level of NT-proBNP is an accurate predictor of anthracycline cardiotoxicity in patients with Hodgkin's lymphoma. Gimeno et al. [5] demonstrated that NT-proBNP>900 pg/mL during MAC is associated in patients with non-Hodgkin's lymphomas with an increased risk of death (adjusted odds ratio of 11.1 with 95% confidence interval from 3.8 to 32.9; p<0.001). In comparison, Sawaya et al. [6] did not establish the prognostic value of NT-proBNP in the development of cardiotoxicity of breast cancer chemotherapy.

The multifaceted specificity of NT-proBNP remains a possible challenge when assessing its diagnostic significance in the detection of cardiotoxicity, since some diseases and physiological indicators have independent effects on its levels. NT-proBNP was shown to increase with age without clinically evident heart failure [7].

Its elevated levels can be observed in renal failure [8], pulmonary embolism [9], or primary pulmonary hypertension [10]. A high percentage of patients with borderline NT-proBNP levels present diastolic heart failure [11, 12].

Given the available data in the literature and the findings of this study, the use of the negative prognostic value of NT-proBNP is reasonable. Thus, normal marker values should be considered as confirmation of the absence of cardiotoxicity signs at this stage of MAC, while elevated levels should be interpreted as a prognostic factor of cardiovascular complications. Thus, despite discussions about the specificity of this marker, patients with elevated NT-proBNP before or during MAC should be monitored and examined carefully, in order to detect cardiovascular complications in good time. In this study, it is this marker which showed the highest sensitivity both before and during MAC. Evaluation of endothelium in patients with indolent lymphomas showed that these patients had signs of ED even before the beginning of therapy, and the use of cytostatics was accompanied by its improvement.

It has been shown that in patients with various CVDs, ED is the basis for remodeling of the vascular walls with increased stiffness, including microcirculatory vessels. This has been demonstrated in several studies of patients with hypertensive heart disease, heart failure, and coronary heart disease [13].

The evaluation of ED in patients with lymphoproliferative diseases continues to show controversial results. Some research groups have obtained data which shows impaired endothelial function during the use of cytostatics [14–16]. At the same time, many works have shown the opposite trend for the ED indicators during anti-tumor therapy, consistent with our findings. Decreased endothelin-1 was shown in patients with lymphomas during therapy [17, 18]. In the study by Fukuda [19], the serum levels of integral membrane glycoprotein (CD44) decreased significantly in patients with indolent lymphomas after long-term MAC. Syrgrios et al. [20] detected significantly elevated serum levels of soluble intercellular adhesion molecule-1 (sICAM-1) and sE-Selectin in patients with newly detected Hodgkin's lymphoma, when compared to healthy volunteers (p<0.0001). Elevated VCAM levels at the moment of diagnosis was significantly correlated with elevated levels of sICAM-1 and sE-Selectin (r=0.5; p=0.03). MAC significantly decreased the levels of sICAM-1 and sE-selectin (p=0.02 and p=0.002, respectively) [20]. It is difficult to give a clear explanation of the improved endothelial function in patients with indolent lymphomas after one course of MAC. Given that ED was detected even before the beginning of MAC, as confirmed by this and several other studies [21], it is suggested that in the absence of clinically

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significant concomitant CVDs, lymphoproliferative disease underlies the development of ED in patients with indolent lymphomas. The administration of cytostatics is accompanied by reduced activity of the tumor process. The weaker activity of the damaging factor, also confirmed by the changes to the acute inflammation tests, is reflected by improved endothelial function. The development of leukopenia (neutropenia) attributable to anti-tumor therapy should be evaluated independently since the oxidative and metabolic function of neutrophils is essential for the functional state of the endothelium in various diseases [22, 23]. Significantly elevated ICAM-1/VCAM-1 in 100 patients with newly detected indolent non-Hodgkin's lymphomas correlated with worse treatment response and overall survival rates ($p<0.002$). This again proves a correlation between lymphoproliferative disease and ED [24].

Conclusion

The study of changes to markers of direct myocardial damage and dysfunction, and endothelium dysfunction indicators in patients with indolent lymphomas receiving antitumor therapy allowed some of the markers to be assessed in a new light, suggesting new risk factors of cardiovascular toxicity and their mechanisms. It is hoped that this will soon help to identify these factors and enable comprehensive prevention of these complications to be performed in a timely manner.

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