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.

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 worldwide1,2. 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 20133. 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 survivors4 and the first cause of death among female survivors from breast cancer5. 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

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), neoregulin-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).
clinical presentation of cardiotoxicity is a dilata-
tion-hypokinetic cardiomyopathy leading to heart
failure. 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 dis-
 ease.

That is why the need to create an integrative
approach has arisen where oncologists and car-
diologists 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, sug-
 suggesting the better management of these patients.

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 che-
motherapy 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. The mechanism
of anthracycline-induced cardiac injury has been
extensively studied and it has not yet been fully
understood.

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-depen-
dent chemical reactions. ROS lead to the peroxi-
dation of myocyte membranes and calcium influx
into the intracellular space, which can ultimately
lead to permanent myocyte damage. In addition,
other mechanisms have been identified, includ-
ing disturbances in topoisomerase function.
Topoisomerase is an enzyme involved in DNA
transcription and replication. There are two iso-
zymes of topoisomerase, topoisomerase 2-alpha
(Top 2-α), overexpressed in rapidly proliferating
cells such as tumor cells, and topoisomerase 2-be-
ta (Top 2-β), expressed in all quiescent cells.
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.

The risk of anthracyclines-induced cardiotoxi-
city is dose-dependent and increases with cu-
mulative dose. For example, doxorubicin is
associated with an incidence of congestive HF
from 3% to 5% with a cumulative dose of 400
mg/m², from 7% to 26% at 550 mg/m², and from
18% to 48% at 700 mg/m².

Moreover, Pein et al 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/
m² compared to patients treated with lower doses
of anthracyclines, confirming a strong associa-
tion 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 usu-
ally within one or two weeks after the treatment
and it is generally characterized by non-specific
electrocardiographic abnormalities such as re-
duction of QRS voltages, QT prolongation and
supraventricular arrhythmias. Early cardio-
toxicity, 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. 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 che-
motherapy, representing a more relevant clini-
cal and prognostic significance, evolving into a
cardiomyopathy and hesitating with heart failure
generally less sensitive to treatment, rarely in
ischemic heart disease.

**Trastuzumab**

Trastuzumab is a monoclonal antibody that
binds to the extracellular domain of the hu-
man 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.
HER2+ tumor cells have a highly proliferative
phenotype, with an increased capacity to dis-
seminate and stimulate angiogenesis.
Anthracycline and trastuzumab-induced cardiotoxicity in breast cancer

Tumor 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. That is why inhibition of HER2 signaling has improved outcomes of patients with HER2+ breast cancer when used in conjunction with conventional chemotherapies. 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). Available research suggests that trastuzumab blocks neureguline-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. 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.

Finally, trastuzumab leads to the down-regulation of the antiapoptotic protein BCL-XL and to the up-regulation of the proapoptotic protein BCL-XS. 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 cardiotoxicity) through the interference with homeostatic mechanisms and pathways of cell survival and repair.

In the phase 3 trial conducted by Slamon et al., 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.

In a 2016 meta-analysis conducted by Mantarro et al. 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.

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.

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.

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/m²), previous LV dysfunction, arterial hypertension and previous radiation therapy.

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\textsuperscript{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\textsuperscript{6}. 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\textsuperscript{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\textsuperscript{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\textsuperscript{6}. 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\textsuperscript{6}. That is why a group of experts from the American Society of Echocardiography and the European Association of Cardiovascular Imaging\textsuperscript{57} published a Consen-
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\textsuperscript{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\textsuperscript{72}.

Finally, Putt et al\textsuperscript{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 be subjected to a further assessment of the LVEF at the end of the chemotherapy\textsuperscript{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\textsuperscript{2} and, after that, every 50 mg/m\textsuperscript{2} \textsuperscript{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\textsuperscript{3,36,70,75}.

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\textsuperscript{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\textsuperscript{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\textsuperscript{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\textsuperscript{79-81}. A similar role has been observed when using nebivolol\textsuperscript{82} but not in studies using non-selective beta-blocker as propanolol\textsuperscript{83}.

In the PRADA trial (PRevention of cArdiac Dysfunction during Adjuvant breast cancer therapy)\textsuperscript{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\(^\text{85}\) 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\(^\text{86}\) in the OVERCOME trial (preventing 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\(^\text{87}\), 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\(^\text{8}\).

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\(^\text{88-91}\). Anthracyclines should be stopped when developing HF\(^\text{8}\).

If cardiotoxicity develops during trastuzumab treatment, the National Cancer Research Institute\(^\text{92}\) 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, cardio-protective therapy interruption can be considered after normalization of LVEF\(^\text{93}\).

**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 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.
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