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Assessment of the dynamics of oxidative stress indicators and early markers of myocardial damage and dysfunction in patients with aggressive lymphoproliferative diseases during of anticancer therapy

Aim	To evaluate the dynamics of indexes of oxidative stress and markers of myocardial injury and dysfunction in patients with aggressive type lymphomas during the antitumor therapy.
Material and methods	This study included 75 patients with lymphoproliferative diseases of aggressive type. The main group consisted of 53 patients who received one course of antitumor therapy during the study. The comparison group consisted of 22 patients who have not received any specific treatment so far. Troponin I (TnI), high-sensitivity troponin (hsTnI), heart-type fatty acid binding protein (H-FABP), N-terminal pro-brain natriuretic peptide (NT-proBNP), superoxide dismutase (SOD), and myeloperoxidase (MPO) were measured in patients of both groups at baseline, and in the main group, they were measured at 4 hours after administration of antitumor agents and on completion of the course. Functional status of the cardiovascular system was evaluated by electrocardiography in all patients at baseline and after the course of antitumor treatment and by echocardiography.
Results	The chemotherapy was associated with increased levels of NT-proBNP, SOD, and MPO (30.670±15.367 vs. 52.309±25.718 pmo l/l; 1.61±0.135 vs. 1.74±0.193 U/ml; and 507.54±91.51 vs. 742.3±49.01 ng/ml, respectively). The study results indicated activation of oxidative stress on the background of the administered antitumor therapy, progressive myocardial dysfunction, and increased frequency of arrhythmic episodes.
Conclusion	The study results allowed identifying NT-proBNP, MPO, and SOD as important indexes for determining a patient group at high risk of cardiotoxicity during the antitumor treatment.

Keywords	Lymphoma; antitumor therapy; oxidative stress; cardiotoxicity; superoxide dismutase; myeloperoxidase
For citation	Antyufeeva O.N., Budanova D.A., Ilgisonis I.S., Gadaev I.Yu., Bochkarnikova O.V., Sokolova I.Ya. et al. Assessment of the dynamics of oxidative stress indicators and early markers of myocardial damage and dysfunction in patients with aggressive lymphoproliferative diseases during of anticancer therapy. Kardiologiia. 2020;60(12):76–82. [Russian: Антюфеева О.Н., Буданова Д.А., Ильгисонис И.С., Гадаев И.Ю., Бочкарникова О.В., Соколова И.Я. и др. Оценка динамики показателей окислительного стресса, ранних маркеров повреждения и дисфункции миокарда у больных лимфопролиферативными заболеваниями агрессивного типа на фоне противоопухолевой терапии. Кардиология. 2020;60(12):76–82]

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In recent decades, the treatment options for cancer patients have increased significantly. This is due to the fact that current anti-tumor therapy affects very complex malignant cell processes. At the same time, there is an inevitable side metabolic disturbance in other organs, which can occur during treatment or months and even years later. This has resulted in the need for interdisciplinary management and treatment of patients, subjected to modern anti-tumor and irradiation therapy. The establishment of integrated departments where oncologists and HCPs work hand-in-hand is becoming more relevant. Cardio-oncology is the pioneer in this direction [1]. Patients with a history of chemotherapy or radiation therapy for blood cancers are more often supervised by cardiologists [2]. According to the WHO (2019), the incidence and mortality of oncohematological diseases is approximately 5%, with lymphoma being the most frequent. It should be noted that tumors of the hematopoietic tissue are among the five leading human tumors and account for about 30% of cases in children up to 5 years of age [3]. More importantly, there is a steady worldwide annual increase in the number of patients with newly detected lymphoproliferative diseases [4]. At the same time, there has been an increase in the age of patients at which lymphoma is diagnosed. This has resulted in high comorbidity in this group of patients, mainly a high rate of concomitant cardiac pathologies and complications during chemotherapy. Therapeutic options in lymphproliferative diseases are

ISSN 0022-9040. Kardiologiia. 2020;60(12). DOI: 10.18087/cardio.2020.12.n1394

rapidly developing. Almost all modern treatment regimens include several drugs of different mechanisms of action. Unfortunately, the cardiotoxic effect during the treatment of lymphoma is typical of almost all available anti-tumor drugs (anthracyclines, alkylating agents, immunomodulators, alkaloids, proteasome inhibitors, etc.). Polychimiotherapy is accompanied by reduced mortality from lymphoproliferative diseases, but results in an increased number of cardiovascular complications. Another important factor is that cardiotoxicity has not been well studied, and the available findings are ambiguous. Thus, it is reasonable to continue research into the cardiotoxicity of anti-tumor therapy in patients suffering from lymphoproliferative diseases and its possible mechanisms.

Objective

To study changes in markers of direct myocardial injury: troponin I (TnI); high-sensitivity troponin I (hsTnI); heart-type fatty acid-binding protein (H-FABP); and N-terminal pro-brain natriuretic peptide (NT-proBNP), as some of the main indicators of myocardial dysfunction during chemotherapy in patients with aggressive lymphomas.

Material and methods

The study included 75 patients between 18 and 75 years of age with verified aggressive lymphoma. The diagnosis was established according to the WHO classification of tumors of lymphoid tissue (2017), based on clinical symptoms, histological and immunohistochemical studies of bone marrow and a lymph node accessible for biopsy, findings of multislice computed tomography, and positron emission computed tomography. All patients were examined and treated in the hematology unit of the University Clinical Hospital No. 1 of the First Moscow State University n.a. I. M. Sechenov (Sechenov University). The treatment group included 53 people who underwent one course of anti-tumor therapy. The reference group included 22 patients Who at the time of inclusion in the study had not yet received a single course of therapy.Troponin I was determined in serum by immunoenzymatic assay using the troponin I (human cardiac-specific) enzyme immunoassay test kit. High-sensitivity troponin I was determined by chemiluminescence immunoassay on an ADVIA CENTAUR XP analyzer, TnI-Ultra test system, NT-proBNP in serum by immunoenzymatic assay, NT-proBNP test system, H-FABP by immunoenzymatic assay using a Human H-FABP ELISA kit test system. At the same time, studying certain cardiotoxicity mechanisms was of interest. According to a number of publications, myocardial injury in various diseases is associated with oxidative stress. For this reason, we monitored the key indicators of this process: superoxide dismutases (SOD); and myeloperoxidase (MPO). Myeloperoxidase and superoxide dismutase were determined by immunoenzymatic assay using Human MPO ELISA Kit and HumanSOD ELISA Kit. All laboratory tests were carried out in the Central laboratory and diagnostic service of the Laboratory hemotransfusiology complex of the Clinical Center of the Sechenov University.

It was important to assess changes in these indicators during anti-tumor therapy in patients with aggressive lymphomas and to identify the most sensitive early cardiotoxicity markers. The above-mentioned indicators were determined in both groups at baseline and in the treatment group 4 hours after administering anti-tumor drugs and upon completing chemotherapy. Markers of acute inflammation and lipid composition of the blood were also tested. In order to assess the functional state of the cardiovascular system, the subjects of the reference group and all patients underwent electrocardiography, echocardiography before chemotherapy and after the course. The study was performed following the Declaration of Helsinki.

Statistical analysis of the obtained data was carried out using Excel and Statistica 10.0. The table data is expressed as mean values with standard deviations and the absolute values with percentage. The parametric and non-parametric methods were used for the statistical processing of the data obtained. The differences between the compared values were statistically significant at $p<0.05$.

Results

Table 1 sets out age and sex characteristics of the subjects, nosologies, stages of the disease according to the Ann-Arbor classification. Both groups were comparable in terms of sex and age. The majority of patients were women over 50 years old. Patients with diffuse large B-cell lymphoma (DLBCL) and stage 3–4 Hodgkin's lymphoma prevailed in both groups.

In both study groups, patients were assessed for risk factors for cardiotoxicity during anti-tumor therapy. These conditionally include: body mass index (BMI) >25 kg/m^2; smoking, hypercholesterolemia (>5.6 mmol/L); hypertriglyceridemia (>1.7 mmol/L); hypertensive heart disease; history of myocardial infarction; diabetes mellitus; and chronic kidney disease (CKD) (Table 2).

In our opinion, the presence of anemia should not be ignored during anti-tumor therapy when assessing the risk of cardiotoxicity, as the sensitivity of the myocardium to damaging factors increases. Anemia was detected in 25% of the patients examined in the reference group and 43.7% of patients in the treatment group during treatment.

Other comorbidities were not exacerbated in patients in both groups and did not influence the indicators of interest. The study did not include patients with a recent history of acute infection (less than six months).

Since different classes of anti-tumor drugs produce adverse effects on the cardiovascular system, and monotherapy of lymphoproliferative diseases is currently almost not used, cardiotoxic effects were studied in different anti-tumor regimens. All patients in the treatment group were included in the study during different chemotherapeutic programs: R-CHOP – n=23 (43.5%); R-COP – n=5 (8.7%); CHOEP – n=5 (8.7%); ABVD – n=11 (21.7%); and BEACOPP – n=9 (17.4%), where R is rituximab, C – cyclophosphamide, A/H – doxorubicin, O – vincristine, P – prednisolone, E – etoposide, D – dacarbazine, B – bleomycin. Most patients received anthracycline during the course of anti-tumor therapy. The cumulative dose of previously administered doxorubicin upon inclusion averaged 109.7±22 mg/m^2; median 63 mg/m^2; minimum 0 mg/m^2; maximum 440 mg/m^2; and 95% confidence interval 64.2–155.2.

Baseline electrocardiographic abnormalities were reported in 44 (82.6%) patients in the treatment group: signs of myocardial hypertrophy (n=16 (30.4%)); rhythm disorders (n=30 (56.5%)), including sinus arrhythmia (n=21 (39.1%)); occasional ventricular extrasystoles (n=9 (17.4%)); and conduction disorders (n=11 (21.7%)). Electrocardiographic abnormalities were reported in 17 (76.9%) patients in the reference group: signs of myocardial hypertrophy (n=10 (46.2%)); rhythm disorders (n=7 (30.8%)); including sinus arrhythmia (n=2 (7.7%)); occasional supraventricular extrasystoles (n=3 (15.4%)); occasional ventricular extrasystoles (n=2 (7.7%)); and conduction disorders (n=4 (15.4%)). According to echocardiogram findings, there were no myocardial contractility disorders during anti-tumor therapy, and left ventricular ejection fraction averaged 62.86±0.94%.

We also estimated the indicators of acute inflammation (Table 3): ESR (2–20 mm/h); C-reactive protein (0–0.8 mg/dL); alpha-2 globulins (5.1–11.8%); lactic dehydrogenase (135–450 U/L). Reference values are given in brackets.

Table 4 shows the baseline levels of TnI, hsTnI, H-FABP, NT-proBNP, SOD, and MPO. Reference values were defined for each indicator: TnI (<1.5 ng/mL), hsTnI (<0.78 ng/mL), H-FABP (<1.6 ng/mL), NT-proBNP (<5.8 pmol/L), SOD (0.005–0.05 U/mL), MPO (0.4–100 ng/mL).

The baseline levels of TnI and hsTnI were not elevated. Baseline H-FABP, NT-proBNP, SOD, and

Table 1. Main characteristics of the subjects

Patient characteristics		Treatment group, n (%)	Reference group, n (%)
Male		9 (17.4)	4 (16)
Female		44 (82.6)	18 (84)
Age			
• Less than 30 years old		7 (13)	4 (16.5)
• 30–49 years old		14 (26)	4 (16.5)
• 50–69 years old		16 (30.5)	9 (41.6)
•> 70 years old		16 (30.5)	5 (25.4)
Mean age, years		53.8±4.1	55.3±5.3
Hodgkin's lymphoma		25 (47.8)	9 (41.6)
DLBCL		21 (39.2)	11 (50)
T-cell lymphoma		7 (13)	2 (8.4)
Stage of the disease	I	2 (4.3)	1 (4.5)
	II	16 (30.4)	6 (27.3)
	III	12 (21.7)	8 (36.4)
	IV	23 (43.5)	7 (31.8)

DLBCL, diffuse large B-cell lymphoma.

Table 2. Risk factors for cardiotoxicity and associated pathology in the study subjects

Patient characteristics		Treatment group, n (%)	Reference group, n (%)
BMI>25 kg/m^2		27 (52.2)	14 (61.5)
Smoking		7 (13)	3 (15.4)
Hypercholesterolemia		21 (39.1)	5 (23.1)
Hypertriglyceridemia		21 (39.1)	7 (30.8)
Elevated VLDL		21 (39.1)	3 (15.4)
Hypertensive heart disease		23 (43.5)	12 (53.8)
Diabetes mellitus		13 (25)	6 (25)
CKD (stages)	I	12 (21.7)	4 (15.4)
	II	37 (69.7)	11 (53.8)
	III	2 (4.3)	4 (15.4)
	IV	2 (4.3)	4 (15.4)

BMI, body mass index; VLDL, very-low-density lipoprotein; CKD, chronic kidney disease.

ISSN 0022-9040. Kardiologiia. 2020;60(12). DOI: 10.18087/cardio.2020.12.n1394

Table 3. Baseline indicators of acute inflammatory processes in the study subjects

Indicator	Treatment group	Reference group
ESR, mm/h	21.7±3.96	20.15±5.23
CRP, mg/dL	2.6±0.84	4.3±5.14
Alpha-2 globulin, %	11.7±0.72	10.71±0.63
LDH, U/L	491.7±63.73	570.69±98.57

ESR, erythrocyte sedimentation rate;
CRP, C-reactive protein; LDH, lactate dehydrogenase.

Table 4. Baseline levels of the indicators of interest in the study subjects

Indicator	Treatment group (mean, median)	Reference group (mean, median)
TnI, ng/mL	0.853±0.030.79	1.19±0.240.79
hsTnI, ng/mL	0.017±0.00.016	0.017±0.0010.016
H-FABP, ng/mL	1.835±0.2031.7	2.1±0.21.7
NT-proBNP, pmol/L	30.7±15.47.1	18.5±6.510
SOD, U/mL	1.61± 0.1351.4	1.25±0.091.11
MPO, ng/mL	507.54±91.51383	342.3±49287

TnI, troponin I; hsTnI, high-sensitivity troponin;
H-FABP, heart-type fatty acid binding protein;
NT-proBNP, N-terminal pro-brain natriuretic peptide;
SOD, superoxide dismutase; MPO, myeloperoxidase.

MPO levels were above the reference levels in both groups.

The following results were obtained during the study. There were no clinically significant changes in TnI and hsTnI during anti-tumor therapy. Their levels were within the reference values during the entire period of observation (Table 5). The mean and median values of H-FABP reduced. NT-proBNP, in turn, increased during anti-tumor therapy. The indicators of oxidative stress, MPO and SOD, also increased during treatment.

The mean and median levels of C-reactive protein, lactic dehydrogenase, alpha-2 globulins, and ESR decreased during anti-tumor therapy (Table 6).

Anti-tumor therapy resulted in increased atherogenesis in the treatment group (mean and median) compared to the baseline: total cholesterol (5.1±0.3 and 5.9±0.4 mmol/L); triglycerides (1.6±0.2 and 1.7±0.2 mmol/L); very low-density lipoprotein (0.8±0.1 and 1.0±0.2 mmol/L); and low-density lipoprotein (3.0±0.2 and 3.4±0.3 mmol/L). It is difficult to interpret the changes identified because the study included patients with comorbidities. Further detailed research is required to draw certain conclusions.

According to ECG, after cytostatic therapy, 6 (13%) patients of the treatment group had episodes of paroxysmal atrial fibrillation, while 20 (39.1%) patients had diffuse changes in ventricular repolarization in the ST-segment, absent at baseline. The echocardiographic indicators remained normal upon completing the course of anti-tumor therapy.

Table 5. Changes in the studied indicators during anti-tumor therapy

Indicator	Before treatment	Four hours after administering cytostatic drugs	Upon completing the course of anti-tumor therapy	p
TnI, ng/mL	0.853±0.038	0.841±0.044	0.857±0.057	0.789
hsTnI, ng/mL	0.017±0.000	0.017±0.000	0.017±0.001	0.480
H-FABP, ng/mL	1.835±0.203	1.775±0.185	1.748±0.231	0.037
NT-proBNP, pmol/L	30.670±15.367	15.479±6.908	52.309±25.718	0.048
SOD, U/mL	1.61±0.135	1.68±0.253	1.74±0.193	0.469
MPO, ng/mL	507.54±91.51	586.07±78.21	742.3±49.01	0.570

TnI, troponin I; hsTnI, high-sensitivity troponin; H-FABP, heart-type fatty acid binding protein;
NT-proBNP, N-terminal pro-brain natriuretic peptide; SOD, superoxide dismutase; MPO, myeloperoxidase.

Table 6. Changes to indicators of acute inflammation during anti-tumor therapy

Indicator	Before treatment	Upon completing the course of anti-tumor therapy	p
ESR, mm/h	21.7±3.96	13.3±2.02	0.453
CRP, mg/dL	2.6± 0.84	2.0±0.59	0.657
Alpha-2 globulin, %	11.7± 0.72	11.2±0.52	0.021
LDH, U/L	491.7±63.73	391.7±23.56	0.165

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; LDH, lactate dehydrogenase.

Discussion

The study did not detect clinically significant changes in the levels of TnI and hsTnI. Their values were within the reference range throughout the study. Troponin is currently considered as the main and the best-studied marker of myocardial injury. The fact that it did not increase during the study can be partly explained by the low cumulative dose of doxorubicin, which averaged 109.7±22 mg/m^2. According to the literature, cardiotoxic effects are most common in patients who have received a cumulative dose of doxorubicin>550 mg/m^2 during all courses of polychemotherapy. However, it is important to note that we did not observe clinically significant changes in these indicators after the course of polychemotherapy. Arguably, no patient had signs of myocardial injury during the study, based on an assessment of TnI and hsTnI (up to 99% accuracy).

The mean and median values of H-FABP were reduced during polychemotherapy. H-FABP was isolated for the first time from the injured myocardium by Glatz et al. [5] in 1988, after which it was proposed as a marker of cardiomyocyte necrosis after several studies [6, 7]. It was found that the blood levels of H-FABP increased diagnostically significantly 1–3 hours after myocardial injury. They attained maximum values in 6–8 hours, and recovered in 12–24 hours. Several papers report that it is more sensitive than myoglobin and less specific than troponin [8]. In our study, mean H-FABP levels were higher than the standard reference values in the reference group, when compared to the baseline levels in the treatment group (2.1±0.2 and 1.835±0.203 ng/mL, respectively)..However, they were significantly below the threshold (>8 ng/mL), which is an independent risk factor for death and fatal cardiovascular complications. This was demonstrated in a large cohort of patients [9]. Given the higher levels of H-FABP in the reference group (not yet treated patients) and their decrease during anti-tumor therapy, it can be assumed that lymphoproliferative disease produces an independent effect on the levels of H-FABP (minimal lymphoproliferative lesions in the heart, soft tissues, and muscles). This requires further research and confirmation.

NT-proBNP is a peptide hormone produced by ventricular cardiomyocytes in response to excessive mechanical stress or volume overload of the cavities. These peptides have been used in cardiology since the 1990 s to diagnose and monitor chronic heart failure [10]. The correlation of changes in NT-proBNP and anti-tumor therapy has not been sufficiently studied. Elevated NT-proBNP was established in patients treated with anthracyclines [11, 12]. However, there is still no consensus on the possibility of using this marker to assess and predict the cardiotoxicity of chemotherapy in patients with blood cancers, since only a few studies have been carried out. Fridrik et al. [13] obtained results in patients with DLBCL indicating the possibility of using NT-proBNP as an early marker of myocardial dysfunction in patients with lymphomas during cytostatic treatment. Increased NT-proBNP preceded a decrease in left ventricular ejection fraction. Ferraro et al. [14] revealed that patients with DVKL and NT-proBNP>600 pg/mL were at a 4-fold higher risk of anthracycline-induced toxicity during anti-tumor therapy. Many studies confirm the direct correlation between increased NT-proBNP and the age of patients, the severity of CKD, and the presence of diabetes mellitus. This can be partly explained by the development of cardiorenal syndrome [15–17]. An analysis of our findings suggests that myocardial dysfunction progresses during anti-tumor therapy, as confirmed by an increased number of episodes of rhythm disorders, ventricular repolarization on ECG. Thus, NT-proBNP is an important predictor of myocardial dysfunction in patients with lymphoproliferative diseases during anti-tumor therapy. Evaluating its changes will enable the group of patients at high risk of cardiotoxicity during cytostatic therapy to be determined, and for timely measures to be taken to correct its manifestations.

Our findings confirm the activation of oxidative stress during anti-tumor therapy, as shown by increased MPO and SOD. Neutrophils, monocytes, tissue macrophages, and endothelial cells produce the largest amounts of MPO. MPO is an important element of phagocyte activity that provides protection of the body by activating oxidative stress, in response to tissue damage of any nature (bacterial, viral, toxic, autoimmune, etc.) [18, 19]. The role of MPO in various heart diseases has been studied in this connection in recent decades [20]. A number of publications suggest that MPO directly damages the myocardium, thus increasing the likelihood of heart failure development and progression [21]. Eleuteri et al. [22] found a direct correlation between MPO and NT-proBNP. The role of MPO was established in the development of endothelial dysfunction. It is characterized by the expression of various pro-inflammatory cytokines and prothrombotic factors that initiate atherogenesis and the prediction of the risk of developing cardiac complications [23, 24]. Increased levels of MPO as a main indicator of oxidative stress result in the compensatory activation of antioxidant protection of

ISSN 0022-9040. Kardiologiia. 2020;60(12). DOI: 10.18087/cardio.2020.12.n1394

the body. This is manifested by increased levels of SOD during anti-tumor therapy, thus maintaining a certain balance between the pro- and anti-oxidant systems in macrophages and neutrophils. The role of SOD in regulating the intensity of oxidative stress in various pathological processes, including inflammatory changes of various origins, toxic damage, anemia, endothelial dysfunction, and atherogenesis, has been actively discussed in the literature [25].

Conclusion

Our findings explain the need to continue studying the effects of anti-tumor therapy on the cardiovascular system in patients with lymphoproliferative diseases. N-terminal pro-brain natriuretic peptide, myeloperoxidase, and superoxide dismutases were determined as possible early markers enabling the identification of patients with lymphomas at high risk of cardiotoxicity during anti-tumor therapy and the need to take timely corrective measures.

Funding

The study was supported by the Project for strengthening the competitive position of leading Russian universities among global leading research and education centers.

The article was received on 06/10/2020

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