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Relationship Between Markers of the Acute Phase of Inflammation, Parameters of Blood Lipid Composition and Intracardiac Hemodynamics During Chemotherapy in Patients With Multiple Myeloma

Aim To evaluate in a pilot study time-related changes in the clinical state, indexes of the acute phase of inflammation, parameters of blood lipid profile, intracardiac hemodynamics, and disorders of cardiac rhythm/conduction in patients who are not candidates for autologous hemopoietic stem cell transplantation, during three bortezomib-containing chemotherapy courses (VCD) followed by a correlation analysis.

Material and methods This pilot study included 20 patients diagnosed with myeloma, who were not candidates for autologous hemopoietic stem cell transplantation and who had undergone three courses of VCD chemotherapy (bortezomib, cyclophosphamide and dexamethasone). In addition to mandatory examinations, measurement of blood lipid profile, transthoracic echocardiography (EchoCG), and 24-h Holter electrocardiogram (ECG) monitoring were performed for all participants before and after a specific therapy.

Results Following three bortezomib-containing courses of chemotherapy, patients of the study group had significant increases in the neutrophil-lymphocyte ratio (NLR) (1.6±0.2 and 2.5±0.4; p=0.05), cholesterol concentration (4.8±1.1 and 5.6±1.1 mmol/l, p=0.05), and low-density lipoprotein concentration (2.8±0.4 and 3.5±0.8 mmol/l, p=0.02). In comparing the changes in parameters of intracardiac hemodynamics, criteria for genuine cardiotoxicity were not met, however, a tendency to emergence/progression of myocardial diastolic dysfunction was noted. No clinically significant disorders of cardiac rhythm/conduction were observed. The correlation analysis performed prior to the start of chemotherapy, showed significant strong, direct correlations between the C-protein concentration and left atrial (LA) volume (r=0.793; p=0.006), right atrial (RA) volume (r=0.857; p=0.002), left ventricular (LV) end-diastolic dimension (EDD) (r=0.589; p=0.043), and LV end-diastolic volume (EDV) (r=0.726; p=0.017). Following the specific treatment, significant, medium-power and strong correlations were found between NLR and EDV (r= –0.673; p=0.033), NLR and end systolic volume (ESV) (r= –0.710; p=0.021), respectively. Significant direct correlations were found between the bortezomib dose per one injection and the serum concentration of triglycerides following the treatment (r=0.78; p=0.05); a single bortezomib dose and parameters of intracardiac hemodynamics: LA (r=0.71; p=0.026), RA (r=0.74; p=0.014), EDD (r=0.837; p=0.003), EDV (r=0.749; p=0.013), ESV (r=0.553; p=0.049).

Conclusion For the first time, a comprehensive evaluation was performed in patients with multiple myeloma, including the dynamics of blood lipid profile, intracardiac hemodynamics and disorders of cardiac rhythm/conduction during bortezomib-containing antitumor therapy, with an analysis of correlation with levels of acute inflammation phase markers. Although in the observation window for genuine cardiotoxicity, clinically significant cardiovascular complications were not detected, the found correlations may evidence a potential role of systemic inflammation activity in myocardial remodeling in the studied patient cohort.

Keywords Inflammation markers; blood lipid composition; intracardiac hemodynamics; multiple myeloma; proteasome inhibitors; bortezomib; cardiotoxicity

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Introduction

According to the GLOBOCAN registry, 2018 first saw 160 thousand new cases of multiple myeloma (0.9% of all registered malignancies) and 106 thousand lethal outcomes in those patients (1.1% of cancer mortality) [1–3]. This statistics reflect the epidemiological significance of this hematologic malignancy. Despite the fact that this disease is incurable, the median survival of patients increased by several years in the past 30 years, which was possible thanks to modern antitumor therapies [4, 5]. The increase in life expectancy of patients with multiple myeloma exacerbated the problem of the effect of antitumor drugs on the cardiovascular system, increased the risk of cardiovascular complications, both de novo pathology and the progression of the underlying cardiovascular pathology. This trend highlights the relevance of cardio-oncology as an independent scientific and clinical discipline in modern medicine.

According to the current Russian clinical guidelines, treatment of patients with newly diagnosed multiple myeloma who are not candidates for high-dose chemotherapy with autologous hematopoietic stem cell transplantation (aHSCT) should be initiated with chemotherapy protocols including targeted proteasome inhibitors [6]. The main antitumor mechanism of proteasome inhibitors is the inhibition of the ubiquitin-proteasome system involved in the degradation of intracellular proteins in pathological plasma cells [7, 8].

There is increasing evidence in the scientific literature that this group of drugs has adverse cardiovascular effects. Dysfunction of the ubiquitin-proteasome system occurs not only in multiple myeloma cells, but also in cardiomyocytes and endothelial cells, leading to the degradation of contractile proteins and sarcoma components, and the endothelial dysfunction (ED) [8, 9]. Clinical cardiovasculotoxic effects include the development of arterial hypertension (AH), heart rhythm/conduction disorders, chronic heart failure (CHF) (up to 25% of cases), manifestation of ischemic complications, cardiomyopathy, thrombotic complications, pulmonary hypertension [8, 10, 11]. Modern principles of cardio-oncology imply the use of special checklists to evaluate the baseline cardio-oncology risk in patients with multiple myeloma who need antitumor therapy including proteasome inhibitors, in order to define the best-possible cardioprotective strategy [12, 13].

The idea of the pathogenesis of cardiovascular diseases (CVDs) is known to be closely related to the concept of the influence of low-intensity systemic inflammation on the processes of CVD initiation/progression through the stages of ED activation, cardiomyocyte dysfunction, proliferation of smooth muscle cells and fibroblasts with further vascular and myocardial remodeling [14–16]. The peculiarities of these pathogenetic components of the CVD development are not well studied in patients with hematologic malignancies receiving various chemotherapy protocols. Thus, it seems relevant to study changes in the indicators of acute inflammation, other laboratory markers, morphological and functional characteristics of the heart, and their correlation and role in the development of cardiovascular complications in patients with multiple myeloma during chemotherapy including proteasome inhibitors.

Objective

Evaluate changes in clinical status, blood lipid profile, acute phase of inflammation, intracardiac hemodynamics, their correlation in patients with multiple myeloma who are not candidates for aHSCT during three VCD (bortezomib, cyclophosphamide, dexamethasone) protocols including the first-generation proteasome inhibitor bortezomib in a pilot study.

Material and Methods

The pilot prospective observational single-center study enrolled 20 patients with newly diagnosed symptomatic multiple myeloma who were followed in the Hematology Department, the Clinical Hospital No. 1, the Sechenov University. The diagnosis of symptomatic myeloma was made based on the 2020 Russian Clinical Guideline for the Diagnosis and Treatment of Multiple Myeloma [1]. All enrolled patients were not candidates for aHSCT using other chemotherapy protocols. The disease was staged using the criteria of the International Staging System (ISS) [2] and the classification by Durie and Salmon [17]. The main exclusion criteria were: age younger than 60 years (candidates for aHSCT), history of acute coronary syndrome or acute cerebrovascular accident within 3 months prior to the study, decompensated chronic obstructive pulmonary disease and/or bronchial asthma, severe liver dysfunction (more than 3-fold elevated hepatic enzymes). The study was conducted following the Declaration of Helsinki. Patients were enrolled after signing the informed voluntary consent.

The enrolled patients were subjected to routine laboratory tests: complete blood count with differential leukocyte count and ESR, calculation of neutrophil-to-lymphocyte ratio (NLR), biochemical profile (ferritin, lipid composition of blood, C-reactive protein), standard coagulogram, including fibrinogen levels. Specific laboratory tests included immunochemical study of serum and urine proteins in all patients. Routine clinical examinations included electrocardiogram, transthoracic echocardiogram, 24-hour Holter monitoring.

The database was created in Microsoft Office 2017. The data obtained were processed using SPSS Statistics for MacOS. The type of variable distribution was determined using the Kolmogorov-Smirnov test. Assuming a normal distribution of the general population, the quantitative parameters are represented as the means (M) and standard errors of mean (m). In a non-normal data distribution, the results were presented as the medians (Me) and the 25 th and 75 th percentiles (Lq; Uq). The qualitative characteristics are expressed as the absolute (n) and relative (%) values. The statistical significance of the differences between the quantitative indicators of the dependent samples was estimated using by the comparison of the mean values using the paired Student's t-test. A correlation analysis was carried out to determine the correlation of the quantitative indicators. The correlation power and direction were estimated using the Spearman's rank correlation coefficient. The results were statistically significant with $p < 0.05$.

Results

The mean age of patients enrolled in the study was 63.5±7.9 years. The study group included 16 female and 4 male patients. According to the ISS classification, 8 patients had multiple myeloma stage II and 12 patients had multiple myeloma stage III. General clinical condition of patients was assessed using a 5-point performance status scale (ECOG: 0 = fully active, able to carry on all pre-disease performance without restriction; 1 = patient is restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; 2 = patient is ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours; 3 = patient is capable of only limited self-care; confined to bed or chair more than 50% of waking hours; 4 = patient is completely disabled; cannot carry on any self-care; totally confined to bed or chair): the performance of 5 patients was assessed as ECOG-1, 13 patients had ECOG-2, and 2 more patients had ECOG-3. Neither patient had significant renal dysfunction. When analyzing other documented cardiovascular risk factors (RFs), it was found that 6 patients had a history of long-term smoking, and 16 patients had a positive family history. At the time of multiple myeloma verification, body mass index (BMI) corresponded to overweight (mean BMI 27.6 ± 6.1 kg/m^2) in 14 patients. All patients had arterial hypertension with various increase in blood pressure (BP); mean systemic BP did not reach the target values. Coronary artery disease (CAD) was verified in 2 patients; 1 patient had a history of MI with subsequent revascularization, CHF functional class (FC) II–III was verified in 2 patients; insulin-independent diabetes mellitus (DM) type 2 was diagnosed in 2 patients. Before treatment of the underlying disease, all patients with CVDs received cardiac therapy: angiotensin-converting enzyme (ACE) inhibitors / angiotensin II receptor blockers (ARBs) in all subjects, beta-blockers in 18 patients, statins in 8 patients, potassium-sparing diuretics in 6 patients, slow calcium channel blockers and antiplatelet drugs in 4 people. When evaluating the baseline cardio-oncology risk (baseline cardiovascular risk in cancer patients receiving chemotherapy [12]), the absolute majority of patients were found to be at a high to very high risk of developing CVDs due to chemotherapy (Table 1).

All patients with multiple myeloma underwent three VCD protocols: proteasome inhibitor (bortezomib) on days 1, 4, 8, and 11 of the protocol, cyclophosphamide on day 1 and day 8, dexamethasone on days 1–4 and days 8–11 in the first protocol and only on days 1–4 in the subsequent protocols. Dosages were calculated individually based on the body surface area and the severity of concomitant pathology. Mean drug dosage per administration was 2.43±0.34 mg of bortezomib, 530±147.57 mg of cyclophosphamide, 38±6.32 mg of dexamethasone, and mean dosage per protocol was 9.72±1.35 mg of bortezomib, 1060±265.14 mg of cyclophosphamide, and 152±25.29 mg of dexamethasone.

After treatment of the underlying disease, the performance status of patients improved: 15 patients had ECOG-1 and 2 patients had ECOG-2. Mean post-treatment systolic BP was 152 ± 14 mm Hg ($p = 0.13$), and diastolic BP was 97 ± 9 mm Hg ($p = 0.341$).

When analyzing the blood count parameters at baseline and after 3 protocols of chemotherapy, a significant increase in neutrophil-to-lymphocyte ratio (NLR) was revealed: 1.6±0.2 and 2.5±0.4, respectively ($p=0.05$). Moreover, there was a consistent increase in hemoglobin (116±17.8 g/L and 127 ± 16.6 g/L, respectively; $p = 0.15$) and a significant decrease in ESR (38.7±10.7 mm/h and 15.9±3.1 mm/h, respectively; $p = 0.03$).

Changes in the indicators of the acute phase of inflammation and the levels of protein fractions are presented in Table 2. After the chemotherapy protocols, CRP levels decreased 2-fold (14.9±7.5 mg/L and 4.7±0.9 mg/L, respectively; $p = 0.312$). There were no statistically significant changes in other indicators of the acute phase of inflammation.

During chemotherapy, all patients in the study group showed a statistically significant increase in the levels of total cholesterol (TC), low-density lipoprotein (LDL) cholesterol and high-density lipoprotein (HDL) cholesterol (Table 3).

Repeat conventional electrocardiography showed impaired repolarization (reduced amplitude of the T

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Table 1. Baseline clinical and anamnestic characteristics of patients with multiple myeloma before chemotherapy

Parameter	Study group (n = 20)
Sex	
• male	4
• female	16
Age, years	63.5 ± 7.9
male	52.5 ± 6.4
female	66.1 ± 5.7
Family history of CVDs, n	16
Smoking, n	6
BMI, kg/m^2 (normal range 18.5–24.9 kg/m^2)	27.6 ± 6.1
AH, n	
Grade 1	4
Grade 2	10
Grade 3	6
DM type 2, n	2
CAD, n	2
Documented MI, n	1
CHF, n	2
SBP, mm Hg (normal range 120–129 mm Hg)	145 ± 15
DBP, mm Hg (normal range 80–84 mm Hg)	93 ± 8
HR, bpm (normal range 60–90 bpm)	74 ± 24
ACE inhibitors/ARBs, n	20
Beta blockers, n	16
SCCBs, n	4
Potassium-saving diuretics, n	6
Antiplatelet drugs, n	4
Statins, n	8
Baseline cardio-oncological risk, n	
• very high	8
• high	10
• moderate	2

BMI, body mass index; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; SCCB, slow calcium channel blocker.

Table 2. Changes in acute inflammatory tests and serum protein fractions before and after chemotherapy

Parameter	Values in patients with multiple myeloma		p
	Before chemotherapy protocols	After chemotherapy protocols	
CRP, mg/L (normal range 0–5 mg/L)	14.9 ± 7.5	7.4 ± 3.3	0.312
Ferritin, μg/mL (normal range 7–200 μg/mL)	244.9 ± 191.4	260.9 ± 255.9	0.838
Fibrinogen, mg/L (normal range 1–4 g/L)	3.7 ± 0.9	4.1 ± 1.1	0.455
ESR, mm/h (normal range 0–20 mm/h)	**38.7 ± 10.7**	**15.9 ± 3.1**	**0.031**
NLR (normal range 1.7–3.5)	**1.6 ± 0.2**	**2.5 ± 0.4**	**0.05**

NLR, neutrophil-lymphocyte ratio. Statistically significant changes are highlighted.

Table 3. Changes in blood lipid profile before and after chemotherapy

Parameter	Values in patients with multiple myeloma		p
	Before chemo-therapy protocols	After three chemo-therapy protocols	
Total cholesterol, mmol/L (normal range 3.2–5.6 mmol/L)	**4.8 ± 1.1**	**5.6 ± 1.1**	**0.05**
VLDL cholesterol, mmol/L (normal range 0.26–1.04 mmol/L)	0.8 ± 0.3	0.7 ± 0.2	0.30
LDL cholesterol, mmol/L (normal range 1.92–4.51 mmol/L)	**2.8 ± 0.4**	**3.5 ± 0.8**	**0.02**
Triglycerides, mmol/L (normal range 0.41–1.8 mmol/L)	1.5 ± 0.8	1.5 ± 0.7	0.99
HDL cholesterol, mmol/L (normal range > 0.7 mmol/L)	**1.1 ± 0.4**	**1.4 ± 0.4**	0.03

VLDL, very low-density lipoprotein; LDL, low-density lipoprotein; HDL, high-density lipoprotein. Statistically significant changes are highlighted.

wave) in all patients, signs of LV hypertrophy (left axis deviation, tall R waves in leads I, V5–V6) in 6 patients, atrioventricular block grade 1 (elongation of PQ to 0.24 s) in 1 (5%) patient. A comparative analysis of the 24-hour Holter monitoring showed a trend to increasing numbers of supraventricular premature beats (SVPB) and ventricular premature beats (VPB): median SVPB was 216 [137; 288] and 424 [211; 543] (p = 0.09), and median VPB was 84 [23; 180] and 156 [55; 233] before and after chemotherapy, respectively (p=0.29). No episodes of allorhythmia were reported; all changes in ECG were of no clinical significance.

The comparison of the indicators of intracardiac hemodynamics revealed no clinically significant changes in the global and local contractile capacity of the myocardium, the degree of LV hypertrophy, or pulmonary hypertension. However, after three protocols of chemotherapy, attention is drawn to a trend to lower LVESV (38.1 ± 6.6 mL and 33.3±7.4 mL; p = 0.18) and LVEDV (87.1±21.9 mL and 81.7±23.9 mL; p=0.55), higher left atrial (LA) volume (60.1±17.7 mL and 62.7±14.5 ml; p=0.75), increased LA volume index (32.1±5.8 and 33.9±6.3; p=0.59), worse LV diastolic function (E/A 1.0±0.2 and 0.8 ± 0.3; p=0.13).

Table 4 shows the data of a correlation analysis of the relationship between NLR and the parameters of blood lipid profile and intracardiac hemodynamics. The analysis

Table 4. Correlation analysis of the relationship between neutrophil-lymphocyte ratio (NLR) and the parameters of blood lipid profile and intracardiac hemodynamics before and after chemotherapy

Blood lipid profile and echocardiogram	NLR before chemotherapy	NLR after chemotherapy
TC	r = –0.249; p = 0.488	r = –0.048; p = 0.896
LDL cholesterol	r = –0.338; p = 0.339	r = 0.090; p = 0.805
VLDL cholesterol	r = –0.217; p = 0.546	r = 0.134; p = 0.712
HDL cholesterol	r = 0.555; p = 0.096	r = –0.236; p = 0.512
TG	r = 0.126; p = 0.728	r = –0.217; p = 0.548
LVPW	r = 0.140; p = 0.711	r = 0.557; p = 0.094
IVS	r = 0.049; p = 0.893	r = 0.359; p = 0.309
LVEF	r = 0.389; p = 0.267	r = –0.361; p = 0.306
E/A	r = –0.158; p = 0.662	r = –0.249; p = 0.412
LA volume	r = –0.191; p = 0.569	r = –0.056; p = 0.879
LA index	r = –0.283; p = 0.428	r = 0.178; p = 0.622
RA volume	r = –0.062; p = 0.866	r = 0.169; p = 0.641
LVEDD	r = 0.047; p = 0.898	r = –0.019; p = 0.957
LVEDV	r = –0.035; p = 0.923	r = –0.673; p = 0.033
LVESV	r = –0.333; p = 0.348	r = –0.710; p = 0.021

LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides; LVPW, left ventricular posterior wall; IVS, interventricular septum; EF, ejection fraction; LA, left atrium; RA, right atrium; LVEDD, left ventricular end-diastolic dimension; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume.

Table 5. Correlation analysis of the relationship between CRP levels and the parameters of blood lipid profile and intracardiac hemodynamics before and after chemotherapy

Blood lipid profile and echocardiogram	CRP before chemotherapy	CRP after chemotherapy
TC	r = –0.050; p = 0.890	r = –0.014; p = 0.970
LDL cholesterol	r = –0.216; p = 0.548	r = –0.970; p = 0.640
VLDL cholesterol	r = 0.426; p = 0.219	r = –0.449; p = 0.193
HDL cholesterol	r = –0.034; p = 0.927	r = 0.526; p = 0.118
TG	r = 0.590; p = 0.072	r = –0.330; p = 0.352
LVPW	r = 0.015; p = 0.966	r = –0.436; p = 0.208
IVS	r = 0.221; p = 0.540	r = –0.079; p = 0.828
LVEF	r = 0.420; p = 0.227	r = 0.354; p = 0.315
E/A	r = –0.146; p = 0.687	r = 0.512; p = 0.130
LA volume	**r = 0.793; p = 0.006**	**r = –0.345; p = 0.329**
LA index	r = 0.347; p = 0.325	r = 0.178; p = 0.622
RA volume	**r = 0.857; p = 0.002**	**r = –0.335; p = 0.343**
LVEDD	**r = 0.589; p = 0.043**	**r = 0.292; p = 0.413**
LVEDV	**r = 0.726; p = 0.017**	**r = –0.208; p = 0.565**
LVESV	r = 0.265; p = 0.459	r = –0.438; p = 0.206

CRP, C-reactive protein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein; HDL, high-density lipoprotein; TG, triglycerides; LVPW, left ventricular posterior wall; IVS, interventricular septum; LVEF, left ventricular ejection fraction; LA, left atrium; RA, right atrium; LVEDD, left ventricular end-diastolic dimension; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume. Statistically significant changes are highlighted.

showed significant moderate and strong NLR-LVEDV and NLR-LVESV correlations after treatment, respectively.

The correlation analysis of CRP levels, blood lipid profile, and intracardiac hemodynamics in patients of the study group, a moderate direct correlation between this acute inflammatory marker and triglyceride levels was found (r_1=0.59; p_1=0.072), which became moderately inverse after chemotherapy (r_2=–0.33; p_2=0.352). Significant direct strong correlations were found between the CRP levels and the LA and right atrial (RA) volumes, LVEDD, and LVEDV before the beginning of specific therapy (Table 5). After chemotherapy, the correlations between CRP, LA and RA volumes, and LVEDV became moderate and mildly inverse (LA: r=–0.345, p=0.343; RA: r=0.301; p=0.452; LVEDV: r=–0.208; p=0.565), and a direct mild correlation was found between CRP and LVEDD (r=0.292; p=0.413).

A statistically significant direct strong correlation was established between bortezomib dosage per administration and serum levels of triglycerides after chemotherapy (r=0.78; p=0.05). A single dose of bortezomib was moderately directly correlated with TC (r=0.41; p=0.238), LDL cholesterol (r=0.441; p=0.241), and very low density lipoprotein (VLDL) cholesterol (r=0.42; p=0.227). Statistically significant strong correlations between bortezomib single dose and indicators of intracardiac hemodynamics: LA volume (r=0.71; p=0.026); RA volume (r=0.74; p=0.014); LVEDD (r=0.837; p=0.003); LVEDV (r=0.749; p=0.013); LVESV (r=0.553; p=0.049).

Discussion

According to the study results, the majority of patients with multiple myeloma are female and over 65 years old, which is consistent with global epidemiological data [2, 3]. The baseline cardio-oncology risk stratification, carried out prior to chemotherapy, may regarded the age-sexual structure of patients with multiple myeloma (postmenopausal women) as an unmodifiable risk factor, which significantly increases the likelihood of CVD manifestation or complications during or after the administration of targeted and cytostatic drugs. Moreover, mean BMI corresponded to overweight in the majority of patients, which also significantly increased the cardiovascular risk [18].

Statistically significant increase in NLR is observed during treatment. Changes in NLR can be explained by two main processes: a decrease in circulating lymphocytes due to use of proteasome inhibitors and alkylating agents,

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АТТР-АМИЛ – ЖИЗНЕУГРОЖАЮЩЕЕ ЗАБОЛЕВАНИЕ

ВИНДАМЭКС® ДЛЯ ПЕРОРАЛЬНОГО ПРИЕМА МОЖЕТ ПОМОЧЬ ПАЦИЕНТАМ ЖИТЬ ДОЛЬШЕ С МЕНЬШЕЙ ЧАСТОТОЙ ГОСПИТАЛИЗАЦИЙ[1]*

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and an increase in neutrophil count, which may be due to the administration of high doses of glucocorticoids.

The study revealed a statistically significant increase in the levels of TC, LDL and HDL cholesterols during the treatment of multiple myeloma. When evaluating the changes of the blood lipid profile as a whole, we determined that baselines levels of TC and LDL exceeded the reference values in 1 (5%) patient, and these indicators exceeded the reference values in 45% of patients after 3 protocols of chemotherapy. Noteworthy, statins were not discontinued during chemotherapy in patients initially taking lipid-lowering drugs. There are single reports in the modern literature on the changes in the blood lipid profile during targeted therapy with proteasome inhibitors. The deterioration of the blood lipid profile can be explained by the direct action of proteasome inhibitors. In the experimental study, Ogura et al. [19] showed the effect of proteasome inhibitors on atherogenesis-specific macrophage proteasomes. When the drugs of this group are used, the scavenging of the ATP-binding transporter (ABCA1) on the surface of the macrophage membrane is disrupted, which leads to the release of endogenous lipoproteins into the systemic circulation [19]. It cannot be denied that systemic glucocorticoids included in the protocol lead to the development of adrenal dysfunction and dyslipidemia [20]. Changes in the blood lipid profile, including those mediated by the activity of systemic inflammation, can contribute to the development/aggravation of ED followed by vascular wall remodeling [21].

The development of clinically insignificant signs of impaired repolarization, such as flat and negative T-wave, in all patients of the study group, increased number of SVPBs and VPBs during the VCD protocol, are most likely explained by the direct effects of drugs used in programmed therapy due to their influence on the cardiomyocyte metabolism [22].

According to modern foreign and Russian consensus papers, a decrease in LVEF by more than 10% of the initial values or less than 53% is one of the definitions of chemotherapy cardiotoxicity [13, 23]. According to the study results, there were no signs of true cardiotoxicity in the study group. However, the data obtained on changes in the heart chamber dimensions (LA and RA volumes, LA volume index, LVESV, LVEDV, LVEDD) and impaired diastolic function of the myocardium (reduced E/A) emphasize the effect of the drugs administered given the spectrum of their cardiovascular effects [24] on the cardiomyocyte function and the development of initial signs of myocardial remodeling.

The presence of direct correlations of CRP levels with blood lipid profile and intracardiac hemodynamics before the beginning of chemotherapy is of particular interest. This emphasizes the role of systemic inflammation activity in the adverse effect on cardiovascular system. The pathogenesis of any malignancy is associated with impaired ratio of pro- and anti-inflammatory cytokines [25]. The pathogenesis of multiple myeloma is realized through several different stages (MGUS, smoldering myeloma, clinically significant multiple myeloma), and this disease is accompanied by chronic cytokine imbalance. The presence of a small clone of abnormal plasma cells results in permanent stimulation of pro-inflammatory cytokine production. Thus, continuous chronic low-intensity inflammation is maintained, which can play a key role in the activation of oxidative stress, the development of vascular atherosclerosis, the activation of profibrotic mechanisms in the myocardium [26]. As a consequence, cardiovascular events may develop and progress more rapidly in patients with paraprotein-associated hematologic malignancies than in those without cancer. The presence of strong inverse correlation of NLR with LVEDV and LVESV after chemotherapy may indicate the involvement of the immune cell link in the pathogenesis of ED, one of the key mechanisms in the development of dysfunctions and remodeling in the cardiovascular system.

Despite a consistent decrease in the levels of acute inflammatory indicators during the treatment of the underlying disease, there are changes in the parameters of intracardiac hemodynamics, such as worsening of diastolic dysfunction, enlargement of atria, which can be explained by the initiation of tissue processes of myocardial remodeling and ED due to a potential cardiovascular toxic effect of the chemotherapy protocol administered. Identified significant correlations between a single dose of bortezomib and LVESV, LVEDV, and LVEDD may be indicative of a dose-dependent effect of this drug on the development of cardiovascular toxicity.

Thus, no true cardiotoxicity and/or clinically significant cardiovascular complications were reported in the pilot study in patients with multiple myeloma after three bortezomib-containing protocols. However, it is not possible to completely exclude the previous cardiotoxic effect of bortezomib-containing chemotherapy protocols due to the lack of data on changes in specific laboratory and clinical examination markers of myocardial damage/dysfunction. We obtained data on the effect of the administered chemotherapy protocols on the levels of pro-atherogenic lipoproteins, changes in the intracardiac hemodynamics, mainly the aggravation of LV diastolic dysfunction. Given the established correlations, it can be assumed that this treatment protocol produces also a vasculotoxic effect via the development/progression of ED in the active pro-inflammatory status. Changes in the blood

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lipid profile suggest from a practical position considering the prescription/correction of lipid-lowering therapy in the studied cohort of patients with multiple myeloma before starting these chemotherapy protocols. Studying the levels of acute inflammatory markers during specific therapy of patients with multiple myeloma may be an indirect criterion for assessing the severity of cardiovascular toxicity of bortezomib-containing chemotherapy protocols. This aspect and the hypolipidemic strategy require further research in a larger patient sample and with a longer follow-up period.

Conclusion

During the study, a comprehensive evaluation of changes in performance status, blood lipid profile, intracardiac hemodynamics during bortezomib-containing protocols was carried out in patients with multiple myeloma for the first time, as well as the correlation analysis with the levels of acute inflammatory markers. Despite the absence of reliable signs of cardiotoxicity and clinically significant cardiovascular complications during treatment, the deterioration in the indicators of diastolic function of the myocardium, blood lipid profile, and their correlations the neutrophil-lymphocyte ratio and C-reactive protein levels can reflect the role of low-intensity systemic inflammation in the development of early cardiac and vascular toxicity in patients of the studied cohort, which requires further research.

Limitations

Relatively small sample size, no control group given the initial status of a pilot study.

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