THE IMPORTANCE OF MULTIDISCIPLINARY CARDIO-ONCOLOGY TEAM IN THE BREAST CANCER TREATMENT WITH ANTHRACYCLINES

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Abstract

The anthracyclines, represented by Doxorubicin, Epirubicin or Idarubicin, are paramount in Oncology due to their antitumoral efficacy in a multitude of solid cancers, making them essential in breast cancer treatment. The biggest disadvantage of anthracyclines, cardiotoxicity, happens as a direct effect of the oncologic treatment on the anatomy and the physiology of the heart and acts also as an element which advances pre-existent cardiovascular disease⁽²⁾.

We are presenting the case of a 51-year-old lady, clinically, with imagistic and biopsy diagnosis of breast cancer cT3N3M0, negative HR, HER 2neu-3+, that was treated with neoadjuvant chemotherapy consisting of anthracyclines and biological therapy with Herceptin (Trastuzumab – monoclonal humanized IgG1 antibodies, administered in HER2 + breast cancer).

By cumulating the current clinical data with the therapeutic challenges of the anthracyclines (antitumoral effect vs cardiotoxicity), we are trying to encourage the multidisciplinary approach (oncology and cardiology), in order to reach the best therapeutic decision for each patient.

Keywords: anthracyclines, Doxorubicin, Trastuzumab, cardiotoxicity, anti-HER2

Rezumat

Antraciclinele, reprezentate de Doxorubicină, Epirubicină sau Idarubicină ocupă un loc important în arsenalul terapeutic oncologic prin eficacitatea antitumorală în cadrul mai multor cancere solide, devenind unul dintre pilonii terapeutici principali în tratamentul neoplasmului mamar. Cardiotoxicitatea, marele dezavantaj al antraciclinelor se manifestă ca efect direct al terapiei oncologice asupra funcției și structurii cardiace, dar și ca element care accelerează dezvoltarea bolilor cardiovasculare deja existente, în special în prezența factorilor de risc tradiționali⁽²⁾.

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Prezentăm cazul unei paciente de 51 de ani care a fost diagnosticată clinic, imagistic și biptic cu neoplasm mamar cT3N3M0, receptori hormonali negativi, HER 2neu-3+, pentru care a urmat chimioterapie (CHT) neoadjuvantă cu antracicline și terapie biologică cu Herceptin (Trastuzumab, anticorp monoclonal umanizat IgG1 administrat în cancerul mamar HER2 pozitiv).

Cumulând datele clinice cunoscute la momentul actual cu provocările terapeutice impuse de antracicline (beneficiu antitumoral vs. cardiotoxicitate) avem ca scop demon-strarea importanței echipei multidisciplinare de cardio-oncologie în luare deciziilor terapeutice.

Cuvinte cheie: antracicline, Doxorubicină, Trastuzumab, cardiotoxicitate, anti-HER2.

Background

It is already known that breast cancer receives a multimodal therapy, based on surgery, chemotherapy and radiation therapy, but current research directions are heading towards customized treatments in order to minimize size effects and mental stress in patients⁽⁷⁾.

Cardiotoxicity is included among the side effects of the oncologic therapy arsenal and its spectrum contains myocardial dysfunction and heart failure (HF), arrhythmias, valvulopathies, thromboembolic events, high blood pressure and pulmonary hypertension, or peripheral vascular damage⁽³⁾. Anthracyclines, antitumor agents belonging to antimetabolites class, became indispensable in breast cancer, and their biggest disadvantage is represented by the cardiotoxicity that varies from direct lesions

on the heart's anatomy and physiology (probably irreversible), to a new rapidly evolving cardiovascular pathology, especially in the presence of some cardiovascular risk factors⁽²⁾.

Objectives

The incompletely elucidated pathophysiological mechanism through which anthracyclines cause cardiovascular damage, leads us to suggest that the target objective is demonstrating the importance of the multidisciplinary cardio-oncology team in the management of patients who have received treatment with these drugs. The incidence of left ventricular (LV) dysfunction is correlated with cumulative dose of cytostatic (table 1), so that if at the cumulative dose of 400 mg/m² doxorubicin, the incidence of LV dysfunction is 5%, at the

Chemotherapy agent:	Incidence
ANTHRACYCLINES	
Doxorubicin 400 mg/m ²	3-5%
Doxorubicin 700 mg/m ²	18-48%
Idarubicin >90 mg/m ²	5-18%
Epirubicin >900mg/m ²	0.9-11.4%
MONOCLONAL ANTIBODIES	
Trastuzumab	1.7-20.1%
Pertuzumab	0.7-1.2 %
ALKYLATING AGENTS	
Cyclophosphamide	7-28%
ANTIMICROTUBULE AGENTS	
Docetaxel	2.3-13%
Paclitaxel	<1%

Table 1. The incidence of LV dysfunction correlated with antitumor medication⁽⁶⁾

Figure 1. Left axillary lymph nodes

Figure 2. Expansive mass with irregular shape and discrete contrast medium uptake

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Demographic and lifestyle risk factors	Previous treatment	Personal medical history
<ul style="list-style-type: none"> • Age (pediatric patients <18 years; >50 years for anti-HER2 therapies; >65 years for anthracyclines) • Family medical history of cardiovascular disorders with onset at a young age (under 50 years old) • Smoking • Increased alcohol intake • Obesity 	<ul style="list-style-type: none"> • Concomitant or previous radiotherapy involving the heart • Concomitant chemotherapy with anthracyclines • Treatment with anti-HER2 therapies • Short period between anthracyclines treatment and anti-HER2 therapy 	<ul style="list-style-type: none"> • Previous cardiovascular disorder • Essential high blood pressure • Diabetes mellitus • Hypercholesterolaemia

Table 2. Risk factors associated with anthracyclines-induced cardiotoxicity⁽⁹⁾

cumulative dose of 700 mg/m², the incidence of LV dysfunction is between 18-48%⁽⁶⁾. Characterized by a progressive decline of the left ventricular ejection fraction (LVEF), cardiotoxicity is divided into acute, early-onset or late-onset toxicity. Acute cardiotoxicity may occur shortly after finishing chemotherapy (several weeks) and it is not dose-dependent, being represented by ventricular dysfunction with or without clinical manifestations for acute heart failure, electrocardiographic changes, arrhythmias or conduction disorders. Early-onset chronic

cardiotoxicity takes the shape of a dose-dependent toxic cardio-myopathy, often with onset in the first years of treatment, evolving into global cardiac decompensation. Late-onset cardiotoxicity manifestations can occur after ten years or more after finishing chemotherapy, many patients being often asymptomatic⁽⁶⁾.

Case presentation

51-year-old female patient, coming from rural area, without personal medical history, was

clinically diagnosed in August 2019 (hard, irregular and painless mass in the upper quadrant of the right breast with a size of about 7 cm), imagistic (mammography and breast ultrasound) and with biopsy diagnosis of breast cancer stage IIIC (cT3N3M0). Immunohistochemistry showed absent hormonal receptors and Her 2neu-3+. It is decided to initiate neoadjuvant chemotherapy with four cycles with cyclophosphamide and anthracyclines - Epirubicin (dose of 90 mg/m²), followed by four cycles with taxanes.

The cardiological evaluation before starting chemotherapy with anthracyclines shows an ECG with normal morphology, a blood pressure value of 125/80 mm Hg, and heart ultrasound shows normal contractions of the LV walls, normal-sized heart cavities, no pericardial effusion and no thrombi in the heart chambers and a LVEF of 73%. Due to the increased cardiovascular risk of anthracyclines, cardiological evaluation is required before and after finishing treatment, heart ultrasound after the last cycle with Epirubicin identifies a LVEF of 65%, 8% lower than the initial examination.

Surgery is performed and a radical mastectomy is made, followed by starting the biological therapy with Trastuzumab, a humanized IgG1 monoclonal antibody administered in HER2-positive breast cancer, with a dose of 6 mg/kg every 21 days, for one year. The patient undergoes adjuvant radiotherapy, an additional risk factor for the occurrence of cardiovascular events with the history of anthracyclines treatment. According to guideline recommendations, in the case of administering anthracyclines and anti-HER2 medication, cardiological evaluations were performed every three months (10), heart ultrasound after three months showed a LVEF of 63%. The following

cardiological evaluations showed no changes, heart ultrasound being normal.

One year after finishing the adjuvant treatment, the patient presents into the Oncology Clinic with right supra-clavicular lymphadenopathy and the aspect of local relapse (the right anterior wall above the scar with edema, tumor infiltrate), and the CT scan shows multiple lymph nodes (ADP) in the left armpit (Figure 1), ADP in the right pulmonary hilum, bilateral ADP in the latero-cervical region, hypoechoic node located in the adipose tissue of the left lateral thoracic wall (Figure 2). Core needle biopsy of the left axillary ADP is required to certify the diagnosis of metastasis of an invasive breast carcinoma of no special type (NST).

In the context of a progressive disease, it is decided to initiate palliative chemotherapy with taxanes and biological therapy with humanized IgG1 monoclonal antibodies: Pertuzumab 420 mg and Trastuzumab 6 mg/kg, every three weeks, recommended in metastatic HER2-positive breast cancer.

The ECG performed during the cardiological evaluation, dictated by the repeated anti-HER2 therapy, is normal, heart ultrasound shows normal-sized heart cavities and a LVEF of 60%.

According to guidelines recommendations, the patient has received regular cardiological evaluations, the first 6 months of treatment had a good clinical tolerance, no serious clinical symptoms, excepting a slight fatigue in average physical activity, sometimes accompanied by sweating or headache.

The next cardiological evaluation indicates normal ECG, blood pressure of 140/70 mm Hg, and heart ultrasound shows a LV without segmental or global kinetic disorders, normal-sized heart cavities, mitral valve surface of 2,6 cm² and LVEF of 55%. Doppler echocardiography shows the presence of

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grade 1 mitral and aortic multiple valvular insufficiency and grade 1 tricuspid regurgitation, uncorrelated with clinical examination. The patient didn't receive cardioprotective therapy, because she was asymptomatic.

Results

Despite the progressive degradation of LVEF, the efficient communication between the cardiologist and the oncologist has allowed to continue the oncologic treatment after the stratification of the individual cardiovascular risk. Summing up the present risk factors associated with anthracyclines-induced cardiotoxicity and anti-Her2 therapy allowed to develop an optimal surveillance strategy, both oncologically and cardiologically.

Discussions

We reported the case of a 51-year-old female patient, diagnosed with stage III C breast cancer, negative hormonal receptors, HER2 positive, for which she underwent neoadjuvant chemotherapy with anthracyclines and taxanes, and she underwent a radical mastectomy surgery, then continued adjuvant treatment with biological therapy with anti-HER2.

The case is particular by a long evolution of breast cancer in a young patient, in which the

evaluation of individual cardiovascular risk factors, as well as the prognosis based on tumor characteristics, allowed the optimization of cancer therapy despite cardiovascular toxicity. By continuing the anti-HER2 therapy and the appropriate chemotherapy, the evolution is favorable, argued both clinically (disappearance of local relapse) and imagistically (regular CT examinations according to guideline recommendations to confirm the absence of secondary lesions).

Anthracyclines have demonstrated the benefit in treating many solid cancers, but the optimal response to their use may be compromised by cardio-toxic side effects, with many patients being initially asymptomatic, with clinical manifestations occurring after a few years after finishing treatment⁽⁹⁾.

The identification of patients with increased risk of cardiotoxicity is performed by analysing the risk factors associated with anthracycline-induced cardiotoxicity, being grouped into demographic factors, lifestyle risk factors, previous administered treatment or the existence of underlying heart disease (table 2)⁽⁹⁾.

According to the recommendations of the present cardio-oncology guidelines, each patient who is suitable for anthracycline medication or anti-HER2 therapy, will be advised before starting the treatment, but

also every three months during the administration, to perform cardiological evaluation.

It consists in electrocardiogram, 2D and 3D echocardiography for LVEF in particular, Doppler echocardiogram and cardiac biomarkers. Heart ultrasound is the election method that allows easy monitoring of cardiac dysfunction caused by antineoplastic therapy, being defined as a progressive decrease in LVEF by more than 10% from baseline, below the lower normal limit. In relation to ACC/AHA/ASE guideline published in 2003, anthracycline-induced cardiotoxicity is defined as a decrease in LVEF below 50%, or the decrease of more than 10 percentage points or more than 20% compared to baseline, or over 5% if the baseline was < 50%⁽¹¹⁾.

Anthracycline-induced cardiotoxicity can be acute, early-onset or late-onset⁽²⁾. Acute cardiotoxicity is usually reversible and may be manifested by electrocardiographic changes such as QT prolongation, supraventricular arrhythmias or transient LV dysfunctions. Late-onset cardiac dysfunction may occur after several years of treatment, taking the form of a cardiac failure, especially in patients over 65 years who have been treated with usual doses of anthracyclines⁽²⁾. Most of the patients, often asymptomatic from the cardiological viewpoint, are underdiagnosed due to the inability to pinpoint whether the cardiac dysfunction is reversible or progressive⁽²⁾.

Various methods have been proposed that have tried to prevent anthracyclines-induced cardiotoxicity, but in the same time maintaining the desired antitumoral efficacy, such as reducing the cumulative dose of drug, the use of non-anthracycline therapeutical agents or liposomal agents⁽⁹⁾.

Estimating the risk of heart damage after

breast radiotherapy is hampered by the long period from exposure to the onset of clinical manifestations of the disease⁽¹⁾.

In the same time, anthracyclines-induced cardiotoxicity depends on the number of cycles performed, the high dose of irradiation (DT > 30-35 Gy), the volume of irradiation, the young age at exposure or previous cardiovascular disorders⁽¹⁾. Expert studies have highlighted the role of adjuvant radiotherapy in breast cancer, with beneficial impact on survival and improvement on patients prognosis, with a decrease in neoplastic mortality, but with the cost of occurring cardiovascular complications⁽³⁾.

Moreover, it has been shown that patients who have performed irradiation on their left breast have a higher risk of coronary events than those irradiated on their right breast, their occurrence being directly proportional with the irradiation dose⁽⁸⁾. The spectrum of radiotherapy-induced cardiovascular damage includes pericardial damage (acute pericarditis during irradiation pericardial effusion with or without tamponade, constrictive pericarditis), myocarditis and post-irradiation endocardial damage, diffuse unspecified interstitial fibrosis that leads to cardiac failure, arrhythmias and conduction disorders or valvular damage⁽³⁾.

In female patients diagnosed with breast cancer that underwent chemotherapy with anthracyclines, the incidence of cardiovascular events after breast irradiation was higher than in women who did not received radiotherapy⁽⁶⁾. The most frequent cardiotoxic effects of the association between radiotherapy and anthracyclines are systolic dysfunction and heart failure. Moreover, radiotherapy associates an additional risk of myocardial infarction occurrence up to 20%, increasing also the incidence of coronary heart disease⁽⁸⁾. In order to identify the

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patients at high risk for coronary heart disease, patient's continuous surveillance is recommended, starting from the first years until finishing irradiation and then continuing the rest of life⁽⁸⁾.

Considering the synergistic cardiotoxic effect of the association between chemotherapy with anthracyclines and breast radiotherapy, reducing the radiation dose, but also decreasing the cardiac volume exposed, become the priorities in preventing cardiovascular complications⁽⁶⁾. Current research directions in the cardio-oncology field highlight modern treatment techniques with promising results in preventing additional cardiotoxic effect for radiotherapy⁽⁶⁾.

These include software systems capable of accurately delineate the boundaries of mass to be irradiated or 3D planning techniques of the treatment plan, but there are neoplasms in which the heart is exposed to irradiation due to its immediate proximity to the target needed to be irradiated, such as left breast cancer or Hodgkin's lymphoma⁽⁵⁾.

Described by overexpression of HER2 oncoprotein, HER2-positive breast cancer differs from other types of breast cancer with its onset at a young age (<55 years), high aggressiveness, negative prognosis, higher lymph nodes invasion rate and incomplete treatment response⁽³⁾.

Introducing anti-HER2 therapies, represented by humanized monoclonal antibodies, such

as trastuzumab (Herceptin) or Pertuzumab, have revolutionized HER2+ breast cancer treatment by improving and prolonging its survival⁽¹⁰⁾. The patients treated with Herceptin have a higher risk of developing cardiac failure or asymptomatic cardiac dysfunction due to structural and functional changes in myocardial cells, being often reversible⁽¹⁰⁾.

There are certain factors associated with the occurrence of cardiovascular events in treatment with Herceptin, such as old age (but also young age), history of heart disease such as high blood pressure or impaired LVEF, previous treatment with anthracyclines or short period between finishing chemotherapy and starting anti-HER2 therapy⁽¹⁰⁾.

Several studies have compared the occurrence of cardiotoxicity in the concomitant administration of anthracyclines and Herceptin therapy, to the administration of Herceptin at 3 months minimum after finishing chemotherapy, with an important decrease in cardiovascular risk in the second situation⁽⁹⁾.

Unlike anthracyclines-induced cardiotoxicity, the cardiotoxic effects of Trastuzumab are not dose-dependent and may occur during treatment. Thereby, through the cumulative cardiotoxicity of these two classes of drugs, it is a priority to understand the importance of the existence of a free time interval between their administration⁽¹⁰⁾. One of the implications of cardiovascular toxicity, with

impact on patient survival by increasing the risk of relapses is the interruption of anti-HER2 therapy, the main reasons being heart failure or asymptomatic decrease of LVEF below 45%⁽⁴⁾. However, clinical experience and continuous surveillance of patients allows restarting the therapy, LV dysfunction and heart failure being reversible in the absence of administration. According to National Cancer Research Institute, if the LVEF decreases <45% or with >10% compared to baseline, Trastuzumab must be interrupted and it can be reinitiated if LVEF is reversible and reaches at least 49%⁽⁴⁾. Depending on the characteristics of each patient, but also the cardiologist's beliefs, the treatment with ACE inhibitors or beta blockers has demonstrated its efficacy in anti-HER2 therapy-induced cardiotoxicity⁽⁵⁾.

Conclusions

Cardiotoxicity represents one of the most disturbing side effects of anthracyclines and anti-HER2 therapy, therefore it requires special attention, especially in the presence of some risk factors⁽⁵⁾. Cancer patients are part of a vulnerable category, and the prevalence of cardiovascular disorders is constantly increasing, which represents a challenge in the multidisciplinary partnership of cardio-oncology⁽⁵⁾. Represented by the continuous degradation of LVEF and afterwards developing the heart failure, cardiotoxic effects can have a strong impact on the survival of patients by compromising the beneficial effects of anthracyclines therapy against cancer⁽⁷⁾.

This work tries to outline the most important

aspects of cytostatic-induced cardiotoxicity, this topic being of current interest, with a permanent usability given the continuous annual increase in the number of cancer cases.

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