Cardiotoxicity in Adjuvant and Neoadjuvant Therapy for Breast Cancer

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Cardiotoxicidade nas Terapias Neoadjuvante e Adjuvante do Câncer de Mama

Cardiotoxicidad en Terapias de Cáncer de Mama Neoadyuvante y Adyuvante

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Abstract

Introduction: Breast cancer is the most common among women worldwide, accounting for almost 25% of all cancer cases. Some drugs have a peculiar characteristic related to cardiotoxicity. **Objective:** Analyze the incidence, clinical characteristics and risk factors associated with cardiotoxicity in patients undergoing protocol doxorubicin and cyclophosphamide followed or not by taxanes and in those who underwent the same protocol associated with trastuzumab. **Method:** Cohort study conducted in a public hospital in Rio de Janeiro. 153 patients were included between September and November 2012. Cardiotoxicity was defined based on the criteria of the Cardiac Review and Evaluation Committee and the Brazilian Society of Cardiology. The relative risk (RR) was calculated using a 95% confidence interval (CI). **Results:** The incidence of cardiotoxicity was 17%. Left ventricular ejection fraction decreased in 31.3% and 52.2% of the patients in the negative and positive *human epidermal growth factor receptor-type* 2 (HER-2) groups, respectively. Three cases of heart failure were identified, two in HER-2 positive patients. Patients using trastuzumab had a higher risk of developing cardiotoxicity (RR=3.53; CI 95%: 1.84-6.79) compared to women in the HER-2 negative group. **Conclusion:** It was possible to verify the occurrence of cases of cardiotoxicity in both groups with higher incidence for the HER-2 positive group.

Key words: Cardiotoxicity; Breast Neoplasms; Doxorubicin; Cyclophosphamide; Trastuzumab.

Resumo

Introdução: O câncer de mama é o mais comum entre as mulheres em todo o mundo, representando quase 25% de todos os casos de câncer. Alguns fármacos possuem características peculiares relacionadas à cardiotoxicidade. **Objetivo:** Analisar a incidência, as características clínicas e os fatores de risco associados à ocorrência de cardiotoxicidade em pacientes submetidas ao protocolo doxorrubicina e ciclofosfamida seguido ou não de taxanos e naquelas que realizaram o mesmo protocolo associado ao trastuzumabe. **Método:** Trata-se de um estudo de coorte realizado em um hospital público do Rio de Janeiro. Foram incluídas 153 pacientes que iniciaram tratamento entre os meses de setembro e novembro de 2012. A cardiotoxicidade foi definida com base nos critérios do *Cardiac Review and Evaluation Committee* e da Sociedade Brasileira de Cardiologia. Foi calculado o risco relativo (RR), utilizando-se um intervalo de confiança (IC) de 95%. **Resultados**: A incidência de cardiotoxicidade foi de 17%. Observou-se queda da fração de ejeção do ventrículo esquerdo em 31,3% e 52,2% das pacientes nos grupos *human epidermal growth factor receptor-type* 2 (HER-2) negativo e positivo, respectivamente. Foram identificados três casos de insuficiência cardíaca, sendo dois em pacientes HER-2 positivas. As pacientes que utilizaram trastuzumabe apresentaram maior risco de desenvolver cardiotoxicidade (RR=3,53; IC 95%: 1,84-6,79) em comparação com as mulheres do grupo HER-2 negativo. **Conclusão:** Foi possível verificar a ocorrência de casos de cardiotoxicidade em ambos os grupos com maior incidência para o grupo HER-2 positivo.

Palavras-chave: Cardiotoxicidade; Neoplasias da Mama; Doxorrubicina; Ciclofosfamida; Trastuzumab.

Resumen

Introducción: El cáncer de mama es el más común entre las mujeres en todo el mundo, y representa casi el 25% de todos los casos de cáncer. Algunos medicamentos tienen característica peculiar relacionada con la cardiotoxicidad. **Objetivo:** Analizar la incidencia, las características clínicas y los factores de riesgo asociados con la cardiotoxicidad en pacientes sometidos al protocolo doxorrubicina y ciclofosfamida seguidos o no por taxanos y en aquellos que se sometieron al mismo protocolo asociado con trastuzumab**.** **Método:** Este es un estudio de cohorte realizado en un hospital público en Río de Janeiro. Se incluyeron 153 pacientes que comenzaron el tratamiento entre septiembre y noviembre de 2012. La cardiotoxicidad se definió según los criterios del Comité de Revisión y Evaluación Cardíaca y la Sociedad Brasileña de Cardiología. El riesgo relativo (RR) se calculó utilizando un intervalo de confianza (IC) del 95%. **Resultados:** La incidencia de cardiotoxicidad fue del 17%. La fracción de eyección del ventrículo izquierdo disminuyó en el 31,3% y el 52,2% de los pacientes en los grupos *human epidermal growth factor receptor-type* 2 (HER-2) negativo y positivo, respectivamente. Se identificaron tres casos de insuficiencia cardíaca, dos en pacientes con HER-2 positivo. Los pacientes que usaban trastuzumab tenían un mayor riesgo de desarrollar cardiotoxicidad (RR=3,53; IC 95%: 1,84-6,79) en comparación con las mujeres en el grupo negativo HER-2. **Conclusión:** Fue posible verificar la aparición de casos de cardiotoxicidad en ambos grupos con mayor incidencia para el grupo HER-2 positivo.

Palabras clave: Cardiotoxicidad; Neoplasias de la Mama; Doxorrubicina; Ciclofosfamida; Trastuzumab.

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INTRODUCTION

Breast cancer is the most common among women worldwide, representing nearly 25% of all the cases of cancer[1]. In Brazil, the estimate is 59,700 new cases of breast cancer for each year of | 2018-2019[2].

The therapeutic modalities for breast cancer may involve local treatment (radiotherapy and surgery) and/or systemic treatment (chemotherapy, hormone therapy and biologic therapy)[3]. The treatment with drugs ensues, most of the times, the appearance of several adverse reactions that are common to many protocols; among them, cardiotoxicity, an adverse event well established for various drugs utilized in the treatment of breast cancer as anthracycline antineoplastic and monoclonal antibody trastuzumab[4].

The cardiac toxicity associated to the oncologic treatment is an increasing source of significant morbidity and mortality and can embrace subclinical myocardial dysfunction and irreversible cardiac insufficiency or even death. Cumulative doses and concomitant use of adjuvant therapies, thoracic radiotherapy combined with other risk factors as preexisting cardiovascular disease, age, obesity, tobacco addiction, hypertension, diabetes and physical inactivity can increase the cardiovascular vulnerability[5].

Among the several clinical manifestations of cardiotoxicity, asymptomatic or symptomatic systolic and diastolic ventricular dysfunction ranges between 5% and 30%, is most frequent in patients with risk factors. Cardiotoxicity can be confirmed by one of the criteria: 1) myocardiopathy with reduction of the measure of left ventricular ejection fraction (LVEF) either globally or affecting more severely the intraventricular septum; 2) symptoms associated to cardiac insufficiency; 3) signs associated to cardiac insufficiency such as gallop S3, tachycardia or both; 4) reduction of LVEF in comparison with baseline of at least 5% until less than 55% with signs or concomitant symptoms of cardiac insufficiency or reduction of LVEF in the range of at least 10% until less than 55% without concomitant signs or symptoms[6,7].

As toxicity can manifest at any moment during the use of the drug or even after the end of the treatment, it is necessary the surveillance of the clinical manifestations. In clinical practice, the modality of the image (echocardiogram, *Multigated Acquisition Scan* - MUGA Scan, or cardiovascular magnetic resonance) is used as main method of detection of cardiotoxicity in patients with cancer. Echocardiogram has been the most utilized option because of its low cost, easy access and non-invasive character[7,8].

Because of the few studies encountered in the Brazilian literature that show the importance of the monitoring and follow up of the detection of cardiotoxicity in patients with breast cancer, this study becomes relevant to evidence the necessity of creating strategies for better surveillance of these reactions in the course of the treatment. Therefore, the objective of this study was to analyze the incidence, the clinical characteristics and the risk factors associated to the occurrence of cardiotoxicity in patients submitted to the protocol doxorubicin and cyclophosphamide (AC) followed or not by taxanes and, also, in these patients who submitted to the same protocol associated to trastuzumab for neoadjuvant and adjuvant treatment for breast cancer.

METHOD

Cohort study conducted in a specialized hospital for breast cancer treatment in the Municipality of Rio de Janeiro.

The hospital has 52 active beds, four surgery rooms, radiologic and radiotherapy center, laboratory and pharmacy.

There are several protocols of chemotherapy adopted in the institution, but the regimens of neoadjuvancy and adjuvancy are regularly used as first line treatment as presented in Plan 1.

The Clinic Oncology Service of the hospital suggests conducting the echocardiogram exams to monitor the cardiotoxic effects provoked by breast cancer drug therapy before the first cycle of protocol AC. In the cases where patients utilized trastuzumab, the monitoring should occur prior to the initiation of the treatment with the

Plan 1. Protocols commonly utilized as first line of neoadjuvant and adjuvant treatment for breast cancer and established in the institution investigated

Protocols	Doses
AC → docetaxel	Doxorubicin 60 mg/m² IV + cyclophosphamide 600 mg/m² IV 4 cycles at every 21 days, followed by docetaxel 100 mg/m² IV 4 cycles at each 21 days
HER-2 positive: AC → docetaxel and trastuzumab	The patients follow the former regimen, but, when initiate docetaxel, it is associated to trastuzumab 8 mg/kg dose of attack, followed by 6 mg/kg IV at every 3 weeks until completing 1 year of trastuzumab
Patients without clinical conditions of receiving docetaxel	AC followed by paclitaxel 80 mg/m² IV weekly during 12 weeks

Captions: AC = doxorubicin and cyclophosphamide; HER-2 = *human epidermal growth factor receptor-type* 2; IV = intravenous.

monoclonal antibody and, also at every three months during therapy.

From September to November 2012, the selection of the patients for the study occurred. The calculation of the sample considered an annual estimate of 400 patients with a margin of error of 5% and confidence interval of confidence of 95%, resulting in a sample with 153 patients.

All the patients in neoadjuvant and adjuvant treatment for breast cancer who submitted to, at least, four cycles of protocol AC were included, followed or not by docetaxel (or paclitaxel), being human epidermal growth factor receptor-type 2 (HER-2) either positive or negative. Those patients who for some reason changed the therapeutic protocol by progression of the disease (change for palliative treatment) or other type of toxicity related to the treatment and who were enrolled for any clinical trial were excluded. All HER-2 negative patients completed the follow up until the last cycle of taxanes, if the case. The patients who were treated with trastuzumab (HER-2 positive) were followed up until the end of the treatment.

Initially, there was the identification of the number of patients in treatment with protocol AC in the period of the study. Screening was based in the month record maps of chemotherapy where the pharmacists noted daily all the patients in treatment and respective drugs and doses.

Once the patients selected previously who initiated chemotherapy treatment in that period occurred, the transcription of the main information from the chart into a field diary listed the following information: number of identification of the patient in ascending numerical order, number of the inscription of the patient, immune-histochemical for HER-2; presence of cardiotoxicity; value of LVEF; symptoms; interruption of the treatment; conduct of the treatment after interruption, if necessary; date of the echocardiogram; frequency of the echocardiogram as recommended by the institution.

The data were compiled into an Excel spreadsheet, version *Microsoft Office Excel* 2003 for organization and further analysis of the results encountered during the study. In the spreadsheet, the name of the patients were sequenced through numeric coding to not expose its identification to which only the principal investigator has access.

The criteria established by the Cardiac Review and Evaluation Committee (CREC) were followed to evaluate the incidence of cardiotoxicity and through search of the main clinical cardiotoxic manifestations described by the I Brazilian Guideline of Cardio-Oncology of the Brazilian Society of Cardiology (*I Diretriz Brasileira de Cardio-Oncologia, Sociedade Brasileira de Cardiologia*)[6]. The results of the echocardiogram attached to the charts and conducted in the institution or elsewhere were verified to obtain the data or online at the Intranet portal. During the review of the charts, it was observed, if there was the presence or not of the symptoms described in the course of the drug therapy[9].

Because it is a trial where it is attempted to identify the occurrence of cardiotoxicity, its incidence was considered elevated if the cases of cardiac insufficiency would have been higher than the encountered in Phase III clinical trials[10,11].

The Relative Risk (RR) of cardiotoxicity was calculated with a Confidence Interval (CI) of 95%.

It was made a comparison between the dates when the therapy cycles began and the date of the echocardiogram to verify the frequency of the echocardiogram as recommended initially by the institution. This been done, it was detected the number of the patients that made the test before the first cycle of AC, how many did the test before docetaxel and trastuzumab and how many did the test at every three months.

The profile of reduction of LVEF was analyzed according to the criteria established by CREC. Therefore, cardiotoxicity was present when the reduction of LVEF in comparison with the baseline was at least of 5% until less than 55% with signs or symptoms of concomitant cardiac insufficiency or when the reduction of LVEF was within the range of at least 10% until less than 55% without concomitant signs and symptoms[9].

The analysis of the profile of reduction of LVEF included a comparison between the absolute values obtained through the echocardiogram done before of the first cycle of AC and the last exam done within the study period.

If the medical conducts complied with the recommendations described in the literature, it were met the proper criteria to interrupt or discontinue the treatment[12,13]. The recommendations are: 1) whether in the HER-2 negative group there was reduction of more than 10% associated to LVEF lower than 50%; 2) if during the therapy with trastuzumab there was symptomatic reduction of LVEF between 10% and 15% and under 55%; or 3) in the cases when it was observed reduction of more than 16% regardless if the absolute value of LVEF was or not within the limit of normality it was considered proper criteria to interrupt or discontinue the treatment.

Upon the recommendations of the literature as criteria to discontinue the treatment, it was verified whether there was any case of interruption or suspension of the treatment because of the cardiotoxic effect based in the chart's medical report.

The study was initiated after the Institutional Review Board of Instituto Nacional de Câncer José Alencar Gomes

da Silva (INCA) issued the approval report number 339793. The Informed Consent Form was waived. Pursuant to the Declaration of Helsinki, the results presented comply with the ethical principles ruling clinical trials with human beings and ensure the confidentiality of the information obtained during the study.

RESULTS

After screening, 165 patients initiated the protocol AC. During the follow up of these patients, in compliance with the exclusion criteria, 12 of them left the study, of which, seven presented progression of the disease and consequently followed another protocol, four had other treatment-associated toxicities and one joined a clinical trial and, in the end, only 153 patients remained. The main causes of exclusion were the progression of the disease detected during the cycles of AC causing changes in the protocol of treatment and intolerance to chemotherapy because of reactions as febrile neutropenia prior to completing the fourth cycle of AC.

Of the 153 patients included, 130 (85%) belonged to the group HER-2 negative and 23 (15%) to HER-2 positive. The median of age was 48 (26-76) years for the group HER-2 negative and 56 (25-71) years for HER-2 positive. The analysis of the two groups revealed that the majority pf the patients failed to present any previous comorbidity. These results showed the characteristic of homogeneity between the two groups.

The incidence of cardiotoxicity was 17%, with 26 patients of the total of the study according to Table 1. The first clinical manifestations observed in the group HER-2 negative revealed that of the 16 patients with cardiotoxicity, 13 (81.2%) had diastolic ventricular dysfunction and one case occurred before the fourth cycle of AC and the others detected few months after the treatment completion. Of these, 11 patients had diastolic ventricular dysfunction grade I, one, grade II and one, grade III. After the fourth cycle of AC, one patient evolved to diastolic dysfunction grade III with increase of volume of the left atrium with echocardiographic aspect suggestive of mitral and aortic marantic endocarditis. In this group, one of the patients who presented diastolic dysfunction grade III evolved to a condition of cardiac insufficiency.

In another case, one patient had alterations of the ventricular repolarization and one, myocardial ischemia after complaining of irradiated pericardium pain to the left upper limb when concluded the last cycle of docetaxel.

Eight patients of the group HER-2 positive developed diastolic dysfunction, seven of them, diastolic dysfunction grade I and one with grade II who evolved with cardiac insufficiency months after the beginning of the therapy with trastuzumab. According to the charts, all of them presented fatigue at small efforts after the first cycle of trastuzumab. In addition, there was one occurrence with a patient who developed cardiac insufficiency after the first month of treatment with trastuzumab in this group.

Neither of the groups presented systolic ventricular dysfunction.

The patients who utilized trastuzumab presented higher risk of developing cardiotoxicity (RR=3.53; CI 95%: 1.84-6.79; p<0.001) in comparison with the women of the group HER-2 negative.

In relation to the frequency, the group HER-2 negative had 118 (90.8%) patients who submitted to echocardiogram before the first cycle of AC and in the other group, 19 (82.6%) patients did the exam before the first cycle of AC (Table 2).

Table 1. Main characteristics among the study groups (HER-2 negative and HER-2 positive)

Characteristics	HER-2 (-) (n=130)	HER-2 (+) (n=23)	Total (n=153)
Staging			
1	5 (3.8%)	2 (8.7%)	7 (4.6%)
2	38 (29.2%)	8 (34.8%)	46 (30.0%)
3	87 (67.0%)	13 (56.5%)	100 (65.4%)
Treatment			
Neoadjuvant	81 (62.3%)	13 (56.5%)	94 (61.4%)
Adjuvant	49 (37.7%)	10 (43.5%)	59 (38.6%)
Events			
Cardiac Insufficiency	1 (0.1%)	2 (8.7%)	3 (2.0%)
Diastolic dysfunction	13 (10.0%)	8 (34.8%)	21 (13.7%)
Cardiotoxicity	16 (12.3%)[a.b]	10 (43.5%)[b]	26 (17.0%)[a.b]

Caption: HER-2 = *human epidermal growth factor receptor-type* 2.
Notes: [a]included the cases of ventricular repolarization and ischemia of the myocardial; [b]one patient, in each subgroup presented two cardiotoxic events (cardiac insufficiency and diastolic dysfunction).

Table 2. Frequency of patients who submitted to echocardiogram according to the guideline established by the institution investigated

Items evaluated	HER-2 (-) n (%)	HER-2 (+) n (%)
Before the 1st cycle of AC	118 (90.8)	19 (82.6)
Before the 1st cycle of docetaxel and trastuzumab	-	17 (74.0)
Frequency of three months after the echocardiogram	-	16 (69.5)

Captions: AC = doxorubicin and cyclophosphamide; HER-2 = *human epidermal growth factor receptor-type* 2.

In the group HER-2 negative, 67 patients did more than one echocardiogram during the study period, 26 (38.8%) had no reduction of LVEF and in the charts of 20 (29.9%) of these, there was no information about LVEF, which hindered the comparison with the baseline. In the group HER-2 positive, all the 23 patients did more than one echocardiogram and 12 (52.2%) patients had reduction of LVEF, as shown in Table 3.

Table 3. Range of values of LVEF observed in the study groups

Range of values of LVEF	HER-2 (-) n (%)	HER-2 (+) n (%)
≤ 5	15 (71.4)	7 (58.3)
6-9	4 (19.1)	3 (25.0)
≥ 10	2 (9.5)	2 (16.7)
TOTAL	21 (100.0)	12 (100.0)

Captions: LVEF = left ventricular ejection fraction; HER-2 = *human epidermal growth factor receptor-type* 2.

One patient of the group HER-2 negative had an asymptomatic reduction of 13% where the baseline LVEF was 80% and, in the end of chemotherapy, reduced to 67% keeping within the limit of normality. Another patient of the same group had asymptomatic reduction of 32% with value of LVEF lower than 55%. In the group HER-2 positive, two patients had reduction of 11% within the normality, one asymptomatic and other, symptomatic.

There was only one case of interruption of the treatment because of cardiotoxicity during the whole study. The patient, after completing the first cycle of trastuzumab, presented symptomatic drop of more than 10% of LVEF, a value within the values of reference range. However, the medical report of one of these patients stated a mild increase of the left atrium with other cavities of normal dimensions, preserved systolic function of the left global and segmental ventricle, diastolic dysfunction stage I (standard of reduction of ventricular relaxation) and mild fibro calcium mitral aortic involvement with mild discrete aortic mitral insufficiency. Furthermore, this patient presented arterial hypertension, diabetes and obesity and used betablocker, hypoglycemiant and diuretic before initiating the therapy.

DISCUSSION

As noticed in this study, the total occurrence of cardiac insufficiency was 2%, lower than the randomized Phase III study *National Surgical Adjuvant Breast and Bowel Project* (NSABP) B-31 (2.7%) and higher than the study *Breast Cancer International Research Group* (BCIRG) 006 (1.2%). The results of the present study show that the incidence of cardiac insufficiency was 0.1% in the group HER-2 negative lower than of the studies NSABP B-31 (1.2%) and BCIRG-006 (0.4%). In the group HER-2 positive, the result of the present study presented high incidence (8.7%) compared with NSABP B-31 (3.8%) and BCIRG-006 (1.9%)[10,11].

These findings indicate that in the three studies, the cardiac incidence is bigger in the group that utilized trastuzumab confirming the hypothesis of having a potentializing effect of cardiotoxicity when trastuzumab is utilized after the use of other drugs with cardiotoxic potential.

Several randomized multicenter studies showed that the addition of trastuzumab to regimens containing anthracycline sequentially kept the events of cardiac insufficiency below 4%. Furthermore, the investigators of the trial BCIRG-006 reported that a subclinical toxic effect persisted for many years in patients who developed cardiac dysfunction in the study arm that received trastuzumab and anthracyclines [7].

While verifying the former results, not all the patients did the echocardiogram. The best result achieved was in the group HER-2 negative, where more than 90% of the patients did the test before the first cycle of AC. For the other items, it was noticed that a portion of the patients did not do the echocardiogram prior to the first cycle of trastuzumab and neither the follow up at every three months as determined by the institution.

Pursuant to the guidelines, for the therapy with anthracyclines the cardiologic monitoring before and after the end of the treatment, regardless of the dose of administration is recommended. For the doses of 240 mg/m^2, the control must be done with six months and one year after the treatment and, after the fifth year of the end of the treatment, the monitoring must follow the medical prescription[6,14].

The risk of cardiomyopathy and cardiac insufficiency grows exponentially with the increase of the cumulative dose of anthracycline and, therefore, the patients who receive high doses of anthracyclines must be monitored

in relation to the asymptomatic reductions of LVEF or cardiac insufficiency. Both the observational and clinical trial data show that the treatment with anthracyclines followed by trastuzumab is associated to higher risks of reduced LVEF and cardiac insufficiency in comparison with the isolated agent[15].

When trastuzumab is in use, the cardiac monitoring should occur before initiating the drug therapy, measuring baseline LVEF as base for comparison of the cardiotoxic effect during the treatment. For this, it is necessary to monitor at each three months. After the conclusion of the treatment, the tests must be followed at every six months during two years by echocardiogram or MUGA[12,16].

Once these guidelines are followed, it is important to evaluate the reasons why these follow up routines were not complied with, mainly those in use of trastuzumab that need to be reassessed at every three months. With this, it is necessary to establish stricter routines for more effective follow up for early detection of these adverse reactions.

The results showed that the reduction of LVEF was more pronounced in the group HER-2 positive (52.2% *vs*. 31.3%). With this, the group who used trastuzumab after chemotherapy with doxorubicin, cyclophosphamide and taxane had higher drop of LVEF than the group who did not use trastuzumab. Similar results were found in study BCIRG-006[17].

One patient (8.3%) of the group HER-2 positive had a reduction of 9% with value below 55%. This result was superior to the study of Dores et al.[18], that noticed that 3.3% of the patients had LVEF below 55%. Nowsheen et al.[19] demonstrated that 73.2% of the patients that had normal baseline LVEF and who were submitted to treatment with trastuzumab after using anthracyclines had a reduction of LVEF in more than 10%, characterizing the cumulative and potentializing effect of these drugs in what concerns cardiotoxicity.

While evaluating cardiotoxicity, considering asymptomatic reduction ≥ 10% with less than 55% as established by CREC, none of the patients of the current study matched this criterion. Unlike this result, 17% of the patients of the study NSABP B-31 had symptomatic drop of LVEF ≥10% to less than 55% in the group HER-2 negative. In the group HER-2 positive, the percent was 34%[17].

The interruption of the treatment with trastuzumab because of the cardiotoxic effect has been the subject of studies. Aitelhaj et al.[20] noticed that 23% of the patients discontinued the treatment, nine received drug treatment with inhibitors of the enzyme conversion of angiotensin or antagonists of the receptor of angiotensin. Hussain et al.[21] showed that of the 23 patients who continued trastuzumab, 61% tolerated trastuzumab without cardiac event, 26% developed LVEF (interval 25% to 42%) resulting in the interruption of trastuzumab and 13% developed a cardiac event.

To minimize the risks of interrupting the treatment because of cardiotoxicity, it is necessary to evaluate the risk factors that can contribute to the appearance of this reaction. The benefits of trastuzumab should surpass the risks if the patient is in good health conditions and does not present risk factors. In the presence of one or two factors, they must be controlled before the administration of trastuzumab; however, if there are three or more factors, the risk-benefit must be evaluated and the caregivers should monitor frequently the cardiac function at every three months[12].

In addition, age, baseline LVEF and LVEF monitoring after chemotherapy should be considered as risk factors for the subsequent development of cardiotoxicity and these parameters must be considered and observed throughout the therapy[13].

In that line, it is worth noticing that the medical conduct adopted in the institution studied appears to have been proper, since not only the reduction of LVEF, but also the presence of risk factors that could harm the patient during the treatment. It is relevant, consequently, to know the risk factors of the patient as well as its control with anti-hypertensive therapy in addition to quarterly cardiovascular monitoring.

The major limitation of the study was not counting with echocardiogram tests as recommended by the institution, which lead to under-notified results. The RR identified could have been overestimated because of the sample size, it was not possible to adjust possible confounding variables.

Regardless of these limitations, the method utilized in the study was adequate and adopted criteria established by CREC, an internationally acknowledged entity to evaluate cardiotoxicity and by the Brazilian Society of Cardiology (Sociedade Brasileira de Cardiologia). In addition, the results of this study demonstrated the relevance of determining the incidence of cardiotoxic reactions in real life situations. However, the outcome of this study showed compatibility with the results of the literature, ratifying the importance of the monitoring and follow up of patients with breast cancer in therapy with cardiotoxic drugs.

CONCLUSION

It was possible to verify the occurrence of cases of cardiotoxicity in both groups with bigger incidence for the group HER-2 positive. The patients who utilized trastuzumab presented higher risk of developing

cardiotoxicity in comparison with women of the group HER-2 negative. It was also noticed a potentializing effect of cardiotoxicity when doxorubicin and trastuzumab were utilized in anticancer therapy demonstrated by the higher incidence of cases of cardiac insufficiency and bigger variation of the drop of LVEF reported in this study in comparison with the group HER-2 negative.

CONTRIBUTIONS

Lívia Christina de Oliveira Pina contributed substantially for the conception or planning of the study, data gathering, analysis and/or interpretation, wording and/or critical review and final approval of the version published. Flávia Axelband and Maria Fernanda Barbosa contributed for the conception and design of the study, critical review with intellectual contribution and final approval of the version for publication. Mario Jorge Sobreira da Silva contributed for the analysis and interpretation of the study date, critical review with intellectual contribution and final approval of the version for publication.

DECLARATION OF CONFLICT OF INTERESTS

There are no conflict of interests to declare.

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