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Assessment of Systemic Inflammation Activity, Myocardial Structure and Functional Features, Their Relationship in Patients With Multiple Myeloma, Receiving Bortezomib Therapy

Aim	To study the dynamics of calculated indices [neutrophil-lymphocyte ratio (NLR); systemic inflammation index (SIV)] and biomarkers of systemic inflammation [interleukin-1β (IL-1β); high-sensitivity C-reactive protein (hsCRP)], parameters of the structure-and-function state of the myocardium and intracardiac hemodynamics, and their relationship in patients newly diagnosed with multiple myeloma (MM) at the onset of the disease and after 6 courses of chemotherapy (CT) containing the proteasome inhibitor bortezomib.
Material and methods	This prospective study included 30 patients aged 63.8±10.0 years diagnosed with MM; 17 (56.7%) of them were men. The following tests were performed for all patients: measurement of IL-1β and hsCRP, calculation of the inflammation indexes NLR and SIV, transthoracic echocardiography before and after 6 courses of bortezomib-containing CT. At the time of study completion, 9 patients dropped out due to reasons not related to cardiovascular complications of CT.
Results	The antitumor therapy was associated with increases of immune-inflammation indexes: NLR increased from 1.54 [1.02; 1.83] to 2.9 [1.9; 4.35] (p=0.009) and SIV increased from 402.95 [230.5; 534.0] to 1102.2 [453.1; 1307.9] (p=0.014). IL-1β increased from 5.15 [4.05; 5.77] to 6.22 [5.66; 6.52] pg/ml remaining within the reference range (p=0.142) whereas hsCRP decreased from 1.02 [0.02; 2.71] to 0.02 [0.02; 0.82] IU/l (p=0.138). Statistically significant changes in parameters of heart remodeling and clinical picture of cardiovascular complications were not observed. A correlation analysis showed significant inverse correlations of hsCRP with left ventricular ejection fraction (LV EF) (r= –0.557; p=0.003), the number of plasma cells (PC) with LV EF (r= –0.443; p=0.023), and a direct correlation of the number of PC with hsCRP (r=0.433; p=0.022).
Conclusion	During the study, the accepted criteria for cardiotoxicity of bortezomib-containing chemotherapy in patients with MM, were not met. The identified correlations between the level of markers for acute inflammation, indexes of intracardiac hemodynamics, and the immediate MM substrate may indicate the role of chronic low-intensity inflammation in the pathogenesis of myocardial remodeling in patients with MM. This necessitates further studies on larger samples of patients to assess the prognostic significance.

Keywords	Cardio-oncology; cardiotoxicity; systemic inflammation; myocardial remodeling; comorbidity; multiple myeloma; proteasome inhibitors
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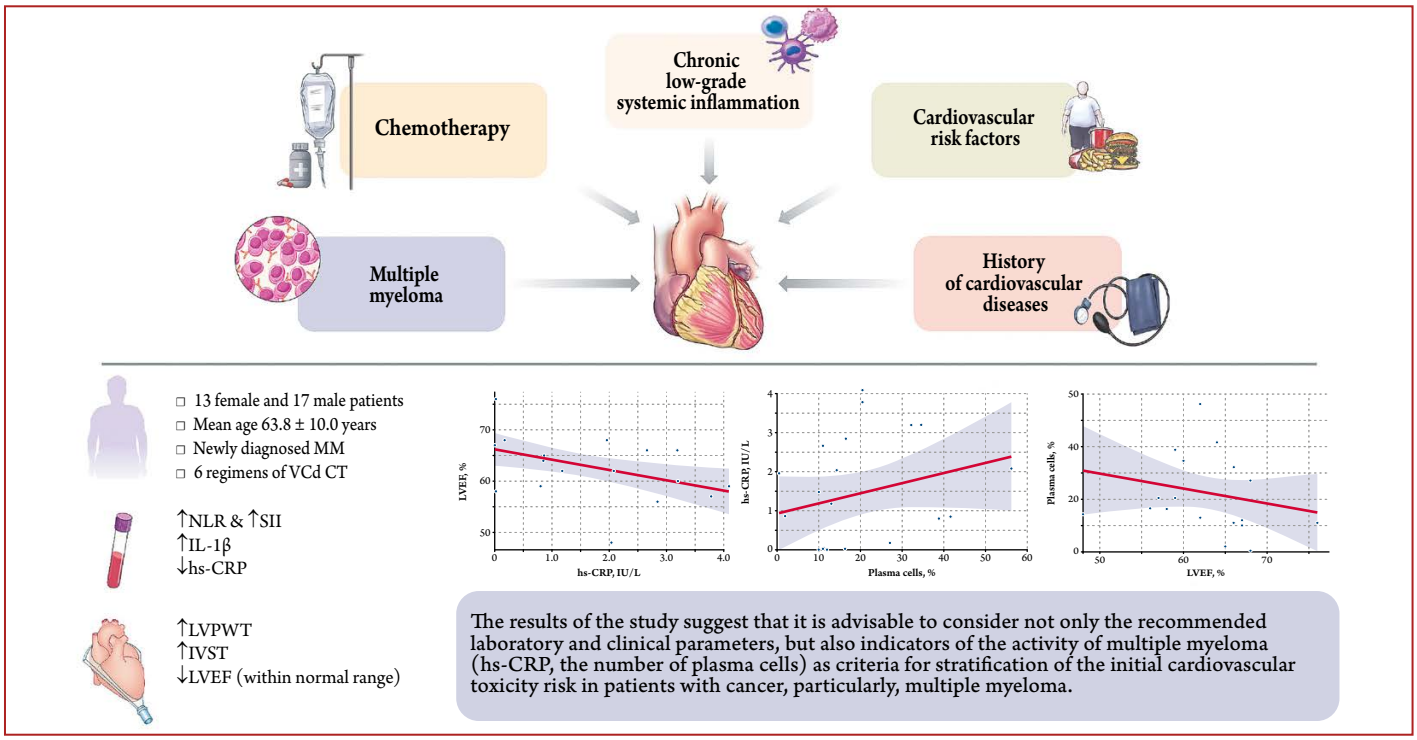
Introduction

Duration and quality of life of cancer patients significantly improved thanks to modern methods of diagnosis and treatment of malignancies. At the same time, the incidence of adverse cardiovascular events increases significantly in this group of patients both during and after the completion of active chemotherapy (CT) and in a delayed period [1, 2]. The direct cardiotoxic action on cardiomyocytes and the indirect vasculotoxic effect of anticancer drugs, which contributes to the violation of myocardial structure and functions, are the main factors in the occurrence of adverse cardiovascular events [3, 4]. Low-intensity chronic systemic inflammation (SI) is a major factor affecting the initial cardiovascular status of cancer patients, the likelihood of the occurrence and progression of adverse cardiovascular events in response to treatment, and likely, the efficacy of therapy and prognosis [5].

Central illustration. Assessment of Systemic Inflammation Activity, Myocardial Structure and Functional Features, Their Relationship in Patients With Multiple Myeloma, Receiving Bortezomib Therapy



Multiple myeloma (MM) is a paraproteinemic hemoblastosis predominantly debuting at the age of 65–70 years, which suggests that patients have documented cardiovascular diseases (CVDs) or several cardiovascular risk factors (RFs). Pathogenetic features of MM (electrolyte disorders, including hypercalcemia, anemic and hyperviscous syndromes, production of monoclonal paraprotein and/or light chains of immunoglobulins, their nephrotoxic effects) also contribute to the development of adverse cardiovascular events in these patients [6, 7].

MM remains an incurable disease despite effective specific therapy. However, there is no doubt that the introduction of proteasome inhibitors (PI) into clinical practice has forever changed the paradigm in the treatment of MM. However, patients with MM are more likely to face the burden of CT-related complications, especially adverse cardiovascular events, which can be as high as 17% for bortezomib [8].

According to the 2022 ESC Guidelines on cardio-oncology, the contemporary definition of cardiotoxicity includes the development of symptomatic and asymptomatic cardiac dysfunction (changes in left ventricular ejection fraction (LVEF)), left ventricular global longitudinal strain (GLS), levels of recommended biomarkers (troponin, brain natriuretic peptide), or heart failure (HF) [9].

Several mechanisms of the effect of bortezomib on cardiomyocytes were described: direct inhibition of cardiomyocyte proteasomes and endotheliocytes, and the development of endothelial dysfunction (ED) due to decreased production of endothelium-dependent relaxation factor nitric oxide (NO), and hyperactivation of oxidative stress processes [10–12].

The predominance of the activity of pro-inflammatory factors (interleukin-1β (IL-1β), IL-6, highly sensitive C-reactive protein (hs-CRP), tumor necrosis factor α (TNF-α), etc.) over anti-inflammatory factors (heat shock proteins, IL-4, IL-10, transforming growth factor β (TGF-β), lipoxin A4 (LXA4)) was shown to affect the expansion of clonal plasma cells in the bone marrow (BM), the progression of MM, cell adhesion, angio- and vasculogenesis in tumor and microenvironment cells [13, 14].

In turn, the role of SI in the pathogenesis of the initiation and course of individual CVDs (atherosclerosis, coronary artery disease, chronic HF) was examined in sufficient detail [15–17]. In this regard, we can suggest that MM patients are more susceptible to the development and progression of cardiac pathology and, consequently, the activity of inflammatory processes in this group of patients is likely to influence the risk of adverse cardiovascular events during anticancer therapy and the prognosis in general.

Thus, it seems relevant to examine the severity of SI processes, their relationship with the parameters of myocardial remodeling during anticancer therapy of MM, since the data obtained can be used to assess the contribution of the studied condition to the initial state of the cardiovascular system (CVS), optimize the stratification of cardio-oncological risk and preventive cardioprotective strategies, to verify the early (subclinical) manifestations of cardiovascular toxicity in patients with severe comorbidities.

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Objective

Examine changes in calculated indices (neutrophil-to-lymphocyte ratio (NLR), systemic inflammation index (SII)) and biomarkers of systemic inflammation (IL-1β, hs-CRP), parameters of the structural and functional state of the myocardium and intracardiac hemodynamics, their correlation in patients with newly diagnosed MM at onset and after 6 regimens of CT containing bortezomib.

Material and Methods

The study included 30 patients with newly diagnosed MM to whom CT with PI is indicated. Diagnosis was verified and patient management strategy was determined according to the 2020 Clinical guideline for the diagnosis and treatment of multiple myeloma [18]. The disease was staged using the International Staging System (ISS) and the classification by Durie and Salmon [19, 20]. The study included patients who were not candidates for high-intensity treatment: over 65 years of age, or under 65 years of age with clinically significant concomitant diseases (Eastern Cooperative Oncology Group (ECOG) score > 3) [21]). The exclusion criteria comprised morphologically confirmed amyloidosis or criteria suggesting the presence of cardiac amyloidosis (Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases, 2021 [22]); history of another malignancy and chemotherapy and/or radiation therapy; decompensated comorbidity, acute cardiovascular event within 3 months before inclusion in the study.

Thirty patients with MM were initially included in the study and 9 patients dropped out after 6 regimens of CT (4 patient died of COVID-19 complications, and the remaining 5 were excluded due to switching to another combination of drugs).

The study was conducted in the Hematology Department of Sechenov University Clinical Hospital No. 1 following the Declaration of Helsinki and approved by the local ethics committee of Sechenov University. Patients were included in the study after signing the informed consent.

The main clinical and laboratory parameters were estimated in patients with MM before starting specific treatment and after 6 bortezomib, cyclophosphamide, dexamethasone (VCD) regimens with the inclusion of PI, which corresponds to 6 months from the start of therapy.

The indices of systemic inflammation NLR and SII were calculated based on the white blood cell differential count using the following formulas:

NLR = absolute neutrophil count (thousand)/ absolute lymphocyte count (thousand);

SII = absolute neutrophil count (thousand)/ absolute lymphocyte count (thousand) × thrombocyte count.

The serum concentrations of IL-1β and hs-CRP were determined by enzyme immunoassay using the Vector-Best commercial kits (Russia).

transthoracic echocardiography was performed using the Acuson Sequoia Ultrasound System to assess the morphofunctional state of the myocardium and intracardiac hemodynamics.

Statistical data processing was performed in StatPlus v.3.0.5 (OOO Stattech, Russia) and SPSS Statistics v.23. The analysis included descriptive and statistical parts. Qualitative variables are presented as the absolute values and percentages. The type of distribution of quantitative variables was determined using the Shapiro-Wilk test. Normally distributed data are presented as the means and standard deviations (M ± SD). Non-normally distributed data are presented as the medians and interquartile ranges (Me [25th percentile; 75th percentile]). The Mann-Whitney U test and Wilcoxon test were used to compare two quantitative variables in the related groups. The correlation analysis was carried out using the Spearman rank correlation method considering the nature of the sample data distribution. The results were statistically significant with $p < 0.05$.

Results

The study included 30 patients of older age group (mean age 63.8 ± 10.0 years), including 13 (43.3%) females and 17 (56.7%) males. At the debut of MM, 23 (76.7%) patients had a burdened family history of CVDs. Such cardiovascular RFs as diabetes mellitus type 2 and smoking were established in 7 (23.3%) and 9 (30.0%) patients, respectively. Moreover, at the time of diagnosing the oncohematological disease,

Figure 1. Distribution of the sample of patients with multiple myeloma depending on the stratification of initial cardio-oncology risk

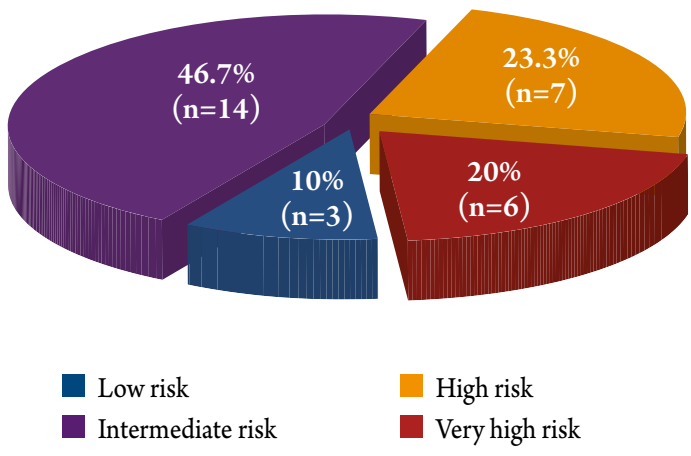

Table 1. Changes in the structure of cardiac therapy in patients with multiple myeloma during chemotherapy

Groups of drugs	Before treatment (n = 30)	After 6 CT regimens (n = 21)	p
Beta-blockers, n (%)	18 (60.0)	20 (95.2)	0.041
ACE inhibitors, n (%)	15 (50.0)	20 (95.2)	0.027
Diuretics, n (%)	8 (26.7)	8 (26.7)	0.765
Statins, n (%)	8 (26.7)	20 (95.2)	0.039
Antiplatelet drugs, n (%)	5 (16.7)	5 (23.8)	0.453
SCCBs, n (%)	4 (13.3)	4 (19.1)	0.046
ARBs, n (%)	2 (6.7)	1 (4.8)	0.797

The data is presented as the absolute and relative values; p-value: statistical significance is evaluated using the Wilcoxon test. SCCB, slow calcium channels blocker; ARB, angiotensin II receptor blocker; ACE, angiotensin-converting enzyme.

Table 2. Changes in the parameters of interest in patients with multiple myeloma during specific anticancer treatment

Parameter	Before treatment (n = 30)	After 6 CT regimens (n = 21)	p
Systemic hemodynamics			
SBP, mm Hg	130 [120; 140]	150 [140; 155]	0.037
DBP, mm Hg	80 [70; 90]	90 [65; 98]	0.324
Immune inflammatory indexes			
NLR (normal range 1–3)	1.54 [1.02; 1.83]	2.9 [1.9; 4.35]	0.009
SII	402.95 [230.5; 534.0]	1102.2 [453.1; 1307.9]	0.014
Markers of systemic inflammation			
IL-1β, pg/mL (normal range < 11 pg/mL)	5.15 [4.05; 5.77]	6.22 [5.66; 6.52]	0.142
hs-CRP, IU/L (normal range 0–1 IU/L)	1.02 [0.02; 2.71]	0.02 [0.02; 0.82]	0.138
Transthoracic echocardiogram			
LVPWT, cm (normal range < 1.0 cm)	0.90±0.14	1.11±0.13	0.026
IVST, cm (normal range < 1.0 cm)	0.94±0.18	1.13±0.23	0.102
LVEF, % (normal range > 55 %)	63.12±6.02	59.57±5.09	0.891
E/A (normal range 1.0–1.5)	1.00 [0.9; 1.17]	0.75 [0.62; 0.92]	0.345
E/e' (normal < 8)	8.1 [6.2; 11.7]	8.4 [6.9; 10.8]	0.765
LA volume, mL (normal range < 52)	56.25±25.51	63.00±23.76	0.600
LAVI, mL/m^2 (normal range < 34 mL/m^2)	30.4 [26.7; 35.2]	29.3 [27.1; 36.7]	0.600
RA volume, mL (normal range < 52)	43 [36; 50]	53 [45; 55.5]	0.786
LVEDD, cm (normal range < 5.2 cm)	4.5 [4.1; 4.9]	4.4 [4.3; 4.7]	0.600
LVEDV, mL (normal range 34–75 mL)	74 [62; 96]	73 [65; 86]	0.917
LVESV, mL (normal range 11–31 mL)	32 [27; 35]	31 [30; 37]	0.674
LVMI, g/m^2 (normal range 43–95 g/m^2)	94 [84; 103]	90 [75; 102]	0.374

Data is presented as the means and standard deviations or as the medians and the 25th percentile and 75th percentile.
The p value is the statistical significance estimated using the Wilcoxon test. CT, chemotherapy; NLR, neutrophil-to-lymphocyte ratio; SII, systemic inflammation index; Il-1β, interleukin-1β; hs-CRP, high-sensitivity C-reactive protein; LVPWT, left ventricular posterior wall thickness; IVST, interventricular septal thickness; E/A, ratio of the peak transmitral velocities of early and late filling; E/e', ratio of the peak early transmitral filling velocity to the peak early diastolic mitral annular velocity; LA, left atrium; LAVI, left atrial volume index; RA, right atrium.

patients had the following CVDs: arterial hypertension (AH) (20 (66.7%) patients), stable coronary artery disease (4 (13.3%) patients), history of myocardial infarction (3 (10.0%) patients).

According to the current guidelines on cardio-oncology [9, 23], all patients were subjected before treatment to the stratification of the initial risk of developing cardiovascular toxicity during CT with PI (Figure 1).

More than 50% of patients initially had a low to intermediate risk, which did not require the administration of de novo cardiac therapy or its modification. The initial characteristics of the cardiac therapy used and its modification during CT are presented in Table 1. The number of patients taking angiotensin-converting enzyme inhibitors, beta-blockers, statins, and slow calcium channel blockers statistically significantly increased by the end of the study.

Analysis of changes in hemodynamic parameters showed that mean systolic blood pressure (SBP) and diastolic blood pressure increased by 20 mm Hg (p = 0.037) and 10 mm Hg (p = 0.324), respectively, after 6 regimens of CT. This

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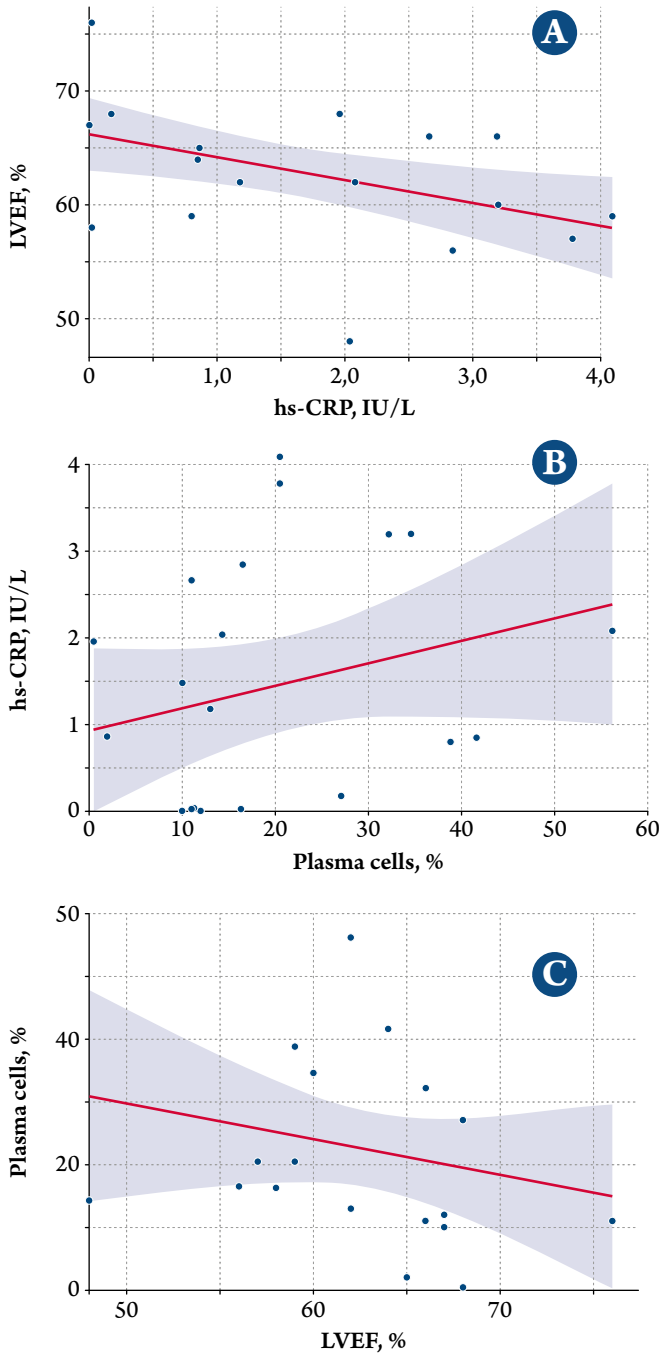
Figure 2. Correlations between hs-CRP and LVEF (A), BM PCs and hs-CRP (B), and LVEF and BM PCs (C) in patients with multiple myeloma at onset



trend was noted during CT despite regular modification of antihypertensive therapy (Table 2).

Mean immune-inflammatory indices of NLR and SII was noted during specific CT, despite the absence of uniform reference values of the latter. However, changes in the levels SI biomarkers were contradictory: despite a slight increase in the levels of IL-1β, its concentration remained within the reference values, and the levels of hs-CRP tended to decrease during long-term CT (Table 2).

Thickening of the left ventricular posterior wall (LVPW) was the only significant result of the analysis of changes in the main transthoracic echocardiographic indicators in the treatment group. Similar changes were noted for the interventricular septum thickness ($p = 0.102$), which may be indicative of the development of myocardial hypertrophy. Moreover, there was a trend during treatment to increase in the volumes of both atria but left atrial volume index (LAVI) showed inverse changes. The parameters of diastolic dysfunction (E/A, E/e', LAVI) tended to change statistically insignificantly during treatment (see Table. 2).

The correlation analysis revealed inverse significant relationships between the levels of hs-CRP and LVEF ($r = –0.557$; $p = 0.003$), direct relationships between the counts of BM plasma cells (PC) and hs-CRP ($r = 0.433$; $p = 0.022$), and inverse relationships between the numbers of BM PCs and LVEF ($r = –0.443$; $p = 0.023$) (Figure 2).

Discussion

In this study, changes of SI indices and markers, structural and functional indicators of myocardial condition were analyzed in patients with MM before and after 6 regimens of CT containing bortezomib, and the correlations of the parameters studied.

The role of chronic SI in the pathogenesis of CVDs was shown [24, 25]. Chronic SI is also an important component in the pathogenesis of any cancer, including MM. However, the effect of this pathogenetic link on the cardiovascular system in this category of patients is understudied [26–28]. Scientists are seeking for the indicators of SI that are easily accessible in clinical settings and reflect the effect of inflammation on the condition of the cardiovascular system as predictors of cardiovascular toxicity of chemotherapeutic agents, including early (subclinical) manifestations. Therefore, the evaluation of SI indices seems promising for routine use and can reflect the activity of the underlying disease and the prognosis for its course, which was proven for certain solid tumors [29, 30]. Some papers describe the role of indices in identifying signs of disease recurrence [31–33]. During this study, a significant increase in the immune-inflammatory indices of interest NLR and SII was found in patients with MM during long-term CT. On the one hand, this is due to higher neutrophil count in the peripheral blood as a direct result of treatment (elimination of infiltrating clonal plasma cells in BM). On the other hand, the contribution is made by high-dose glucocorticoids included in the CT regimen protocol and granulocyte colony-stimulating factor used to accelerate the restoration of hematopoiesis and the prevention of febrile neutropenia.

Unlike the SI indices, acute inflammatory markers IL-1β and hs-CRP are specific and more reliable to reflect the action of chronic SI on the initial state of the cardiovascular system (CANTOS [34, 35]) and the pathogenesis of cancer, including MM [36]. Based on the results obtained,

the levels of IL-1β before treatment and after 6 regimens of CT containing bortezomib did not exceed the upper normal limit, but its concentration tended to increase. This is presumably due to the inhibition of BM function in MM, since the specified cytokine is produced mainly by neutrophils, monocytes, and macrophages [37]. Changes in the levels of hs-CRP is characterized, according to the data obtained, by initially elevated levels with a tendency to decrease during treatment, which is explained by the efficacy of hemoblastosis therapy. Similar data were obtained by Lust et al. [38] in the analysis of long-term results of a phase II clinical trial: the use of an IL-1 receptor antagonist (anakinra) – in combination with low-dose dexamethasone in case of stabilization/progression of the disease after 6 months from the initiation of treatment – in patients with smoldering and indolent MM allowed postponing/preventing the development of symptomatic MM. The decrease in hs-CRP levels was correlated with an increase in progression-free and overall survival, which was considered by the authors as a consequence of the effect on the IL-1 – IL-6 axis, since IL-1 is one of the main cytokines responsible for the production of IL-6 microenvironment cells, which are essential for the growth of plasma cells [38].

No statistically significant changes in the structural and functional state of the myocardium and the main hemodynamic parameters were detected during 6 regimens of CT containing bortezomib. Attention is drawn to the increased thickness of LVPW with a minimal trend an increase in E/e', a decrease in E/A without significant changes in LVPW. It is important to keep in mind when calculating LAVI, that a cancer patient's body surface area is a dynamic parameter. For example, body weight may increase due to the regression of symptoms of intoxication, long-term use of high-dose glucocorticoids included in the CT protocol. These changes may cause the onset of diastolic myocardial dysfunction as a manifestation of subclinical cardiotoxicity or as a consequence of an increase in the number of patients with instable BP. The current clinical guidelines for cardiac oncology place fundamental importance on not meeting the criteria of anticancer therapy cardiotoxicity – no signs of HF and changes in LVEF [9, 23]. There are few studies examining changes in transthoracic echocardiography in patients with MM who receive CT containing bortezomib. After analyzing the data of 49 patients with MM (n = 35 with newly diagnosed MM, n = 14 with refractory/relapsed MM) subjected to CT containing bortezomib, Shnalieva and Salogub [39] regarded the trend to a decrease in LVEF in this cohort of patients (61.2 ± 2.4% and 56.0 ± 1.8% before and after the end of CT, respectively) as asymptomatic LV dysfunction. Moreover, the observed changes were reversible: during therapy with ACE inhibitors and/or bets-blockers, LVEF increased by a mean of 59.5 ± 1.6% 4 months after the end of treatment [39]. There were no other clinically significant adverse cardiovascular events (arrhythmias, conduction disorders, ischemia, pericarditis) were detected during the study.

The correlation analysis showed a direct relationship between the number of PCs and the levels of hs-CRP, which confirms the cytokine-mediated mechanism of MM progression. Clonal plasma cells affect the paracrine secretion of IL-6, which is key in the development of MM, by producing IL-1β [40]. IL-6 is able to stimulate the production of proteins of acute liver inflammation, including hs-CRP. Therefore, this biomarker may be reliable and sensitive to estimate the degree of MM activity [36]: MM therapy is accompanied by a decrease in the levels of hs-CRP due to the elimination of the PC tumor clone, which reflects the achieved therapeutic effect. Significant inverse correlation detected between the levels of hs-CRP and LVEF emphasizes the contribution of chronic persistent SI to the pathogenesis of CVDs and characterizes the influence of MM activity on systolic function, which deteriorates due to myocardial remodeling associated with microcirculatory ED due to oxidative stress and chronic SI [41].

There is contradictory information on the cardiotoxicity of PI bortezomib, which is included in the first-line CT regimens for MM. Some studies demonstrate that no significant adverse cardiovascular events develop during bortezomib therapy [42, 43]. According to other authors, the incidence of adverse cardiovascular events could increase to 11.6%, especially if patient received therapy containing other groups of anticancer drugs, for example, anthracycline antibiotics [44]. HF is the most common complication [45] followed by cardiac conduction disorders [46] and arrhythmias, such as atrial fibrillation [47]. Cardiotoxicity of bortezomib may also be confirmed by case reports of the onset coronary artery complications [48], pericardial effusion [49] during treatment.

However, as well as bortezomib, the VCD regimen also includes alkylating agent cyclophosphamide and dexamethasone – a synthetic analogue of prednisolone – each produces some adverse cardiovascular effects in addition to anticancer activity. Cyclophosphamide-induced cardiotoxicity is formed due to oxidative stress, cardiomyocyte apoptosis, myocarditis, ED, damage to the endoplasmic reticulum and mitochondria, and a decrease in the production of adenosine triphosphate in cardiomyocytes [50]. Long-term administration of high-dose glucocorticoids causes an increase in vascular tone, cardiosclerosis, myocardial hypertrophy, which is a natural adaptive response of the myocardium to dexamethasone-induced AH [51]. Thus, it is not possible to consider the contribution of each individual chemotherapeutic agent to the development of cardiovasculotoxic complications

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of chemotherapy, which is why it advisable to conduct a comprehensive estimation of a specific CT regimen.

In this study, changes in immunoinflammatory indices (NLR and SII) and markers of SI (IL-1β and hs-CRP), structural and functional parameters, and intracardiac hemodynamics in patients with MM to whom high-dose CT is not indicated, were evaluated for the first time at onset of the disease and after 6 regimens of CT containing PI bortezomib. Chronic persistent low-intensity inflammation plays an important role in the development and progression of MM; thus, it is pathogenetically reasonable to determine indices and markers of SI. High pro-inflammatory activity of MM directly affects structural and functional parameters of the myocardium. No cardiotoxicity criteria, according to the modern definition, were met in either patient, which may be due to a small patient sample, a short follow-up period, the use of drugs with a potential cardioprotective effect (beta-blockers, ACE inhibitors, and statins).

Thus, the initial state of cardiovascular system and the parameters of the underlying disease, persistent chronic SI and toxic effects of chemotherapeutic agent determine the entire spectrum of adverse cardiovascular events, which once again emphasizes the relevance and importance of cardio-oncology as a section of cardiology aiming to solve the issues of prevention and treatment of adverse cardiovascular events arising during anticancer treatment.

Conclusion

Cardio-oncology is clearly one of the most promising areas in modern clinical medicine. A multidisciplinary approach should be applied for cardiac patients not only at the stage of treatment, but also for the prevention of cardiovascular toxicity of modern chemotherapeutic agents, including targeted ones. It is necessary to have a broad understanding of the initial effects of the processes associated with malignancy on the cardiovascular system in order to take timely and effective measures aimed at cardiovascular protection in cancer patients. Given the effect of chronic systemic inflammation on the development of cardiovascular diseases, hematological patients are of particular interest due to the presence of initial active immune-inflammatory response. During the study, the criteria for cardiotoxicity of chemotherapy containing bortezomib were not met, according to the accepted definition, in patients with multiple myeloma. Initial indicators reflecting the activity and prevalence of multiple myeloma can serve as predictors of possible subclinical cardiotoxicity of chemotherapy (levels of high-sensitivity C-reactive protein, number of plasma cells in the bone marrow before treatment) and be considered as stratification criteria for the initial cardio-oncological risk for patients with multiple myeloma. Limited information on this issue is presented in the modern literature, which requires conducting further large prospective studies.

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