

Research Article

Cardiotoxicity of Anthracycline-based Chemotherapy in Breast Cancer Patients: A Case Series

Zhenisgul Sh. Tlegenova¹, Saule K. Balmagambetova^{2*}, Bekbolat K. Zholdin¹, Gulnara L. Kurmanalina¹, Iliada Zh. Talipova¹, Arip K. Koyshybaev², Gulmira A. Sultanbekova¹, Kulparshan I. Kubenova³, Mira B. Baspayeva³, Saule S. Madinova³, and Ayganym Amanova¹

¹Department of Internal Diseases-2, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan

²Department of Oncology, West Kazakhstan Marat Ospanov Medical University, Aktobe, Kazakhstan

³University's Medical Center, Aktobe, Kazakhstan

ORCID:

Zhenisgul Sh. Tlegenova: <https://orcid.org/0000-0002-3707-7365>

Saule K. Balmagambetova: <https://orcid.org/0000-0003-4080-5383>

Bekbolat K. Zholdin: <https://orcid.org/0000-0002-4245-9501>

Gulnara L. Kurmanalina: <https://orcid.org/0000-0002-0937-2949>

Iliada Zh. Talipova: <https://orcid.org/0000-0002-5450-7056>

Arip K. Koyshybaev: <https://orcid.org/0000-0002-6164-8009>

Gulmira A. Sultanbekova: <https://orcid.org/0000-0002-7714-4673>

Kulparshan I. Kubenova: <https://orcid.org/0000-0002-2018-6733>

Mira B. Baspayeva: <https://orcid.org/0000-0001-6361-4841>

Saule S. Madinova: <https://orcid.org/0000-0002-8216-1224>

Ayganym Amanova: <https://orcid.org/0009-0001-9787-7583>

Corresponding Author: Saule K. Balmagambetova; email: sau3567@gmail.com

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Abstract

In Kazakhstan, breast cancer (BC) remains the leading cause of cancer morbidity and mortality among women. The presented case series aims to summarize cardiovascular events that resulted in anthracycline-based chemotherapy discontinuation or suspension during the ongoing project on studying the cardiotoxicity effects. Case 1. Classic acute cardiotoxicity with asystole. Patient Sh., 46 years old, was admitted with a baseline LVEF of 64% and GLS of 22.4%. After the first dose of doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m², the patient experienced two episodes of asystole. She was prescribed Trimetazidine at a dose of 80 mg. Eventually, Sh. completed the courses of anthracycline therapy after a 1-month delay at a cumulative dose of 455 mg/m². Case 2. Subacute cardiotoxicity with ventricular extrasystole. Patient Zh., aged 47, developed single, paired, and group ventricular extrasystoles after the 2nd course of chemotherapy with doxorubicin 200 mg/m² (23 days after admission). Carvedilol was prescribed at 25 mg twice daily and Trimetazidine at 80 mg once a day. After 1 month of monitoring, ventricular extrasystoles disappeared. With a month's delay, the patient completed chemotherapy at a cumulative dose of 400 mg/m².

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Case 3. Severe cardiotoxicity due to pre-existing cardiovascular disease with discontinuation of chemotherapy. Patient M., aged 58, was referred to the very high-risk group for developed atrial fibrillation and heart failure with LVEF 51%. M. received Enalapril 5 mg two times per day, Bisoprolol 5 mg, Eplerenone 50 mg, Dapagliflozin 10 mg, and Dabigatran 150 mg twice daily. After 3 months, anthracycline therapy was canceled at a cumulative dose of 260 mg/m² due to the deterioration of the patient's condition (LVEF 41%). Discontinuation or the delay of vitally needed chemotherapy in BC patients deteriorate their prognosis for survival. Patients should be constantly monitored during and after anticancer treatment.

Keywords: anthracyclines, chemotherapy, cardiotoxicity, Kazakhstan, case series

1. Introduction

Reportedly, the burden of breast cancer (BC) is predicted to increase to over 3 million new cases and 1 million deaths yearly by 2040 [1]. In Kazakhstan, BC remains the leading cause of cancer morbidity and mortality among women. The all-cause mortality rate for BC within 2014-2019 was 16%. The prevalence rate increased to 50.6 in 2019, and the incidence rate varied from 4.5 per 10,000 population to 7.3 [2, 3].

Along with that, the number of cancer survivors continues to grow, primarily due to improved strategies for early detection and advances in antitumor pharmacological treatment, particularly chemotherapy. However, most cancer survivors must cope with the physical effects of cancer and its treatment, leading to functional and cognitive impairments [4, 5]. It has been established that BC survivors are three times more likely to develop heart failure (HF) within 5 years of cancer diagnosis than the general population [6]. According to Chinese researchers, the most vulnerable period for cardiovascular events development in BC patients, including death, is 30-64 years, it has been observed that the risk peaks usually within the first few months after diagnosis [7]. Cardiovascular complications in cancer patients include coronary artery disease, hypertension, QT prolongation, arrhythmias, stroke, peripheral arterial disease, valvular heart disease, pericardial disease, and venous thromboembolism. Among the cardiotoxic effects of chemotherapy, now defined in the literature as cancer therapy-related cardiac dysfunction (CTRCD), the development of left ventricular dysfunction (LVD) is the most common and serious [8].

Overall, there are two types of cardiotoxicities caused by antitumor treatment and two main groups of pharmaceuticals associated with these types. CTRCD type 1 is characterized by irreversible myocardial damage, while CTRCD type 2 leads to reversible myocardial dysfunction [9]. Anthracyclines, the most widely used class of chemotherapy agents in BC treatment, induce cardiotoxicity type 1, which is dose-dependent, and often manifests as HF and arrhythmias [10-12]. The incidence of HF is estimated to reach 5% at a cumulative dose of 400 mg/m² of anthracyclines, increasing to 16% at 500 mg/m², 26% at 550 mg/m², and 48% at 700 mg/m² [10, 13]. Trastuzumab (herceptin), 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 [14-16]. Trastuzumab is the most widely used pharmaceutical in human epidermal growth factor receptor 2 (HER2)-positive BC patients as it is a mainstay of targeted therapy [15]. 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%) [17-19].

The 2022 cardio-oncology guidelines contain an updated definition of asymptomatic CTRCD, classifying it as mild (left ventricular ejection fraction (LVEF) \geq 50% and new relative global longitudinal strain (GLS) reduction $>15\%$ compared to baseline and/or new elevation of cardiac biomarkers); moderate ($\geq 10\%$ to 40–49% reduction in LV ejection fraction or $<10\%$ to 40–49% reduction in LV ejection fraction and relative GLS reduction $>15\%$ or elevated cardiac biomarkers); or severe (LV ejection fraction $<40\%$), aligning with the European Society of Cardiology (ESC) HF guiding principles classification [20]. These guidelines also comprehensively summarize the role of clinical risk factors in assessing the potential cardiotoxicity of upcoming chemotherapy and highlight the strategy for stratifying patients' cardiovascular risk at baseline. The potential risk of CTRCD emergence is calculated during baseline clinical examination. In line with the current strategy, the risk scores are calculated considering all possible risk factors - existing (recorded) cardiovascular diseases, the toxicity of chemotherapy prescribed, and lifestyle risk factors. At the time of examination, patients with one moderate risk factor or absence of risks were allocated to the low-risk group. Two to four scores of moderate risk were assigned to the moderate risk group. Scores more than five of moderate risk or at least one high-risk factor were allocated to the high-risk group. Respectively, patients with one very high-risk factor were allocated to the very high-risk group. "Very high" risk means the presence of existing chronic heart failure or dilated cardiomyopathy; "high" risk includes previous severe valvular heart disease, past myocardial infarction and/or revascularization, baseline LVEF $<50\%$, stable angina, or preceding radiation therapy.

Patients with very high, high, and moderate risk are given medications according to indications: ACE inhibitors/ARBs (angiotensin converting enzyme inhibitors/angiotensin II receptor blockers), beta-blockers, statins, trimetazidine/analogues, and others. According to the 2022 ESC Guidelines on cardio-oncology, the stratification of cancer patients by cardiovascular risk groups is one of the crucial steps in their management.

The chemotherapeutic regimen in cancer patients is selected according to the disease status and risk factors. Trastuzumab is mostly presented at a standard regimen every 3 weeks for up to 18 courses, with an initial dose of 8 mg/kg and then 6 mg/kg [21]. For HER2-negative patients, anthracycline-based chemotherapy remains the primary option for treatment. Most of the patients who are administered anthracyclines receive AC or AC-T regimens. The AC regimen is 60 mg/m² doxorubicin and 600 mg/m² cyclophosphamide, which was used on the first day and administered every 21 days for four courses. The AC-T regimen is the same dose of AC during the first four courses, after which T (paclitaxel or docetaxel) is given at 90 mg/m² for four courses (every 21 days) [22].

The presented case series aims to summarize and analyze the entity of cardiovascular events that resulted in anthracycline-based chemotherapy discontinuation or suspension, which occurred in the chemotherapy division of the Aktobe Oncologic Center during the ongoing project on studying the cardiotoxicity effects in breast cancer patients.

Overall, we faced a series of three such cases among the cohort of 128 enrolled BC patients treated with anthracyclines and/or trastuzumab.

2. Case series report

2.1. Case 1. Classic acute cardiotoxicity with asystole

Patient Sh., 46 years old, ST IIB T3NxM0, had no CV diseases in history and revealed risk factors on admission to the chemotherapy division on March 17, 2022. Baseline LVEF was 64%, GLS 22.4%. Primary biomarkers value at baseline: cardiac Troponin I (cTnI) - 0.1 ng/ml and B-type natriuretic peptide (BNP) - 43.8 pg/ml. The initial risk of forthcoming anthracycline therapy seemed insignificant, and the patient was allocated to the low-risk group. After the first dose of doxorubicin 60 mg/m² and cyclophosphamide 600 mg/m² (AC regimen), the patient experienced two episodes of asystole at Holter monitoring (HM), 9327 msec and 4051 msec, respectively. This case was referred to as acute cardiotoxicity because it occurred less than a week after administering 60 mg/m² of

doxorubicin. As the patient developed rhythm disturbances, defined as asystole, we prolonged observation after relieving 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 essential, 31.7%. Nonetheless, Sh. completed the courses of anthracycline therapy after a 1-month delay at a cumulative dose of 455 mg/m².

Furthermore, 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. In very high and high-risk patients, the predicted risk of antitumor therapy cardiotoxic complications fluctuated from 10% to 19%, that is, CTCD 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% [23]. This case is critical to understanding the nuances of patients' baseline allocation into risk groups and was briefly reported [24].

2.2. Case 2. Subacute cardiotoxicity with ventricular extrasystole

Patient Zh., aged 47, newly diagnosed with invasive breast carcinoma, was admitted to the division on November 5, 2021. The baseline risk of cardiotoxic complications was estimated as low.

After the 2nd course of chemotherapy with doxorubicin 200 mg/m² (23 days after admission), complaints of interruptions in heart function appeared. Single, paired, and group ventricular extrasystoles (VES) were recorded at HM, totaling 10,895 and a maximum of 1211 per hour. Table 1 displays summary data on arrhythmias. These data are also presented graphically (Figure 1)

Holter monitoring, conclusion:

Dynamic 24-hour ECG examination was conducted using three channels for 23:42 min. The main rhythm was sinus. There were a total of 118,376 QRS complexes, with maximum heart rate 170 beats/min (walking.) Minimum heart rate 47 beats/min (sleep.) Average heart rate 83 beats/min. Increased ectopic activity: Single VES 10,895. Maximum number of VES = 1211 (23:00). VES - Bigeminy = 88. VES - Trigeminy = 932. Single VES = 64. ST analysis: No ischemic changes in the ST segment were observed.

Carvedilol was prescribed at 25 mg twice daily and Trimetazidine at 80 mg once a day. Cardio protectants were prolonged until the normalization of HM performance. After 1 month of monitoring, no VES was observed in the control HM. Eventually, the

TABLE 1: Summary data on arrhythmias during the Holter monitoring in patient Zh.

Ventricular activity								
Time	Max HR	Min HR	Average HR	Total complexes	Total VES	Single VES	Bigeminy	Trigeminy
Total	0	0	83	118,376	10,895	10,895	88	932
10:45–12:00	148	64	89	6669	344	344	3	17
12:00–13:00	133	60	85	5129	505	505	2	32
13:00–14:00	137	68	95	5703	321	321	4	11
14:00–15:00	147	78	101	6065	233	233	0	5
15:00–16:00	103	75	83	4962	538	538	0	9
16:00–17:00	119	51	77	4597	316	316	2	8
17:00–18:00	93	62	72	4342	670	670	23	31
18:00–19:00	140	64	91	5474	184	184	2	5
19:00–20:00	126	67	94	5624	155	155	3	6
20:00–21:00	137	59	94	5656	147	147	0	2
21:00–22:00	110	74	56	3371	108	108	0	7
22:00–23:00	123	74	91	5457	257	257	1	20
23:00–00:00	117	70	81	4857	1211	1211	28	80
00:00–01:00	107	50	79	4741	1098	1098	19	83
01:00–02:00	114	47	68	4056	671	671	1	53
02:00–03:00	102	59	70	4194	595	595	0	78
03:00–04:00	94	61	69	4148	632	632	0	99
04:00–05:00	93	60	69	4118	588	588	0	92
05:00–06:00	125	55	70	4174	706	706	0	96
06:00–07:00	102	58	68	4070	757	757	0	99
07:00–08:00	128	53	74	4421	668	668	0	88
08:00–09:00	170	73	125	7500	109	109	0	7
09:00–10:00	157	81	112	6720	65	65	0	6
10:00–10:28	117	80	97	2328	17	17	0	1

patient completed chemotherapy at a cumulative dose of 400 mg/m², with 1-month delay. Upon 12 months of monitoring, no signs of developed CTRCD were observed except for BNP performances evidencing incremental subclinical cardiotoxicity (Table 2).

TABLE 2: Monitoring of possible CTRCD development in patient Zh.

Cardiotoxicity monitoring:	Visit 1	Visit 2 (3 months after the treatment commencement)	Visit 3 (6 months after the treatment commencement)	Visit 4 (9 months after the treatment commencement)	Visit 5 (12 months after the treatment commencement)
cTnI, ng/ml	0.1	0.1	0.1	0.1	0.1
BNP, pg/ml	49.64	53.20	38.20	56.38	99.54
CRP, mg/ml	2.98	3.41	4.28	3.87	1.80
D-dimer, mg/l	3.22	2.43	0.27	0.22	0.23
LVEF, %	57	56	55	55	56
GLS, %	-14.3	-16.7	-14.6	-17.8	-15.8

The patient needs scrutinized monitoring during the follow-up according to the principles summarized in ESC cardio-oncology guidelines 2022 [20].

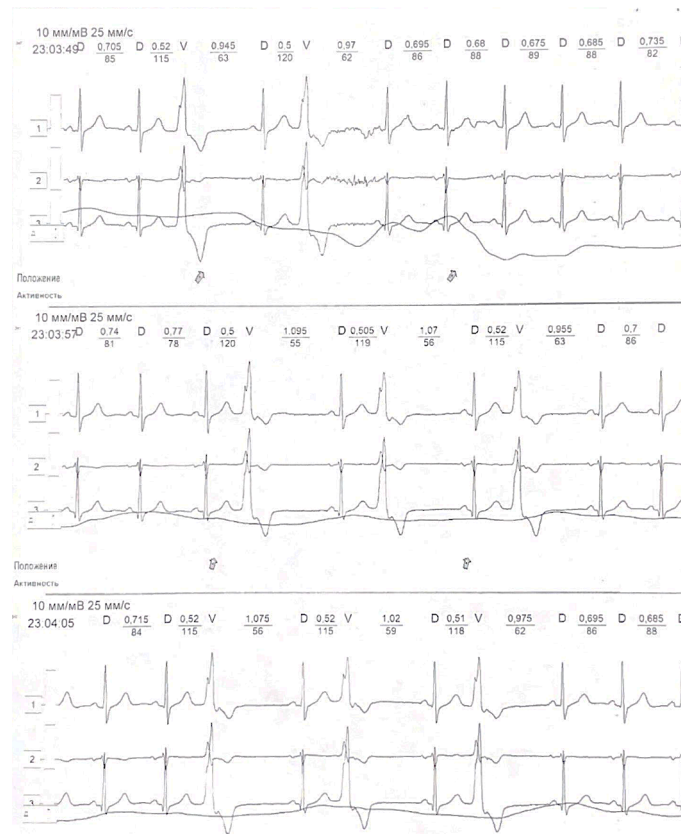


Figure 1: Data on Holter monitoring in patient Zh.

2.3. Case 3. Severe cardiotoxicity due to pre-existing CV disease with discontinuation of chemotherapy

In our cohort of 128 patients, three (2.3%) had a recorded history of cardiovascular disease. However, the only patient, M., aged 58, was referred to the very high-risk group for developed atrial fibrillation and HF with LVEF 51%. The patient had been suffering from AH since 2000, and atrial fibrillation emerged in 2010. In 2017, HF with declined LVEF (38%) was diagnosed. Due to the treatment for atrial fibrillation and HF with 38% EF, LVEF eventually recovered to 51% (HF with improved LVEF). Breast carcinoma was newly diagnosed in 2021. The patient's history is screened in Figure 2.

Transthoracic echocardiography (TTE) with speckle tracking as of October 18, 2022. Both the atria were enlarged; the pumping and contractile functions of the LV were reduced; LVEF 51%; global longitudinal deformation was reduced -12.6%; LV myocardial hypertrophy; mild aortic regurgitation; mitral regurgitation of 2nd degree. Tricuspid regurgitation grade 1.5; minimal regurgitation on the pulmonary valve; pulmonary hypertension (pulmonary artery systolic pressure (PASP) 41 mmHg). Interventricular septum

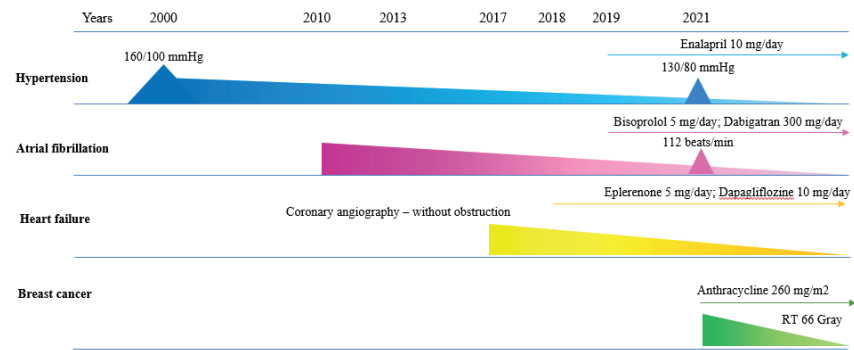


Figure 2: Case 3 graphical presentation. The patient was examined by a cardiologist. Conclusion: Arterial hypertension 1, risk 4. Permanent form of atrial fibrillation, CHA₂DS₂-VASc (congestive HF, hypertension, Age ≥ 75 years (doubled), Diabetes mellitus, prior Stroke or TIA or thromboembolism (doubled), vascular disease, age 65-74 years, sex category) score 3 points*. HF with improved LVEF (51%) NYHA class II.

(IVS) echo-enhanced - a small amount of fluid in the pericardial cavity. No fluid was detected in the pleural cavities.

Considering the LVEF is 50-55%, the clinical signs of chronic heart failure (CHF), AH, and increased cardiac markers, M. was included in the very high-risk group. As being HER2-negative, she was subject to anthracycline therapy. According to ESC Guidelines, cardioprotective therapy was administered immediately after the diagnosis and before she started chemotherapy. So, M. received Enalapril 5 mg 2 times per day, Bisoprolol 5 mg, Eplerenone 50 mg, Dapagliflozin 10 mg, and Dabigatran 150 mg twice daily (Figure 2).

TTE in the dynamics (after 3 months of observation): LVEF 41%. Mitral regurgitation grade 2. Tricuspid regurgitation grade 1.5-2. The pulmonary artery had been expanded. Regurgitation on the pulmonary valve of 1-1.5 degrees. Pulmonary hypertension (PASP 56 mmHg). The oval window was open - a small amount of fluid in the pericardial cavity. No fluid was detected in the pleural cavities.

Anthracycline therapy was canceled at a cumulative dose of 260 mg/m² due to the deterioration of the patient's condition (LVEF 41%). Anticancer treatment was continued with Tamoxifen (antihormonal treatment) and courses of radiation therapy (at a total focal dose of 66 Gray). Cardiotoxicity monitoring data in patient M. are shown in Table 3.

* The CHA₂DS₂-VASc (congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke or transient ischemic attack (TIA), vascular disease, aged between 65 and 74 years, sex category) score is a validated tool to predict the risk of stroke and systemic emboli in patients with non-valvular atrial fibrillation.

TABLE 3: Monitoring of CTRCD development in patient M.

Cardiotoxicity monitoring:	Visit 1	Visit 2 (3 months after the treatment commencement)	Visit 3 (6 months after the treatment commencement)	Visit 4 (9 months after the treatment commencement)	Visit 5 (12 months after the treatment commencement)
cTnI, ng/ml	0.4	0.35	0.19	0.1	0.1
BNP, pg/ml	124.78	115.60	67.60	109.51	131.30
CRP, mg/ml	5.30	6.30	2.98	15.00	1.87
D-dimer, mg/l	0.72	0.98	0.36	1.03	0.45
LVEF, %	51	41	43	43	43
GLS, %	-12.6	-12.5	-12.7	-11.3	-10.2

3. Conclusion

Discontinuation, suspension, or the delay of vitally needed chemotherapy in BC patients essentially deteriorates their prognosis for survival. The development of CTRCD during or after chemotherapy is the predominant factor for decreased quality of life after the antineoplastic treatment. Cardiotoxicity can occur in patients at any time, irrespective of their baseline risks. All BC patients should be constantly monitored during and after the treatment according to the principles summarized in ESC cardio-oncology Guidelines 2022.

Authors contribution

SB, ZT, and BZ were responsible for the general editing of the manuscript and key issues of the report presentation. SB was a major contributor to writing all sections of the manuscript. GK, IT, and AK edited the “Background” section. AA and GS were responsible for the selection of references and participated in searching the medical records. KK, MB, and SM were responsible for data curation and validation. All authors read and approved the final manuscript.

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Conflict of Interest

The authors declare that there is no conflicts of interest.

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