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Stratifying breast cancer patients by baseline risk of cardiotoxic complications linked to chemotherapy

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Abstract

A majority of modern antitumor pharmaceuticals are accompanied by cardiotoxicity. The **study aims** to present practical approaches to stratifying the baseline risk of antitumor therapies' cardiotoxicity in patients newly diagnosed with breast cancer started on anthracyclines and/or trastuzumab.

Material and methods: Stratifying the risks of antitumor therapy was carried out according to the European Society of Cardiology recommendations. A therapist examined all patients for existing cardiovascular diseases and risk factors detection. The blood levels of glucose, cholesterol, creatinine, cardiac troponin I, and brain natriuretic peptide were determined. Electrocardiography and echocardiography with an assessment of the myocardium global longitudinal strain were performed.

Results: In total, 128 breast cancer patients with a mean age of 54.3±11.0 years were included in the study. Of them, 84.4% had tumor stages I and II, and 21.1% were HER2-positive. Chronic heart failure and ischemic heart disease were detected in 2.3%. Among the risk factors, the most common were arterial hypertension (51.6%), obesity (29.7%), age 65-70 years (18%), significant smoking history (15.6%), and diabetes mellitus (11.7%). Elevated cardiac troponin I and brain natriuretic peptide baseline levels were present in 5.5% and 7.0% of patients, respectively. To a high-risk group for cardiotoxic complications, 7.8% were allocated, 35.7% were assigned to the moderate-risk group, and 54.7% had low risk. High/very high and moderate-risk patients (43.5%) were referred to a cardiologist. Cardioprotective treatment was started immediately in high/very high-risk patients.

Conclusion: All revealed differences between the cardiovascular risk groups were related to age, cardiovascular system condition, and the severity of comorbid pathologies. The baseline stratification of patients into risk groups is a crucial step in preventing the cardiotoxicity of anticancer therapy. Comprehensive assessing the patient's condition before and during chemotherapy allows for avoiding the development of fatal cardiovascular complications in at-risk patients.

Key words: cardiotoxicity, chemotherapy, breast cancer, cardiovascular risks

Introduction

Over the past decades, owing to achievements in early diagnosis of the tumor process and the introduction of effective antitumor therapies into clinical practice, the prognosis of cancer patients improved drastically [1]. At the same time, numerous studies have demonstrated various side effects caused by chemotherapy and radiation therapy, among which cardiotoxicity has the most significant prognostic value [2,3]. Clinical manifestations of antitumor therapies' cardiotoxicity vary widely from asymptomatic subclinical changes recorded only by special imaging techniques such as global longitudinal strain measurement (GLS) and 3D-Echocardiography (EchoCG) to severe clinical

symptoms evidencing heart failure and requiring emergency hospital admission [4]. Cardiotoxicity, or, according to the current definition, cancer treatment-related cardiovascular disease (CTRCD), can develop both during antitumor therapy and in the first year or even years after chemotherapy completion [5]. CTRCD may be irreversible due to myocardial injury (type 1) and reversible due to myocardial dysfunction (type 2). Type 1 CTRCD is associated with anthracyclines and often manifests as heart failure (HF) and arrhythmias [6]. Trastuzumab, vascular endothelial growth factor (VEGF) inhibitors, checkpoint and/or proteasome inhibitors are responsible for the development of type 2 CTRCD, manifesting as HF, arrhythmias, arterial hypertension (AH), and myocardial ischemia [7-9]. Myocarditis, pericarditis, ischemic heart disease (IHD), valvular disease, conduction disorders, and thoracic aorta calcification (porcelain aorta) are more common after radiotherapy [10].

CTRCD can occur in the treatment with anthracyclines (1-26%), trastuzumab (2-28%), tyrosine kinase inhibitors (0.005-11%), or high doses of cyclophosphamides (7-28%) [11].

When managing cancer patients, there are three essential periods. The first period commences after the diagnosis of a tumor disease. Determining the baseline risk of cardiotoxic complications before initiating antitumor treatment is necessary. There are very-high, high, intermediate, and low-risk categories. Allocation into risk groups is based on assessing existing cardiovascular diseases (CVD) and CV risk factors, an objective examination focused on the CV system, measurement of blood pressure, ECG, EchoCG, laboratory blood tests, and performing the tests on cardiac troponin I (cTnI) and brain natriuretic peptide (BNP). In addition, the previous anticancer therapy must be considered [12,13].

An individual monitoring program for cardiotoxic complications is being created for each risk category. Patients at very high and high risk of such complications are started with preventive cardioprotective treatment. The next step involves monitoring at planned intervals (depending on baseline risk) for the onset of symptoms or signs of CTRCD, focusing on detecting early preclinical signs. The final stage begins when the anticancer treatment is completed. This period includes monitoring patients who experienced CTRCD and the entire cohort of cancer patients, as late CV complications may still occur [14].

The study **aims** to demonstrate practical approaches to baseline CTRCD risk stratification in patients with breast cancer (BC) who are administered anthracyclines and/or trastuzumab.

Material and methods

In total, 128 women newly diagnosed with BC and started antitumor chemotherapy with doxorubicin and/or trastuzumab at the University's Medical Center from September 2021 to August 2022 were enrolled in the study. The eligible patients were those with verified BC of any stage, at age ≥18 years, and started on mentioned antitumor therapy. Exclusion criteria: Simpson left ventricular ejection fraction (LVEF)≤40%; decompensation of any comorbid pathology. The study was approved by the Bioethics Committee of the West Kazakhstan Medical University (Ref. No. 5, 13/05/2020) and registered in the international registry of clinical trials ISRCTN, ID 12628444. The study protocol was published [15]. Figure 1 displays the research design.

We assessed the tumor's clinical, molecular-genetic subtypes in BC patients. We established the presence of existing CV diseases and risk factors, such as stable angina pectoris, previous myocardial infarction, myocardial revascularization in history, AH, chronic heart failure (CHF), atrial fibrillation, diabetes mellitus (DM), and obesity. Besides, we detected the baseline levels of glucose, cholesterol, creatinine, cTnI, and BNP [16]. The glomerular filtration rate was calculated using the CKD-EPI formula. Patients underwent computerized ECG using the Poly-Spectrum-8 device (Neurosoft, Russia).

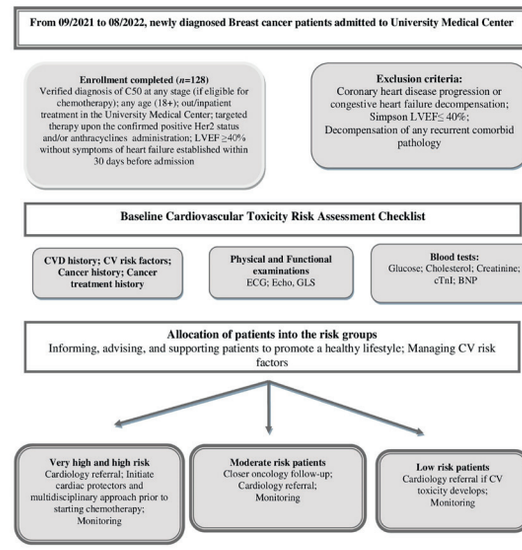

Figure 1 - Study flowchart

Table 1 An example of patients stratifying according to baseline cardiovascular toxicity risk (by Heart Failure Association-International Cardio-Oncology Society).

Baseline CV toxicity risk factors	Anthracycline-based chemotherapy	Patient's code: 17
Previous cardiovascular diseases		
Heart failure or cardiomyopathy	Very high	0
Severe valvular heart disease	High	0
Myocardial infarction or previous coronary revascularization (PCI* or CABG**)	High	0
Stable angina	High	0
Cardiac imaging		
Baseline LVEF <50%	High	0
Borderline LVEF 50–54%	Medium 2	0
Cardiac biomarkers		
Elevated baseline cardiac troponin	Medium 1	0
Elevated baseline natriuretic peptides (BNP/ NT- proBNP)	Medium 1	0
Age and cardiovascular risk factors		
Age ≥80 years	High	0
Age 65–79 years	Medium 2	2
Arterial hypertension	Medium 1	1
Chronic kidney disease	Medium 1	1
Diabetes mellitus	Medium 1	1
Previous exposure to		
Anthracycline-based chemotherapy	High	0
Radiotherapy to left chest or mediastinum	High	0
Non-anthracycline-based chemotherapy	Medium 1	0
Lifestyle risk factors		
Current smoker or significant smoking history	Medium 1	0
Obesity (BMI>30 kg/m2)	Medium 1	1
Summary M 6 - High risk		
*PCI - Percutaneous Coronary Intervention **CABG - Coronary Artery Bypass Grafting		

EchoCG was performed on a GE Vivid 9 machine (GE Healthcare). Measurement of LVEF was carried out by the biplane method, according to Simpson. GLS measurement was performed from the apical 3-chamber (3C), 4-chamber (4C), and 2-chamber (2C) positions. The apical positions were taken so that the myocardial wall's thickness along the entire length of the left ventricle fell into the study area.

Table 2 Descriptive and comparative statistics of BC patients allocated into risk groups.

Parameters	Total, n=128	High risk, n=10	Moderate risk, n=48	Low risk, n=70	p
Age, years	54,3±11.0	68,3±5.4	58.8±8.9	49,3±9.8	**<0.001**
Ethnicity: Asian, n (%) European, n (%)	 89(69.5) 39(30.6)	 3(30.0) 7(70.0)	 27(56.3) 21(43.7)	 59(84.3) 11(15.7)	 **<0.001**
Heredity, n (%)	16(12.5)	3(30.0)	3(6.3)	10(14.3)	0.094
Menopause, n (%)	87(68.0)	10(100.0)	42(87.5)	35(50.0)	**<0.001**
Localization: Right Left Both sides	 56(43.7) 70(54.7) 2(1.6)	 5(50.0) 5(50.0) -	 16(33.3) 31(64.6) 1(2.1)	 35(50.0) 34(48.6) 1(1.4)	 0.193
Clinical stage: I, n (%) IIA, n (%) IIB, n (%) IIIA, n (%) IIIB, n (%) IV, n (%)	 6(4.7) 44(34.4) 58(45.3) 5(3.9) 10(7.8) 5(3.9)	 - 4(40.0) 3(30.0) 1(10.0) 2(20.0) -	 3(6.3) 17(35.4) 24(50.0) 1(2.1) 2(4.2) 1(2.1)	 3(4.3) 23(32.9) 31(44.3) 3(4.9) 6(8.6) 4(5.7)	 0.706
Tumor histotype, n (%) Invasive carcinoma, unspecified; Invasive ductal carcinoma; Invasive lobular cancer; Angiosarcoma	 89(69.5) 34(26.6) 4(3.1) 1(0.78)	 9(90.0) 4(40) 1(10.0) -	 33(68.8) 15(31.3) 1(2.1) 1(2.1)	 47(67.1) 15(21.4) 2(2.9) -	 0.286
*Breast cancer types, n (%) 1 - Nodular cancer 2 - Mastitis-like cancer 3 - Edematous-infiltrative 4 - Paget disease of BC 5 - Armor-like cancer 6 - Erysipelas-like 7 - Diffuse forms - other	 106(82.8) 2(1.6) 10(7.8) 1(0.78) 9(7.0) - -	 8(80.0) - 1(10.0) - 1(10.0) - -	 44(91.6) - 3(6.3) - 1(2.1) - -	 54(77.1) 2(2.8) 6(8.6) 1(1.4) 7(10.0) - -	 0.630
Imminohistochemistry, n(%) 1 - Triple negative (TNBC); 2 - Luminal A type; 3 - Luminal B (positive); 4 - Luminal B (negative); 5 - Her2-positive	 23(18.0) 35(27.3) 18(14.1) 43(33.6) 9(7.0)	 2 (20.0) 2(20.0) 1(10.0) 5(50.0) -	 10(20.8) 15(31.3) 7(14.6) 14 (29.2) 2(4.2)	 11(15.7) 18(25.7) 10(14.3) 24(34.3) 7(10.0)	 0.826
Smoking, n(%)	20(15.6)	1(10.0)	9(18.7)	10(14.3)	0.708
IBM, kg/m2	27.0(23.3;30.9)	29.5(27.4;34.6)	30.8(26.6;35.3)	23.6(22.3;28.4)	**<0.001**
**SBP, mmHg	120±17.5	122±14.0	130±17.6	113±14.6	**<0.001**
DBP, mmHg	75±9.6	74±6.7	80±9.6	72±8.5	**<0.001**
Heart rate	76(70;80)	76(74;88)	76(68;80)	76(72;80)	0.449
Charlson Comorbidity index, points	5(3;6)	6.5(5;7)	5(4;6)	4(3;5)	**<0.001**
Hb, g/L	124.2±13.5	123.5±14.4	126.5±13.6	122.7±13.4	0.398
Creatinine, μmol/L	67.8(59.6;77.2)	68.2(55.0;70.5)	68.4(60.9;79.0)	66.9(58.8;76.5)	0.543
eGFR, mL/min/1,73m2	90.1±17.5	82.0±13.2	84.8±16.3	95.0±17.6	**0.003**
Glucosae, mmol/L	5.2(4.7;5.6)	5.8(5.2;6.0)	5.2(4.7;5.6)	5.1(4.6;5.4)	**<0.001**
Cholesterol, mmol/L	5.2±1.0	4.9±0.6	5.2±1.1	5.2±1.0	0.645
Baseline LVEF, %	59.7±3.9	55.8±4.5	58.8±3.5	60.8±3.6	**0.001**
Baseline GLS, %	18.2±3.0	16.2±4.1	17.8±3.1	18.8±2.5	**0.028**
Baseline cTnI, ng/mL	0.10(0.10;0.27)	0.23(0.10;0.40)	0.10(0.10;0.29)	0.10(0.10;0.22)	0.240
Baseline BNP, pg/mL	54.9(36.1;86.7)	109.0(93.8;124.8)	53.3(37.8;72.8)	49.7(35.2;74.6)	**<0.001**
***6MWT, m	398.0(322;448.0)	363.0(313.0;407.0)	358.0(298.5;408.5)	432.0(354.0;469.0)	**<0.001**

*According to BC types clinical classification adopted in our country.
**SBP, DBP - systolic, diastolic blood pressure.
***6 Minute Walk Test.

We accepted the normal GLS value at (-)18%. All obtained information was entered into particular forms developed by the European Society of Cardiologists (ESC) experts for stratifying the CV risk of future therapy with anthracyclines and/or trastuzumab. All risk factors for CV complications included in the forms are evidence-based or have been discussed by experts [17]. An example of a filled-in form is presented in Table 1.

The statistical data analysis was carried out using the software package Statistica (StatSoft, Inc., Tulsa, OK, USA, v. 10). The Kolmogorov-Smirnov test was used to check the normality of the quantitative variables distribution. A comparison of three groups (very high/high, intermediate, and low risk) was performed using the Kruskal-Wallis H-test. Accordingly, the critical value of the significance level was set at $p<0.017$ (given the three groups of pairwise comparisons under analysis). As we tested the three statistical hypotheses, we used a smaller critical significance level of p. This level was calculated using the formula 1-0.951/3 = 0.017 [18,19]. To analyze the differences between groups regarding qualitative and rank variables, the Pearson criterion $\chi 2$ was applied.

Results

The average age of participants was 54.3±11.0 years. Summarized patients' data are presented in Table 2.

Table 2 shows no statistically significant differences between the CV risk groups regarding the tumor clinical staging or biological features. All revealed differences were related to age, CV system condition, and the severity of comorbid pathologies.

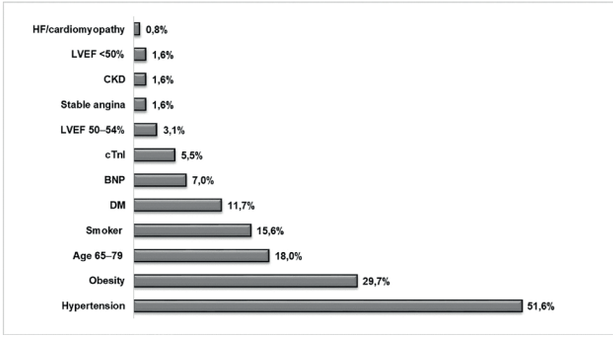

Figure 2 - Baseline cardiovascular toxicity risk factors

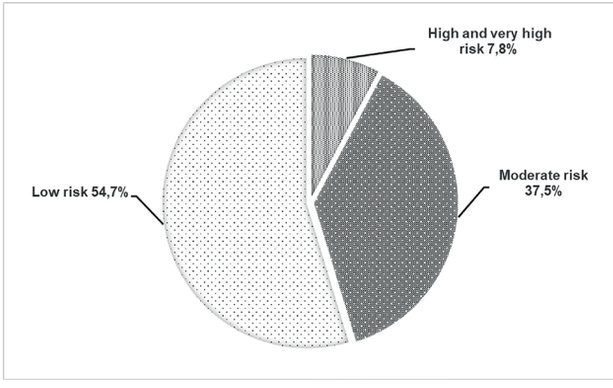

Figure 3 - Baseline cardiovascular toxicity risk stratification

The occurrence of significant CV diseases and risk factors before the start of chemotherapy is shown in Figure 2. At baseline, three patients (2.3%) had CVD; two had a history of stable angina Class II, and one suffered from CHF with a permanent form of atrial fibrillation. Among the risk factors for CVD, AH was the most common (66 individuals out of 128), then obesity (BMI> 30 kg/m2) - 38 (29.7%), age 65-70 years - 23 (18%), active smoker or significant smoking history - 20 (15.6%), and DM - 15 (11.7%). After EchoCG and determining blood biomarkers, four patients were assigned to the moderate-risk group, receiving two points each for LVEF lower than 54%. For elevated baseline levels of cTnI, seven (5.5%), and nine patients (7.0%) for elevated BNP, received one point each and were also assigned to the moderate-risk group.

Patients were stratified into risk groups, as shown in Figure 3. Overall, 70 out of 128 were identified as low-risk patients, 48 were counted as patients at moderate risk, and ten were referred to the high- and very high-risk groups. Almost half (45.3%) of patients were assigned to very high/high and moderate-risk groups, according to points calculation for comorbidities and other risk factors, as demonstrated in Table 1.

We united very-high and high-risk patients; they were ten (7.8%). But, for clarity, only one was referred to the very-high-risk group, and the rest nine were high-risk patients. They were those who received the highest points, according to Table 1. As mentioned above, three (2.3%) had a history of cardiovascular disease. So, the only patient, M., 58 years old, referred to the very-high-risk group developed atrial fibrillation due to stable angina II before enrollment in the study. According to ESC Guidelines, cardioprotective therapy was administered immediately after the diagnosis and before she started chemotherapy. Patient M. has been prescribed, except for routine cardiac medications, Mineralocorticoid Receptor Antagonists (MRA), Sodium-glucose Cotransporter-2 (SGLT2) Inhibitors, and oral anticoagulants. So, M. received Enalapril 5 mg x 2 times per day; Bisoprolol 5 mg; Eplerenone 50 mg; Dapagliflozin 10 mg; and Dabigatran 150 mg twice a day. Afterward, after three months of observation, LVEF fell from 51% to 41%, and anthracycline therapy was canceled at a summary dose of 260 mg/m2 due to the deterioration of her condition. Anticancer treatment was continued with Tamoxifen and courses of radiation therapy.

All ten high- and very-high-risk patients have been prescribed Angiotensin-converting enzyme inhibitors / Angiotensin-receptor blockers (ACE-I/ARBs); Beta-blockers were additionally administered to nine of them, and eight of them were provided by statins.

Out of 48 patients at moderate risk, 40 (83.3%) were provided with cardioprotectors before chemotherapy started, according to indications. As most of them suffered from arterial hypertension (40 from the moderate risk group out of total 66 with AG), they were provided with appropriate antihypertensive medications.

Chemotherapy of BC patients, given the tumor process and the risk of cardiotoxic complications, is displayed in Figure 4. An overwhelming majority of patients (85.9%) started on an anthracycline-based regimen. In this cohort, the cumulative effect of anthracyclines and the possible development of irreversible type 2 CTRCD should be expected.

During the present study, we faced a case of classic acute cardiotoxicity. Patient Sh., 46 years old, ST IIB T3NxM0, had no CV diseases in history and revealed risk factors. Baseline LVEF 64%, GLS 22.4%, cTnI 0.1 ng/ml; BNP 43.8 pg/ml. The initial risk of forthcoming anthracycline therapy seemed to be low. After the first dose of doxorubicin 60 mg/m2 and cyclophosphamide 600 mg/m2, the patient experienced two episodes of asystole at Holter monitoring, 9327 msec, and 4051 msec, respectively (Figure 5).

This case proves the necessity of scrutinizing and constantly monitoring patients undergoing chemotherapy with potentially cardiotoxic agents, particularly anthracyclines having cumulative effects.

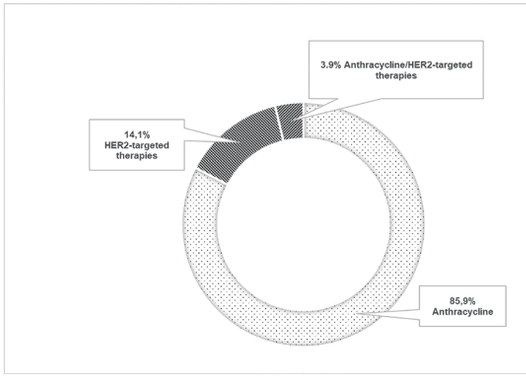

Figure 4 - Cancer treatment groups

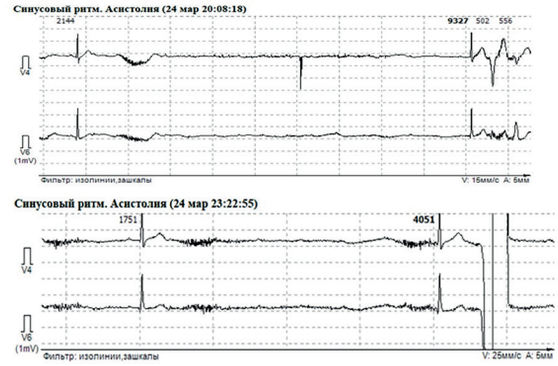

Figure 5 - A fragment of Holter monitoring in patient Sh., 46 years old, with acute anthracycline-induced cardiotoxicity

Discussion

As stated above, the baseline risk of cardiotoxic complications was very-high/high in 7.8% and moderate in 37.5% of BC patients. Anthracyclines, associated with the most severe and irreversible cases of CTRCD, have been administered to 85.9% of patients. Thus, the study identified groups of patients who would benefit the most from a multidisciplinary approach. In very high and high-risk patients, the predicted risk of antitumor therapy cardiotoxic complications fluctuates from 10% to 19%, i.e., CTRCD can develop in each fifth patient. In the presence of 2 to 4 moderate risk factors, the predicted risk of cardiotoxic complications is 2-9%; if there are no risk factors or one moderate risk factor, then the risk is defined as low, <2% [20]. In our cohort of patients, the following diseases and conditions, such as HF/cardiomyopathy, stable angina, and LVEF<50%, were associated with a very high and high risk of CTRCD. However, the majority of patients, 60%, were assigned to this group as they scored more than five moderate risk points. The most common moderate risk factors were AH, obesity, age 65+ years, active smoking, DM, and high baseline BNP and cTnI (Figure 2). Baseline risk stratification should be performed quickly without delaying antitumor treatment. Cardiology referral is recommended in high-risk, very high-risk, and moderate CV toxicity risk patients before chemotherapy. Anticancer therapy can be paused/changed by the decision of an interdisciplinary team consisting of an oncologist and a cardiologist only in patients at high and very high risk of CV complications. Patients should be informed of the risk of CV complications and may be involved in the treatment choice. All patients with a very high and high risk of CT complications should start primary prevention, including treatment of existing CV diseases, proper control of CV risk factors, scheduling optimal antitumor therapy, and the most appropriate chest radiation regimen [21]. If surgical treatment is required, patients undergo a preoperative risk assessment for surgical intervention.

The next stage is regular monitoring of CTRCD development during anticancer treatment. CTRCD is a continuous event that begins with damage to myocardial cells and then manifests as a progressive decrease in LVEF and overt HF. Suppose we evaluate the symptoms of HF (dyspnea, fatigue, orthopnea, cardiac asthma attacks, weight gain) and signs of CV insufficiency (galloping rhythm, tachycardia, tachypnea, crackles in the lungs, jugular vein swelling, peripheral edema, pleural effusion, liver enlargement, ascites). In that case, cardiotoxicity was detected late. If we focus on a decrease in LVEF, we can see cardiotoxicity a few months after the process starts. We can catch subclinical cardiotoxicity if we assess the degree of damage to myocardial cells using GLS technology and biomarkers like troponin and natriuretic peptides [22].

Thus, only comprehensive monitoring of echoCG parameters and biomarkers allows for revealing myocardial dysfunction at the preclinical stage. The frequency of monitoring depends on the patient's risk group. For very high and high-risk patients, echoCG is recommended every two cycles of chemotherapy and within three months after treatment completion. In patients at moderate to low risk of cardiotoxic complications, echoCG is recommended after a cumulative dose of ≥250 mg/m2 of doxorubicin or equivalent. In high and very high-risk patients, monitoring of cTnI and natriuretic peptides (BNP, NT-proBNP) is recommended before every cycle during anthracycline chemotherapy and 3 and 12 months after therapy completion. In moderate- and low-risk patients receiving a cumulative dose of ≥250 mg/m2 of doxorubicin or equivalent, cTn and NP monitoring should be considered every two cycles during anthracycline chemotherapy and within three months after therapy completion [23]. During echocardiography, the preferred method for assessing LVEF is 3D-echoCG (2D-LVEF if 3D is unavailable); also, GLS should be evaluated [24]. During the examination, systolic and diastolic function, the state of the heart valves, the pericardium, the right ventricle, the right atrium, and the inferior vena cava should be assessed. The criterion for subclinical myocardial dysfunction is a decrease in LV GLS ≥15% from baseline, confirmed by repeat imaging after two weeks [25]. In such a clinical situation, it is necessary, together with the oncologist, to discuss the possibility of modifying anticancer therapy to reduce its cardiotoxicity and proceed with CHF secondary drug prevention.

In a study by Cardinale et al., 2625 patients who received anthracyclines were followed up for a median value of 5.2 (2.6–8) years, and 226 (9%) developed CTRCD. In 98% of cases, cardiotoxicity developed one year after the chemotherapy completion (median 3.5 months). During cardioprotective therapy with enalapril and beta-blockers (carvedilol or bisoprolol), 82% had partial or complete recovery of LV systolic function. Cardiotoxicity in this study was associated with LVEF at the end of chemotherapy (RR 1.37, 95% CI 1.33;1.42) and doxorubicin dose per 50 mg/m2 (RR 1.09, 95% CI 1.04;1.15) [26].

The meta-analysis by de Baat et al. showed that dexrazoxane in anthracycline patients demonstrated cardioprotective effects; in three studies, n=417 (RR 0.37, 95% CI 0.24;0.56), and in two studies, n=534 (RR 0.46, 95% CI 0.33;0.66) dexrazoxane reduced the risk of cardiotoxicity [27]. Meta-analysis of randomized clinical trials revealed the benefit of ACEI/ARBs and beta-blockers in patients on trastuzumab- and anthracycline-associated cardiotoxicity [28]. Anthracycline infusion for more than 6 hours or longer reduces the risk of clinical and subclinical cardiotoxicity and is also considered a potential cardioprotective

strategy [29]. According to another meta-analysis, liposomal doxorubicin reduced the development of HF without changing antitumor efficacy and overall survival - OR 0.34 (0.24;0.47) [30]. If LVEF falls below 40% or any symptom of heart failure is present, treatment with anthracyclines and trastuzumab should be discontinued [31].

In general, acute, subacute, and chronic cardiotoxicity can occur during anthracycline therapy. Acute and subacute myocardial injury is a rarer type of cardiotoxicity; it can happen within a week after taking an anthracycline drug and appears as arrhythmia, myocarditis, pericarditis, or acute left ventricular failure [32].

We have presented the above case with patient Sh., acute cardiotoxicity that occurred less than a week after the first administration of 60 mg/m2 doxorubicin. As the patient developed rhythm disturbances as asystole, we prolonged observation after the relief of acute episodes. Holter data came to normal values a week after the event. She has been prescribed Trimetazidine at a dose of 80 mg. After a year of observation, LVEF decreased from 64% at baseline to 58%, GLS from [-22.4%] to [-15.3%], and reduction was 31.7%. Nonetheless, Sh. successfully completed the courses of anthracycline therapy at a summary dose of 455 mg/m2. Of note, the patient was not transferred to other risk groups as there were no indications of allocation to the high- or very high-risk, or moderate-risk group. This case is critical to understand the nuances of patients' baseline allocation into risk groups. Episodes of acute or subacute cardiotoxicity can occur in patients at any time, irrespective of their baseline risks.

The final stage occurs after the chemotherapy treatment completion. Meticulous monitoring is required for patients who have developed cardiotoxic complications or have potential risk factors, such as a total dose of doxorubicin ≥250 mg/m2, an amount of radiation therapy ≥30 Gy, and treatment with HER2-targeted agents. Patients treated due to the onset of CTRCD conditions require long-term follow-up. Educating and supporting cancer patients to make appropriate healthy lifestyle choices is strongly recommended. Cancer patients should also receive education on recognizing CVD's early signs and symptoms. Regular exercise for at least 150 minutes per week and a healthy balanced diet must be included in the list of recommendations.

In asymptomatic high-risk patients, echoCG and cardiac serum biomarkers are recommended at 3 and 12 months after completion of antitumor therapy. In asymptomatic moderate and low-risk patients, echoCG and cardiac serum biomarkers should be considered within 12 months after the therapy completion. Annual CV risk assessment, including ECG and natriuretic peptides (BNP; Pro-BNP), and CV risk factors management is recommended in cancer survivors (CS) treated with potentially cardiotoxic cancer medications or radiotherapy. CV toxicity risk restratification is recommended for five years after therapy to arrange long-term follow-up. EchoCG at years 1, 3, and 5 after completion of cardiotoxic cancer therapy and, subsequently, every five years, should be considered in asymptomatic very high- and early high-risk adults (CS). Echocardiography may also be considered every five years in asymptomatic moderate-risk adult CS [23].

Patients diagnosed with cardiotoxic events, irrespective of the time passed from the event, should be treated and followed up by a cardiologist for as long as necessary.

Conclusion

We found no statistically significant differences between the CV risk groups regarding the tumors' clinical staging or biological features. All revealed differences were related to age, CV system condition, and the severity of comorbid pathologies.

Thus, the baseline stratification of patients into risk groups is a key step in the primary prevention of anticancer therapy cardiotoxicity. In our cohort of BC patients, 43.5% had a baseline very high/high risk and a moderate risk of cardiotoxic complications. These patients should have an opportunity to be examined by a cardiologist to monitor and manage cardiovascular complications in a cancer treatment division under the conditions of a multifunctional hospital. In the long run, every multifunctional hospital should be provided with a specialist in cardio-oncology.

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