Cancer Therapeutics-Related Cardiac Dysfunction among Patients with Active Breast Cancer: A Cardio-Oncology Registry

Michal Laufer-Perl MD, Liat Mor MS, Assi Milwidsky MD, Matthew Derakhshesh MS, Nadav Amrami MD, Yonatan Moshkovits MS, Joshua Arnold MS, Yan Topilsky MD, Yaron Arbel MD and Zach Rozenbaum MD

Department of Cardiology, Tel Aviv Sourasky Medical Center, affiliated with the Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

ABSTRACT **Background:** Progress in the treatment of breast cancer has led to substantial improvement in survival, but at the cost of increased side effects, with cardiotoxicity being the most significant one. The commonly used definition is cancer therapeutics-related cardiac dysfunction (CTRCD), defined as a left ventricular ejection fraction reduction of > 10%, to a value below 53%. Recent studies have implied that the incidence of CTRCD among patients with breast cancer is decreasing due to lower doses of anthracyclines and low association to trastuzumab and pertuzumab treatment.

Objectives: To evaluate the prevalence of CTRCD among patients with active breast cancer and to identify significant associates for its development.

Methods: Data were collected as part of the Israel Cardio-Oncology Registry, which enrolls all patients who are evaluated at the cardio-oncology clinic at our institution. Patients were divided to two groups: CTRCD and no-CTRCD.

Results: Among 103 consecutive patients, five (5%) developed CTRCD. There were no significant differences in the baseline cardiac risk factors between the groups. Significant correlations of CTRCD included treatment with trastuzumab ($P = 0.001$) or pertuzumab ($P < 0.001$), lower baseline global longitudinal strain (GLS) ($P = 0.016$), increased left ventricular end systolic diameter ($P < 0.001$), and lower e' septal ($P < 0.001$).

Conclusions: CTRCD is an important concern among patients with active breast cancer, regardless of baseline risk factors, and is associated with trastuzumab and pertuzumab treatment. Early GLS evaluation may contribute to risk stratification and allow deployment of cardioprotective treatment.

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KEY WORDS: cancer therapeutics-related cardiac dysfunction (CTRCD), cardio-oncology, cardiotoxicity

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Breast cancer is one of the most common types of cancer [1], representing 15% of all new cancer cases in the United States. Approximately 12.4% of all women will be diagnosed with breast cancer during their lifetime [2]. In the past decades, a decrease in cancer-related mortality is evident as a result of early screening and improved therapeutic options [3]. Nonetheless, breast cancer survivors face long-term treatment side effects, with cardiotoxicity being the most significant one, which lead to increased morbidity and mortality [4].

Echocardiography is a commonly used modality to assess cardiac function in patients with breast cancer. According to the American and European Society of Echocardiography Expert Consensus, a left ventricular ejection fraction (LVEF) reduction of > 10%, to a value below 53% is defined as cancer therapeutics-related cardiac dysfunction (CTRCD) [5]. CTRCD might be drug-induced, radiation-induced [6], or a combination of both [7].

Breast cancer patients are particularly susceptible to CTRCD as treatment regimens include cardiotoxic drugs, primarily anthracyclines and anti-human epidermal growth factor receptor 2 (anti-HER2) agents (recombinant humanized monoclonal antibodies directed against HER2 such as trastuzumab and pertuzumab) [8] as well as chest radiation. However, recent studies have implied that the incidence of CTRCD among patients with breast cancer is decreasing due to lower doses of anthracyclines [9] and lower association between anti-HER-2 agents and CTRCD as described in the APHINITY study [10,11].

Although LVEF is a sensitive marker for the development of cardiac dysfunction, studies show that a significant LVEF reduction manifests only after major, and mostly irreversible, damage to the myocardium [12,13]. Novel means for early detection of myocardial damage were recently examined in order to potentially allow for the initiation of cardioprotective therapy or change of drug regimen [7]. In recent years, two-dimensional (2D) speckle tracking echocardiography (2D-STE) was demonstrated as a useful imaging technique for evaluation of ventricular dynamics [14]. One parameter of 2D STE known as global longitudinal strain (GLS) has been shown to precede the decrease in LVEF, both during and after anthracyclines chemotherapy [15]. Accordingly, the American and European Society of Echocardiography Expert Consensus strongly supports a GLS-based follow-up during and after cancer therapy [5].

The objectives of the current study were to evaluate the prevalence of CTRCD among patients with breast cancer and its association to specific treatment regimens and to assess echocardiographic parameters that can aid in early detection of cardiotoxicity.

PATIENTS AND METHODS

STUDY POPULATION

The study population is part of the Israel Cardio-Oncology Registry (ICOR), a prospective registry that enrolls all patients evaluated in the cardio-oncology clinic at Tel Aviv Sourasky Medical Center. All patients signed an informed consent during the first visit to the clinic and are followed prospectively. The registry was approved by the local ethics committee and is registered at www.clinicaltrials.gov (Identifier: NCT02818517). The clinic follows adult patients who are currently receiving cancer therapy. In general, the registry includes three types of populations: patients who developed cardiovascular complications during therapy, high risk patients with baseline cardiac risk factors, and as of February 2017 preventively all patients planned for anthracyclines therapy. From October 2016 to May 2018, 110 patients with active breast cancer were evaluated. Overall, seven patients were excluded: one due to the absence of a second echocardiograph examination and the other six due to LVEF < 55% at the initial echocardiographic evaluation. There were no other exclusion criteria.

Overall, 103 patients were included in the study, of which 49 (48%) were referred to the clinic before the beginning of therapy due to either high-risk baseline factors or planned anthracyclines therapy. Metastatic disease was present in 37 (36%) patients. Patients were treated according to our practical use protocol. Patients with anthracyclines therapy were treated with four cycles of doxorubicin at a cumulative dose of 240 mg/m^2 combined with cyclophosphamide every 2 weeks. Two weeks later, therapy with 12 cycles of paclitaxel was added once a week. Patients with positive HER2 continued therapy with trastuzumab and pertuzumab. Breast radiation was added individually at the discretion of the oncologist.

STUDY PROTOCOL

All study participants underwent a full medical history evaluation including chronic diseases, specifically cardiac risk factors, cancer type, and cancer therapy. In addition, participants underwent a physical examination, vital signs assessment, blood tests (including complete blood count and renal function), and at least two echocardiograms.

ECHOCARDIOGRAPHY

All trans-thoracic echocardiograms (TTE) were performed by the same vendor, technician, and interpreting cardiologist. To prevent inter-vendor variability, we used a General Electric (GE) system, model Vivid S70 (General Electric Company, USA). Routine left ventricle (LV) echocardiographic parameters included LV diameters, and LVEF [16]. Early trans-mitral flow velocity (E), late atrial contraction (A) velocity, deceleration time, and early diastolic mitral annular velocity (medial and lateral e') were measured in the apical 4-chamber view to provide an estimate of LV diastolic function [17]. The peak E/peak e' ratio was calculated (average mitral E/e' ratio) from the average of at least three cardiac cycles. Left atrium (LA) volume index was calculated using the biplane area length method at end-systole [18]. All exams included 2D-STE longitudinal evaluation [19].

Before each acquisition, images were optimized for endocardial visualization by adjusting the gain, compress, and time-gain compensation controls. Images were acquired using high frame rate (> 50 frames/s) apical views (four, two, and three chambers) [20]. Images were stored digitally and used for offline analysis. Analysis was performed using 2D-STE software to measure GLS from images acquired using the above scheme and tracking within an approximately 5 mm wide region of interest, which is thinner than the default. LV boundaries were initialized in an end-systolic frame and then automatically tracked throughout the cardiac cycle. Manual corrections were performed as needed to optimize boundary tracking throughout the cardiac cycle. Normal peak GLS was defined as ≤ -19% [21,22], which adhered to the standard benchmark set by previous studies.

STATISTICAL ANALYSIS

All data were summarized and displayed as a mean ± standard deviation for continuous variables and as a number (percentage) of patients for categorical variables. Categorical variables were analyzed using the Pearson's Chi-square test. Continuous variables were analyzed using the independent sample *t* test or Mann-Whitney test, as appropriate. A two-tailed *P* value of < 0.05 was considered significant. Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software, version 20 (SPSS, IBM Corp, Armonk, NY, USA).

RESULTS

BASELINE PARAMETERS

Among the 103 patients included, 5 (5%) developed CTRCD and were defined as the CTRCD group. The other 98 patients (95%) were defined as the no-CTRCD group. The mean time for CTRCD diagnosis was 171 days (66–231). Moreover, 10 patients (10%) developed LVEF reduction of 5% and above. To confirm the accuracy of the EF difference we performed an intra-observer exam by evaluating the LVEF among a sample of 20 patients, both at the first and second echocardiography exam and found that there was a high level of agreement with an inter-class correlation coefficient (ICC) of 0.91 ($P < 0.001$) and 0.862 ($P < 0.001$), respectively.

There were no significant differences in patient characteristics between both groups, including mean age, metastatic disease, and cardiac risk factors such as hypertension, diabetes mellitus, hyperlipidemia, smoking, atrial fibrillation, and ischemic stroke [Table 1]. Lower systolic blood pressure was the only significant vital sign related to CTRCD development (100 ± 13 vs. 130 ± 22, $P = 0.006$) [Table 1]. Finally, blood count (white blood cells, hemoglobin, and platelets) and creatinine levels showed no significant difference between the groups [Table 1].

ECHOCARDIOGRAPHY PARAMETERS

Baseline echocardiography revealed a number of parameters associated with CTRCD development, including lower GLS (-18 ± 3% vs. -21 ± 2%, $P = 0.016$), higher left ventricle end systolic diameter (LVESD) (35 ± 6 mm vs. 25 ± 4 mm, $P < 0.001$) and lower e' septal (5.2 ± 0.5 cm/s vs. 7.4 ± 2.6 cm/s, $P < 0.001$) [Table 2]. Other parameters, such as E/A, deceleration time, e' lateral, E/e' average, and tricuspid annular plane systolic excursion showed no significant association to CTRCD.

CHEMOTHERAPEUTIC AGENTS

Patients with CTRCD were treated more frequently with trastuzumab (80% vs. 18%, $P = 0.001$) and pertuzumab (80% vs. 14%, $P < 0.001$), but not with doxorubicin (a type of anthracycline) [Table 3]. The maximum dose of anthracyclines was 240 mg/m^2.

OUTCOMES

During follow-up one patient from the CTRCD group developed heart failure. A total of two patients died due to non-cardiac reasons, and were both from the no-CTRCD group.

DISSCUSION

In this study the authors demonstrated that CTRCD is still an important concern among patients with active breast cancer and should be considered during cancer therapy. Our study reports a 5% prevalence of CTRCD. Moreover, 10% of the patients showed a 5% and above reduction in LVEF, which in longer follow-up may progress to CTRCD.

Past studies [5,7,23] suggested that a comprehensive pre-treatment evaluation may unveil predisposing cardiac risk-factors and identify patients at risk for CTRCD development. In our study, none of the known cardiac risk factors, such as hypertension, diabetes mellitus, and hyperlipidemia were associated with CTRCD development. Moreover, the patients in the CTRCD group had no baseline cardiac risk-factors [Table 1]. This finding raises the question of whether routine cardiac assessment of all patients with breast cancer treated with cardiotoxic drugs is warranted. Interestingly, patients in the CTRCD group had baseline lower systolic blood pressure, which might be explained as more unstable hemodynamic state and an obstacle for administration of cardioprotective therapy and therefore more prone for developing LV dysfunction. Regarding the chemotherapeutic agents associated with CTRCD, anthracyclines is still considered to be the most significant cardiotoxic drug and it is known to be dose-dependent [7]. Currently it is given in considerably low doses (240 mg/m^2) to patients with breast cancer, and therefore is estimated to cause less cardiotoxicity among this population [10]. Our study supports this estimation as we saw no association between CTRCD development and anthracyclines therapy. Trastuzumab and pertuzumab are also known

Table 1. Baseline characteristics according to cancer therapeutics-related cardiac dysfunction

	No-CTRCD (n=98)	CTRCD (n=5)	*P* value
Age, years (mean ± SD)	57 ± 16	55 ± 15	0.788
Hypertension (n, %)	36 (37%)	0 (0%)	0.093
Diabetes mellitus (n, %)	26 (26%)	0 (0%)	0.183
Hyperlipidemia (n, %)	28 (28%)	0 (0%)	0.161
Ischemic heart disease (n, %)	5 (5%)	0 (0%)	0.605
Atrial fibrillation (n, %)	3 (3%)	0 (0%)	0.691
Ischemic stroke (n, %)	2 (2%)	0 (0%)	0.747
Heart rate (mean ± SD)	79 ± 14	86 ± 30	0.838
Systolic blood pressure (mean ± SD)	130 ± 22	100 ± 13	0.006
Diastolic blood pressure (mean ± SD)	73 ± 11	65 ± 20	0.108
O2 saturation (mean ± SD)	97 ± 2	98 ± 0	0.598
Body surface area (mean ± SD)	1.7 ± 0.2	1.5 ± 0.3	0.148
ACEI (n, %)	17 (17%)	3 (60%)	0.019
ARB (n, %)	9 (9%)	0 (0%)	0.478
Beta blockers (n, %)	18 (18%)	4 (80%)	0.001
Spironolactone (n, %)	1 (1%)	0 (0%)	0.820
Hemoglobin g/dl (mean ± SD)	12.1 ± 1.5	11.6 ± 0.9	0.473
White blood cells 10e3/µl (mean ± SD)	7.2 ± 3	6.4 ± 2.2	0.603
Platelets10e3/µl (mean ± SD)	255 ± 85	271 ± 95	0.708
Creatinine mg/dl (mean ± SD)	0.7 ± 0.2	0.6 ± 0.1	0.182

ACEI = angiotensin-converting-enzyme inhibitor, ARBs = angiotensin II receptor blockers, CTRCD = cancer therapeutics-related cardiac dysfunction, SD = standard deviation

Table 2. Echocardiographic parameters according to cancer therapeutics-related cardiac dysfunction

	No-CTRCD (n=98)	CTRCD (n=5)	*P* value
Ejection fraction 1* % (mean ± SD)	60 ± 1	57 ± 3	0.090
Global longitudinal strain 1* % (mean ± SD)	-21 ± 2	-18 ± 3	0.016
Left ventricular end diastolic dimension 1* mm (mean ± SD)	45 ± 5	48 ± 6	0.180
Left ventricular end systolic dimension 1* mm (mean ± SD)	25 ± 4	35 ± 6	< 0.001
LV MASS 1* g (mean ± SD)	146 ± 40	134 ± 43	0.558
E/A 1* (mean ± SD)	0.6 ± 0.1	1.1 ± 0.5	0.541
Deceleration time 1* ms (mean ± SD)	180 ± 47	160 ± 21	0.401
E' septal 1* cm/s (mean ± SD)	7.4 ± 2.6	5.2 ± 0.5	< 0.001
E' lateral 1* cm/s (mean ± SD)	9.2 ± 3	8 ± 2	0.298
E/e' septal 1* (mean ± SD)	11.6 ± 5.3	14 ± 2.9	0.085
E/e' lateral 1* (mean ± SD)	9.4 ± 4.1	9.6 ± 3.5	0.746
E/e' average 1* (mean ± SD)	10.3 ± 4.3	11.3 ± 3.2	0.317
Left atrium volume index 1* ml/m2 (mean ± SD)	32 ± 13	39 ± 0.5	0.433
Tricuspid annular plane systolic excursion 1*cm (mean ± SD)	24 ± 3	26 ± 5	0.213
Ejection fraction2* % (mean ± SD)	60 ± 1	44 ± 7	0.006
Global longitudinal strain 2* % (mean ± SD)	-20 ± 2	-15 ± 1	< 0.001

CTRCD = cancer therapeutics-related cardiac dysfunction, SD = standard deviation
1* are parameters measured at initial echocardiography evaluation.
2* are parameters measured at follow-up echocardiography.

to cause CTRCD [7]; however, the APHINITY study recently reported a substantial low rate of 0.6% [10]. Our study contradicts those finding, demonstrating a higher number of CTRCD development, with a high prevalence of trastuzumab and pertuzumab therapy among the CTRCD group. Since patients with breast cancer are frequently treated with a combination of those medications, larger trials are needed to examine the impact of each treatment and its synergism.

Table 3. Chemotherapy according to cancer therapeutics-related cardiac dysfunction

	No-CTRCD (n=98)	CTRCD (n=5)	*P* value
Doxorubicin (n, %)	44 (45%)	3 (60%)	0.508
Cyclophosphamide (n, %)	42 (43%)	2 (40%)	0.900
Paclitaxel (n, %)	37 (38%)	3 (60%)	0.319
Trastuzumab (n, %)	18 (18%)	4 (80%)	0.001
Pertuzumab (n, %)	14 (14%)	4 (80%)	< 0.001
Chest radiation (n, %)	22 (22%)	2 (40%)	0.365

CTRCD = cancer therapeutics-related cardiac dysfunction

Since the toxicity of anthracyclines is considered to be irreversible [24], a routine echocardiographic evaluation during the course of treatment possibly enables early diagnosis of cardiac dysfunction. As LVEF reduction manifests only after major damage to the myocardium [12,13], novel and more sensitive means are needed. Echocardiographic predictors of CTRCD as demonstrated in this study were low GLS and increased LVESD. GLS is considered to be a sensitive predictor of LVEF reduction [5], but due to the lack of large randomized control trials as well as low availability and experience of the technique, GLS is still not measured routinely. Compared to previous studies, our study includes a relatively large homogenous population of patients with breast cancer followed routinely and prospectively by GLS. Another advantage of our study is that all GLS exams were performed by the same vendor, technician, and interpreting cardiologist, which made the exam more accurate and less prone to bias. We showed that even a trend of reduced GLS is associated with CTRCD development. As to other echocardiographic parameters, a higher LVESD and a lower e' septal were associated significantly with CTRCD development, while other parameters of diastolic function and right ventricular function were not [Table 2]. Therefore, our study supports the use of routine GLS follow-up among patients with active breast cancer.

In our study only one patient developed heart failure during follow-up. Moreover, we did not observe any cardiac death. This finding however does not imply that heart failure and cardiac death are not a concern, as there can be multiple explanations for the low incidence. First, the close follow-up of patients revealed the early decrease in LVEF and allowed initiation of cardioprotective therapy, thus preventing deterioration in LVEF and possibly the development of heart failure and death. Furthermore, the follow-up period of the trial was relatively short and cardiac outcomes may still develop in the long term. In addition, this cohort was composed of relatively young women. As so, it fairly reflected the population of breast cancer patients and allowed the isolated cardiac damages of cancer therapy to be more clearly evident due to less initial cardiac morbidity. Per-

haps a larger cohort with more age diversity would have shown even more cases of CTRCD and heart failure, as age is the main predictor of cardiotoxicity [7].

LIMITATIONS

Our study has several limitations. First, it was a single-center, observational study. Second, we acknowledge that the relatively small number of patients reduces the statistical power of our results. Finally, the relative short period of follow-up might have influenced the results, with the possibility of LVEF reduction and development of cardiac outcomes occurring later in the course of follow-up.

CONCLUSIONS

Our study demonstrates that CTRCD is still an important concern among patients with active breast cancer and is associated with trastuzumab and pertuzumab treatment. Furthermore, our findings imply that even patients who are considered low risk may develop CTRCD. Finally, we showed that a lower baseline GLS is associated with CTRCD development, which may support a routine use for risk stratification and early diagnosis of cardiotoxicity.

Correspondence
Dr. M. Laufer-Perl
Dept. of Cardiology, Tel Aviv Sourasky Medical Center, Tel Aviv, 6423906 Israel
Phone: (972-3) 697-4509
Fax: (972-3) 697-4388
email: michalpela@gmail.com

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We are social creatures to the inmost centre of our being.
The notion that one can begin anything at all from scratch, free from the past,
or unindebted to others, could not conceivably be more wrong.
Karl Popper (1902–1994), Austrian-born British philosopher of science,
academic and social commentator