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A first approach to identifying cardiotoxic effects of breast cancer chemotherapeutic treatment in Kazakhstan

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Abstract

As known, the clinical efficacy of chemotherapy is limited by the cardiotoxicity of drugs used.

The study aimed to clarify cardiotoxic complications of chemotherapy from the Aktobe Medical Center database for 2018-2019.

Material and methods: We performed a register study on essential parameters of the oncological process, drugs used, duration of chemotherapy, types of complications, and outcomes, including survival.

Results: We found a total of 305 breast cancer cases. Chemotherapy was completed without complications in 65.9% of patients; treatment was interrupted due to complications - 10.5%; 6.2% of cardiovascular complications were identified. The two groups of patients, EchoCG + and EchoCG -, showed significant difference in the number of detected CV complications (p<.001) but no difference in the survival rate (p .814). The survival rate in patients with documented CV complications was 28.1 months vs. 34.3 months in the group without ones (p.005). The survival rate in those who completed the treatment without complications, was 34.9 months vs. 17.6 in individuals whose treatment was interrupted due to complications (p<.001). We performed a detailed review of four cases of cardiotoxicity with fatal outcomes.

Conclusion: The analysis indicates the absence of a systematic approach to recording crucial information regarding cardiotoxicity. There is a lack of concordance in the actions of cardiologists and oncologists in the management of BC patients. The presence of lethal outcomes of chemotherapy with an established cause of cardiac death indicates the need to revise the cancer register management from the standpoint of cardio-oncology. In general, there is a need to develop local protocols for screening and monitoring patients undergoing cardiotoxic chemotherapy and radiation therapy.

Key words: breast cancer, cancer register, chemotherapy, cardiovascular events, cardiotoxicity

Introduction

Breast cancer (BC) consistently ranks first among the causes of death from cancer in women [1,2]. According to the International Agency for Research on Cancer (IARC), in 2020, the proportion of BC worldwide was 10-18% of all new cases of malignant neoplasms [3]. In Kazakhstan, the relative survival rate for BC ranges within 28.7% [4].

The prognosis of BC treatment depends on the tumor tissue's histochemical properties, the tumor's aggressiveness, the cancer process staging, and the cardiotoxicity of chemotherapy [5-7].

As known, the clinical efficacy of chemotherapy is limited by the cardiotoxic (CT) effect on the heart and blood vessels with accelerated development of chronic heart failure (CHF), rhythm and conduction disturbances,

a tendency to thrombosis, etc. [8]. Studies have shown an increase in the relative risk of developing fatal cardiovascular (CV) complications of chemotherapy up to 2.2 times in patients with BC and the risk of developing CHF up to 4.9 times. At the same time, attempts to treat the long-term consequences of CT complications of chemotherapy are not always effective [5].

Chemotherapy in breast cancer patients implies using several groups of pharmaceuticals, mostly Anthracyclines and targeted therapy - monoclonal antibodies, low molecular weight tyrosine kinase inhibitors, proteasome inhibitors, etc.

Currently, researchers identify Anthracycline-mediated irreversible type 1 cardiotoxicity, due to the death of cardiomyocytes (the degree of myocardial damage, in this case, depends on the cumulative dose) and Trastuzumab-mediated reversible type 2 cardiotoxicity due to mitochondrial and protein damage (the effect is not dose-dependent) [9]. In patients treated with Anthracyclines, complications usually develop within the first year after stopping chemotherapy and proceed as progressive CHF, up to the development of dilated cardiomyopathy [10].

Trastuzumab, the mainstay of therapy for human epidermal growth factor receptor-2 (HER2) positive breast cancer, reduced mortality from BC by one-third but did not justify expectancies concerning severe cardiac complications. Up to 3% of BC patients treated with Trastuzumab experience severe CT complications, while the combined uptake of Anthracycline and Trastuzumab leads to a 7-fold increase in CHF risk [11, 12].

Breast cancer chance, like a risk of emerging CV events, increases with age; therefore, most patients with BC will require the close attention of cardiologists and oncologists to balance the antitumor chemotherapy concerning the risk of CT complications [13]. The early detection of chemotherapy cardiotoxicity and timely correction of complications becomes the priority in cancer patients management [6].

Identifying high-risk CT complications can provide a range of additional preventive measures to improve BC patients' outcomes, such as possibly changing the dosage and the grugs administration regimen, applying their new combinations, and/or cardioprotectors with proven efficacy [14,15]. It has been shown that regular echocardiography (EchoCG) reveals significant left ventricular myocardial dysfunction in 98% of patients during the first year of chemotherapy. Cardiac protection using ACE-inhibitors, and beta-blockers can normalize left ventricular ejection fraction (LVEF) in 82% of patients, thus significantly improving the prognosis of the underlying disease [16].

Meanwhile, Cardioncology that studies the cardiotoxic effects of chemotherapy, methods of their detection, and preventive measures, has not yet come into practice in Kazakhstan.

The presented work is the first attempt to scrutinize information from the Cancer register (EROB, electronic register of oncologic patients) on CT effects of Breast cancer chemotherapy.

The study aimed to analyze the overall outcomes of chemotherapy in patients with breast cancer who have undergone treatment at the Aktobe Oncology Center in the period 2018-2019, focusing on the patients' survival and their cardiovascular system condition.

Tasks:

1. To present the overall patients profile, essential parameters of chemotherapy treatment, including the degree and quality of its completion, outcomes, and survival.

2. To select a group of patients with adverse chemotherapy outcomes due to cardiotoxic effects of treatment to analyze the identified complications.

Material and methods

This research performed at Marat Ospanov West Kazakhstan Medical University is a single-center register study presenting the retrospective stage of a joint project of cardiologists and oncologists. The study design and protocol were approved by the University Bioethical Committee (No. 7 dated 09.09.2020). The sample of the retrospective stage was formed by including the medical records of all patients admitted to chemotherapy with a verified diagnosis of C50 and registered in the Cancer register (EROP), with a search depth of two years, 2018-2019. The informed consent was not required due to the register nature of the study. Extracting information from the Cancer register was carried out in pairs - an oncologist and a cardiologist, in several directions:

1) General data: age of patients, IBM, hereditary factor, comorbidity index;

2) Characteristics of the cardiovascular system: baseline intake of cardiac protectors, baseline data on blood pressure, heart rate, ECG, LVEF;

3) Characteristics of the oncological process: staging, clinical classification, and tumor histotype, immunohistochemical data;

4) Characteristics of the treatment performed: class of chemotherapy drugs, type, and duration of chemotherapy, degree of courses completion, and reasons for the interruption;

5) Complications and outcomes of chemotherapy, including death, cardiovascular death, chemotherapy course interruption, and tumor progression.

Statistical analysis

The statistical software packages Statistica.10 (StatSoft - Russia, version 10) and SPSS (IBM, version 25) were used. To determine the normal distribution of quantitative variables, the Kolmogorov-Smirnov method was used. Variables with normal distribution are presented as M (SD). Variables with non-Gaussian distribution are presented as median and 25/75 percentiles, Me (25; 75).Categorical variables are presented as an absolute value and a percentage. Quantitative variables were compared using the nonparametric Mann-Whitney U-test for unrelated samples. The Pearson $\chi 2$ test was used to identify intergroup differences for categorical variables. Event-free survival of Breast cancer patients was determined using the Kaplan-Meier method with a graphical presentation of the results. Differences in survival between groups were determined using the following criteria: log-rank test, Breslow test, Tarone-Ware test. For all tests, a two-sided type I error ($p \leq 0.05$) was assumed statistically significant at a 95% CI.

Results

According to the Cancer register for 2018-2019, in total, 305 patients were admitted to the Chemotherapy department of the Aktobe oncology center in both inpatient and outpatient mode. The average age of patients Me 56.0 (47-64), min-max 24-84 years; BMI min-max 17-53; Charlson comorbidity index min-max 1-15; the duration of chemotherapy was min-max 1-26 months. Echocardiographic monitoring is the most essential in diagnosing cardiotoxicity; therefore, the sample was analyzed from the standpoint of the presence/absence of EchoCG monitoring. The quantitative representation of the sample is shown in Table 1.

The prevailing part of patients are women aged 60+ years (41.6%), in menopause, with metabolic disorders, in the majority with a normal baseline ECG (76.1%), with nodular cancer,

Table 1 Descriptive statistics of patients in the context of EchoCG monitoring, characteristics of the tumor process, and treatment.

Parameter	All, n=305	EchoCG (+), n=60	EchoCG (-), n= 245	p-value
Age, years	55.4±11.4	55.9±12.5	55.3±11.2	0.527
Age groups, n (%) 18-29 30-39 40-49 50-59 60 +	 3 (1.0) 25 (8.2) 72 (23.6) 78 (25.6) 127 (41.6)	 1 (1.7) 7 (11.7) 11 (18.3) 12 (20.0) 29 (48.3)	 2 (0.82) 18 (7.4) 61 (24.9) 66 (26.9) 98 (40.0)	 p= 0.400
Heredity+, n (%)	41 (13.44)	6 (10.0)	35 (14.3)	p= 0.383
Menopause +, n (%)	215 (70.5)	43 (71.7)	172 (70.2)	p=0.824
IBM*, kg/м2	28.4±5.7	28.8±5.6	28.3±5.7	p 0.344
Baseline LVEF*, n 117 (56.1%)	60.7±4,0	61.7±3.4	60.2±4.2	p 0.012
Tumor staging, n (%) I IIA IIB IIIA IIIB IV	 16 (5.3) 127 (41.6) 112 (36.7) 18 (5.9) 24 (7.9) 8 (2.6)	 6 (10.0) 17 (28.3) 24 (40.0) 5 (8.3) 5 (8.3) 3 (5.0)	 10 (4.1) 110 (44.9) 88 (35.9) 13 (5.3) 19 (7.8) 5 (2.0)	 p = 0.109
Tumor histotype, n (%) Invasive carcinoma Intraductal carcinoma Infiltrating ductal Lobular carcinoma Carcinosarcoma	 175 (57.6) 16 (5.3) 107 (35.2) 3 (1.0) 3 (1.0)	 29 (49.2) 5 (8.5) 24 (40.7) 0 (0.00) 1 (1.7)	 146 (59.6) 11 (4.5) 83 (33.9) 3 (1.2) 2 (0.82)	 p=0.399
Immunohistochemical data, n (%) Triple negative Luminal A type Luminal B positive Luminal B negative Her-2 neu negative Not determined	 58 (19.0) 29 (9.5) 35 (11.5) 136 (44.6) 39 (12.8) 8 (2.6)	 9 (15.0) 3 (5.0) 14 (23.3) 20 (33.3) 13 (21.7) 1 (1.7)	 49 (20.0) 26 (10.6) 21 (8.6) 116 (47.4) 26 (10.6) 7 (2.9)	 p=0.003
Tumor's clinical forms, n (%) Nodular Mastitis-like Edematous infiltrative Erysipelas-like Others, without specification	 287 (94.1) 1 (0.33) 9 (3.00) 1 (0.33) 7 (2.3)	 54 (90.0) 0 (0.00) 3 (5.00) 0 (0.00) 3 (5.0)	 233 (95.1) 1 (0.41) 6 (2.5) 1 (0.41) 4 (1.6)	 p=0.397
Charlson comorbidity index, scores Me(25;75)	5[4;7]	5[4;8]	5[4;6]	p 0.169
Cardioprotectors, n (%) Foregoing intake No intake Unknown	 34 (11.15) 120 (39.34) 151 (49.51)	 12 (20.0) 13 (21.7) 35 (58.3)	 21 (8.6) 107 (43.7) 117 (47.8)	 p=0.002
Chemotherapy, n (%) Neoadjuvant Neoadjuvant and adjuvant Adjuvant Due to tumor progression	 11 (3.6) 183 (60.0) 84 (27.5) 27 (8.9)	 2 (3.3) 28 (46.7) 27 (45.0) 3 (5.0)	 9 (3.7) 155 (63.3) 57 (23.3) 24 (9.8)	p = 0.008
Administered treatment, n (%) Anthracyclines Anthracyclines + MCA* Monoclonal antibodies Other	 199 (65.3) 41 (13.4) 30 (9.8) 35 (11.5)	 24 (40.0) 20 (33.3) 9 (15.0) 7 (11.7)	 175 (71.4) 21 (8.6) 21 (8.6) 28 (11.4)	 p<0.001
Chemotherapy duration, months Me(25;75)	5[4;7]	6[4;10]	5[3;7]	p 0.027
Chemotherapy duration before interruption, n (%) 25% 50% 75% 100%	 9 (3.0) 25 (8.2) 41 (13.4) 230 (75.4)	 1 (1.7) 7 (11.7) 7 (11.7) 45 (75.0)	 8 (3.3) 18 (7.4) 34 (13.9) 185 (75.5)	 p=0.639
Quality of completed courses, n (%) Without complications, successfully A correction was required Interrupted due to complications Interrupted for non-medical reasons (refusal, moving)	 201 (65.9) 36 (11.8) 32 (10.5) 36 (11.8)	 36 (60.0) 11 (18.3) 9 (15.0) 4 (6.7)	 165 (67.4) 25 (10.2) 23 (9.4) 32 (13.1)	 p= 0.102
Chemotherapy complications, n (%) Cardiovascular complications Hematological From the gastrointestinal tract A combination of complications (allergic, skin, gastrointestinal, hematol.) Not indicated	 19 (6.2) 20 (6.6) 10 (3.3) 243 (79.7) 13 (4.3)	 11 (18.3) 4 (6.7) 2 (3.3) 40 (66.7) 3 (5.0)	 8 (3.3) 16 (6.5) 8 (3.3) 203 (82.9) 10 (4.1)	 p< 0.001
Chemotherapy outcomes, n (%) Alive, no complications CV* death / interruption of the course due to CT* complications Death, / interruption of the course due to other complications Progression	 258 (84.6) 4 (1.3) 21 (6.9) 22 (7.2)	 49 (81.7) 2 (3.3) 3 (5.0) 6 (10.0)	 209 (85.3) 2 (0.82) 18 (7.4) 16 (6.5)	 p=0.309
Observations, days	657.9±242.3	722.0±260.6	642.3±235.5	p 0.022

*Abbreviations:
CT - cardiotoxic (complications); CV - cardiovascular (death); IBM - index body mass; LVEF - left ventricular ejection fraction; MCA - monoclonal antibodies

Table 2 Kaplan-Meier survival curves indices for the presence of EchoCG monitoring, the presence of recorded CV events, and the quality of chemotherapy courses.

Parameters	%	Months	SE	95% CI	log-rank p
Presence (absence) of EchoCG monitoring					
EchoCG + (1), n 53	90.6	34.0	1.01	32.1;36.1	
EchoCG - (2), n 229	91.3	33.9	0.52	32.9;34.9	.814
Presence (absence) of cardiovascular complications					
Complications not revealed (0), 92.5 33.7 0.44 33.6;35.2 n 266 Recorded (1), n 16 68.8 28.1 3.1 22.0;34.2 .005					
Successfulness of chemotherapy courses completion*					
Without complications (1), n 190	94.5	34.9	0.45	33.9;35.8	
Correction was required (2), n 24	68.6	29.2	1.94	25.4;33.0	<.001
Interrupted due to complications (3), n 11	34.4	17.6	1.63	14.4;20.8	

* Note: individuals who did not complete treatment courses for personal reasons (refusal, relocation) were not included in the statistics.

Figure 1 - Structure of recorded cardiovascular events in Breast cancer patients.

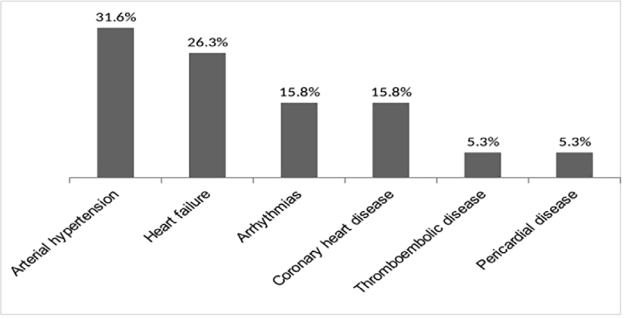
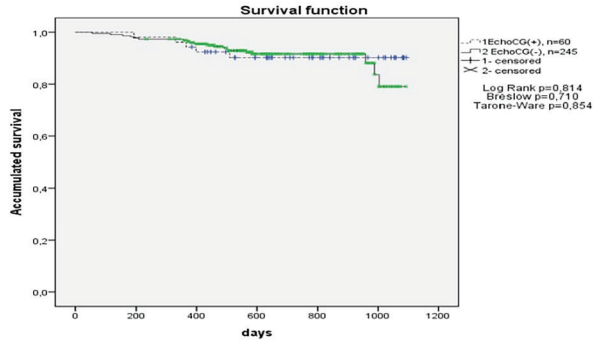


Figure 2 - Kaplan-Meier survival curves for the presence (absence) of EchoCG monitoring.



invasive carcinoma stage IIA, and 7 out of 10 with Her2-neu negative status, cutting off the opportunity for targeted therapy. Information on intaking cardioprotectors before and during treatment is either unknown (49.5% of all patients) or evidencing that no cardioprotectors were prescribed (39.3%). The data of echocardiographic monitoring, the most significant for the early detection of cardiotoxicity, are not entered into the register on a systematic basis: slightly more than half of the patients have baseline LVEF (56.1%, n 117), but only one of five was examined over time (19.7%, n 60). At the same time, a quarter of the total number of patients, 23.9%, shows an abnormal baseline ECG before starting chemotherapy courses. Two-thirds of patients (65.9%) completed chemotherapy without complications, but in every tenth, the treatment was interrupted due to complications (10.5%). In the structure of complications, 6.2% are CV ones. Table 1 also demonstrates a significant difference regarding CV complications between the two groups of patients - EchoCG+ and EchoCG- (p<0.001). One of the explanations for this difference is that in the EchoCG+ group, 33.3% of patients underwent a combined therapy of Anthracyclines + monoclonal antibodies, with a highly increased risk for cardiotoxicity development, vs. 8.6% in the EchoCG- group. Figure 1 shows the structure of CV complications according to Cancer register data (n 19, 6.2%).

Arterial hypertension and heart failure that developed in the course of chemotherapy account for more than half of all cases of CV complications (57.9%). The Kaplan-Meier survival curves were performed for the most significant indicators of the chemotherapy effectiveness in terms of cardiotoxicity - the presence/absence of EchoCG monitoring (LVEF changings during treatment), the presence/absence of recorded CV complications, and the quality of courses completed. The results are presented graphically and in Table 2 (the calculation was performed as event-free).

As follows from Table 2 and Figure 2, there was no difference in the survival of both groups, EchoCG+ and EchoCG- (log-rank p. 814). The analysis of contingency tables indicates a statistically significant difference between these groups in some key parameters. For instance, in the EchoCG+ group, the luminal B positive type predominates (23.3% vs. 8.6%, p.003) in the immunohistochemical structure of tumors, therefore, the proportion of patients in this group undergoing Anthracyclines + targeted therapy is higher (33.3% vs. 8.6%, p<.001) and the course of chemotherapy is longer (p.027).

The survival rate in the group of patients with documented CV complications appeared expectedly lower, 28.1 months. vs. 34.3 months (log-rank p .005), Figure 3.

The overall survival of patients (event-free), depending on the completeness and quality of chemotherapy courses, can be considered demonstrative (Figure 4).

For those who completed the chemotherapy course without complications, the survival rate was 34.9 months. vs. 17.6 in persons whose duration of treatment was interrupted due to complications, and 29.2 months in those with treatment adjusted (log-rank p<.001).

Table 3 presents data from the Cancer register on four identified cases of cardiotoxicity with an unfavorable outcome, but not correctly and timely documented in the register.

Comments on register data:

In Patient 1, death from acute coronary syndrome occurred six months after starting chemotherapy, after an entire course of Anthracyclines and radiation therapy. With that, there was no data on LVEF during chemotherapy in the Cancer register, as well as neither baseline nor prescribed cardiac protection during treatment. The patient died from CV complications detected posthumously, but there was no proper monitoring of probable CT signs during follow-up. There is reason to believe that Patient 1 developed late-onset cardiotoxicity due to the cumulative effect of Anthracyclines.

When an additional searching for information, Patient 2 was found to be developed sinus tachycardia during treatment, heart rate increased from 83 at baseline to 107-115 over five months of follow-up. Still, the register did not contain data on either the baseline ECG and EchoCG or the proceeding ECG, as well as cardiac correction data. The patient took Anthracyclines, Trastuzumab, and antihormonal drugs almost simultaneously, but the register did not reflect proper monitoring of her condition.

During additional information retrieval, we also found

Table 3 Data of patients where cardiotoxicity of chemotherapy was revealed postmortem.

Parameters:	Patient 1	Patient 2	Patient 3	Patient 4
Registration date	19.07.2018	20.02.2019	08.10.2018	27.05.2019
Age (yrs)	55	64	62	61
IBM	25.4	30.0	33.3	36.0
CV risk factors	Arterial hypertension, diabetes mellitus	Arterial hypertension, diabetes mellitus, obesity	Arterial hypertension, diabetes mellitus, obesity	Arterial hypertension, obesity
Baseline ECG	Sinus rhythm, heart rate 88 (normal)	No data	Sinus rhythm, norm	Sinus rhythm,norm
ECG during chemotherapy	Sinus tachycardia, heart rate 100, moderate violations of repolarization	No data	Sinus bradycardia 54, supraventricular extrasystole, moderate violations of repolarization	Sinus rhythm 85, frequent ventricular extrasystoles, unstable ventricular tachycardia, severe violations of repolarization
Baseline BP, HR	120/80; 80	130/70; 68	130/80; 72	110/70; 66
BP, HR during treatment	120/80; 96	120/70; 80	150/80; 68	150/100; 88
Baseline LVEF	55%	No data	58%	69%
LVEF during treatment	No data	56%, hypokinesia zones	No data	56% (in four months)
Baseline cardioprotective treatment	No data	No data	No data	Micardis Plus 80/25 (Telmisartan)
Cardioprotective treatment during chemotherapy	No data	No data	No data	Micardis Plus 80/25 (Telmisartan/ Hydrochlorthiazide)
Charlson comorbidity index	6 scores (diabetes mellitus)	13 scores (moderate or severe liver damage; metastatic tumors; diabetes)	6 scores (diabetes mellitus)	6 scores (moderate liver damage)
TNM diagnosis	St. IIApT2N0M0	St. IIBT2N1M0	St. IIBpT2N1M0	St. I T1NxM0
Tumor histotype	Invasive carcinoma	Invasive carcinoma	Invasive carcinoma	Invasive carcinoma
IHC data	Luminal A subtype	Luminal B subtype	Luminal A subtype	HER-2 positive
Tumor's clinical form	Nodular	Nodular	Nodular	Nodular
Treatment administered	Surgery; adjuvant radiation and chemotherapy	Neoadjuvant chemotherapy; Surgery	Surgery; adjuvant radiation and chemotherapy	Surgery; adjuvant radiation and targeted chemotherapy
Treatment prescribed	Anthracyclines (doxorubicin) 4 courses	Anthracyclines (doxorubicin) Trastuzumab hormone therapy 4 + 4	Other (4 courses) + hormone therapy	Trastuzumab
Duration before interruption (amount of treatment received)	3 months (100%)	5 months (50%)	3 months (100%)	13 courses (75%)
Quality of Chemotherapy courses	No complications	Interrupted	Correction required (not specified which)	Interrupted
Identified cardiotoxic complication (indication in Cancer registry)	I 20.0 Unstable angina (posthumous)	I 42 Cardiomyopathy (posthumous)	I 25.8 Other forms of chronic coronary artery disease (posthumously)	Decreased LVEF> 10%, ventricular extrasystoles, unstable ventricular tachycardia
Chemotherapy outcomes	Death (02.16.2019), after 6 months from the start of treatment.	Interruption of the course due to CT complications; death after 5 months from the start of treatment (08/07/2019).	Death after 6 months from the start of treatment (08.02.2020).	Interruption of the course due to CT complications, admission in the Cardiology division (05/26/2020). Death 31.08.21, after 26 months from the start of treatment, the death cause COVID-19.

Note: CV - cardiovascular; BP - blood pressure; HR - heart rate; LVEF - left ventricular ejection fraction; IHC - immunohistochemistry (conclusion).

Figure 3 - Kaplan-Meier survival curves for the presence (absence) of CV complications.

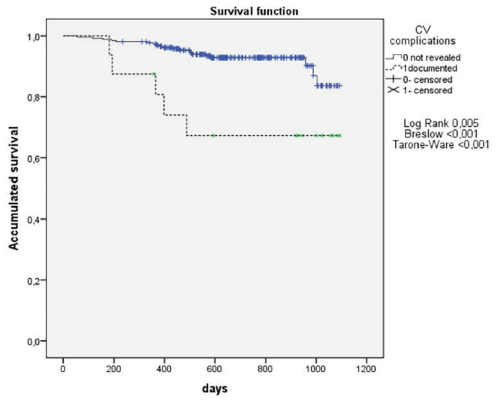
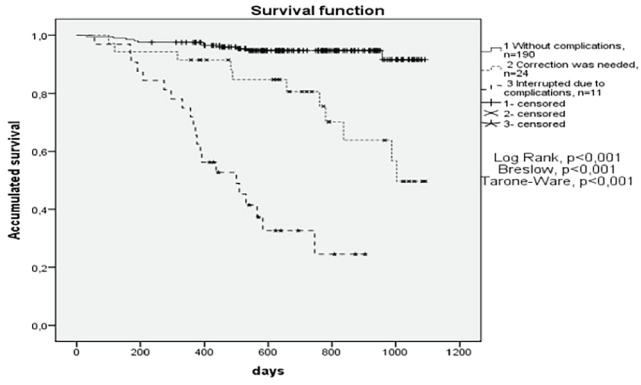


Figure 4 - Kaplan-Meier survival curves on the successfulness of chemotherapy courses completion.



that Patient 3 was administered cardiac protector Valsartan/ Amlodipin 160/10, but there were no data in the register. The register also did not contain data on what kind of chemotherapy correction was required for the patient. Proceeding assessment of LVEF in this patient was also absent.

The death of Patient 4 occurred 26 months after the date of registration, the cause of death recorded as Covid-19. Nonetheless, this case can be attributed to the developed chronic cardiotoxicity.

Discussion

According to a retrospective analysis of data from 305 patients who had undergone breast cancer chemotherapy from 2018 to 2019, the rate of CT complications was 6.2%. Arterial hypertension (31.6%) and CHF (26.3%) prevailed in the structure of CT complications. Transthoracic Echocardiography to detect left ventricular myocardial dysfunction was performed only in 19.7% of patients. The survival rate in the group with documented CT complications was lower (OR = 3.8, 95% CI 1.3; 11.1) than in the group without ones. Baseline assessment of cardiovascular system condition in patients and cardioprotective therapy administered to them were insufficient.

CV diseases can lead to premature disability and the death of cancer survivors. Such events can result from 1) cardiotoxicity, i.e. due to the direct effect of anticancer therapy; 2) accelerating the development of CV diseases in the presence of conventional CV risk factors [17]. It has been established that the risk of left ventricular dysfunction or the development of heart failure in patients with existing CV risk factors increases with the administration tyrosine kinase inhibitors; prescribing Trastuzumab simultaneously with or after Anthracyclines, or even without them; with radiation therapy in combination with chemotherapy, especially with cancer of the left breast; when prescribing VEGF inhibitors [6, 18]. Antineoplastic drugs for the treatment of breast cancer cause both early and delayed (late-onset) cardiotoxic effects. Acute events consist mainly of changes on the ECG, while delayed cardiomyopathy leads to dysfunction of the left ventricle with subsequent development of heart failure [19]. In our sample of unfavorable Chemotherapy outcomes, three of four patients underwent adjuvant radiation and chemotherapy, which deteriorated their condition through the development of severe heart failure signs that resulted in death.

Although the frequency of the chemotherapy cardiotoxic effects depends mainly on the class of drugs prescribed, there are other predisposing factors. Reportedly, the incidence of cardiotoxicity among Anthracyclines ranges from 8.9% (chronic) up to 27.2% (acute); however, the incidence is based on the cumulative dose and other risk factors, such as poor compliance with cardiac monitoring recommendations [20]. According to leading Italian experts (ICOS-ONE Study Investigators), the incidence of Anthracycline-induced cardiac events was 1.1% within the sample of N 273 [21]. The Trastuzumab-induced cardiotoxicity is reversible, unlike the irreversible Anthracycline-induced one, but this combination of drugs being administered together, increases the risk of cardiac events up to 7-fold, despite a relatively favorable safety profile of Trastuzumab [12, 22]. In our Cancer register, we identified 6.2% of documented cases of CV complications in 2 years for all classes of chemotherapy drugs, including 5-FU and other drugs. Regrettably, due to a small sample (n 19) and missed some crucial data in the register, we failed to present a prevalence of cardiotoxicity effects by classes of drugs.

As known, cardiotoxicity can be prevented by screening and modifying existing risk factors, aggressively monitoring for symptoms as chemotherapy is administered, and continuing follow-up after completion of a course or the entire treatment [23]. In this relation, EchoCG is considered a method cost-effective and reliable enough to monitor cardiac function, despite the emerging data on cardiac markers supremacy. Generally, echocardiographic monitoring of the CV system is an integral part of cardiac patient management [22, 24]. LVEF is recognized as a good predictor of CV outcomes, but lacks the sensitivity to detect early subclinical changes in cardiac function. A more sensitive marker for predicting dysfunction of the left ventricle in patients during and after cancer therapy is an assessment of global longitudinal myocardial deformation [25, 26]. Cardiac troponin may also be helpful for early assessment and monitoring of CV events [22, 27]. In our study, we did not find a significant difference in survival between patients of the two groups, where EchoCG monitoring was carried out and where it was none (log rank p.814). Contrary to current guidelines, this situation might have been due to many unaccounted-for confounding factors and incomplete filling of the registry. In particular, we found that in half of the patients (49.5%), cardioprotective treatment was absent in the records, and in 34.3% of them was not prescribed before the treatment. There was no data on baseline cardiac protection or ongoing treatment in three patients with a fatal outcome directly due to the cardiotoxicity of therapy.

Currently, there are no specific medicines to diminish the side effects of chemotherapeutic drugs. The only FDA and EMA-approved cardioprotective drug is Dexrazoxane,

which provides effective primary cardioprotection against Anthracycline-induced cardiotoxicity, in the meantime saving its activity. Under our conditions, Dexrazorane is unavailable so far. Generally, pharmacological treatment of most cardiac events induced by chemotherapy is symptomatic. Various cardioprotectors can be applied to reduce the adverse effects of chemotherapy, depending on symptoms. For instance, compared to placebo, administration of an ACE inhibitor Lisinopril, or the beta-blocker Carvedilol reduces the frequency of interruptions in Trastuzumab treatment and increases survival without CT complications - RR 0.49 (95% CI 0.27; 0.89) for Carvedilol and 0.53 (95% CI 0.30; 0.94) for Lisinopril - in HER2-positive BC patients [28]. In Patient 4, Micardis 80/25 (Telmisartan) was administered at baseline and further, thus providing 13 courses of targeted therapy and relatively long survival comparing to other patients from the sample of unfavorable outcomes.

At least three of our patients out of four who died showed developed chronic or late-onset cardiotoxicity not diagnosed timely due to improper filling in the Cancer register and herein improper cardiac monitoring.

Conclusion

According to Cancer registry data for 2018-2019, CV complications were recorded in 6.2% of patients. The survival rate of these patients is lower than in the group without ones (28.1 months vs. 34.3 months, log-rank p .005).

With that, the database analysis indicates the absence of a systematic approach to the registration of crucial information regarding cardiotoxicity (monitored EchoCG data recorded only in 19.7% of patients, 49.5% of patients had no data on cardioprotective therapy). There is a lack of concordance in the actions of cardiologists and oncologists in the management of Breast cancer patients who need careful monitoring of heart function due to cardiotoxicity of the drugs used.

The lethal outcomes of chemotherapy with an established cardiac death indicate the need to revise the Cancer registry management from the standpoint of cardio-oncology. All Breast cancer patients undergoing chemotherapy require careful cardiac monitoring during treatment and follow-up. In general, there is a need to develop local protocols for screening and monitoring patients undergoing cardiotoxic chemotherapy and radiation therapy.

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