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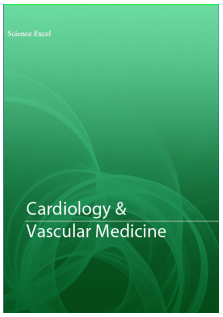

Anthracyclines and Trastuzumab-induced Cardio-toxicity in Breast Cancer Patients: Testing a Clinical Risk Score in the First Cardio-Oncology Unit in Morocco

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Breast cancer, Trastuzumab, Anthracyclines, Cardio-toxicity, Clinical risk score, Cardio-oncology

Abbreviations

CRS : Cardiotoxicity Risk Score; ASCO : American Society of Clinical Oncology; HER-2: Human Epidermal Growth Factor Receptor-2; LVEF: Left Ventricular Ejection Fraction; LV: Left Ventricule; LGS: the Longitudinal Global Strain; RT: Radiotherapy; CTRCD: cancer therapeutics–related cardiac dysfunction; CVD: Cardiovascular disease; HF: Heart failure; TIC: Trastuzumab-induced cardiotoxicity

Abstract

Background: Recent advances in the early detection and treatment of cancer have led to a significant improvement of cancer survival worldwide. However, long-term cardio-toxic side effects affect both patient survival and quality of life.

Aim: To assess the utility of the Cardio-toxicity Risk Score (CRS) to predict cardio-toxicity among our patients.

Material and Methods: We conducted a prospective observational study for 3 years in the first cardio-oncology unit in Morocco. For each breast cancer candidate to an adjuvant treatment with anthracyclines and/or trastuzumab, we calculated The CRS proposed by the ASCO, and classified the patients in 2 groups (high and low risk). We then performed sensitivity and correlation analysis between cardio-toxicity and the patients' CRS.

Results: In total, 413 patients were included, and when applying the CRS to them, 136 (32.9%) were considered at high risk and 277 (67.1%) at low risk. During follow-up, 42 patients (10.1%) experienced cardio-toxicity. Sensitivity analysis showed that the CRS applied to our population had a sensitivity of 83% [95% CI: 0.78, 0.92], a specificity of 65% [95% CI: 0.54, 0.71], with a positive predictive value of 21% [95% CI: 0.08, 0.39] and a negative predictive value of 97% [95% CI: 0.90, 0.99]. On the other hand, correlation analysis found a significant positive correlation with both transient and permanent cardio-toxicity.

Conclusion: The CRS demonstrated good sensitivity and negative predictive value for the development of cardio-toxicity in our population, suggesting that intensive cardiac monitoring may not have as much interest in low-risk patients that in high-risk patients.

Introduction

Breast cancer is becoming an increasingly urgent problem worldwide. In fact, it is the world's most common cancer among women according to the International Agency for Research on Cancer (IARC) latest global cancer data [1]. In 2018, 24.2% and about one in 4 of all new cancer cases diagnosed in women worldwide are breast cancer. Moreover, it is the leading cause of cancer death in women (15.0%) [1,2].

In Morocco, it is also by far the most common cancer in women with an incidence of 19.2% in 2018 (10 136 new cases), and the second cause of death by cancer after lung cancer, according to the same source [1].

Over these last decades, Cancer survival and patients' outcome significantly improved by major advances in treatment options especially in targeted agents such as Trastuzumab, a humanized monoclonal antibody against HER2 [3], and also in early detection and screening of its short and long-term side-effects.

However, despite these advances, morbidity associated with breast cancer treatment affect both patient's survival and quality of life [4].

Cardio-toxicity is one of the most feared and undesirable side effect of cancer treatments, occurring in approximately 10% of the patients [5], It is usually multifactorial, due to combined protocols as adjuvant chemotherapy especially anthracycline- based regimen, trastuzumab and radiation therapy. Its onset depends also on other parameters like the patient's predisposition or risk (comorbidities, history, and medication's intake).

Currently, although several risk scores have been proposed [6,7], among which the clinical risk score (CRS), developed by the American Society of Clinical Oncology (ASCO) [8], and the Framingham risk score (FRS) [9], it is difficult to predict which patients are at highest

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risk of developing cardio-toxicity from chemotherapy or targeted therapy .

The aim of our study was to assess the utility of the CRS to predict anthracyclines and trastuzumab-induced cardio-toxicity in breast cancer patients in a Moroccan Cardio-oncology unit in order to implement a standardized risk score in routine clinical practice.

Material and Methods

This was a prospective observational study, conducted in the cardio-oncology unit of Casablanca, the first cardio-oncology unit in Morocco, from November 2017 to December 2019. We included all new cases of early-stage (I–III) breast cancer patients, who are candidates to receive an adjuvant treatment with anthracyclines associated or not with trastuzumab in the HER2+ patients.

We excluded from our study patients having metastatic disease, or a cardiac disease at the time of the diagnosis.

For all our patients, a baseline cardiac assessment was performed, and we collected information concerning their medical history (with Data on demographics, cancer characteristics, cardiac risk factors etc.), in addition to clinical examination, biological exams including Troponins I, Brain natriuretic peptides (BNP) and lipid level. We also performed an electrocardiogram and an echocardiography with assessment of Left Ventricular Ejection Fraction (LVEF) and Longitudinal Global Strain (LGS).

After this baseline work-up, we assessed our patients' risk accordingly to the ASCO CRS in order to define patients at increased risk for developing a cardiac dysfunction, considering the following criteria [8]:

- Treatment that includes any of the following:

  - High-dose anthracycline (eg, doxorubicin ≥ 250 mg/m^2, epirubicin ≥ 600 mg/m^2)

  - High-dose Radiotherapy (RT) (≥ 30 Gy) where the heart is in the treatment field.

  - Low-dose anthracycline (eg, doxorubicin < 250 mg/m^2, epirubicin < 600 mg/m^2) in combination with low-dose RT (< 30 Gy) where the heart is in the treatment field.

- Treatment with low-dose anthracycline (eg, doxorubicin < 250 mg/m^2, epirubicin < 600 mg/m^2) or trastuzumab alone, and presence of any of the following risk factors:

  - Multiple cardiovascular risk factors (≥ two risk factors), including smoking, hypertension, diabetes, dyslipidemia, and obesity, during or after the therapy's completion.

  - Old age (≥ 60 years) at the cancer treatment's time.

  - Compromised cardiac function (eg, borderline low LVEF [50% to 55%], history of myocardial infarction, ≥ moderate valvular heart disease) at any time before or during treatment

- Treatment with low dose anthracycline (eg, doxorubicin < 250 mg/m^2, epirubicin < 600 mg/m^2) followed by trastuzumab (sequential therapy)

Following this criteria, we classified our patients in two groups: High risk and low risk of developing cancer therapeutics–related cardiac dysfunction (CTRCD)

Patients receiving anthracyclines and/or trastuzumab were followed prospectively from the treatment initiation's time, and according to the European Society of Cardiology 2016 guidelines [10].

For low-risk patients (normal baseline echocardiogram, no clinical risk factors), an assessment of cardiac function was performed after a cumulative total doxorubicin (or equivalent) dose of 200 mg/m^2 or epirubicin 400 mg/m^2 or even earlier if clinical symptoms and/or an increase in cardiac enzymes was observed, and then at 3,6,9,12 months after the end of the treatment. For the anti-HER2 therapy, cardiac monitoring was performed every 4 cycles of the treatment, and then every 3 and 6 months after its completion.

More frequent monitoring was performed for patients with abnormal baseline echocardiography (reduced or low normal LVEF, structural heart disease) and those with higher clinical risk at baseline (prior anthracyclines, previous myocardial infarction, and treated heart failure).

The importance of this follow-up was the screening and the early detection of CTRCD that was defined as a decrease of the LVEF more than 10% , and below the lower limit of 50%, with or without symptoms [10,11]. CTRCD was considered transient if the patient's LVEF returned to the baseline value during the study period, and permanent if the LVEF was sustained either below 50% or more than 10% below the baseline LVEF's value .

Statistical analysis

First, we performed a sensitivity analysis using SPSS 21.0. A true positive was defined as a patient in the high-risk score group who experienced a CTRCD during the follow-up period, and a true negative was defined as a low-risk patient who experienced no cardio-toxicity during the study. Using those cut-points, sensitivity and specificity, as well as positive and negative prediction values were calculated.

In the second analysis, we evaluated the correlation between the patients' risk and the degree of recovery of the LVEF using the Pearson correlation coefficient. We aimed to assess whether or not a high risk accordingly to the CRS was correlated to a permanent cardiotoxicity and if a low-risk was correlated with a transcient CTRCD.

Ethical approval

The participation in the study was voluntary; consent was free and clear, written or oral. The study was conducted in compliance with the ethical standards of the responsible institution on human subjects as well as with the Helsinki Declaration.

Results

During the study period, 413 new cases of early-stage breast cancer patients, who were candidates to receive an adjuvant treatment with anthracyclines, and/or trastuzumab, were referred to the cardio-oncology unit of Casablanca.

Their baseline characteristics are assessed in Table 1.

Mean age in the cohort was 51 years (range: 23–88 years; standard deviation: 11 years).

Concerning the cardiovascular risk factors, 10.1% had hypertension, 7% diabetes Mellitus, 15.5% dyslipidemia and more than half the women were menopausal. Almost 25% of our patients had non-cardiovascular associated comorbidities including asthma, dysthyroidism etc.

41% of our patients had stage II disease at the time of diagnosis (169 (40.9%)), and 94% (n = 387) were candidates to adjuvant chemotherapy including Anthracyclines in 86% of cases. Median

Characteristics	Value
Number of patients	413
Mean age (years)	51±11.7
Mean Body Mass Index	27.1±6
Pre-existing cardiovascular conditions and risk factors [n (%)]	
Hypertension	42 (10;1%)
Diabetes mellitus	29 (7,0%)
Smoking	5 (1,2%)
Hyperlipidemia	64 (15,5%)
Menopause	217 (52,5%)
Coronary artery disease	9 (2,1%)
Significant valvular disease	5 (1,2%)
Renal failure	11 (2,6%
Stroke	4 (0,9%)
Number of non-cardiovascular comorbidities [n (%)]	
None	305 (73,9%)
1 to 2	103 (24,9%)
>3	5 (1,2%)
Tumor stage [n (%)]	
I	71 (17,2 %)
II	169 (40,9%)
III	82 (19,9%)
Unknown	91 (22,0%)
Chemotherapy [n (%)]	
Adjuvant	387 (93,7%)
Neoadjuvant	26 (6,3%)
Antracyclines based	95 (23,0%)
Trastuzumab	34 (8,2%)
Anthracyclines plus trastuzumab	261 (63,2%)
Anthracyclines cumulative dose [n (%)]	
High dose	31 (7,5%)
Low dose	319 (77,2%)
Unknown	63 (15,3%)
Radiotherapy [n (%)]	176 (42,6%)
Radiotherapy cumulative dose n (%)]	
High dose >30 Gy	19 (10,7%)
Low dose <30 Gy	87 (49,5%)
Unknown	70 (39,8%)
Mean baseline LVEF	58%±9%
Mean baseline LGS	21%±4%

Table 1. Patients' characteristics at baseline

Variables	Clinical risk score	
	Low-risk	High-risk
Patients [n (%)]	277 (67,1%)	136 (32,9%)
CTRCD [n (%)]	7 (16,6%)	35 (83,4%)
Transient CTRCD [n (%)]	7 (100%)	24 (68,5%)
Permanent CTRCD [n (%)]	0 (0%)	11 (31,5%)

Table 2. Cancer therapeutics–related cardiac events stratified according to the CRS

Variables	Value	CI 95%
Sensitivity	0.83	[0.78, 0.92]
Specificity	0.65	[0.54, 0.71]
Positive predictive value	0.21	[0.08, 0.39]
Negative predictive value	0.97	[0.90, 0.99]

CI = confidence interval

Table 3. Sensitivity analysis.

	Low-risk		High- risk	
	Pearson correlation	p value	Pearson correlation	p value
Transient CTRCD	0.092	0.062	0.354	<0.001
Permanent CTRCD	--	--	0.236	<0.001

Table 4. Correlation analysis between CRS and CTRCD reversibility.

baseline LVEF was 58% (standard deviation 9%), and mean baseline LGS in absolute value was 21% (standard deviation 4%).

When applying the CRS to our study population, 136 of them (32.9%) were considered at high risk and 277 (67.1%) at low risk.

In the study period, 42 patients (10.1%) experienced CTRCD among which 79,1% were asymptomatic and 20.9% had heart failure. Moreover, 31 patients (73,8%) had full recovery of their LVEF.

The majority of patients who experienced CTRCD were in the high-risk group (83.4%, n = 35) against 7 patients (16.6%) in the low-risk group.

Also, 100% of the low-risk patients completely recovered their cardiac function during the 3 years follow-up versus 68.5% (n= 24) in the high-risk group, with permanent CTRCD in more than a third of our patients.

Table 2 details all the cases of cardio-toxicity in our patients stratified by the CRS and the degree of LVEF within 3 years of therapy initiation.

After this, we performed a sensitivity analysis where we calculated sensitivity and specificity, and also positive and negative prediction values (Table 3). The results showed that when applying the CRS to our population, the sensitivity was 83% [95% CI: 0.78, 0.92], the specificity 65% [95% CI: 0.54, 0.71], with a positive predictive value of 21% [95% CI: 0.08, 0.39] and a negative predictive value of 97% [95% CI: 0.90, 0.99]

In the second analysis, we evaluated the correlation between the patients' risk and the degree of recovery of the LVEF (Table 4)

In high risk patients, the results showed a significant positive correlation with both transient and permanent CTRCD, with however, a significant correlation between high-risk patients and transient CTRCD (0.354, p<0.001). On the other hand, no significant correlation was assessed between low-risk patients and transient CTRCD (0.092, p=0.062).

Discussion

Breast cancer is the most common cancer diagnosed in Morocco, with an estimated 10 136 new cases in 2018 based on the Moroccan cancer registry, the second most common cancer in terms of mortality rate, responsible of 10.7% of deaths among cancer patients [1,2]. In cancer survivors, cardiovascular disease (CVD) is the second cause of long-term morbi-mortality [12] and the first cause of death among female survivors from breast cancer [13].

These past decades, advances in chemotherapy and targeted therapies significantly increased cancer patients' survival, hence the long-term side-effects of cancer therapy, especially chemotherapy. Some molecules like anthracyclines and herceptine were found to be associated with an important risk of cardiac damage, including left ventricular (LV) dysfunction and heart failure (HF), thromboembolic complications, hypertension as well as arrhythmias. Many breast cancer patients die of causes independent of the cancer itself but related to treatments cardiovascular side-effect, which draws attention to the importance of managing cardiovascular risk factors for the long-term care of patients diagnosed with breast cancer [13].

Anthracyclines

Anthracycline-based chemotherapy regimens used as adjuvant or neo-adjuvant in breast cancer treatment displayed survival improvement [14], however, they carry a well-known cytotoxicity on cardiomyocytes that may be responsible for a cardiomyopathy, that can often be irreversible [15].

The mechanism of anthracycline-induced cardiac injury has been the subject of several studies and yet has not been fully explained [16,17].

The risk of cardio-toxicity secondary to anthracyclines is mostly dose-dependent and depends on the cumulative dose. For instance, doxorubicin is responsible of an incidence of congestive HF ranging from 3% to 5% with a cumulative dose of 400 mg/m^2, from 7% to 26% at 550 mg/m^2, and from 18% to 48% at 700 mg/m^2 [18,19].

Pein et al [20] analyzed 229 patients treated with anthracycline and reported a relative risk of HF of 1.93 in patients who received 250-400 mg/m^2 compared to those treated with lower doses of anthracyclines, confirming a strong relationship between cumulative dose and cardio-toxicity.

Trastuzumab

Trastuzumab, is a monoclonal antibody directed against the HER2 that significantly improve survival in women with HER2-positive early-stage breast cancer [21]. However, trastuzumab-induced cardiotoxicity (TIC), mainly reversible left ventricular dysfunction, may limit its use [22]. TIC severity is quite variable and can go from asymptomatic decline in LVEF to symptomatic HF, and does not seem to be associated to either dose or duration [22]. It is usually a type 2 cardio-toxicity unlike anthracyclines that are classified among type 1 cardio-toxicity [23]. Indeed, contrary to anthracyclines that directly cause structural damage to cardiomyocytes, its mechanisms of action include cytotoxicity through inhibition of signal transduction, neoangiogenesis and repair of DNA damage caused by other treatments (type 2 cardio-toxicity) [23].

In Mantarro et al meta-analysis [24], including approximately 29000 patients, severe TIC was found in about 3% of patients, with an increasing incidence up to 19% among older patients, smokers and patients with diabetes, hypertension or cardiovascular disease. However, after TIC diagnosis, trastuzumab is often interrupted, which is associated with a higher rate of cancer recurrence [25,26]. In our study we found the same factors with similar proportions.

Risk assessment

Predicting patients at high risk of developing cardio-toxicity following a sequential anthracycline-based chemotherapy and trastuzumab still remains a challenge for the cardio-oncologist.

Although no guidelines are available, the strategy mostly used to reduce and to prevent cardio-toxicity is a precise analysis of cardiovascular risk factors or underlying subclinical cardiovascular damage in addition to an accurate assessment of the optimal therapy and maximal cumulative dose [27]. This was the approach we adopted in our unit, which allowed us to establish a database and results close to the literature series.

So far, few risk prediction scores have been published in the literature [27-29].

The CRS proposed by the ASCO takes both patient characteristics and treatment risk factors into consideration, however it doesn't include treatment doses and hasn't been tested in real life clinical prospective settings, therefore, it has not been validated nor recommended by savant societies [10].

In order to produce a clinical risk stratification model, the score should include treatment with dosage related risk factors; patient related risk factors and should be tested in real world clinical setting.

Treatment related risk factors

The various regimens used in treatment of breast cancer carries different risk of cardio-toxicity alongside with the dosage used [19].

Molecules used for chemotherapy are divided into 4 categories based on incidence of myocardial contractile damage; and group 4 alone accounts over 10% of cardio-toxicity. The most common breast cancer treatment used which belong to group 4 are Anthracyclines and Trastuzumab.

LV dysfunction seems to be more frequent in case of:

- High-dose anthracycline (doxorubicin > 250 mg/m^2 or epirubicin > 600 mg/m^2); observed in 7.5% in our series.
- Lower-dose anthracycline in combination with lower-dose radiation therapy (RT < 30 Gy) where the heart is in the treatment field;
- Patients with cardiovascular risk factor including advanced age and structural heart abnormality;
- Sequential therapy: treatment with anthracycline followed by trastuzumab.

One of the limits of our study was the high proportion of the indeterminate status of Radiotherapy and anthracyclines cumulative doses (in 39.8% and 15.3% of the cases respectively).

Patient-related risk factors

Among patients' related risk factor, the ones most frequently reported in the literature are age of exposure (<15 or >65 year old), heart centered radiation therapy, obesity, hypertension and diabetes mellitus besides demographic features (female sex, black ethnicity) [29].

Combining more than 3 of these risk factors is related to 5 times higher risk of cardio-toxic adverse effects versus patients without any risk factors [29].

These risk factors are found in our series however it was difficult for us to calculate the relative risk of cardio-toxicity with the lack of appropriate statistical methodology.

Detection and Monitoring of cardiotoxicity

A clinical risk stratification score may represent an effective, inexpensive tool to help managing development of cardio-toxicity after treatment initiation and reduce early discontinuation of therapy by early detection and treatment.

Besides clinical risk factors, baseline and post chemotherapy strain imaging using echocardiography and cardiac biomarkers has been included in cardio-toxicity prediction. In this perspective, a group of experts from the American Society of Echocardiography and the European Association of Cardiovascular Imaging [30] defined cardio-toxicity as a decrease in LVEF (measured by the Simpson biplane method) of more than 10% from the reference value to a value below the lower limit of normal [31], as it was the case in our study. GLS is also a reproducible echocardiographic method to measure changes in left ventricular contractility before ejection fraction declines [30].

Cardiac biomarkers are a useful tool to identify patients with higher risk of toxicity. Elevated troponin level has been useful for detection of in the early cardio-toxicity related to chemotherapy [32,33].

Based on clinical features, imaging and cardiac biomarkers, elaborating a prediction model that can enhance sensitivity to detect high risk patients to develop chemotherapy-related toxicity and should benefit from close intense monitoring.

On the other hand, it allows identifying low risk patients who will not need long term cardiac monitoring, saving its cost for high risk group.

Cardio-oncology clinicians and researchers should focus on assessment and applicability of such risk stratification model in more extensive prospective and long term settings. According to our study, the hypothesis that a high risk was positively correlated with permanent cardio-toxicity and that low risk had a negative correlation with transient CTRCD was not true in our analysis as shown in Table 4.

Conclusion

In conclusion, in our study, the CRS was proven to be an effective tool to assess breast cancer patients' risk and to predict the development of CTRCD. It demonstrated good sensitivity and negative predictive value for the development of cardio-toxicity in a real-world population of breast cancer patients undergoing anthracyclines and/or trastuzumab based therapy. These findings suggest that intensive cardiac monitoring may not have interest in low-risk patients, but that high-risk patients must benefit from early consultation in a cardio-oncology unit, due to the increased risk of cardiac events.

Conflicts of interest

The authors declare they have no conflict of interest.

Authors' contributions

All the authors contributed equally in the drafting of the manuscript. All the authors read and agreed to the final manuscript.

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References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries [published correction appears in CA Cancer J Clin. 2020 Jul;70(4):313]. CA Cancer J Clin. 2018;68(6):394-424
2. Coughlin SS, Ekwueme DU. Breast cancer as a global health concern. Cancer Epidemiol. 2009;33(5):315-318.
3. Viani GA, Afonso SL, Stefano EJ, De Fendi LI, Soares FV. Adjuvant trastuzumab in the treatment of her-2-positive early breast cancer: a meta-analysis of published randomized trials. BMC Cancer. 2007;7:153.
4. Binkley JM, Harris SR, Levangie PK, et al. Patient perspectives on breast cancer treatment side effects and the prospective surveillance model for physical rehabilitation for women with breast cancer. Cancer. 2012;118(8 Suppl):2207-2216.
5. Cardinale D, Colombo A, Bacchiani G, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation. 2015;131(22):1981-1988.
6. Romond EH, Jeong JH, Rastogi P, et al. Seven-year follow-up assessment of cardiac function in NSABP B-31, a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel (ACP) with ACP plus trastuzumab as adjuvant therapy for patients with node-positive, human epidermal growth factor receptor 2-positive breast cancer. J Clin Oncol. 2012;30(31):3792-3799.
7. Ezaz G, Long JB, Gross CP, Chen J. Risk prediction model for heart failure and cardiomyopathy after adjuvant trastuzumab therapy for breast cancer. J Am Heart Assoc. 2014;3(1):e000472.
8. Armenian SH, Lacchetti C, Barac A, et al. Prevention and Monitoring of Cardiac Dysfunction in Survivors of Adult Cancers: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2017;35(8):893-911.
9. Law W, Johnson C, Rushton M, Dent S. The Framingham risk score underestimates the risk of cardiovascular events in the HER2-positive breast cancer population. Curr Oncol. 2017;24(5):e348-e353.
10. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC) [published correction appears in Eur Heart J. 2016 Dec 24;:]. Eur Heart J. 2016;37(36):2768-2801.
11. Gavila J, Seguí MÁ, Calvo L, et al. Evaluation and management of chemotherapy-induced cardiotoxicity in breast cancer: a Delphi study. Clin Transl Oncol. 2017;19(1):91-104.
12. Mertens AC, Liu Q, Neglia JP, et al. Cause-specific late mortality among 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. J Natl Cancer Inst. 2008;100(19):1368-1379.
13. Patnaik JL, Byers T, DiGuiseppi C, Dabelea D, Denberg TD. Cardiovascular disease competes with breast cancer as the leading cause of death for older females diagnosed with breast cancer: a retrospective cohort study. Breast Cancer Res. 2011;13(3):R64.
14. Polychemotherapy for early breast cancer: an overview of the

randomised trials. Early Breast Cancer Trialists' Collaborative Group. Lancet. 1998;352(9132):930-942.

15. Ades F, Zardavas D, Pinto AC, Criscitiello C, Aftimos P, de Azambuja E. Cardiotoxicity of systemic agents used in breast cancer. Breast. 2014;23(4):317-328.
16. Volkova M, Russell R 3rd. Anthracycline cardiotoxicity: prevalence, pathogenesis and treatment. Curr Cardiol Rev. 2011;7(4):214-220.
17. Zhang S, Liu X, Bawa-Khalfe T, et al. Identification of the molecular basis of doxorubicin-induced cardiotoxicity. Nat Med. 2012;18(11):1639-1642.
18. Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer. 2003;97(11):2869-2879.
19. Von Hoff DD, Layard MW, Basa P, et al. Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med. 1979;91(5):710-717.
20. Pein F, Sakiroglu O, Dahan M, et al. Cardiac abnormalities 15 years and more after adriamycin therapy in 229 childhood survivors of a solid tumour at the Institut Gustave Roussy. Br J Cancer. 2004;91(1):37-44.
21. Moja L, Tagliabue L, Balduzzi S, et al. Trastuzumab containing regimens for early breast cancer. Cochrane Database Syst Rev. 2012;2012(4):CD006243
22. Tripathy D, Slamon DJ, Cobleigh M, et al. Safety of treatment of metastatic breast cancer with trastuzumab beyond disease progression. J Clin Oncol. 2004;22(6):1063-1070.
23. Pondé NF, Lambertini M, de Azambuja E. Twenty years of anti-HER2 therapy-associated cardiotoxicity. ESMO Open. 2016;1(4):e000073.
24. Mantarro S, Rossi M, Bonifazi M, et al. Risk of severe cardiotoxicity following treatment with trastuzumab: a meta-analysis of randomized and cohort studies of 29,000 women with breast cancer. Intern Emerg Med. 2016;11(1):123-140.
25. Yu AF, Yadav NU, Lung BY, et al. Trastuzumab interruption and treatment-induced cardiotoxicity in early HER2-positive breast cancer. Breast Cancer Res Treat. 2015;149(2):489-495.
26. Suter TM, Procter M, van Veldhuisen DJ, et al. Trastuzumab-associated cardiac adverse effects in the herceptin adjuvant trial. J Clin Oncol. 2007;25(25):3859-3865.
27. Herrmann J, Lerman A, Sandhu NP, Villarraga HR, Mulvagh SL, Kohli M. Evaluation and management of patients with heart disease and cancer: cardio-oncology. Mayo Clin Proc. 2014;89(9):1287-1306.
28. Dranitsaris G, Rayson D, Vincent M, et al. The development of a predictive model to estimate cardiotoxic risk for patients with metastatic breast cancer receiving anthracyclines. Breast Cancer Res Treat. 2008;107(3):443-450.
29. Lotrionte M, Biondi-Zoccai G, Abbate A, et al. Review and meta-analysis of incidence and clinical predictors of anthracycline cardiotoxicity. Am J Cardiol. 2013;112(12):1980-1984.
30. Plana JC, Galderisi M, Barac A, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2014;27(9):911-939.
31. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28(1):1-39.e14.
32. Cardinale D, Sandri MT, Colombo A, et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. Circulation. 2004;109(22):2749-2754.
33. Cardinale D, Sandri MT, Martinoni A, et al. Left ventricular dysfunction predicted by early troponin I release after high-dose chemotherapy. J Am Coll Cardiol. 2000;36(2):517-522.