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Characteristic of cardiovascular status and intracardiac hemodynamics in patients with multiple myeloma before the start of antitumor therapy

Aim	To evaluate risk factors, the cardiovascular status, and the condition of intracardiac hemodynamics in patients with multiple myeloma (MM) before the start of specific antitumor treatment.
Material and methods	The study included 2 groups with equal number of patients: group 1, 25 patients newly diagnosed with MM; group 2 (comparison group), 25 patients with documented cardiovascular diseases (CVDs), including arterial hypertension (AH) and ischemic heart disease (IHD). Standard laboratory tests, instrumental studies (electrocardiography, echocardiography, 24-h Holter electrocardiographic monitoring), and analysis of documented CVD risk factors were performed for all included patients.
Results	Comparison of these two groups showed that the condition of the cardiovascular system (CVS) of patients with MM was comparable with that of patients with documented CVDs. Patients of the main group showed significant, moderate positive correlations between indexes of systemic inflammation, blood lipid composition, and intracardiac hemodynamics, i.e., concentrations of C-reactive protein (CRP) and triglycerides ($r=0.415$; $p<0.05$); CRP and very low-density lipoproteins ($r=0.345$; $p=0.09$); CRP concentration and left atrial volume ($r=0.434$; $p<0.05$); and CRP concentration and end-diastolic volume ($r=0.30$; $p<0.05$). The high risk of cardiovascular complications at baseline, in MM patients, may be due to cardiac remodeling associated with active systemic inflammation.
Conclusion	Considering the use of potentially cardio- and vasculotoxic drugs for the treatment of MM, evaluation of the cardiovascular status and cardio-oncologist/cardiologist consultation with selection of therapy should be a mandatory stage preceding the start of specific treatment.

Keywords	Cardiovascular system; multiple myeloma; cardio-oncology; cardiotoxicity; proteasome inhibitors; prevention of cardiotoxicity
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Introduction

Cardiovascular diseases (CVDs) and cancer remain the leading contributors to the global mortality rate. In 2019, the incidence of cardiovascular diseases (CVDs) in the Russian Federation was 35 per 1,000 people, while the occurrence of any type of cancer was 11 per 1,000 people [1].

Modern techniques supporting early diagnosis and effective treatments of cancer, including hematologic malignancy, have significantly reduced the mortality of the underlying disease. However, the increased survival rate and life expectancy among cancer patients contributes to the pressing issue of the effects of antitumor therapy on the cardiovascular system, resulting in the new and rapidly developing discipline of cardio-oncology [2]. By decreasing global myocardial contractility, many chemotherapeutic agents indirectly produce vasculotoxic effects. Moreover, modern target drugs and their combinations have cardiovasculotoxic properties, as do conventional cytostatics.

For this reason, it is of particular importance to assess risk factors (RFs) of CVDs in cancer patients before starting any specific therapy. The European Society of Cardiology (ESC) has approved guidelines for stratifying cardiotoxicity risks depending on the chemotherapeutic treatment used [3]. However, there are no clear protocols that specify the timing and scope of the necessary cardiological/cardio-oncological follow-

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up of patients undergoing antitumor regimens. Therefore, the present work investigates RFs of developing CVDs and intracardiac hemodynamics in patients with multiple myeloma at the time of verifying the underlying disease compared to cardiovascular patients without cancer to assess the effects of the hematologic malignancy on the cardiovascular system.

Multiple myeloma (MM) comprises a malignancy of hematopoietic tissue, in which the tumor substrate represents a clone of proliferating malignant plasma cells producing pathological immunoglobulin [4]. The second most common hematopoietic malignancy, MM makes up 1–2% of all malignant neoplasms worldwide [5]. The mean age of patients at the time of diagnosis is 65–70 years [6, 7]. In the Russian Federation, the incidence of MM was 2.8 per 100 thousand people in 2018 [8]. The number of such patients is likelyu to progressively increase.

Before starting a specific chemotherapy intervention and comparing it with patients with documented CVDs, it is necessary to assess the state of the cardiovascular system in patients with MM. This should take into account the epidemiological features of the paraproteinemic hemoblastosis (mean age of manifestation is 65 years and older, a documented CVD – or, at least, RFs of developing CVDs), as well as the possible direct (deposition of the fragments and/or the intact molecule of monoclonal paraprotein, fibrillar protein amyloid in the interstitial myocardium, plasma cell infiltration of the heart tissue) and indirect (electrolyte imbalance, anemia syndrome, hyperviscosity syndrome) pathophysiological effects on the myocardium and the vascular endothelium.

Aim

To assess the initial intracardiac hemodynamics and RFs of CVDs in patients with MM prior to commencing combination chemotherapy.

Materials and Methods

The study included two patient groups. The study group (n=25) comprised patients with newly diagnosed MM, who were not candidates for autologous hematopoietic stem cell transplantation (aHSCT). All patients were followed up in the Hematology Department of Clinical Hospital No. 1 of the Sechenov University. The diagnosis of MM was verified based on the criteria of the 2016 Russian Clinical Guidelines for the Diagnosis and Treatment of Multiple Myeloma [9]. The stage of the disease was determined following the criteria of the International Staging System (ISS) [10] and the Salmon-Durie classification [11]. The comparison group (n=25) included patients at ages comparable with those of the study group and with documented CVDs: hypertensive heart disease (HHD) and coronary artery disease (CAD) without heart failure phenomena who were followed up in the First Cardiology Department of Clinical Hospital No. 1 of the Sechenov University. All patients included in the study underwent standard laboratory tests (complete blood count with differentiated white blood cell count, total protein, creatinine, potassium, sodium, hepatic transaminases, lipid profile, markers of acute inflammation) and clinical examinations (electrocardiography (ECG), echocardiography, 24-hour Holter ECG monitoring); known RFs of CVDs (sex, age, family history of CVDs, smoking, body mass index (BMI)) were analyzed.

Transthoracic echocardiography was conducted using an Acuson Sequoia (Siemens, Germany) device to assess intracardiac hemodynamics. The examination was performed under the standard protocol in the M- and B-modes, as well as using Doppler ultrasound and pulse-wave modes. Cardiac morphology and function were analyzed.

The database was created in Excel 2017. The data obtained were processed in StatPlus and SPSS Statistics for MacOS. Normally distributed quantitative variables were presented as mean and mean error deviations (M (m)). Qualitative variables were expressed as absolute and relative values (n (%)). The significance of differences in the quantitative indicators of two independent groups was determined using the paired Student's t-test subject to normal distribution. The significance of differences in the qualitative indicators was determined using Fisher's exact test. Differences were considered statistically significant if the p-value was less than 0.05. A correlation analysis was carried out to assess the correlation of the quantitative indicators of interest. The correlation power and direction were estimated using Spearman's rank correlation coefficient. Hypotheses were tested at the level of significance of p=0.05.

Results

As shown in Table 1, the mean age of patients was 67.4±6.9 and 66.7±7.5 years in the study group and comparison group, respectively. In both groups, female patients predominated: female patients – 56% (n=14); male patients – 44% (n=11).

Following verification of MM diagnosis, 15 (60%) patients were found to have a history of hypertensive heart disease (HHD) of varying severity, 50% of whom had received continuous antihypertensive therapy with angiotensin-converting enzyme (ACE) inhibitors; 1 (4%) patient with HHD and coronary artery disease (CAD) received continuous heart-rate lowering therapy with an ACE inhibitor and beta-blockers; no clinical

signs of chronic heart failure (CHF) were detected. Paroxysmal atrial fibrillation (PAF) was found in 2 (8%) patients. Moreover, 2 (8%) patients of the study group had a comorbidity such as impaired glucose tolerance; the same number of patients had diabetes mellitus (DM) type 2. An analysis of continuous cardiac therapy administered prior to starting MM treatment showed that 6 (24%) patients received ACE inhibitors/ARBs, 8 (32%) patients administered beta-blockers, 3 (12%) patients received thiazide diuretics and lipid-lowering statin therapy, 4 (16%) patients used calcium channel blockers (CCBs), while 1 (4%) patient did not receive antihypertensive therapy. Anticoagulant therapy was administered to 3 (12%) patients, while only 1 (4%) patient received antiplatelet therapy. The remaining 9 (36%) patients with MM had no history of CVDs and did not receive cardioprotective therapy.

An analysis of non-modifiable RFs of CVDs revealed that most patients with MM had a family history of CVDs (n=21; 84%); 17 (68%) patients were over 65 years old. The evaluation of modifiable RFs of CVDs showed that patients from the study group had a significantly lower BMI (mean BMI was 25.9±5.2 kg/m^2 and 30.1±5.9 kg/m^2 in the study group and the comparison group, respectively; p=0.009), which may be a manifestation of tumor intoxication related to pathophysiological changes in cancer.

Elevated blood pressure (BP) was detected in all patients in the comparison group, while only 14 (56%) patients from the study group had BP higher than the target levels: mean systolic blood pressure (SBP) was 138.8±14.1 mm Hg and mean diastolic blood pressure (DBP) was 83.6±7.79 mm Hg.

Among patients with MM, 9 (36%) individuals were smokers. The same number of patients were smokers in the comparison group at the time of inclusion.

Laboratory tests (Table 2) revealed normochromic normocytic anemia characteristic of MM in most patients in the study group (n=18; 72%): hemoglobin levels were 114.1±2.3 g/L and 137.3±11.9 g/L in the study group and the comparison group, respectively (p=0.005). Levels of C-reactive protein (CRP) differed

Table 1. Clinical and anamnestic characteristics of the patients of the study group and the comparison group

Parameter	Study group (n=25)	Comparison group (n=25)	p
Sex	Male (n=11) Female (n=14)	Male (n=11) Female (n=14)	0.082
Age, years	67.4±6.9	66.7±7.5	0.307
BMI, kg/m^2 (normal range 18.5–24.9)	25.9±5.2	30.1±5.9	0.009
Family history of CVDs	21 (84)	23 (92)	0.394
Smoking	9 (36)	9 (36)	0.497
CAD	1 (4)	21 (84)	0.034
Documented MI	0	5 (25)	0.019
HHD grade I	7 (28)	2 (8)	0.066
HHD grade II	5 (20)	18 (72)	0.072
HHD grade III	3 (12)	5 (20)	0.222
AF	2 (8)	5 (20)	0.222
DM type 2	4 (16)	4 (16)	0.543
SBP, mm Hg (normal range 120–139)	138.8±14.1	154.3±12.8	0.020
DBP, mm Hg (normal range 80–89)	83.6±7.79	93.2±7.4	0.010
HR, bpm (norm 60–80)	74.2±24.5	70.3±9.9	0.010
Risk of developing cardiovascular events			
• very high risk (4)	6 (24)	13 (52)	0.071
• high risk (3)	7 (28)	8 (32)	0.095
• moderate risk (2)	3 (12)	4 (16)	0.020
ACE inhibitors/ARBs	6 (24)	15 (60)	0.020
Beta-blockers	8 (32)	19 (76)	0.004
Antiplatelet drugs	1 (4)	13 (52)	0.008
Anticoagulant drugs	3 (12)	5 (20)	0.149
Statins	3 (12)	19 (76)	0.001
Thiazide diuretics	3 (12)	5 (20)	0.149

The data are expressed as absolute and relative values (n (%)) unless otherwise specified. BMI – body mass index; CVD – cardiovascular disease; CAD – coronary artery disease; MI – myocardial infarction; AF – atrial fibrillation; DM – diabetes mellitus; SBP – systolic blood pressure; DBP – diastolic blood pressure; HR – heart rate; ACE – angiotensin-converting enzyme; ARB – angiotensin II receptor blocker

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significantly between patients with MM and patients with CVDs: 15.3±3.2 mg/L and 1.75±1.5 mg/L, respectively (p=0.052). This indicated the presence of systemic inflammation, a known independent factor of an unfavorable prognosis in CVDs [12]. Of note, kidney function was significantly deteriorated in patients with MM as compared to patients with CVDs; this was due to kidney damage related to the underlying disease: creatinine levels were 128.3±75.6 μmol/L and 85.6±20.3 μmol/L (p=0.02), glomerular filtration rate (CKD-EPI) 54.7±19.5 mL/min/1.73 m^2 and 70.7±19.2 mL/min/1.73 m^2 (p>0.05) in the study group and the comparison group, respectively. All indicators of the lipid and carbohydrate profiles in patients of the study group were comparable to those of the comparison group (Table 2). However, total cholesterol and low-density lipoprotein (LDL) levels were above the normal range in 10 (40%) patients with MM; levels of very-low-density lipoprotein (VLDL) and triglycerides were elevated in 4 (16%) and 7 (28%) patients, respectively; high-density lipoprotein (HDL) levels were lower than the reference values in 15 (60%) patients from the study group. The comparison of the indicators between the two groups revealed that patients with MM had higher levels of pro-atherogenic factors.

When assessing the 10-year risk of cardiovascular events in patients with verified CVDs, it was found that 6 (24%), 7 (28%), and 3 (12%) patients from the study group were at a very high, high, and moderate risk of developing cardiovascular events, respectively (Table 1).

24-hour Holter ECG monitoring showed that 14 (56%) patients with MM had no rhythm/conduction disorders. Paroxysms of supraventricular tachycardia (SVT), single supraventricular/ventricular premature beats, sinus bradycardia with atrioventricular (AB) conduction disorder (AV blockade grade I) were registered in 2 (8%), 5 (20%) and 2 (4%) cases, respectively (Figure 1). Two patients had PAF, including clinically significant events, for which antiarrhythmic and anticoagulant therapy was administered. In other cases, rhythm/conduction disorders were clinically silent, detected by ECG or 24-hour Holter ECG monitoring and not life-threatening. All patients had sinus rhythm at the time of inclusion.

The comparative analysis of the parameters of intracardiac hemodynamics of both groups (Table 3) provided the following data: prior to starting specific combination chemotherapy, only 2 (8%) patients of the study group had decreased left ventricular ejection fraction (LVEF) according to the echocardiographic findings. The same patients had a history of CVDs (CAD, HHD, PAF). The rest of the study group had normal global LV contractility. In the group of patients with CVDs, LVEF was decreased in 5 (20%) patients, while signs of diastolic dysfunction (E/A<1.0) were observed in 11 (44%) patients.

Patients with documented CVDs had LV concentric hypertrophy and diastolic dysfunction. It is of particular interest that, in the absence of myocardial thickening and in normal LV relaxation, patients with MM had higher left atrial (LP) volume than in the group without MM (59.2±19.3 mL and 55.4±15.1 mL, respectively; p=0.374) and lower left ventricular end-diastolic volume (LVEDV), which may indirectly indicate increased myocardial stiffness.

A correlation analysis of the parameters of interest was additionally conducted to reveal a significant positive correlation of the mean power of systemic inflammation activity with the indicators of lipid profile and parameters of intracardiac hemodynamics: between the levels of CRP and triglycerides (TG; r=0.415; p<0.05), CRP and VLDL (r=0.345; p=0.09), CRP and LA volume (r=0.434; p<0.05), and CRP and LVEDV (r=0.30; p<0.05).

Table 2. Laboratory findings of hemoglobin, indices of kidney function, markers of acute inflammation, as well as carbohydrate and lipid profiles in the study and comparison groups

Parameter	Study group (n=25)	Comparison group (n=25)	p
Glucose, mmol/L (normal range 3.3–5.5)	5.52±0.9	5.7±0.99	0.050
Total cholesterol, mmol/L (normal range 3.2–5.6)	5.73±3.44	5.25±1.42	0.897
VLDL, mmol/L (normal range 0.26–1.04)	0.97±1.43	0.66±0.46	0.837
LDL, mmol/L (normal range 1.92–4.51)	3.18±1.26	3.28±1.16	0.954
Triglycerides, mmol/L (normal range 0.41–1.8)	2.07±1.1	1.62±0.94	0.757
HDL, mmol/L (normal range >0.7)	1.44±1.01	1.38±0.41	0.956
Hemoglobin, g/L (normal range 117–180)	114.1±12.3	137.3±11.9	0.005
ESR, mm/h (normal range 0–15)	53.8±31.6	10.12±6.02	0.021
Creatinine, mmol/L (normal range 44–115)	128.3±75.6	85.6±20.3	0.019
GFR (CKD EPI), mL/min/1.73 m^2	54.7±19.5	70.7±19.2	0.562
CRP, mg/L (normal range 0–5)	15.3±3.2	1.75±1.5	0.052

VLDL – very-low-density lipoprotein; LDL – low-density lipoprotein; HDL – high-density lipoprotein; ESR – erythrocyte sedimentation rate; GFR – glomerular filtration rate; CRP – C-reactive protein.

Discussion

Our findings confirmed MM to be most prevalent in the elderly patients (over 65 years old) as consistent with global data [13]. Most of the patients in the study group were postmenopausal women, which is also an important RF of CVDs.

Mean BMI was significantly lower in the study group than in the comparison group. These differences, which are probably associated with tumor intoxication syndrome, are not indicative of a lower risk of developing cardiovascular accidents.

Following verification of hematologic malignancy, over 50% of patients had documented CVDs. However, even when excluding the hematologic malignancy, the life expectancy prognosis was significantly lowered by the fact that they either did not receive continuous cardiac therapy or took it irregularly.

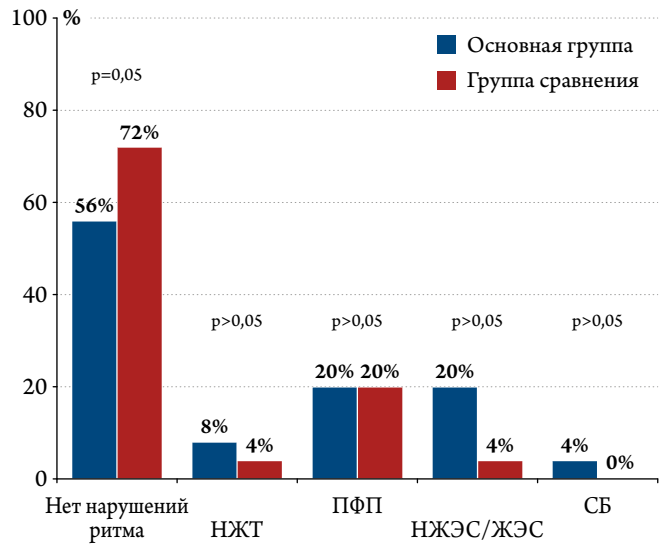
Blood lipid profile indicators were comparable in patients with MM and those in the comparison group. Since only a few patients of the study group received continuous lipid-lowering therapy at the time of inclusion, most patients did not achieve the target values of the relevant pro-atherogenic parameters. These changes objectively increase the risk of atherosclerotic lesions and the development of cardiovascular events during the management of the underlying disease, especially with immunomodulators and glucocorticosteroids having prothrombogenic activity [14].

According to the evaluation of the risk of cardiovascular events using the SCORE scale, patients with MM are at higher risk of developing fatal conditions.

It also seems significant that the mean hemoglobin level was lower in the study group than in patients with CVDs. Lower hemoglobin levels are also significant RF of severe ischemic complications, such as myocardial infarction type 2 [15].

The current understanding of myocardial and vascular remodeling is closely related to the concept of systemic inflammation [16]. Cardiovascular events are often driven, for example, by complications associated with the instability of an atherosclerotic plaque (ulceration, bleeding, atherothrombosis with subsequent occlusion of arteries). Here, chronic inflammation characteristic of the plaque microenvironment plays a significant role in the pathogenesis. Its activity is often caused by an increase in the levels of pro-inflammatory cytokines interleukins (IL) – 6 and –8. When IL-6 and IL-8 levels increase, hepatocytes more actively produce CRP. Therefore, CRP is currently considered as a reliable biomarker of systemic inflammation and a significant predictor of atherothrombotic complications in patients who do not have a history of cancer [3]. Somatic mutations occurring during the development of a malignancy clearly increase the expression of key pro-inflammatory cytokines (IL-6, IL-8, tumor necrosis

Figures 1. Rhythm and conduction disorders in patients of the study group and the comparison group



SVT – supraventricular tachycardia; PAF – paroxysmal atrial fibrillation; SVPB – supraventricularpremature beat; VPB – ventricular premature beat; SB – sinus bradycardia – AV conduction disorder.

Table 3. Main echocardiographic indices in the patients of the study and comparison groups

Parameter	Study group (n=25)	Comparison group (n=25)	p
LV ejection fraction, % (normal range>55)	60.2±4.17	58.4±7.5	0.352
LV posterior wall thickness, cm (normal range <1.0)	0.95±0.28	1.14±0.13	0.004
Interventricular septal thickness, cm (normal range <1.0)	1.03±0.2	1.5±0.7	0.521
LV diastolic dysfunction (E/A) (normal range 1.0–1.5)	1.1±0.2	0.8±0.2	0.294
Left atrial volume, mL (normal range <52)	59.2±19.3	55.4±15.1	0.374
Right atrial volume, mL (normal range <52)	46.6±13.5	47.2±14.8	0.976
LV end-diastolic dimension, cm (normal range <5.2)	4.84±0.5	4.59±0.27	0.662
LV end-diastolic volume, ml (normal range 34–75)	90.8±19.3	99.8±37.6	0.364
LV end-systolic volume, ml (normal range 11–31)	40.2±14.7	43.9±22.9	0.892

LV, left ventricular.

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factor (TNF)), and thus, higher levels of CRP. Moreover, the following pathological aspects of elevated CRP levels were demonstrated in terms of vascular wall remodeling: faster conversion of macrophages into foam cells due to increased uptake of LDL by macrophages [17]; activation of the conventional pathway of complement components with an increased risk of thrombosis [18]; production of a large amount of tissue factor during the activation of macrophages; increased expression/activity of plasminogen activator inhibitor 1 (PAI-1) followed by the inhibition of fibrinolysis [12].

The direct effect of chronic systemic inflammation on myocardial and vascular remodeling can occur through the activation of fibroblasts by the stimulation of fibrogenic macrophages and lymphocytes. Long-term sluggish inflammation can cause necrosis of cardiomyocytes, contributing to the development of reparative fibrosis [19]. Such processes have a significant impact on changes in intracardiac hemodynamics. For example, there are publications that describe the presence of a reliable inverse correlation of IL-6 levels with LVEF and a direct correlation with LVEDV [19, 20]. The development of compensatory hypertrophy may progress to clinically significant heart failure due to reduced LV contractility [21].

Changes in the parameters of the heart cavities are well described in diseases directly related to processes of chronic systemic inflammation. Echocardiography often shows increased LA dimensions and fibrosis in such patients, which are not associated with impaired intracardiac hemodynamics. This is explained by the thicker layer of epicardial adipose tissue, which also produces pro-inflammatory mediators that affect the closely located LA when released [22, 23]. Thus, CRP, which is most widely used in clinical practice to assess the activity of inflammatory processes, is directly related to the increased LA dimensions and fibrosis, significantly increasing the risk of hemodynamically significant rhythm disorders [24].

Although mean E/A was within the normal range in patients of the study group, it was reduced in almost 50% of patients with MM; in patients with documented CVDs and without LV hypertrophy, LVEDV was lower and LA more significant. Such changes in patients with paraproteinemic hemoblastosis may indicate increased LV stiffness, which could be due to direct (deposition of the fragments and/or the intact molecule of monoclonal paraprotein, fibrillar protein amyloid in the interstitial myocardium, plasma cell infiltration of the heart tissue) and indirect (anemia, hypercalcemia) pathophysiological effects of MM on the myocardium and vascular endothelium. Attention is drawn to the correlation analysis showing that increased levels of CRP are significantly correlated with elevated levels of VLDL and TG, increased LA volume, as well as decreased LVEDV in the study population. Such correlations showing that systemic inflammation plays a central role in the development of primary manifestations of cardiovascular remodeling in hematologic malignancy indicate the need for further study.

The current scientific literature provides extensive evidence of the cardiotoxic effects of first-line MM therapy (proteasome inhibitors such as bortezomib; immunomodulators such as lenalidomide) [25]. The main mechanism of action of proteasome inhibitors excludes proteasome (which is necessary for the degradation of intracellular protein molecules) from cell metabolism. Meanwhile, the accumulation of non-functional proteins activates the processes of apoptosis. These drugs produce the greatest effect on cells that actively synthesize protein structures, including cardiomyocytes and endotheliocytes [24, 25]. The main mechanism of action of immunomodulators consists in the inhibition of pro-inflammatory cytokines (TNF, IL-1β, IL-6, IL-12) and the induction of the T-cell proliferation, which increases the activity of cytotoxic killers [26]. Both drug groups produce cardiotoxic effects such as the development of arterial hypertension, the manifestation of various rhythm and conduction disorders, coronary complications, cardiomyopathies, thromboembolism, as well as heart failure. However, the mechanisms of their pathogenesis and clinical particularities are not yet well known [3, 27].

Conclusion

Patients with multiple myeloma are initially at a high risk of developing cardiovascular events. Primary manifestations of cardiac remodeling associated with systemic inflammation were also detected. Thus, patients in need of combination chemotherapy regimens using potentially cardiovasculotoxic drugs should be examined by a cardiologist/cardio-oncologist prior to the administration of a specific therapy for early detection, prevention and rational management of cardiovascular events.

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