ORIGINAL ARTICLE

Hematotoxicity and functional impacts related to chemotherapy with doxorubicin and cyclophosphamide for invasive ductal breast carcinoma: a study in clinical records

Hematotoxicidade e impactos funcionais relacionados à quimioterapia com doxorrubicina e ciclofosfamida para carcinoma ductal invasivo da mama: um estudo em prontuários clínicos

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Abstract

Objective: To evaluate the occurrence of hematological and functional toxicities during chemotherapy with doxorubicin and cyclophosphamide in women with breast invasive ductal carcinoma. **Methods:** This was a descriptive, cross-sectional and quantitative study, involving the data collection in clinical records of 119 women undergoing chemotherapy for breast invasive ductal carcinoma in an oncology outpatient clinic, carried out between February 2014 and February 2015. **Results**: The investigated toxicities and their respectively occurrences in patients exposed to doxorubicin and cyclophosphamide were hemoglobinemia (26,5%), leukopenia (21,6%), neutropenia (10,8%), thrombocytopenia (none) and reduced hematocrit (28,4%), in addition to fatigue (93,1%), fever (20,6%), gain (35,3%) and weight loss (22,5%). In these variables, there were no significant differences between the exposed and not exposed patients. The association with taxanes showed a significant reduction in hematocrit values (p=0.019) and the toxicities distributed by age group were not significant within the exposed group. **Conclusions**: Exposure to doxorubicin and cyclophosphamide was not associated with an increase in the occurrence of hematotoxicities and functional impacts in women with breast ductal invasive carcinoma, except when associated with taxane agents.

Keywords: Breast Neoplasms; Antineoplastic Agents; Toxicity.

Resumo

Objetivo: Avaliar a ocorrência de toxicidades hematológicas e funcionais durante a quimioterapia com doxorrubicina e ciclofosfamida para neoplasias de mama em mulheres com carcinoma ductal invasivo da mama. **Métodos**: Trata-se de um estudo descritivo, transversal e quantitativo, envolvendo a coleta de dados em prontuários médicos de 119 mulheres em tratamento quimioterápico para carcinoma ductal invasivo da mama em um ambulatório de oncologia, realizado entre fevereiro de 2014 e fevereiro de 2015. **Resultados**: As toxicidades investigadas e as respectivas ocorrências em pacientes expostas à doxorrubicina e à ciclofosfamida foram hemoglobinemia (26,5%), leucopenia (21,6%), neutropenia (10,8%), plaquetopenia (nenhuma) e hematócrito reduzido (28,4%), além da fadiga (93,1%), febre (20,6%), ganho (35,3%) e perda de peso (22,5%). Para essas variáveis, não houve diferenças significativas entre o grupo exposto e o não exposto. A associação com taxanos apresentou redução significativa nos valores do hematócrito (p=0.019), e as toxicidades distribuídas por faixa etária não foram significativas dentro do grupo exposto. **Conclusões**: A exposição à doxorrubicina e à ciclofosfamida não esteve associada ao aumento da ocorrência de hematotoxicidades e impactos funcionais em mulheres com carcinoma ductal invasivo da mama, exceto quando associados a agentes taxanos.

Palavras-chave: Neoplasias da Mama; Antineoplásicos; Toxicidade.

INTRODUCTION

The occurrence of hematotoxicity during chemotherapy is a limiting factor in the prognosis of neoplasms. Hematopoietic cells, precursors of the red and white blood lines (erythrocytes, leukocytes, and thrombocytes), are found inside the bones in an organized trabecular network. Chemotherapy can suppress this hematopoietic system, reducing the amount of red marrow in the trabecular bone and increasing the amount of yellow marrow (rich in lipids), which is not associated with blood cells production, causing the reduction of these cell lines[1,2].

Chemotherapy treatment, regardless of the antineoplastic agents used, is essential to the success of oncological

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Conflict of interest: The authors declare that there is no conflict of interest.
Received: 2021 Apr 16; Revised: 2021 Apr 19; 2021 Oct 10; Accepted: 2021 Oct 14

therapies for breast cancer[2,3]. In addition, the combination of chemotherapeutic agents is classically more effective than single-drug therapies. In this context, doxorubicin, an anthracycline, and cyclophosphamide, an alkylating agent, are often combined and adopted in different protocols. Although effective, especially in advanced tumors, the side effects of this combination on the bone marrow are commonly reported, impairing the hematopoietic function of patients undergoing chemotherapy[3,4].

In the past 40 years, especially in the advanced stages of breast cancer, doxorubicin has been widespread in clinical practice. The association with other drugs, such as cyclophosphamide, has improved the success of therapies and breast cancer mortality rates[2]. However, toxicities related to the combination of doxorubicin and cyclophosphamide include, in addition to the reduction of blood cells, the increased risk of anemia, hemorrhage and infections, comorbidities that contribute negatively to breast cancer outcomes in women who experience chemotherapy agents over the course of cancer treatment[3].

Studies in animal models suggest that several drugs, including doxorubicin and cyclophosphamide, can cause damage to bones and bone marrow. Thus, understanding the mechanisms by which anthracyclines and alkylating agents combined cause hematotoxicities during chemotherapy for breast cancer becomes a priority in new studies[2,5].

In addition to blood toxicities, chemotherapy treatment can cause other side effects that directly interfere with the quality of life and functionality of women with breast cancer, especially fatigue and changes in body composition. Chemotherapy-related changes in the body may involve loss of muscle mass and increase in fat mass, reflecting clinically in patients as muscle weakness, tiredness, and weight gain or loss. These functional changes can favor the emergence of comorbidities, such as diabetes and cardiovascular diseases, affecting the cancer prognosis[6,7].

Knowledge about the occurrence of toxicities helps to prevent related complications. Considering the aforementioned possible changes associated with doxorubicin and cyclophosphamide combination, this knowledge becomes even more necessary, especially when considering that these toxicities have not yet been fully understood[3,4]. Thus, the objective of this study was to evaluate the occurrence of hematological and functional toxicities during chemotherapy with doxorubicin and cyclophosphamide in women with breast invasive ductal carcinoma. The investigated hypothesis is that women who were exposed to the combination of these chemotherapeutic agents had a high occurrence of hematological and functional changes.

METHODS

This was a cross-sectional and quantitative study developed using clinical records from a private chemotherapy outpatient clinic, carried out between February 2014 and February 2015. It is important to report that the clinical-epidemiological profile of this sample has been previously presented[8], this being a second investigation in the same population, based on another research hypothesis. In order to ensure the originality and copyright of both publications, only additional data related to the new study hypothesis were described in this method section.

Of the 125 women who met the inclusion criteria for the description of the clinical-epidemiological profile, only 119 met the criteria for this investigation. However, the re-presentation of these samples remains restricted to the new hypothesis and their results, as well as the readers, should seek the original publication for more details on their acquisition and distribution, including the clinical-epidemiological profile[8].

The variables selected to achieve the proposed objective were the serum levels of hematological components (hemoglobin, hematocrit, leukocytes, neutrophils, and platelets) and cancer-related functionalities (fatigue, fever, and weight gain or loss), in addition to the presence or absence of osteoporosis. In the data obtained from laboratory exams, all the results described in the clinical record of each patient up to the time of collection were considered.

The values of the hematological components were determined according to the methods and parameters proposed by the clinical analysis laboratories during the period in which the samples were collected. However, considering the recent results of the National Health Survey (PNS) in Brazil for average values of laboratory blood tests[9], the parameters considered low in the exams of the patients in the sample remain below the average of the Brazilian population.

The data were evaluated in the entire sample and compared between exposed and unexposed participants. To assess the effects of the simultaneously delivered doxorubicin and cyclophosphamide drug combination (with or without other drugs), the patients were first divided into two groups: group 1 (G1: exposed to the combination at some point in the chemotherapy treatment) and group 2 (G2: not exposed to the combination at any time during the chemotherapy treatment). Subsequently, to assess the effect of age on the occurrence of toxicities in women exposed to the combination, group G1 was subdivided into two groups: group 3 (G3: <55 years) and group 4 (G4: ≥55 years). Likewise, to assess the association with subsequent taxanes, group G1 was again subdivided into two groups: group 5 (G5: not exposed to taxanes) and group 6 (G6: exposed to taxanes).

The data obtained were tabulated in a single spreadsheet by the Google Sheets tool® for further analysis by statistical tests. The software used was PAST: *Paleontological Statistics Software Package for Education and Data Analysis* (Oslo, Norway, 1999). Descriptive statistics were performed and Pearson's chi-square (x^2) and exact Fisher (expected values less than five

in contingency tables) tests were applied. The results with a p-value less than 5% were considered statistically significant (α = 0.05).

RESULTS

The sample consisted of 119 women (N = 119) undergoing chemotherapy for invasive ductal breast carcinoma. Of these, 102 (85,7%) underwent a combination of doxorubicin and cyclophosphamide at some point in the systemic antineoplastic therapy. Table 1 shows the general and age-related occurrence of hematological and functional toxicities in this group, while Table 2 proportionally compares the occurrence of hematological and functional changes in relation to the unexposed group according to the clinical-epidemiological, hematological, and functional variables. Table 3 shows the comparison between women exposed in relation to age, as well as table 4 shows the comparison in relation to the subsequent administration of taxanes in hematotoxicity.

Table 1. General and age-related occurrence of hematological and functional toxicity during breast cancer chemotherapy with doxorubicin and cyclophosphamide (n = 102).

Toxicities	Absolute frequency	Relative frequency (%)	< 55 years (%)	≥ 55 years (%)
Hemoglobinemia	27	26,5	16,7	9,8
Reduced hematocrit	29	28,4	18,6	9,8
Leukopenia	22	21,6	14,7	6,9
Neutropenia	11	10,8	6,9	3,9
Thrombocytopenia	0	-	-	-
Fatigue	95	93,1	56,8	36,3
Fever	21	20,6	15,7	4,9
Weight gain	36	35,3	22,5	12,7
Weight loss	23	22,5	11,8	10,8

Table 2. Comparisons between groups exposed and unexposed to simultaneous doxorubicin and cyclophosphamide during chemotherapy treatment in relation to hematological and functional variables.

Variables	G1		G2		Overall		
Participants	102		17		119		
Mean age	52.4		59.7		53.4		p-value§
Standard deviation	±10.9		±12.4		±11.4		
	N	%	N	%	N	%	
Hemoglobin (g/dL)							
≥ 11,5	75	63	14	11,8	89	74,8	0.556†
< 11,5 e ≥ 10,0	22	18,5	2	1,7	24	20,2	
< 10,0	5	4,2	1	0,8	6	5	
Hematocrit (%)							
≥ 36	73	61,3	15	12,6	88	73,9	0.232†
< 36 e ≥ 30	28	23,5	2	1,7	30	25,2	
< 30	1	0,8	0	0	1	0,8	
Leukocytes (cel/mm³)							
≥ 4.000	80	67,2	15	12,6	95	79,8	0.518†
< 4.000 e ≥ 3.000	20	16,8	1	0,8	21	17,6	
< 3.000 e ≥ 2.000	2	1,7	1	0,8	3	2,5	
Neutrophils (cel/mm³)							
≥ 1.600	91	76,5	16	13,4	107	89,9	1†
< 1.600 e ≥ 1.500	5	4,2	0	0	5	4,2	
1.500 e ≥ 1.000	6	5	1	0,8	7	5,8	

Platelets (mil/mm³)							
≥ 150	102	85,7	16	13,4	118	99,2	0.142†
< 150 e ≥ 75	0	0	1	0,8	1	0,8	
Fatigue							
No	7	5,9	1	0,8	8	6,7	1†
Yes	95	79,8	16	13,4	111	93,3	
Mild or moderate	66	59,5	13	11,7	79	71,2	
Severe	29	26,1	3	2,7	32	28,8	
Fever (°C)							
No	81	68,1	14	11,8	95	79,8	1†
Yes	21	17,6	3	2,5	24	20,2	
≥ 38 e < 39	18	75	1	4,2	19	79,2	
≥ 39	3	12,5	2	8,3	5	20,8	
Weight gain (%)							
No	66	55,5	9	7,6	75	63	0.352
Yes	36	30,3	8	6,7	44	37	
≥ 5 e < 10	27	61,4	6	13,6	33	75	
≥ 10	9	20,5	2	4,5	11	25	
Weight loss (%)							
No	79	66,4	16	13,4	95	79,8	0.189†
Yes	23	19,3	1	0,8	24	20,2	
≥ 5 e < 10	12	50	1	4,2	13	54,2	
≥ 10	11	45,8	0	0	11	45,8	

G1: exposed to chemotherapy with simultaneous doxorubicin and cyclophosphamide; G2: unexposed group; N: absolute frequencies; %: relative frequencies; DP: standard deviation; *: p-value <0,05; §: x^2 - Pearson's chi-squared test; †: Fisher's exact test.

Table 3. Comparison of hematological and functional changes associated with doxorubicin and cyclophosphamide by age.

Variables	**G3**		**G4**		**Overall**		
Participants	60		42		102		
Mean age	45.3		62.6		52.4		
Standard deviation	±6.8		±6.7		±10.9		
	N	**%**	**N**	**%**	**N**	**%**	**p-value§**
Hemoglobin (g/dL)							
≥ 11,5	43	42,2	32	31,4	75	73,5	0.610
< 11,5 e ≥ 10,0	16	15,7	6	5,9	22	21,6	
< 10,0	1	1	4	3,9	5	4,9	
Hematocrit (%)							
≥ 36	41	40,2	32	31,4	73	71,6	0.386
< 36 e ≥ 30	19	18,6	9	8,8	28	27,4	
< 30	0	0	1	1	1	1	
Leukocytes (cel/mm³)							
≥ 4.000	45	44,1	35	34,3	80	78,4	0.313
< 4.000 e ≥ 3.000	14	13,7	6	5,9	20	19,6	
< 3.000 e ≥ 2.000	1	1	1	1	2	2	

Neutrophils (cel/mm³)							
≥ 1.600	53	52	38	37,3	91	89,2	1†
< 1.600 e ≥ 1.500	4	3,9	1	1	5	4,9	
< 1.500 e ≥ 1.000	3	2,9	3	2,9	6	5,9	
Platelets (mil/mm³)							
≥ 150	60	58,8	42	41,2	102	100	1†
< 150 e ≥ 75	0	0	0	0	0	0	
Fatigue							
No	2	2	5	4,9	7	6,9	0.120†
Yes	58	56,9	37	36,3	95	93,1	
Mild or moderate	34	35,8	32	33,7	66	69,5	
Severe	24	25,3	5	5,3	29	30,5	
Fever (°C)							
No	44	43,1	37	36,3	81	79,4	0.069
Yes	16	15,7	5	4,9	21	20,6	
≥ 38 e < 39	13	61,9	5	23,8	18	85,7	
≥ 39	3	14,3	0	0	3	14,3	
Weight gain (%)							
No	37	36,3	29	28,4	66	64,7	0.442
Yes	23	22,5	13	12,7	36	35,3	
≥ 5 e < 10	17	47,2	10	27,8	27	75	
≥ 10	6	16,7	3	8,3	9	25	
Weight loss (%)							
No	48	47,1	31	30,4	79	77,4	0.502
Yes	12	11,8	11	10,8	23	22,5	
≥ 5 e < 10	4	17,4	8	34,8	12	52,2	
≥ 10	8	34,8	3	13	11	47,8	

G3: exposed to chemotherapy combined with doxorubicin and cyclophosphamide aged <55 years; G4: exposed to chemotherapy combined with doxorubicin and cyclophosphamide aged ≥ 55 years; N: absolute frequencies; %: relative frequencies; DP: standard deviation; *: p-value <0,05; §: x^2 - Pearson's chi-squared test; †: Fisher's exact test.

Table 4. Comparison of hematological changes associated with doxorubicin and cyclophosphamide delivered with taxane agents.

Variables		**G5**		**G6**		**Overall**	**p-value§§**
Participants		27		75		102	
Mean age		54.6		51.6		52.4	
Standard deviation	±12.3	±10.3	±10.9				
	N	**%**	**N**	**%**	**N**	**%**	
Hemoglobin (g/dL)							
≥ 11,5	23	22,5	52	51	75	73,5	0.109
< 11,5 e ≥ 10,0	1	1	21	20,6	22	21,6	
< 10,0	3	2,9	2	2	5	4,9	
Hematocrit (%)							
≥ 36	24	23,5	49	48	73	71,6	0.019*
< 36 e ≥ 30	3	2,9	25	24,5	28	27,4	

< 30	0	0	1	1	1	1	
Leukocytes (cel/mm³)							
≥ 4.000	22	21,6	58	56,9	80	78,4	0.653
< 4.000 e ≥ 3.000	5	4,9	15	14,7	20	19,6	
< 3.000 e ≥ 2.000	0	0	2	2	2	2	
Neutrophils (cel/mm³)							
≥ 1.600	25	24,5	66	64,7	91	89,2	0.723†
< 1.600 e ≥ 1.500	0	0	5	4,9	5	4,9	
< 1.500 e ≥ 1.000	2	2	4	3,9	6	5,9	
Platelets (mil/mm³)							
≥ 150	27	26,5	75	73,5	102	100	1†
< 150 e ≥ 75	0	0	0	0	0	0	

G5: exposed to chemotherapy combined with doxorubicin and cyclophosphamide without taxanes; G6: exposed with associated taxane agent (simultaneously or in sequence); N: absolute frequencies; %: relative frequencies; DP: standard deviation; *: p-value <0,05; §: x^2 - Pearson's chi-squared test; †: Fisher's exact test.

DISCUSSION

It is necessary to report, as an important limitation for the interpretation and application of these results, that the included hematological changes took into account the information available in the medical records up to the collection period. Although hematological toxicity is considered acute and dependent on myelosuppressive antineoplastic drugs in the treatment of breast cancer, chronic toxicity still lacks more consistent approaches[3,4]. Other limitations are presented in the first publication[8], such as the lack of training to fill in clinical records and the absence of sample sizing.

Although the probability of toxicity is higher, the use of combinations of antineoplastic drugs is the best strategy to reduce drug resistance and maintain an acceptable cytotoxic function. However, the hematopoietic damage caused by these combinations is one of the main causes of therapeutic failures associated with chemotherapy[3,5].

Currently, in experimental models, there is evidence that doxorubicin associated with cyclophosphamide induces a reduction in hematopoietic cellularity and causes an increase in lipids within the bone marrow, increasing the area filled with adipocytes. The increase in these cells can be justified by the increase in mRNA of genes regulating adipogenesis, such as PPARc and FABP[4]. In addition, this combination may cause an increase in tumor necrosis factor-alpha (TNF-α), a cytokine that negatively regulates hematopoiesis, inhibiting it[2].

Considering the inhibition of hematopoiesis, an important connection involves breast cancer patients treated with myelosuppressive chemotherapy. Changes in bone mineral density (BMD) can be related to the occurrence of breast cancer, as well as chemotherapy in pre-menopausal women can reduce estrogen levels and affect BMD. In addition, breast cancer in postmenopausal women can accentuate mineral loss. Lastly, a dysregulation in bone metabolism and inadequate activities of osteoblasts and osteoclasts can result in the production of proteins that inhibit the formation of blood cells, such as osteopontin[10]. In the findings of this sample, 10 women (8,4%) had osteoporosis, establishing an important link between conditions.

Other animal experiments indicate that the slow infusion rate of doxorubicin can cause several acute and significant toxicities when compared to the faster infusion rate. In murine models, after 48 hours of administration, doxorubicin caused hepatic, renal, and cardiovascular toxicity verified by several lesion markers, as well as increased serum levels of interleukin 6 (IL-6) and TNF-α[11]. In addition, doxorubicin can cause intestinal lesions that trigger the increase of endotoxins from the intestinal flora to the circulation, as well as increased expression of Toll-like receptor 4 (TLR4) in macrophages, making them more susceptible to intestinal endotoxins, increasing induced toxicity[12].

On the other hand, it is worth noting that chemotherapy with bone marrow depressant drugs and hematopoiesis can cause anemia due to the reduced amount of serum hemoglobin. When anemia is present prior to cancer diagnosis, it can be aggravated by treatment and the prognosis can worsen. In addition, low levels of hemoglobin increase the secretion of erythropoietin, correlated with the emergence of tumor cells resistant to chemotherapy[13]. Considering the patients who manifested some toxicity during the chemotherapy, 26% presented a reduction in hematocrit and 25,2% in hemoglobin.

Evidence also supports that neutropenias may be recurrent in patients using doxorubicin and cyclophosphamide due to the susceptibility of neutrophils to chemotherapeutic agents. Patients with reduced neutrophils may be more affected by

fevers and infections. In the findings of this sample, 9,2% of the patients who manifested toxicity had neutropenia when exposed to the combination of doxorubicin and cyclophosphamide. Anemias and neutropenias are the most frequent hematological toxicities in women with breast cancer treated with myelosuppressive chemotherapy[13,14,15].

In fact, women undergoing chemotherapy are prone to the development of hematological toxicities, especially those over 65 years of age. In addition, they may also be more likely to interrupt treatment or die from complications associated with damage caused by antineoplastic agents in the bone marrow. Overall, women with breast cancer may be 14,6 times more susceptible to neutropenia and three times more susceptible to anemia[16]. When comparing the findings by age group, it was not observed such differences were associated with age at the border of 55 years.

Considering other drugs present in the therapeutic arsenal for breast cancer and identified in the sample, a meta-analysis did not identify recurrent hematological changes associated with anastrozole or tamoxifen. For these drugs, hematological adverse effects were related only to thromboembolic events, especially with the use of tamoxifen[17]. In this sample, thrombocytopenias associated with doxorubicin and cyclophosphamide were not reported.

An epidemiological study involving women with breast cancer older than 65 years identified that 6.272 underwent chemotherapy with simultaneous administration of doxorubicin and cyclophosphamide. In their results, the authors identified that there is a significant risk for the development of anemia and the risk of bone marrow toxicity was greater in women who used protocols involving anthracyclines, alkylants, and taxanes[16].

In the results of this investigation, paclitaxel and docetaxel were the most frequent taxane antineoplastic agents in patients who did not expose to doxorubicin and cyclophosphamide, observed in 35,3% and 17,6% of the sample (alone or in combination with other drugs than simultaneous doxorubicin and cyclophosphamide), respectively. Considering the low occurrence of hematotoxicity due to anastrozole and tamoxifen, cases of hematological changes in the unexposed group may be associated with these drugs. In addition, in the group exposed to doxorubicin and cyclophosphamide with subsequent use of taxane, there was a significant reduction in hematocrit ($p=0.019$), reinforcing this probable association.

A comparative meta-analysis between combinations of antineoplastic agents and general toxicities in women with advanced breast cancer concluded that, in relation to febrile neutropenia, the combination of doxorubicin and cyclophosphamide was less toxic than the combination of doxorubicin and paclitaxel or docetaxel. However, for metastatic breast cancer, the literature presents evidence that doxorubicin and paclitaxel are first-line drugs and have better response and survival rates compared to other drugs[18].

Moreover, the clinical relevance of understanding phenomena related to changes in body composition consists, among other aspects, in the influence of self-image during chemotherapy treatment, considering the quality of life and self-esteem of women with breast cancer. In addition to this perspective, the increase in fat mass and the reduction of lean mass may increase mortality in this population[6,7,19]. In the findings of this sample, more than 35% of patients who manifest some toxicity increased at least 5% of their initial body weight after chemotherapy. However, the combination of doxorubicin and cyclophosphamide was not associated with this outcome in relation to the unexposed group.

Available meta-analyzes on the topic infer that the gain of 10% or more of body weight increases mortality, as well as the percentage of fat mass, can interfere with the occurrence of toxicities during chemotherapy treatment, reducing the dose of antineoplastic agents. In addition, during chemotherapy for breast cancer, patients may experience an average gain of 2,7 kg[20,21]. It is worth noting that obesity is related to an increased risk of breast cancer since excess adipose tissue produces cytokines and inflammatory mediators that favor the invasion of neoplastic cells, in addition to changes in self-image[22].

Fatigue, on the other hand, is one of the most recurrent functional symptoms experienced by women undergoing chemotherapy, associated with systemic inflammatory markers often elevated in women with breast cancer. Cases of severe or persistent fatigue are related to recurrence and increased mortality from breast cancer, although the mechanisms that cause this condition have not yet been fully elucidated[23,24]. Currently, among other possible causes, it is known that radiotherapy can also trigger fatigue in women with breast cancer undergoing treatment[25]. Considering the need to manage this condition to prevent impacts on health and quality of life, several approaches have been investigated, including dietary guidance, yoga practice, and physical exercises[25,26,27].

CONCLUSION

During chemotherapy treatment of women with invasive ductal breast carcinoma who were exposed to the combination of doxorubicin and cyclophosphamide, when comparing them with unexposed patients, a greater occurrence of hematotoxicities or functional impacts was not observed, except when associated with taxanes. On the other hand, expressive frequencies of these toxicities were observed in the sample, indicating that women who were exposed to breast cancer chemotherapy treatment can often manifest them, requiring preventive measures.

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Como citar este artigo/ How to cite this article:
Kameo SY, Ramos MJO, Lima RB, Amorim BF, Santos JC, Marinho PML, et al. Hematotoxicity and functional impacts related to chemotherapy with doxorubicin and cyclophosphamide for invasive ductal breast carcinoma: a study in clinical records. J Health Biol Sci. 2021; 9(1):1-8.