Is Paclitaxel Less Cardiotoxic in the Treatment of Breast Cancer Before or After Doxorubicin?

Qual Estratégia Terapêutica é Menos Cardiotóxica no Tratamento do Câncer De Mama: Uso de Paclitaxel Antes ou Depois da Doxorrubicina?

André Luiz Cerqueira de Almeida[1], Edval Gomes dos Santos Júnior[2], Aluísio José de Oliveira Monteiro Neto[3], Thyago Monteiro do Espírito Santo[1], Paulo André A. Almeida[4], Samuel Oliveira Affonseca[1], Caroline de Souza Almeida[1], Matheus Pamponet Freitas[1], Cecília Lopes Viana Santos[1], Vitória Régia Beserra Barbosa Ximenes[1], Mariana Andrade Falcão[1], Israel Costa Reis[1], Suzane Pereira de Souza[2], Maurício Gomes da Silva Serra[2], Ana Beatriz Menezes de Oliveira[2], Tayla Silva Santos[1], Nilson Lima Lopes[1], Marcelo Dantas Tavares de Melo[3]

[1]Santa Casa de Misericórdia of Feira de Santana, Feira de Santana, BA - Brazil. [2]State University of Feira de Santana, Feira de Santana, BA - Brazil. [3]Federal University of Paraíba, João Pessoa, PB - Brazil. [4]UNIFACS Course of Medicine, Salvador, BA - Brazil.

Abstract

Background: The combination of doxorubicin (DOX) with paclitaxel (PTX) effectively treats breast cancer (BC). However, DOX-associated cardiotoxicity (CTX) is aggravated by the use of PTX. Consensus is lacking about which drug sequence involves the most CTX.

Objectives: To evaluate whether DOX followed by PXT or the reverse sequence has the greatest cardiotoxic potential in the treatment of BC.

Methods: Prospective study of women with primary BC who received four cycles of DOX and 12 infusions of PTX. Participants were divided into Group 1 (G1; PXT before DOX) and Group 2 (G2; DOX before PXT) at the discretion of the oncologist. CTX was defined as an absolute reduction in left ventricular ejection fraction (LVEF) > 10% to a value <53%. Patients underwent clinical evaluations and echocardiography before treatment (Phase 1) and one year after treatment (Phase 2).

Results: Sixty-nine women were evaluated: 19 in G1 and 50 in G2. The groups had similar clinical characteristics. The doses of radiation, DOX, and PTX used were similar. Eight (11.6%) patients developed CTX: two (10.5%) in G1 and six (12.0%) in G2 (p=0.62). The mean LVEF was similar between groups in Phase 1 (G1=65.1±3.5%; G2=65.2±3.9%; p=0.96), with a significant reduction noted after one year in both groups: G1=61.4±8.1% (p=0.021) and G2=60.8±7.6% (p<0.001). Although lower, mean LVEF remained similar between groups after Phase 2 (p=0.79).

Conclusions: In women with BC who underwent chemotherapy, the incidence of CTX at the end of the first year of treatment was similar regardless of whether DOX was used before or after PTX.

Keywords: Cardiotoxicity, Paclitaxel, Doxorubicin, Breast neoplasm.

Resumo

Fundamento: *A combinação de doxorrubicina com paclitaxel é eficaz no tratamento do câncer de mama. No entanto, a cardiotoxidade associada à doxorrubicina é agravada pelo uso do paclitaxel. Não há consenso sobre qual sequência é mais segura.*

Objetivos: *Avaliar qual sequência tem maior potencial cardiotóxico no tratamento do câncer de mama: doxorrubicina seguida de paclitaxel ou o inverso.*

Métodos: *Estudo prospectivo de mulheres com câncer de mama primário. Todos os participantes receberam quatro ciclos de doxorrubicina e 12 infusões de paclitaxel. Os participantes foram divididos em dois grupos, a critério do oncologista: Grupo 1, que recebeu paclitaxel antes da doxorrubicina, e Grupo 2, que teve doxorrubicina antes do paclitaxel. Definiu-se cardiotoxicidade como uma redução absoluta na fração de ejeção ventricular esquerda >10% para <53%. Os pacientes foram submetidos a avaliação clínica e ecocardiografia antes do tratamento (fase 1) e 1 ano após o tratamento (fase 2).*

Resultados: *Foram avaliadas 69 mulheres: 19 no Grupo 1 e 50 no Grupo 2. Os grupos apresentavam características clínicas semelhantes. As doses*

Mailing Address: Marcelo Dantas Tavares de Melo •

E-mail: marcelot@alumni.usp.br
Manuscript received 2/6/2022; revised 3/16/2022; accepted 4/12/2022

DOI: 10.47593/2675-312X/20223502eabc289

de radiação, doxorrubicina e paclitaxel utilizadas foram semelhantes. Oito (11,6%) pacientes desenvolveram cardiotoxicidade: dois (10,5%) no Grupo 1 e seis (12,0%) no Grupo 2 (p=0,62). A fração de ejeção ventricular esquerda se mostrou semelhante entre os grupos da fase 1 (Grupo 1 = 65,1±3,5; Grupo 2=65,2±3,9; p=0,96), com redução significativa após 1 ano em ambos os grupos: Grupo 1 = 61,4±8,1% (p=0,021) e Grupo 2 = 60,8±7,6% (p<0,001). Embora menor, a fração de ejeção ventricular esquerda permaneceu semelhante entre os grupos após a Fase 2 (p=0,79).

Conclusão: *Nas mulheres com câncer de mama submetidas à quimioterapia, a incidência de cardiotoxicidade ao final do primeiro ano de tratamento foi semelhante, independentemente do uso de doxorrubicina antes ou após o paclitaxel.*

Palavras-chave: *Cardiotoxicidade; Paclitaxel; Doxorrubicina; Neoplasias de mama.*

Introduction

Approximately 1.7 million new cases of cancer will be diagnosed in the United States in 2019. Of them, 270,000 will be breast cancer (BC)[1,2]. In Brazil, the National Cancer Institute estimates approximately 600,000 new cases of cancer in 2019, including 60,000 of BC[3]. From 1991 to 2016, the overall cancer mortality rate steadily declined in the US by 27%, translating into approximately 2.6 million fewer cancer deaths than would be expected had mortality rates remained at their peak[2]. The mean 5-year survival rate of patients with BC is approximately 90%[2]. The causes of this improvement in survival are multifactorial. Advances in antineoplastic therapy play an important role in this favorable outcome, but this type of therapy is also associated with undesirable cardiotoxic effects[4].

Doxorubicin (DOX) and paclitaxel (PTX) are potent chemotherapeutic drugs that were introduced in the therapeutic arsenal in the 1960s and 1980s, respectively[5]. The combination of DOX with PTX is widely used in BC patients because of its efficacy against cancer cells[6]. DOX is a chemotherapeutic agent of the anthracycline class that, depending on the dose used, may feature left ventricular (LV) dysfunction as a side effect in 3–48% of cases[4]. PTX and DOX belong to the taxane class (antimicrotubule agents), which have an incidence of cardiotoxicity (CTX) of 1–13%[4]. DOX-associated CTX is aggravated by PTX use[6-10]. In experimental study models, PTX may synergistically aggravate DOX-induced CTX. This result is reportedly more pronounced when PTX is used 24 hours after DOX[11]. Data from the FinHer trial, in contrast, suggested that CTX may remain low when a taxane (docetaxel) is given prior to the anthracycline[12]. Whether due to the therapeutic benefits or possible side effects, consensus is lacking about which drug should be used first in the treatment of BC patients[6,13].

Echocardiography is an important tool in the follow-up of patients who are antineoplastic therapy candidates. In this scenario, left ventricular ejection fraction (LVEF) is the most commonly used echocardiographic parameter for monitoring ventricular function[14]. Although useful, LVEF has low sensitivity for detecting small changes in ventricular function. The evaluation of myocardial deformation through the study of strain by the speckle tracking technique allows detection of subclinical LV dysfunction in several scenarios[15]. The reduction in global longitudinal strain (GLS) in patients undergoing chemotherapy is a sign of subclinical myocardial alterations that occur secondary to cancer therapy[16]. The change in GLS in this scenario usually occurs before any change in LVEF is detected[16,17].

The primary objective of this study was to evaluate which sequence has greater cardiotoxic potential in the treatment of BC patients: DOX followed by PTX or the reverse order. The secondary objective was to evaluate GLS and LVEF at the end of the first year of treatment of BC patients undergoing chemotherapy and compare GLS and LVEF between the DOX and PTX use sequences.

Methods

This prospective study included women diagnosed with BC indicated for treatment with DOX and PTX who were admitted to the oncology service of our hospital for chemotherapy during the period of 06/2014 to 07/2015. The exclusion criteria were an LVEF < 55%, previous cancer treatment, segmental dysfunction detected on echocardiography, diagnosis of heart failure by the Framingham criteria, inadequate echocardiographic window for GLS analysis, complex arrhythmia, valvular heart disease, any type of cardiomyopathy, and LV hypertrophy greater than discrete. All patients received four cycles of DOX (60 mg/m^2) with intervals of three weeks between cycles and 12 weekly infusions of PTX (80 mg/m^2). The sequence of use of both drugs was at the discretion of the treating oncologist. Participants were divided into Group 1 (PTX before DOX) and Group 2 (DOX before PTX). Patients underwent clinical evaluation and echocardiography prior to treatment initiation (Phase 1) and one year after initiation of DOX (Phase 2). CTX was defined as an absolute reduction in LVEF>10%, to a value <53%, one year after starting DOX[14]. The study was approved by our institution's research ethics committee. All patients signed an informed consent form.

Echocardiography

Transthoracic echocardiography was performed using a Vivid 6 or Vivid I cardiovascular ultrasound system (GE Healthcare, Milwaukee, WI, USA). All echocardiographic variables were analyzed off-line at the workstation of our service's echocardiography laboratory. EchoPAC software version 112.0.x (GE Healthcare) was used for these analyses. LVEF was calculated using the modified biplane Simpson method with four- and two-chamber apical views of the LV. The other echocardiographic measurements were calculated based on American Society of Echocardiography guidelines[18].

Grayscale images of the two-dimensional echocardiograms were obtained in four-, three-, and two-chamber apical views for the measurement of the LV subjective global assessment (SGA). The aortic valve closure time was obtained using pulsed Doppler flow tracing in the aortic valve synchronized with the electrocardiogram.

The professionals involved in the strain image acquisition received previous training to ensure the acquisition of adequate images for GLS analysis. The images corresponding to the GLS measurement were acquired with a frame rate of 50–80 cycles/s in three total cycles for each image. Proper tracking of points was checked and adjusted manually if necessary.

The LV SGA was calculated by the mean longitudinal strain values in the basal, mid-, and apical segments obtained in the four-, three-, and two-chamber LV apical views (Figure 1). To avoid confusion and following previous recommendations, GLS is expressed as the absolute value (aGLS), thus eliminating the negative sign[18,19].

Reproducibility

To determine intraobserver variability, echocardiograms from 20 randomly selected patients were retested by the same evaluator (FTAA) six months after the initial analysis. To determine interobserver variability, the data of these 20 patients were analyzed by a second evaluator (VRBBX) using the same exams and the same cycles for each.

Statistical analysis

The statistical analysis was performed using SPSS 2.0. The distribution of the studied variables was analyzed using the Shapiro-Wilk test. Quantitative variables are expressed as mean ± standard deviation and were compared by the *t* test for independent samples or Wilcoxon signed-rank test, while qualitative variables are expressed as frequency and percentage and were compared by the chi-square test or Fisher's exact test. The paired *t* test was used to determine if the mean of the differences between two paired samples differed from zero. The interobserver and intraobserver agreements were evaluated by the intraclass correlation coefficient (ICC) with 95% confidence interval (CI). Values of $p<0.05$ were considered statistically significant.

RESULTS

Sample

A total of 76 women with BC were treated with DOX and PTX during the study period. Of them, seven were excluded: two who requested exclusion and five who died before the evaluation in Phase 2 (two of sepsis, one of brain metastasis, one of sudden death, and of unknown cause). Of the 69 patients who composed the sample, 19 (27.5%) were treated with PTX before DOX (Group 1) and 50 (72.5%) were treated with DOX before PTX (Group 2).

The patients' main characteristics are summarized in Table 1. At the start of the study, the two groups were similar in age, systolic blood pressure, diastolic blood pressure, body mass index, and waist circumference. The same was observed in terms of the main cardiovascular risk factors and the use of cardiovascular drugs.

Table 1 – Patient characteristics by group.

Variable	Group 1 (n=19)	Group 2 (n=50)	P value
Age (years)	50±13	49±13	0.76
SBP (mmHg)	133±18	131±26	0.79
DBP (mmHg)	83±12	81±13	0.63
BMI (kg/m²)	26.9±5.1	27.3±4.7	0.74
Waist circumference (cm)	90±12	88±14	0.71
Cardiovascular risk factors, n (%)			
Hypertension	9 (47)	20 (41)	0.63
Diabetes	4 (21.1)	4 (8.5)	0.21
Smoking	0 (0)	3 (6.5)	0.55
Sedentary lifestyle	15 (83.3)	36 (81.8)	1.0
Dyslipidemia	1 (5.3)	3 (6.5)	1.0
Radiation therapy	16 (84.2)	40 (80)	1.0
Trastuzumab	3 (15.8)	14 (28)	0.36
Cardiovascular medication, n (%)			
ACEI	2 (13.3)	8 (22.2)	0.70
Beta-blocker	0 (0)	2 (5.6)	1.0
ARB	5 (33.3)	5 (13.2)	0.09
Antineoplastic treatment (n of doses)			
DOX (mg/m²)	240±11	237±14	0.38
PTX (mg)	1570±138	1567±236	0.96
Radiation (Gy)	58±5	56±6	0.39

Continuous variables are presented as mean ± standard deviation, while categorical variables are shown as frequency (percentage). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; DBP, diastolic blood pressure; DOX, doxorubicin; PTX, paclitaxel; SBP, systolic blood pressure.

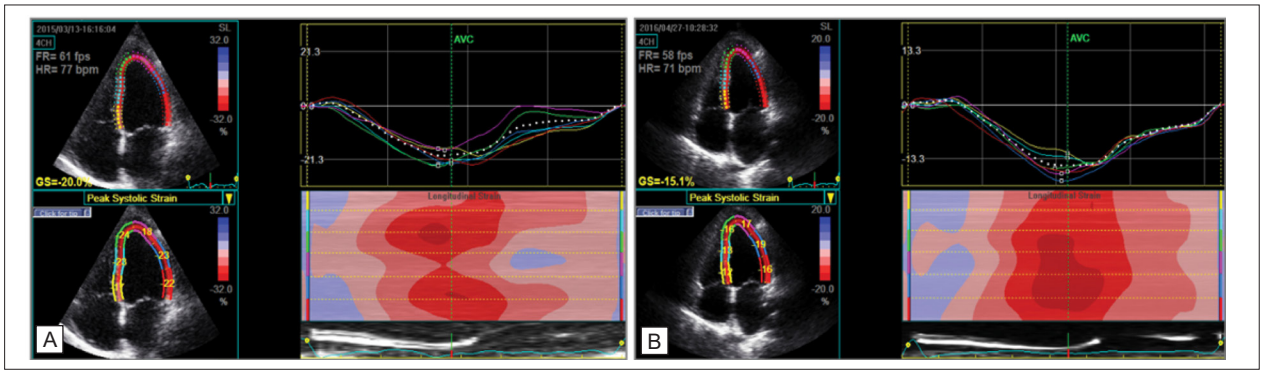

Figure 1 – *Normal longitudinal strain before chemotherapy (A) and decreased longitudinal strain after chemotherapy (B).*

One patient (1.4%) in Group 2 had bilateral BC. Of the others, 34 (49.3%) had right BC, and 34 (49.3%) had left BC. Seven (37%) Group 1 patients had right BC, while 27 (54%) Group 2 patients had right BC (p=0.18).

Eight patients (11.6%) developed CTX by the end of the study: two (10.5%) in Group 1 and six (12.0%) in Group 2 (p=0.62) (Figure 2).

Antineoplastic treatment

The cumulative dose of DOX and the total dose of PTX did not differ between groups (p=0.38 and p=0.96 for Groups 1 and 2, respectively; Table 1).

Radiation therapy was used in 16 (84.2%) patients in Group 1 and 40 (80%) patients in Group 2 (p=1.0). There was no intergroup difference in the radiation dose used (p=0.39; Table 1).

Seventeen (24.6%) patients were classified as being *HER2*-positive and, therefore, were treated with trastuzumab: 3 (15.8%) in Group 1 and 14 (28%) in Group 2 (p=0.36; Table 1).

Echocardiographic variables

The main echocardiographic variables in Phases 1 and 2 are presented in Table 2.

LVEF at baseline was similar between groups (Group 1, 65.1±3.5% versus Group 2, 65.2±3.9%; p=0.96; Table 3). There was a significant decrease in LVEF after one year in both groups (Table 2). The LVEF decreased by 3.7% in Group 1 (from 65.1±3.5% to 61.4±8.1%; p=0.021) and by 4.4% in Group 2 (from 65.2±3.9% to 60.8±7.6%; p<0.001). One year after treatment, although lower, LVEF remained similar between groups (Group 1, 61.4±8.1% versus Group 2, 60.8±7.6%; p=0.79; Table 3).

The aGLS results were similar to the LVEF results. There was no intergroup difference in aGLS before treatment (Group 1, 19.9±2.0% versus Group 2, 20.0±2.4%; p=0.90; Table 3). A significant decrease in aGLS was noted in both groups at the end of the first year of chemotherapy (Table 2), but the decreases were similar between them (Table 3).

Other variables associated with LV systolic function (mitral annular plane systolic excursion [MAPSE], mitral S' wave, and systolic longitudinal strain rate [LSRs]) followed the same pattern as LVEF and aGLS (Table 2). The same occurred in the ratio of early diastolic transmitral velocity-to-early diastolic tissue velocity ratio (E/E' ratio), a variable related

Table 2 - Echocardiographic parameters by group and study phase.

Variable	Group 1 (n=19)		Group 2 (n=50)	
	Phase 1	Phase 2	Phase 1	Phase 2
LVDD (mm)	44.7±3.8	44.2±5.6	44.8±3.9	45.5±4.8
LVSD (mm)	28.8±3.0	29.3±5.9	29.0±3.0	30.1±4.9*
LVEF (%)	65.1±3.5	61.4±8.1†	65.2±3.9	60.8±7.6*
E/A ratio	1.12±0.40	1.09±0.32	1.09±0.33	1.09±0.37
E/E' ratio	8.6±2.7	9.9±3.4†	7.9±2.6	9.5±3.1*
Mitral S' wave (cm/s)	6.7±1.0	6.0±1.1†	7.2±1.3	6.3±1.3*
MAPSE (mm)	13.2±1.3	12.2±2.3†	13.4±1.8	12.2±1.7*
aGLS (%)	19.9±2.0	18.4±2.3†	20.0±2.4	18.9±2.7*
LSRs $^{(-1)}$	1.00±0.15	-0.90±0.13†	-1.02±0.17	-0.95±0.22*

*aGLS, absolute global longitudinal left ventricular strain; LSRs, systolic longitudinal strain rate; LVDD, left ventricular diastolic diameter; LVSD, left ventricular systolic diameter; LVEF, left ventricular ejection fraction; MAPSE, mitral annular plane systolic excursion. *p<0.05 versus Phase 1 results. #p<0.05 versus Phase 1 results.*

Table 3 - LVEF and global longitudinal strain.

Variable	Group 1 (n=19)	Group 2 (n=50)	P value
Phase 1, %			
LVEF (%)	65,1±3,5	65,2±3,9	0,96
aGLS (%)	19,9±2,0	20,0±2,4	0,90
Phase 2, %			
LVEF (%)	61,4±8,1	60,8±7,6	0,79
aGLS (%)	18,4±2,3	18,9±2,7	0,48

Data are presented as mean ± standard deviation. aGLS, absolute global longitudinal strain of the left ventricle; LVEF, left ventricular ejection fraction

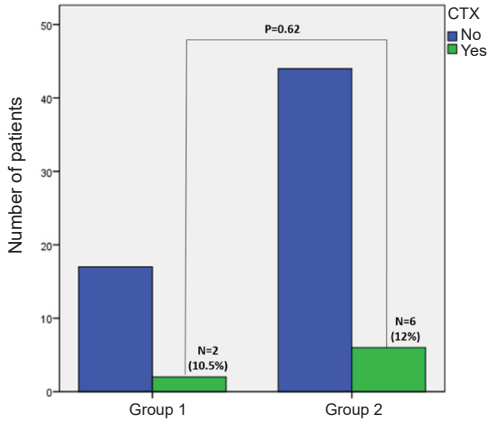

Figure 2 – *Cardiotoxicity after 1 year.*

to LV diastolic function. However, no change was noted in the early-to-late diastolic transmitral flow velocity ratio (E/A ratio) of mitral flow.

Reproducibility

There was excellent intraobserver agreement in aGLS (ICC, 0.94; 95% CI, 0.84–0.98) and interobserver (ICC, 0.92; 95% CI, 0.80–0.97).

Discussion

The present study demonstrated no difference in the incidence of CTX when DOX followed PTX or, conversely, when PTX followed DOX in the treatment of BC patients. Despite this, a significant decrease in aGLS and LVEF was noted at the end of the first year of chemotherapy. This decrease, however, was similar between the two groups regardless of the drug use sequence.

Other variables evaluated in our study, such as MAPSE, mitral annulus S' wave, and LSRs, followed the pattern observed for LVEF and aGLS. These data confer greater robustness to our results because they also provide important information about LV systolic function.[14] In addition, because it is not possible to evaluate aGLS by using the speckle tracking technique, MAPSE and mitral annulus S' wave are the variables recommended to ensure an adequate evaluation of LV longitudinal function[14].

DOX-associated CTX is aggravated by PTX treatment[6-9]. The latter increases the plasma concentration of the former[8,9]. PTX also stimulates the formation of DOX metabolites, which play a key role in the mechanism of CTX[9]. The effect of PTX on DOX metabolites can reportedly be attributed to interference by the PTX carrier in the biliary elimination of the anthracycline molecule, explaining the greater toxicity of the PTX-DOX association versus DOX alone[7]. Studies in laboratory animals have shown that PTX can aggravate DOX-induced CTX, especially when a taxane (paclitaxel) is used after DOX[11]. Another chemotherapeutic taxane, docetaxel, has effects similar to those of PTX[9]. However, the FinHer study showed that docetaxel, when used before DOX, was associated with low CTX rates[12]. Focan et al.[20] demonstrated that the use of an anthracycline (epirubicin) on day 1 followed by a taxane (PTX) on day 2 decreased the risks of hematological complications, especially neutropenia. However, the CTX, as in our study, did not change regardless of drug sequence[20].

The incidence of CTX in our sample was low (11.6%), similar to the 9% reported by Cardinale et al.[21] but lower than those of other reports in the literature[4,22]. This relatively low incidence of CTX may be attributed to the low dose of DOX used by our patients (238±13 mg/m^2). Higher rates are usually seen with higher doses. The increase in CTX related to the DOX-PTX combination is currently prevented by limiting the cumulative dose of DOX to 360 mg/m^2 or separating the infusion of the two drugs by an interval of more than four hours[8]; both approaches were used with our patients. Our patients were at low risk of developing CTX, and some were already using cardioprotective drugs. These factors may also be associated with the low incidence of CTX in our sample.

The use of more sensitive methods for detecting subclinical ventricular dysfunction, such as GLS, has been very useful for monitoring patients undergoing chemotherapy[14]. The data are very consistent regarding the diagnostic value of GLS in CTX screenings among these patients. A relative reduction in aGLS > 15% compared to baseline is strong evidence of subclinical ventricular dysfunction in patients undergoing chemotherapy; furthermore, it is a predictor of an LVEF decrease and subsequent development of heart failure[14]. Charbonnel et al.[23] demonstrated that even at low doses of DOX (150 mg/m^2), aGLS was an independent predictor of future CTX associated with anthracycline use. Our study demonstrated a decrease in aGLS at one year after the start of DOX treatment, a finding that did not depend on the sequence of DOX and PTX use. The patients who composed the sample in our study continue to be followed up to enable the future analysis of the prognostic value of aGLS in patients at high risk for cardiovascular events.

The choice of the sequence of anthracycline and taxane administration in BC patients is currently based on classical biological factors as well as clinical and demographic factors associated with the risk of disease recurrence[6]. It is customary to use an anthracycline followed by a taxane based on the above information and on historical development, as anthracyclines were introduced first in clinical practice. This influences the routine of many services. However, recent studies reported using taxanes before anthracyclines[24], which has served as an example for other centers. Virtually all of these studies had the main objective of evaluating the therapeutic efficacy of the drugs; in most of them, there was no specific design to evaluate the cardiotoxic potential associated with the anthracycline and taxane administration sequences. Focan et al.[20] was one of the few that made this evaluation; epirubicin was the anthracycline used. Our study also performed this evaluation, but we used DOX instead. Based on our results, either sequence of DOX and PTX administration is safe from a cardiovascular standpoint since neither increases the risk of CTX in patients with BC. This information can give peace of mind to oncology services when choosing the treatment sequence. However, further studies are needed with larger numbers of patients that use the currently recommended doses and evaluate the CTX potential of possible anthracycline and taxane administration sequences in BC patients.

Limitations

Our study has some limitations. Its relatively small number of patients may have contributed to the lack of statistically significant intergroup differences. As the number of patients who developed CTX was small, our findings require confirmation in a larger sample. The fact that the patients come from a single center raises the possibility of selection bias. This issue is attenuated by the fact that the sample comprised all the women who met the study inclusion criteria within one year and were admitted to our hospital's oncology department for chemotherapy. Due to the variability in GLS among the different manufacturers of echocardiography devices, we cannot guarantee that our results can be replicated with devices of brands other than

the one used here. The professionals who acquired the echocardiogram images were not blinded to the examination phase, which may have led to observation bias. And finally, it was not possible to measure biomarker levels, but this was not the objective of our study.

Conclusion

In the present sample of BC patients referred to begin chemotherapy, the incidence of CTX at the end of the first year of treatment was similar regardless of whether DOX was used before or after PTX. The study also showed significant and similar decreases in aGLS and LVEF at the end of the first year of treatment regardless of the chemotherapeutic agent use sequence.

Author contributions

Conception and design: Almeida ALC, Melo MDT; Data collection: Melo MDT, Santo TME, Monteiro Neto AJO, Almeida CS, Santos CLV, Souza SP, Serra MGS, Oliveira ABM, Santos TS, Lopes NL, Ximenes VRBB, Lopes NL, Reis IC; Data analysis and interpretation: Santos Junior EG, Affonseca SO, Santo TM, Melo MDT, Almeida ALC; Statistical analysis: Santos Junior EG, Almeida ALC; Writing the manuscript: Almeida ALC, Monteiro Neto AJO, Melo MDT, Almeida PAA; Critical review for intellectual content: Melo MDT, Santos Júnior EGS, Almeida ALC, Affonseca SO.

Conflict of interest

The authors have declared that they have no conflict of interest.

References

1. American Cancer Society. Cancer facts & figures 2018. Atlanta: American Cancer Society; 2018.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69(1):7-34. doi: https://doi.org/10.3322/caac.21551
3. Estimativa 2018: incidência de câncer no Brasil. Instituto Nacional de Câncer José Alencar Gomes da Silva/ Ministério da Saúde; 2017. Available at: http://www.inca.gov.br/estimativa/2018
4. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, et al.; ESC Scientific Document Group. 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(36):2768-2801. doi: https://doi.org/10.1093/eurheartj/ehw211. Erratum in: Eur Heart J. 2016 Dec 24; PMID: 27567406
5. de Moor JS, Mariotto AB, Parry C, Alfano CM, Padgett L, Kent EE, et al. Cancer survivors in the United States: prevalence across the survivorship trajectory and implications for care. Cancer Epidemiol Biomarkers Prev. 2013;22(4):561-70. doi: https://doi.org/10.1158/1055-9965.EPI-12-1356
6. Bines J, Earl H, Buzaid AC, Saad ED. Anthracyclines and taxanes in the neo/adjuvant treatment of breast cancer: does the sequence matter? Ann Oncol. 2014;25(6):1079-85. doi: https://doi.org/10.1093/annonc/mdu007
7. Gianni L, Viganò L, Locatelli A, Capri G, Giani A, Tarenzi E, et al. Human pharmacokinetic characterization and in vitro study of the interaction between doxorubicin and paclitaxel in patients with breast cancer. J Clin Oncol. 1997;15(5):1906-15. doi: https://doi.org/10.1200/JCO.1997.15.5.1906
8. Gianni L, Salvatorelli E, Minotti G. Anthracycline cardiotoxicity in breast cancer patients: synergism with trastuzumab and taxanes. Cardiovasc Toxicol. 2007;7(2):67-71. doi: https://doi.org/10.1007/s12012-007-0013-5
9. Salvatorelli E, Menna P, Cascegna S, Liberi G, Calafiore AM, Gianni L, et al. Paclitaxel and docetaxel stimulation of doxorubicinol formation in the human heart: implications for cardiotoxicity of doxorubicin-taxane chemotherapies. J Pharmacol Exp Ther. 2006;318(1):424-33. doi: https://doi.org/10.1124/jpet.106.103846
10. Gianni L, Dombernowsky P, Sledge G, Martin M, Amadori D, Arbuck SG, et al. Cardiac function following combination therapy with paclitaxel and doxorubicin: an analysis of 657 women with advanced breast cancer. Ann Oncol. 2001;12(8):1067-73. doi: https://doi.org/10.1023/a:1011655503511
11. Saad SY, Najjar TA, Alashari M. Cardiotoxicity of doxorubicin/paclitaxel combination in rats: effect of sequence and timing of administration. J Biochem Mol Toxicol. 2004;18(2):78-86. doi: https://doi.org/10.1002/jbt.20012
12. Joensuu H, Bono P, Kataja V, Alanko T, Kokko R, Asola R, et al. Fluorouracil, epirubicin, and cyclophosphamide with either docetaxel or vinorelbine, with or without trastuzumab, as adjuvant treatments of breast cancer: final results of the FinHer Trial. J Clin Oncol. 2009;27(34):5685-92. doi: https://doi.org/10.1200/JCO.2008.21.4577
13. Wildiers H, Forceville K, Paridaens R, Joensuu H. Taxanes and anthracyclines in early breast cancer: which first? Lancet Oncol. 2010;11(3):219-20. doi: https://doi.org/10.1016/S1470-2045(10)70025-5
14. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2014;15(10):1063-93. doi: https://doi.org/10.1093/ehjci/jeu192.
15. Geyer H, Caracciolo G, Abe H, Wilansky S, Carerj S, Gentile F, et al. Assessment of myocardial mechanics using speckle tracking echocardiography: fundamentals and clinical applications. J Am Soc Echocardiogr. 2010;23(4):351-69; quiz 453-5. doi: https://doi.org/10.1016/j.echo.2010.02.015. Erratum in: J Am Soc Echocardiogr. 2010;23(7):734
16. Thavendiranathan P, Poulin F, Lim KD, Plana JC, Woo A, Marwick TH. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: a systematic review. J Am Coll Cardiol. 2014;63(25 Pt A):2751-68. doi: https://doi.org/10.1016/j.jacc.2014.01.073
17. Almeida AL, Silva VA, de Souza Filho AT, Rios VG, Lopes JR, de Afonseca SO, et al. Subclinical ventricular dysfunction detected by speckle tracking two years after use of anthracycline. Arq Bras Cardiol. 2015;104(4):274-83. doi: https://doi.org/10.5935/abc.20140209
18. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015;28(1):1-39.e14. doi: https://doi.org/10.1016/j.echo.2014.10.003.
19. Feigenbaum H, Mastouri R, Sawada S. A practical approach to using strain echocardiography to evaluate the left ventricle. Circ J. 2012;76(7):1550-5. doi: https://doi.org/10.1253/circj.cj-12-0665.
20. Focan C, Graas MP, Beauduin M, Canon JL, Salmon JP, Jerusalem G, et al. Sequential administration of epirubicin and paclitaxel for advanced breast cancer. A phase I randomised trial. Anticancer Res. 2005;25(2B):1211-7.

21. Cardinale D, Colombo A, Bacchiani G, Tedeschi I, Meroni CA, Veglia F, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation. 2015;131(22):1981-8. doi: https://doi.org/10.1161/CIRCULATIONAHA.114.013777

22. Sawaya H, Sebag IA, Plana JC, Januzzi JL, Ky B, Tan TC, et al. Assessment of echocardiography and biomarkers for the extended prediction of cardiotoxicity in patients treated with anthracyclines, taxanes, and trastuzumab. Circ Cardiovasc Imaging. 2012;5(5):596-603. doi: https://doi.org/10.1161/CIRCIMAGING.112.973321

23. Charbonnel C, Convers-Domart R, Rigaudeau S, Taksin AL, Baron N, Lambert J, et al. Assessment of global longitudinal strain at low-dose anthracycline-based chemotherapy, for the prediction of subsequent cardiotoxicity. Eur Heart J Cardiovasc Imaging. 2017;18(4):392-401. doi: https://doi.org/10.1093/ehjci/jew223

24. Bear HD, Tang G, Rastogi P, Geyer CE Jr, Robidoux A, Atkins JN, et al. Bevacizumab added to neoadjuvant chemotherapy for breast cancer. N Engl J Med. 2012;366(4):310-20. doi: https://doi.org/10.1056/NEJMoa1111097.