European Review for Medical and Pharmacological Sciences 2018; 22: 2175-2185

Anthracycline and trastuzumab-induced cardiotoxicity in breast cancer

M.A. NICOLAZZI[1], A. CARNICELLI[1], M. FUORLO[1], A. SCALDAFERRI[2], R. MASETTI[2], R. LANDOLFI[1], A.M.R. FAVUZZI[1]

[1]Department of Medical Sciences, A. Gemelli University Foundation, Catholic University of the "Sacred Heart", School of Medicine, Rome, Italy
[2]Department of Surgery, Breast Unit, A. Gemelli University Foundation, Catholic University of the "Sacred Heart", School of Medicine, Rome, Italy

Abstract. – OBJECTIVE: Breast cancer is the most common cancer among women. In the last twenty years early diagnosis, neoadjuvant and adjuvant systemic treatment that targeted to specific molecular targets have significantly reduced the mortality from breast cancer. However, the increase in survival has allowed to observe the cardiotoxic effects of anticancer therapy and increased mortality from cardiovascular causes, resulting in a large literature where experts try to identify the correct management of this critical problem. Even thought the increased attention in this field, many questions have not yet answers and new studies are needed.

MATERIALS AND METHODS: We conducted a broad search of the English-language literature in Medline using the following search terms: cardiotoxicity, anthracyclines, trastuzumab, breast cancer, left ventricular dysfunction, heart failure. A manual examination of the articles found has been performed.

RESULTS: We provide a comprehensive assessment of the current knowledge about cardiotoxicity induced by anthracycline plus trastuzumab in women affected by breast cancer.

CONCLUSIONS: Early identification and prompt treatment of subclinical cardiotoxicity may improve cardiologic prognosis of these patients and may allow oncologists to avoid withdrawal of chemotherapy. That is why it becomes always more important the creation of multidisciplinary teams where cardiologists and oncologists work together to ensure optimal care to oncologic patients treated with cardiotoxic agents.

Key Words:
Cardiotoxicity, Anthracyclines, Trastuzumab, Breast cancer, Heart failure, Left ventricular dysfunction.

Abbreviations

Cardiovascular disease (CVD), left ventricular (LV), heart failure (HF), European Society of Cardiology (ESC), reactive oxygen species (ROS), topoisomerase 2-alpha (Top 2-α), topoisomerase 2-beta (Top 2-β), epidermal growth factor receptor 2 (HER2), epidermal growth factor receptor tyrosine kinases (ErbB), neoreguline-1 (NRG-1), left ventricular ejection function (LVEF), global systolic longitudinal myocardial strain (GLS), troponin I (TNI), N-terminal pro-B-type natriuretic peptide (NT-proBNP), myeloperoxidase (MPO), angiotensin-converting-enzyme (ACE).

Introduction

Breast cancer is the most common cancer in women counting about 125 per 100000 per year new cases in the United States and about 1.4 million new cases worldwide[1,2]. Over the last 10 years, the rates for new female breast cancer cases have been stable, while death rates have been falling on average 1.8% each year over 2005-2014 with a 5-year survival rate of 89.7% from 2007 to 2013[3]. That is probably due to the increase in screening, adjuvant systemic treatment and therapy targeted to specific molecular targets.

On the other side, the increase in survival has allowed to observe the onset of side effects of anticancer therapy and increased the morbidity and mortality from other causes. Cardiovascular disease (CVD) is now the second leading cause of long-term morbidity and mortality among cancer survivors[4] and the first cause of death among female survivors from breast cancer[5]. Conventional chemotherapy and targeted therapies are associated with an increased risk of cardiac damage, including left ventricular (LV) dysfunction and heart failure (HF), hypertension, vasospastic and thromboembolic ischemia, as well as rhythm disturbances. The drugs employed for years in the treatment of breast cancer (anthracyclines and trastuzumab) are often associated with the development of cardiotoxicity. The most common

Corresponding Author: Maria Anna Nicolazzi MD; e-mail: marianna.nicolazzi@libero.it

clinical presentation of cardiotoxicity is a dilatation-hypokinetic cardiomyopathy leading to heart failure[6]. The development of cardiotoxicity, even if asymptomatic, not only adversely affects the cardiac prognosis of the patient, but significantly limits the therapeutic possibilities in oncology, when an additional anticancer treatment becomes necessary for the recovery/relapse of cancer disease[7].

That is why the need to create an integrative approach has arisen where oncologists and cardiologists work together to ensure optimal care to oncologic patients treated with cardiotoxic agents. Even thought the increased attention in this field, many questions have not yet answers and there are not clinical practice guidelines. In the last years experts have focused attention on this topic giving rise to a large literature, as the recent 2016 European Society of Cardiology (ESC) position paper, to assist physicians, suggesting the better management of these patients[8].

The aim of the present review is to provide a comprehensive assessment of the cardiotoxicity induced by anthracycline plus trastuzumab and to explore the diagnostic and therapeutic tools to prevent or minimize this complication.

Anthracyclines

Anthracyclines, a class of highly effective chemotherapy agents, are nowadays one of the major components of chemotherapy regimens both for solid and hematologic cancers. In particular, in breast cancer doxorubicin and epirubicin are used both in the neoadjuvant and adjuvant setting, as well as in metastatic patients[9]. The mechanism of anthracycline-induced cardiac injury has been extensively studied and it has not yet been fully understood[10,11].

Anthracyclines cardiac toxicity is represented by structural cardiomyocyte alterations and cell death (type 1 cardiotoxicity), it is generally not reversible and mediated at least in part by reactive oxygen species (ROS) generated in iron-dependent chemical reactions. ROS lead to the peroxidation of myocyte membranes and calcium influx into the intracellular space, which can ultimately lead to permanent myocyte damage[12-17]. In addition, other mechanisms have been identified, including disturbances in topoisomerase function. Topoisomerase is an enzyme involved in DNA transcription and replication. There are two isozymes of topoisomerase, topoisomerase 2-alpha (Top 2-α), overexpressed in rapidly proliferating cells such as tumor cells, and topoisomerase 2-beta (Top 2-β), expressed in all quiescent cells[18-20]. In mammalians adult cardiomyocytes express only Top 2-b. The cardiac toxicity of anthracyclines is thought to be mediated through the binding of anthracyclines to DNA and Top 2-b resulting in a cleavage complex that ultimately leads to cell death, and, consequently to cardiac damage[21].

The risk of anthracyclines-induced cardiotoxicity is dose-dependent and increases with cumulative dose. For example, doxorubicin[22,23] is associated with an incidence of congestive HF 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.

Moreover, Pein et al[24] analyzed 229 patients treated with anthracycline-containing regimens and observed a relative risk of cardiac failure of 1.93 in patients who had received 250-400 mg/m^2 compared to patients treated with lower doses of anthracyclines, confirming a strong association between cumulative dose and cardiotoxicity.

The cardiotoxicity from anthracyclines can be acute, early or late. The acute cardiotoxicity, a rather rare and transient side effect, occurs usually within one or two weeks after the treatment and it is generally characterized by non-specific electrocardiographic abnormalities such as reduction of QRS voltages, QT prolongation and supraventricular arrhythmias[25-27]. Early cardiotoxicity, the most frequent one, manifests itself as a subclinical LV dysfunction, generally occurring within the first year of treatment as described in the study of Cardinale et al[28]. Among 2625 patients treated with anthracycline-containing therapy, 9% of them developed cardiotoxicity and 98% of these cases occurred within the first year. On the contrary, late effects occur generally after several years (on average 7 years) after chemotherapy[29], representing a more relevant clinical and prognostic significance, evolving into a cardiomyopathy and hesitating with heart failure generally less sensitive to treatment, rarely in ischemic heart disease[30].

Trastuzumab

Trastuzumab is a monoclonal antibody that binds to the extracellular domain of the human epidermal growth factor receptor 2 (HER2). HER2 is part of the transmembrane epidermal growth factor receptor tyrosine kinases (ErbB) and helps in growth, proliferation, and repair[31]. HER2+ tumor cells have a highly proliferative phenotype, with an increased capacity to disseminate and stimulate angiogenesis HER2+ tu-

mor cells found in up to 30% of breast cancers. They are generally associated with a decreased response to hormonal therapy and a higher risk of metastasis, recurrence and death[32]. That is why inhibition of HER2 signaling has improved outcomes of patients with HER2+ breast cancer when used in conjunction with conventional chemotherapies[33-35]. Trastuzumab-induced cardiotoxicity remains at least in part unclear regarding its pathophysiology but it is known that, opposite 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 cardiotoxicity)[36]. Available research suggests that trastuzumab blocks neoreguline-1 (NRG-1)-mediated activation of HER2 reducing fundamental intracellular mechanisms of cardiomyocytes such as the ability to maintain the structure and function of sarcomeres and scavenging of proapoptotic oxidative subproducts of ATP production in a cell that has high and constant ATP demands[37,38]. In addition, oxidative stress leads to the upregulation of angiotensin II. Angiotensin II is an inhibitor of NRG-1 that prevents its binding to other ErbB family receptors to compensate for HER2 blockade, leading to even more inhibition of the pathway, and thus to more oxidative stress. Also, it activates NADPH oxidase leading to mitochondrial dysfunction and cell death. Furthermore, angiotensin II also induces apoptosis through the AT1 receptor[39].

Finally, trastuzumab leads to the down-regulation of the antiapoptotic protein BCL-XL and to the up-regulation of the proapoptotic protein BCL-XS[40]. In contrast to anthracycline-induced cardiotoxicity, trastuzumab-cardiotoxicity is not dose dependent, and it is often reversible. These mechanisms of damage may explain the increased risk of cardiotoxicity associated with the concurrent use of trastuzumab and anthracyclines. Trastuzumab (type 2 cardiotoxicity) can exacerbate and precipitate the damage caused by previous anthracyclines treatments (type 1 cardiotoxocity) through the interference with homeostatic mechanisms and pathways of cell survival and repair[41]. In the phase 3 trial conducted by Slamon et al[31], 469 patients affected by metastatic breast cancer were randomly assigned to receive either a combination of doxorubicin and cyclophosphamide or paclitaxel monotherapy both with or without trastuzumab. In this study authors observed that about 27% of patients in the doxorubicin and cyclophosphamide plus trastuzumab arm experienced HF *vs.* 8% in the doxorubicin and cyclophosphamide alone arm, 13% in the paclitaxel plus trastuzumab arm and 1% in the paclitaxel alone arm.

Since cardiac toxicity was increased in chemotherapeutic regimens involving the concomitant administration of anthracycline and trastuzumab, adjuvant trials provide treatment schedules, which avoid concomitant administration. Trastuzumab cardiotoxicity is actually reduced when administration is delayed with respect to anthracyclines[42,43].

In a 2016 meta-analysis conducted by Mantarro et al[44] including a cohort of about 29000 patients, severe cardiotoxicity associated with trastuzumab was observed in about 3% of patients, with an increasing incidence up to 19% among older patients, smokers and patients suffering from diabetes, hypertension or cardiovascular disease. One of the most relevant implication of trastuzumab-induced cardiotoxicity is treatment interruption, which is associated with an increase in cancer recurrence[45,46].

Pre-Treatment Assessment and Cardiovascular Risk Factors Evaluation

Although no guidelines are available, it is common opinion that the first strategy to reduce and to prevent chemotherapy-induced cardiotoxicity is an accurate analysis of pre-existing cardiovascular risk factors or subclinical cardiovascular damage and an assessment of the optimal type and cumulative dose of therapy[47].

According to literature, the main risk factors associated with anthracycline-induced cardiotoxicity are cumulative dose, female sex, age > 65 years old, renal failure, concomitant or previous radiation therapy involving the heart, concomitant chemotherapy with alkylating or antimicrotubule agents or immuno- and targeted therapies, pre-existing conditions such as cardiac diseases associating increased wall stress, arterial hypertension, and genetic factors[8,23,48,49].

Moreover, risk factors associated with trastuzumab-induced cardiotoxicity are previous or concomitant anthracycline treatment, short time between anthracycline and anti-HER2 treatment, age >65 years, high body mass index (> 30 kg/m^2), previous LV dysfunction, arterial hypertension and previous radiation therapy[50-52].

Risk assessment prior than treatment beginning should always include a clinical history collection, physical examination and measure-

ment of vital signs. Detection and correction of modifiable cardiovascular risk factors, such as hypertension or diabetes mellitus, smoking habit or overweight, should always be considered.

In the recent years several authors have tried to identify a clinical risk score to help physician to early identify patients at high risk to develop cardiotoxicity[53]. However, none of these risk scores has been validated, so each patient should be individually evaluated and an overall definition of the cardiovascular risk is left to each physician's judgment.

Moreover, an assessment of the LV performance is always recommended before the beginning of a potential cardiotoxic treatment to detect any pre-existing condition of LV dysfunction. Cardiac biomarkers measurement (such as natriuretic peptides or troponins) may be considered at baseline to detect subclinical cardiac abnormalities[8]. When a pre-existing LV dysfunction is found, the patient should be discussed by a multidisciplinary team to identify the need for cardioprotection and the optimal chemotherapy regimen.

To decrease the risk of cardiotoxicity, a preliminary assessment of the optimal chemotherapy regimen is critical. For example, anthracycline cumulative dose is often limited to <550 mg/m^2 and a slow infusion during a period of 6 hours or more is generally preferred over bolus therapy, based on data from multiple studies[54,55].

Definition and Early Detection of Cardiotoxicity

Cardiac Imaging

Cardiac imaging has a key role in the preliminary evaluation and early detection of LV dysfunction. The imaging methods approved are echocardiography, nuclear imaging and cardiac magnetic resonance[8]. The choice of the diagnostic method depends on the local availability and expertise, but echocardiography remains the preferred one for its wide diffusion, lack of radiation and less time and source consuming, even if its main limitation is the reproducibility and inter-observer variability. In the last decades several definitions of cardiotoxicity have been used due to the lack of strong evidence and the absence of guidelines to guide clinical trials and clinical practice[56]. That is why a group of experts from the American Society of Echocardiography and the European Association of Cardiovascular Imaging[57] published a Consensus paper to make light on this topic. In particular, cardiotoxicity was defined as a decrease in the left ventricular ejection function (LVEF) (measured with the two-dimensional biplane Simpson method) of > 10% from baseline to a value below the lower limit of normal[58]. Unfortunately, a significant decrease in LVEF is often recognized too late and a delayed diagnosis is correlated with poor clinical outcome. Thus, in the last years there has been interest in finding other echocardiographic parameters, which may be used in detecting subclinical myocardial dysfunction preceding a drop in LVEF. Several studies have suggested the importance of global systolic longitudinal myocardial strain (GLS) in the prediction of a LV dysfunction[59-61]. In the work of Sawaya et al[62], early GLS decrease was predictive of the later development of cardiotoxicity, meant as a significant LVEF reduction. In a prospective study conducted by Fallah-Rad et al[63] in patients with breast cancer receiving trastuzumab, a decrease in GLS but not in LVEF was observed as early as 3 months in patients who later developed cardiotoxicity. Although these findings suggest GLS as useful parameter that could detect early sign of cardiotoxicity, it should be used with caution in patient with comorbidities such as valvular disease, infiltrative disease, LV hypertrophy, and myocardial infarction, conditions which can impact LV strain[64-66]. With all these limitations, at the moment, GLS is considered to be the gold standard to detect early LV dysfunction in patients treated with cardiotoxic chemotherapy; a relative percentage reduction of GLS of 15% from baseline is considered abnormal and a marker of early LV subclinical dysfunction[67]. Evidence of diastolic dysfunction is also described in cancer patients treated with cardiotoxic chemotherapy. In recent study conducted in childhood leukemia survivors treated with anthracyclines, a decreased E/A ratio and an increase in E/e' ratio was observed. Despite these findings, at the moment there is yet no strong evidence of correlation between diastolic dysfunction and future reduction in LVEF[68].

Biomarkers

Several cardiac biomarkers have been studied to help physicians to early detect and stratify patients who could develop cardiotoxicity[62,69]. In the prospective study of Cardinale et al[70], 251 women treated with trastuzumab underwent measurement of level of troponin I (TNI) before, every 3 month during trastuzumab therapy and

every 6 month afterward. 62% of the patients who developed trastuzumab-induced cardiotoxicity presented an early TNI elevation with TNI elevation as the strongest independent predictor of cardiotoxicity. In addition, 60% of patients presenting cardiotoxicity had LVEF recovered after trastuzumab interrupting with a less number of recovering in TNI elevated patients. This work suggests that TNI could detect early and subclinical cardiotoxicity and predict which patients will not recover.

Moreover, in the study of Ky et al[71], elevation of TNI was associated with a greater risk to develop cardiotoxicity in 78 patients treated with doxorubicin and trastuzumab. In the same study, other biomarkers were tasted [C-reactive protein, N-terminal pro-B-type natriuretic peptide (NT-proBNP), growth differentiation factor-15, placental growth factor, soluble fms-like tyrosine kinase receptor-1, and galectin-3] but no one was demonstrated to have significant correlation with the development of cardiotoxicity.

The use of NT-proBNP to detect HF is widely established and even very low levels can identify high-risk patients and guide therapy. In the context of chemotherapy-induced LV dysfunction NT-proBNP may be useful, but its role in routine surveillance is not established[72].

Finally, Putt et al[73] suggested a possible role of myeloperoxidase (MPO) to predict the risk of cardiotoxicity. In this study, increases in MPO are associated with cardiotoxicity over the entire course of doxorubicin and trastuzumab therapy.

In conclusion, available evidence is still limited and future studies are needed to guide clinicians to determine the optimal biomarker and, moreover, the timing of biomarker measurement.

Surveillance Timing

In the last decades a lack of universal agreement has generated confusion also in the optimal surveillance timing rising different protocol strategies in each cardio-oncology center.

However, in order to identify subclinical myocardial injury, it is common opinion that patients treated with anthracyclines-containing regimens should always be subjected to a further assessment of the LVEF at the end of the chemotherapy[8,74]. Also, when dealing with high risk patients or when using high doses of anthracyclines, a LVEF assessment is recommended after a cumulative dosage of doxorubicin (or equivalent) of 240 mg/m^2 and, after that, every 50 mg/m^2 [75]. Moreover, measurement of TNI should be considered after each cycle of anthracyclines-containing therapy. When the treatment with anthracyclines is followed by trastuzumab, due to the unpredictability of the cardiotoxicity appearance, an echocardiography performance is recommended every 3 months during the trastuzumab therapy; TNI measurement at each trastuzumab cycle is suggested, at least in patients at high risk[8,36,70,75].

Due to the existence of a late cardiotoxicity developing even after several years after the end of cardiotoxic chemotherapy, especially when dealing with high-dose anthracycline-containing regimens or with patients who developed subclinical cardiotoxicity during chemotherapy, a long-term surveillance is recommended[76].

Treatment Strategies and Cancer Therapy Change

Increasing attention towards early detection of LV dysfunction has led to a consequent increasing interest in investigating possible cardioprotective strategies[77]. In the last decades, several studies have been conducted to detect the possible role of conventional congestive HF therapy in the prevention and treatment of LV dysfunction in cancer patients. Cardinale et al[78] suggested that enalapril, an angiotensin-converting-enzyme (ACE) inhibitor, could prevent late cardiotoxicity in patients with elevated TNI after treatment with high-dose chemotherapy. Moreover, several studies suggested a possible protective role of beta-blockers in the prevention of anthracycline-induced cardiotoxicity. Carvedilol has been shown to be an effective antioxidant and an iron chelating which can prevent cardiac damage and reduce the risk of cardiotoxic complication caused by anthracyclines[79-81]. A similar role has been observed when using nebivolol[82] but not in studies using non-selective beta-blocker as propanolol[83].

In the PRADA trial (PRevention of cArdiac Dysfunction during Adjuvant breast cancer therapy)[84] a 2 × 2 factorial, randomized, placebo-controlled, double-blind trial, 130 women with early breast cancer treated with adjuvant anthracycline-containing regimens with or without trastuzumab and radiation were included. The women, all of them without significant cardiovascular comorbidities, were randomly treated with candesartan (an angiotensin receptors blockers), metoprolol, in combination or alone, compared with placebo. After three years of follow-up, in the candesartan groups a significant reduction

in LV dysfunction was observed, compared with placebo, while no protective effect of metoprolol was observed.

In a recent randomized placebo-controlled trial, however, Boekhout et al[85] did not observe a significant reduction in LV dysfunction among patients undergoing trastuzumab therapy preventively treated with candesartan, compared with placebo.

Moreover, Bosch et al[86] in the OVERCOME trial (preventiOn of left Ventricular dysfunction with Enalapril and caRvedilol in patients submitted to intensive ChemOtherapy for the treatment of Malignant hEmopathies) suggested that combined enalapril and carvedilol may have additive protective effect against chemotherapy induced cardiotoxicity compared with placebo.

In addition, data from the MANTICORE study[87], a randomized trial of perindopril in comparison to bisoprolol and placebo in patients treated with adjuvant trastuzumab, show that bisoprolol significantly prevented reduction in LVEF and trastuzumab treatment interruptions when compared with perindopril or placebo. An ongoing trial (NCT01009918) is evaluating the prophylactic role of lisinopril plus carvedilol in preventing trastuzumab cardiotoxicity.

Though the results of these randomized trials are interesting, it is very important to note that all these studies have small samples and few years of follow-up. Moreover, all these trials include women without cardiovascular comorbidities, so more large trials are needed to better understand the optimal cardioprotective strategy. Therefore, on the basis of the most recent evidence, a prophylactic cardioprotective treatment is strongly recommended when patient is at high risk of developing cardiotoxicity (e.g. previous CVD or poorly controlled cardiovascular risk factor) and can be considered when a high-dose anthracycline-containing therapy is needed, even if at low baseline cardiovascular risk.

During surveillance, it is recommended to start a cardioprotective therapy when observing an increase in TNI values or when subclinical LV dysfunction is detected during echocardiogram controls[8].

If developing HF during cardiotoxic chemotherapy, complete HF therapy according to the current guidelines should be started. The patient should be evaluated by a multidisciplinary team where cardiologists and oncologists decide the necessity and the duration of chemotherapy interruption.

When detecting subclinical LV dysfunction during anthracycline therapy, several strategies can be used to minimize the cardiotoxic effect such us reduction in the cumulative dose, use of continuous infusions to decrease peak plasma levels, withdraw the use of anthracyclines and replace them with analogues or liposomal formulations or, when there is evidence of equal efficacy, start a non-anthracycline regimen[88-91]. Anthracyclines should be stopped when developing HF[8].

If cardiotoxicity develops during trastuzumab treatment, the National Cancer Research Institute[92] recommends to use the following algorithm: if LVEF > 50% trastuzumab can be continued; if LVEF decreases < 10% from baseline to a value between 49% and 45%, trastuzumab may be continued but an ACE inhibitor should be initiated; if LVEF decreases > 10% from baseline to a value between 49% and 45% or < 44%, trastuzumab should be interrupted and ACE inhibitors should be started. In case of trastuzumab interruption, a further assessment of LVEF should be performed after 3 weeks and if restored to normal values or between 49 and 45% with a drop <10% from baseline trastuzumab treatment can be restarted.

At the end of the cardiotoxic treatment, cardioprotective therapy interruption can be considered after normalization of LVEF[93].

Conclusions

The increase in number of long-surviving cancer patients and the appearance of the side effects of chemotherapies have raised new and important challenges for physicians. Early detection and correct management of cardiotoxicity are nowadays-critical issues for cardiologists and oncologists especially because lots of points still remain unclear and new studies are needed.

An adequate preliminary stratification of cardiotoxicity risk an and early identification and treatment of subclinical cardiac damage may allow oncologists to avoid withdrawal of chemotherapy and cardiologists to improve the patient's prognosis avoiding irreversible cardiovascular dysfunction. A multidisciplinary approach is required and it is always more important the development of cardio-oncology teams.

Conflict of Interest

The Authors declare that they have no conflict of interests.

References

1) Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin 2016; 66: 7-30.
2) Tao Z, Shi A, Lu C, Song T, Zhang Z, Zhao J. Breast cancer: epidemiology and etiology. Cell Biochem Biophys 2015; 72: 333-338.
3) Howlader N, Noone AM, Krapcho M, Miller D, Bishop K, Kosary CL, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). SEER Cancer Statistics Review, 1975-2014, National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2014/, based on November 2016 SEER data submission, posted to the SEER web site, April 2017.
4) Mertens AC, Liu Q, Neglia JP, Wasilewski K, Leisenring W, Armstrong GT, Robison LL, Yasui Y. Cause-specific late mortality among 5-year survivors of childhood cancer: the childhood cancer survivor study. J Natl Cancer Inst 2008; 100: 1368-1379.
5) Patnaik JL, Byers T, Di Guiseppi 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: R64.
6) Shan K, Lincoff AM, Young JB. Anthracycline-induced cardiotoxicity. Ann Intern Med 1996; 125: 47-58.
7) Felker GM, Thompson RE, Hare JM, Hruban RH, Clemetson DE, Howard DL, Baughman KL, Kasper EK. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. N Engl J Med 2000; 342: 1077-1084.
8) Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, Habib G, Lenihan DJ, Lip GY, Lyon AR, Lopez Fernandez T, Mohty D, Piepoli MF, Tamargo J, Torbicki A, Suter TM; Authors/Task Force Members; ESC Committee for Practice Guidelines (CPG). 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). Eur Heart J 2016; 37: 2768-2801.
9) Blum RH, Carter SK. Adriamycin. A new anticancer drug with significant clinical activity. Ann Intern Med 1974; 80: 249-259.
10) Volkova M, Russell R 3rd. Anthracycline cardiotoxicity: prevalence, pathogenesis and treatment. Curr Cardiol Rev 2011; 7: 214-220.
11) Zhang S, Liu X, Bawa-Khalfe T, Lu LS, Lyu YL, Liu LF, Yeh ET. Identification of the molecular basis of doxorubicin-induced cardiotoxicity. Nat Med 2012; 18: 1639-1642.
12) Davies KJ, Doroshow JH. Redox cycling of anthracyclines by cardiac mitochondria. I. Anthracycline radical formation by NADH dehydrogenase. J Biol Chem 1986; 261: 3060-3067.
13) Doroshow JH, Davies KJ. Redox cycling of anthracyclines by cardiac mitochondria. II. Formation of superoxide anion hydrogen peroxide and hydroxyl radical. J Biol Chem 1986; 261: 3068-3074.
14) Kotamraju S, Chitambar CR, Kalivendi SV, Joseph J, Kalyanaraman B. Transferrin receptor-dependent iron uptake is responsible for doxorubicin-mediated apoptosis in endothelial cells role of oxidant-induced iron signaling in apoptosis. J Biol Chem 2002; 277: 17179-17187.
15) Minotti G, Recalcati S, Menna P, Salvatorelli E, Corna G, Cairo G. Doxorubicin cardiotoxicity and the control of iron metabolism: quinone-dependent and independent mechanisms. Methods Enzymol 2004; 378: 340-361.
16) Minotti G, Menna P, Salvatorelli E, Cairo G, Gianni L. Anthracyclines molecular advances and pharmacologic developments in antitumor activity and cardiotoxicity. Pharmacol Rev 2004; 56: 185-229.
17) Cole MP, Chaiswing L, Oberley TD, Edelmann SE, Piascik MT, Lin SM, Kiningham KK, St Clair DK. The protective roles of nitric oxide and superoxide dismutase in adriamycin-induced cardiotoxicity. Cardiovasc Res 2006; 69: 186-197.
18) Vejpongsa P, Yeh ET. Topoisomerase 2β: a promising molecular target for primary prevention of anthracycline-induced cardiotoxicity. Clin Pharmacol Ther 2014; 95: 45-52.
19) Lyu YL, Lin CP, Azarova AM, Cai L, Wang JC, Liu LF. Role of topoisomerase IIbeta in the expression of developmentally regulated genes. Mol Cell Biol 2006; 26: 7929-7941.
20) Lyu YL, Kerrigan JE, Lin CP, Azarova AM, Tsai YC, Ban Y, Liu LF. Topoisomerase IIbeta mediated DNA double-strand breaks: implications in doxorubicin cardiotoxicity and prevention by dexrazoxane. Cancer Res 2007; 67: 8839-8846.
21) Capranico G, Tinelli S, Austin CA, Fisher ML, Zunino F. Different patterns of gene expression of topoisomerase II isoforms in differentiated tissues during murine development. Biochim Biophys Acta 1992; 1132: 43-48.
22) Swain SM, Whaley FS, Ewer MS. Congestive heart failure in patients treated with doxorubicin: a retrospective analysis of three trials. Cancer 2003; 97: 2869-2879.
23) Von Hoff DD, Layard MW, Basa P, Davis HL Jr, Von Hoff AL, Rozencweig M, Muggia FM. Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med 1979; 91: 710-717.
24) Pein F, Sakiroglu O, Dahan M, Lebidois J, Merlet P, Shamsaldin A, Villain E, de Vathaire F, Sidi D, Hartmann O. 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: 37-44.
25) Bloom MW, Hamo CE, Cardinale D, Ky B, Nohria A, Baer L, Skopicki H, Lenihan DJ, Gheorghiade M, Lyon AR, Butler J. Cancer therapy-related cardiac

dysfunction and heart failure: part 1: definitions, pathophysiology, risk factors, and imaging. Circ Heart Fail 2016; 9: e002661.

26) Bristow MR, Thompson PD, Martin RP, Mason JW, Billingham ME, Harrison DC. Early anthracycline cardiotoxicity. Am J Med 1978; 65: 823-832.

27) Buzdar AU, Marcus C, Smith TL, Blumenschein GR. Early and delayed clinical cardiotoxicity of doxorubicin. Cancer 1985; 55: 2761-2765.

28) Cardinale D, Colombo A, Bacchiani G, Tedeschi I, Meroni CA, Veglia F, Civelli M, Lamantia G, Colombo N, Curigliano G, Fiorentini C, Cipolla CM. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation 2015; 131: 1981-1988.

29) Abu-Khalaf MM1, Juneja V, Chung GG, DiGiovanna MP, Sipples R, McGurk M, Zelterman D, Haffty B, Reiss M, Wackers FJ, Lee FA, Burtness BA. Long-term assessment of cardiac function after dose-dense and -intense sequential doxorubicin (A) paclitaxel (T) and cyclophosphamide (C) as adjuvant therapy for high-risk breast cancer. Breast Cancer Res Treat 2007; 104: 341-349.

30) Steinherz LJ, Steinherz PG, Tan CT, Heller G, Murphy ML. Cardiac toxicity 4 to 20 years after completing anthracycline therapy. JAMA 1991; 266: 1672-1677.

31) Slamon DJ, Godolphin W, Jones LA, Holt, JA, Wong SG, Keith DE, Levin WJ, Stuart SG, Udove J, Ullrich A. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. Science 1989; 244: 707-712.

32) Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, Fleming T, Eiermann W, Wolter J, Pegram M, Baselga J, Norton L. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001; 344: 783-792.

33) Pritchard KI, Shepherd LE, O'Malley FP, Andrulis IL, Tu D, Bramwell VH, Levine MN; National Cancer Institute of Canada Clinical Trials Group. HER2 and responsiveness of breast cancer to adjuvant chemotherapy. N Engl J Med 2006; 354: 2103-2111.

34) Goldenberg MM. Trastuzumab, a recombinant DNA-derived humanized monoclonal antibody, a novel agent for the treatment of metastatic breast cancer. Clin Ther 1999; 21: 309-318.

35) Piccart-Gebhart MJ, Procter M, Leyland-Jones B, Goldhirsch A, Untch M, Smith I, Gianni L, Baselga J, Bell R, Jackisch C, Cameron D, Dowsett M, Barrios CH, Steger G, Huang CS, Andersson M, Inbar M, Lichinitser M, Láng I, Nitz U, Iwata H, Thomssen C, Lohrisch C, Suter TM, Rüschoff J, Suto T, Greatorex V, Ward C, Straehle C, McFadden E, Dolci MS, Gelber RD; Herceptin Adjuvant (HERA) Trial Study Team. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. N Engl J Med 2005; 353: 1659-1672.

36) Pondé NF, Lambertini M, de Azambuja E. Twenty years of anti-HER2 therapy-associated cardiotoxicity. ESMO Open 2016; 1: e000073.

37) Kuramochi Y, Guo X, Sawyer DB. Neuregulin activates erbB2-dependent src/FAK signaling and cytoskeletal remodeling in isolated adult rat cardiac myocytes. J Mol Cell Cardiol 2006; 41: 228-235.

38) El Zarrad MK, Mukhopadhyay P, Mohan N, Hao E, Dokmanovic M, Hirsch DS, Shen Y, Pacher P, Wu WJ. Trastuzumab alters the expression of genes essential for cardiac function and induces ultrastructural changes of cardiomyocytes in mice. PLoS One 2013; 8: e79543.

39) Nakagami H, Takemoto M, Liao JK. NADPH oxidase-derived superoxide anion mediates angiotensin II-induced cardiac hypertrophy. J Mol Cell Cardiol 2003; 35: 851-859.

40) Grazette LP, Boecker W, Matsui T, Semigran M, Force TL, Hajjar RJ, Rosenzweig A. Inhibition of ErbB2 causes mitochondrial dysfunction in cardiomyocytes: implications for herceptin-induced cardiomyopathy. J Am Coll Cardiol 2004; 44: 2231-2238.

41) Guglin M, Cutro R, Mishkin JD. Trastuzumab-induced cardiomyopathy. J Card Fail 2008; 14: 437-444.

42) Ewer MS, Ewer SM. Cardiotoxicity of anticancer treatments: what the cardiologist needs to know. Nat Rev Cardiol 2010; 7: 564-575.

43) Marty M. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. J Clin Oncol 2005; 23: 4265-4274.

44) Mantarro S, Rossi M, Bonifazi M, D'Amico R, Blandizzi C, La Vecchia C, Negri E, Moja L. 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: 123-140.

45) Yu AF, Yadav NU, Lung BY, Eaton AA, Thaler HT, Hudis CA, Dang CT, Steingart RM. Trastuzumab interruption and treatment-induced cardiotoxicity in early HER2-positive breast cancer. Breast Cancer Res Treat 2015; 149: 489-495.

46) Suter TM, Procter M, van Veldhuisen DJ, Muscholl M, Bergh J, Carlomagno C, Perren T, Passalacqua R, Bighin C, Klijn JG, Ageev FT, Hitre E, Groetz J, Iwata H, Knap M, Gnant M, Muehlbauer S, Spence A, Gelber RD, Piccart-Gebhart MJ. Trastuzumab associated cardiac adverse effects in the Herceptin adjuvant trial. J Clin Oncol 2007; 25: 3859-3865.

47) 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: 1287-1306.

48) Hershman DL, McBride RB, Eisenberger A, Tsai WY, Grann VR, Jacobson JS. Doxorubicin, cardiac risk factors, and cardiac toxicity in elderly patients with diffuse B-cell non-Hodgkin's lymphoma. J Clin Oncol 2008; 26: 3159-3165.

49) Domercant J, Polin N, Jahangir E. Cardio-Oncology: a focused review of anthracycline-, Human Epidermal Growth Factor Receptor 2 inhibitor-, and radiation-induced cardiotoxicity and management. Ochsner J 2016; 16: 250-256.

50) Russell SD, Blackwell KL, Lawrence J, Pippen JE Jr, Roe MT, Wood F, Paton V, Holmgren E, Mahaffey KW. Independent adjudication of symptomatic heart failure with the use of doxorubicin and cyclophosphamide followed by trastuzumab adjuvant therapy: a combined review of cardiac data from the National Surgical Adjuvant Breast and Bowel Project B-31 and the North Central Cancer Treatment Group N9831 clinical trials. J Clin Oncol 2010; 28: 3416-3421.

51) Bowles EJ, Wellman R, Feigelson HS, Onitilo AA, Freedman AN, Delate T, Allen LA, Nekhlyudov L, Goddard KA, Davis RL, Habel LA, Yood MU, McCarty C, Magid DJ, Wagner EH; Pharmacovigilance Study Team. Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment: a retrospective cohort study. J Natl Cancer Inst 2012; 104: 1293-1305.

52) Ewer SM, Ewer MS. Cardiotoxicity profile of trastuzumab. Drug Saf 2008; 31: 459-467.

53) Rushton M, Johnson C, Dent S. Trastuzumab-induced cardiotoxicity: testing a clinical risk score in a real-world cardio-oncology population. Curr Oncol 2017; 24: 176-180.

54) Casper ES, Gaynor JJ, Hajdu SI, Magill GB, Tan C, Friedrich C, Brennan MF. A prospective randomized trial of adjuvant chemotherapy with bolus versus continuous infusion of doxorubicin in patients with high-grade extremity soft tissue sarcoma and an analysis of prognostic factors. Cancer 1991; 68: 1221-1229.

55) van Dalen EC, van der Pal HJ, Caron HN, Kremer LC. Different dosage schedules for reducing cardiotoxicity in cancer patients receiving anthracycline chemotherapy. Cochrane Database Syst Rev 2009; CD005008.

56) Khouri MG, Douglas PS, Mackey JR, Martin M, Scott JM, Scherrer-Crosbie M, Jones LW. Cancer therapy-induced cardiac toxicity in early breast cancer: addressing the unresolved issues. Circulation 2012; 126: 2749-2763.

57) Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, Ganame J, Sebag IA, Agler DA, Badano LP, Banchs J, Cardinale D, Carver J, Cerqueira M, DeCara JM, Edvardsen T, Flamm SD, Force T, Griffin BP, Jerusalem G, Liu JE, Magalhaes A, Marwick T, Sanchez LY, Sicari R, Villarraga HR, Lancellotti P. 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. Eur Heart J Cardiovasc Imaging 2014; 15: 1063-1093.

58) Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, Flachskampf FA, Foster E, Goldstein SA, Kuznetsova T, Lancellotti P, Muraru D, Picard MH, Rietzschel ER, Rudski L, Spencer KT, TsangW, Voigt JU. 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: 1-39.e14.

59) Mavinkurve-Groothuis AM, Groot-Loonen J, Marcus KA, Bellersen L, Feuth T, Bökkerink JP, Hoogerbrugge PM, de Korte C, Kapusta L. Myocardial strain and strain rate in monitoring subclinical heart failure in asymptomatic long-term survivors of childhood cancer. Ultrasound Med Biol 2010; 36: 1783-1791.

60) Karakurt C, Kocak G, Ozgen U. Evaluation of the left ventricular function with tissue tracking and tissue doppler echocardiography in pediatric malignancy survivors after anthracycline therapy. Echocardiography 2008; 25: 880-887.

61) Jiji RS, Kramer CM, Salerno M. Non-invasive imaging and monitoring cardiotoxicity of cancer therapeutic drugs. J Nucl Cardiol 2012; 19: 377-388.

62) Sawaya H, Sebag IA, Plana JC, Januzzi JL, Ky B, Cohen V, Gosavi S, Carver JR, Wiegers SE, Martin RP, Picard MH, Gerszten RE, Halpern EF, Passeri J, Kuter I, Scherrer-Crosbie M. Early detection and prediction of cardiotoxicity in chemotherapy-treated patients. Am J Cardiol 2011; 107: 1375-1380.

63) Fallah-Rad N, Walker JR, Wassef A, Lytwyn M, Bohonis S, Fang T, Tian G, Kirkpatrick ID, Singal PK, Krahn M, Grenier D, Jassal DS. The utility of cardiac biomarkers, tissue velocity and strain imaging, and cardiac magnetic resonance imaging in predicting early left ventricular dysfunction in patients with human epidermal growth factor receptor II-positive breast cancer treated with adjuvant traztuzumab therapy. J Am Coll Cardiol 2011; 57: 2263-2270.

64) Miyazaki S, Daimon M, Miyazaki T, Onishi Y, Koiso Y, Nishizaki Y, Ichikawa R, Chiang SJ, Makinae H, Suzuki H, Daida H. Global longitudinal strain in relation to the severity of aortic stenosis: a two-dimensional speckle tracking study. Echocardiography 2011; 28: 703-708.

65) Sun JP, Stewart WJ, Yang XS, Donnell RO, Leon AR, Felner JM, Thomas JD, Merlino JD. Differentiation of hypertrophic cardiomyopathy and cardiac amyloidosis by two-dimensional strain imaging echocardiography. Am J Cardiol 2009; 103: 411-415.

66) Takamura T, Dohi K, Onishi K, Tanabe M, Sugiura E, Nakajima H, Ichikawa K, Nakamura M, Nobori T, Ito M. Left ventricular contraction-relaxation coupling in normal, hypertrophic, and failing myocardium quantified by speckle-tracking global strain and strain rate imaging. J Am Soc Echocardiogr 2010; 23: 747-754.

67) Voigt JU, Pedrizzetti G, Lysyansky P, Marwick TH, Houle H, Baumann R, Pedri S, Ito Y, Abe Y, Metz S, Song JH, Hamilton J, Sengupta PP, Kolias TJ, d'Hooge J, Aurigemma GP, Thomas JD, Badano LP. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document

of the EACVI/ASE/Industry Task Force to standardize deformation imaging. Eur Heart J Cardiovasc Imaging 2015; 16: 1-11.

68) Dorup I, Levitt G, Sullivan I, Sorensen K. Prospective longitudinal assessment of late anthracycline cardiotoxicity after childhood cancer: the role of diastolic function. Heart 2004; 90: 1214-1216.

69) Thakur A, Witteles RM. Cancer therapy-induced left ventricular dysfunction: interventions and prognosis. J Card Fail 2014; 20: 155-158.

70) Cardinale D, Colombo A, Torrisi R, Sandri MT, Civelli M, Salvatici M, Lamantia G, Colombo N, Cortinovis S, Dessanai MA, Nolè F, Veglia F, Cipolla CM. Trastuzumab-induced cardiotoxicity: clinical and prognostic implications of troponin I evaluation. J Clin Oncol 2010; 28: 3910-3916.

71) Ky B, Putt M, Sawaya H, French B, Januzzi JL Jr, Sebag IA, Plana JC, Cohen V, Banchs J, Carver JR, Wiegers SE, Martin RP, Picard MH, Gerszten RE, Halpern EF, Passeri J, Kuter I, Scherrer-Crosbie M. Early increases in multiple biomarkers predict subsequent cardiotoxicity in patients with breast cancer treated with doxorubicin, taxanes, and trastuzumab. J Am Coll Cardiol 2014; 63: 809-816.

72) Ledwidge M, Gallagher J, Conlon C, Tallon E, O'Connell E, Dawkins I, Watson C, O'Hanlon R, Bermingham M, Patle A, Badabhagni MR, Murtagh G, Voon V, Tilson L, Barry M, McDonald L, Maurer B, McDonald K. Natriuretic peptide-based screening and collaborative care for heart failure: the STOP-HF randomized trial. JAMA 2013; 310: 66-74.

73) Putt M, Hahn VS, Januzzi JL, Sawaya H, Sebag IA, Plana JC, Picard MH, Carver JR, Halpern EF, Kuter I, Passeri J, Cohen V, Banchs J, Martin RP, Gerszten RE, Scherrer-Crosbie M, Ky B. Longitudinal changes in multiple biomarkers are associated with cardiotoxicity in breast cancer patients treated with doxorubicin, taxanes, and trastuzumab. Clin Chem 2015; 61: 1164-1172.

74) Drafts BC, Twomley KM, D'Agostino R Jr, Lawrence J, Avis N, Ellis LR, Thohan V, Jordan J, Melin SA, Torti FM, Little WC, Hamilton CA, Hundley WG. Low to moderate dose anthracycline-based chemotherapy is associated with early non invasive imaging evidence of subclinical cardiovascular disease. JACC Cardiovasc Imaging 2013; 6: 877-885.

75) Hamo CE, Bloom MW, Cardinale D, Ky B, Nohria A, Baer L, Skopicki H, Lenihan DJ, Gheorghiade M, Lyon AR, Butler J. Cancer therapy-related cardiac dysfunction and heart failure: part 2: prevention, treatment, guidelines, and future directions. Circ Heart Fail 2016; 9: e002843.

76) Conway A, McCarthy AL, Lawrence P, Clark RA. The prevention, detection and management of cancer treatment-induced cardiotoxicity: a meta-review. BMC Cancer 2015; 15: 366.

77) Seicean S, Seicean A, Alan N, Plana JC, Budd GT, Marwick TH. Cardioprotective effect of β-adrenoceptor blockade in patients with breast cancer undergoing chemotherapy: follow-up study of heart failure. Circ Heart Fail 2013; 6: 420-426.

78) Cardinale D, Colombo A, Sandri MT, Lamantia G, Colombo N, Civelli M, Martinelli G, Veglia F, Fiorentini C, Cipolla CM. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. Circulation 2006; 114: 2474-2481.

79) Oliveira PJ, Bjork JA, Santos MS, Leino RL, Froberg MK, Moreno AJ, Wallace KB. Carvedilol-mediated antioxidant protection against doxorubicin-induced cardiac mitochondrial toxicity. Toxicol Appl Pharmacol 2004; 200: 159-168.

80) Elitok A, Oz F, Cizgici AY, Kilic L, Ciftci R, Sen F, Bugra Z, Mercanoglu F, Oncul A, Oflaz H. Effect of carvedilol on silent anthracycline-induced cardiotoxicity assessed by strain imaging: a prospective randomized controlled study with six-month follow-up. Cardiol J 2014; 21: 509-515.

81) Kalay N, Basar E, Ozdogru I, Er O, Cetinkaya Y, Dogan A, Inanc T, Oguzhan A, Eryol NK, Topsakal R, Ergin A. Protective effects of carvedilol against anthracycline-induced cardiomyopathy. J Am Coll Cardiol 2006; 48: 2258-2262.

82) Kaya MG, Ozkan M, Gunebakmaz O, Akkaya H, Kaya EG, Akpek M, Kalay N, Dikilitas M, Yarlioglues M, Karaca H, Berk V, Ardic I, Ergin A, Lam YY. Protective effects of nebivolol against anthracycline-induced cardiomyopathy: a randomized control study. Int J Cardiol 2013; 167: 2306-2310.

83) Choe JY, Combs AB, Folkers K. Potentiation of the toxicity of adriamycin by propranolol. Res Commun Chem Pathol Pharmacol 1978; 21: 577-580.

84) Gulati G, Heck SL, Ree AH, Hoffmann P, Schulz-Menger J, Fagerland MW, Gravdehaug B, von Knobelsdorff-Brenkenhoff F, Bratland A, Storas TH, Hagve TA, Rosjo H, Steine K, Geisler J, Omland T. Prevention of cardiac dysfunction during adjuvant breast cancer therapy (PRADA): a 2 × 2 factorial, randomized, placebo-controlled, double-blind clinical trial of candesartan and metoprolol. Eur Heart J 2016; 37: 1671-1680.

85) Boekhout AH, Gietema JA, Milojkovic Kerklaan B, van Werkhoven ED, Altena R, Honkoop A, Los M, Smit WM, Nieboer P, Smorenburg CH, Mandigers CM, van der Wouw AJ, Kessels L, van der Velden AW, Ottevanger PB, Smilde T, de Boer J, van Veldhuisen DJ, Kema IP, de Vries EG, Schellens JH. Angiotensin II-Receptor inhibition with candesartan to prevent trastuzumab-related cardiotoxic effects in patients with early breast cancer: a randomized clinical trial. JAMA Oncol 2016; 2: 1030-1037.

86) Bosch X, Rovira M, Sitges M, Domènech A, Ortiz-Pérez JT, de Caralt TM, Morales-Ruiz M, Perea RJ, Monzó M, Esteve J. Enalapril and carvedilol for preventing chemotherapy-induced left ventricular systolic dysfunction in patients with malignant hemopathies: the OVERCOME trial (preventiOn of left Ventricular dysfunction with Enalapril and caRvedilol in patients submitted to in-

tensive ChemOtherapy for the treatment of Malignant hEmopathies). J Am Coll Cardiol 2013; 61: 2355-2362.

87) Pituskin E, Mackey JR, Koshman S, Jassal D, Pitz M, Haykowsky MJ, Pagano JJ, Chow K, Thompson RB, Vos LJ, Ghosh S, Oudit GY, Ezekowitz JA, Paterson DI. Multidisciplinary Approach to Novel Therapies in Cardio-Oncology Research (MANTICORE 101-Breast): a randomized trial for the prevention of trastuzumab-associated cardiotoxicity. J Clin Oncol 2017; 35: 870-877.

88) Boyle EM, Morschhauser F. Pixantrone: a novel anthracycline-like drug for the treatment of non-Hodgkin lymphoma. Expert Opin Drug Saf 2015; 14: 601-607.

89) Safra T, Muggia F, Jeffers S, Tsao-Wei DD, Groshen S, Lyass O, Henderson R, Berry G, Gabizon A. Pegylated liposomal doxorubicin (Doxil): reduced clinical cardiotoxicity in patients reaching or exceeding cumulative doses of 500 mg/m2. Ann Oncol 2000; 11: 1029-1033.

90) Rafiyath SM, Rasul M, Lee B, Wei G, Lamba G, Liu D. Comparison of safety and toxicity of liposomal doxorubicin vs. conventional anthracyclines: a meta-analysis. Exp Hematol Oncol 2012; 1: 10.

91) Sparano JA, Makhson AN, Semiglazov VF, Tjulandin SA, Balashova OI, Bondarenko IN, Bogdanova NV, Manikhas GM, Oliynychenko GP, Chatikhine VA, Zhuang SH, Xiu L, Yuan Z, Rackoff WR. Pegylated liposomal doxorubicin plus docetaxel significantly improves time to progression without additive cardiotoxicity compared with docetaxel monotherapy in patients with advanced breast cancer previously treated with neoadjuvant-adjuvant anthracycline therapy: results from a randomized phase III study. J Clin Oncol 2009; 27: 4522-4529.

92) Jones AL, Barlow M, Barrett-Lee PJ, Canney PA, Gilmour IM, Robb SD, Plummer CJ, Wardley AM, Verrill MW. Management of cardiac health in trastuzumab-treated patients with breast cancer: updated United Kingdom National Cancer Research Institute recommendations for monitoring. Br J Cancer 2009; 100: 684-692.

93) Ewer MS, Ewer SM. Cardiotoxicity of anticancer treatments. Nat Rev Cardiol 2015; 12: 620.