RESEARCH ARTICLE

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Evaluation of Pathological Complete Response Rate in Patients with *HER2*-Positive Breast Cancer Undergoing Neoadjuvant Trastuzumab and Chemotherapy With or Without Anthracycline

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Abstract

Objective: This study aimed to evaluate the pathological complete response rate (pCR) in *HER2* breast cancer by comparing anthracycline-containing and anthracycline-free regimens. **Methods:** A retrospective cohort study was performed to obtain data from women undergoing neoadjuvant chemotherapy associated with two groups: • AC-TH patients: treated with trastuzumab with confirmed *HER2*-positive breast cancer using an anthracycline-based therapy followed by taxane. • CTH patients: recieved trastuzumab concurrently during taxane use in an anthracycline-free regime (carboplatin plus a taxane). Clinical data, pCR, free-disease survival, and overall survival were compared using chi-square, log-rank Mantel-cox, multinomial logistic and Cox regression tests ($p < 0.05$, SPSS v20.0). **Results:** There are no differences between AC-TH and CTH in terms of: • pCR (p=0.745), •Disease- free survival (p=0.840), • Overall survival (p=0.642). The major prognostic factor for overall survival were: • Nodal metastasis (p=0.043, HR = 0.263 (CI95% = 0.072-0.959) and • Dose reduction (p=0.021, HR = 0.070 (CI95% = 0.007-0.667) and For disease-free survival: • Age (p=0.038, HR = 3.288, CI95% 1.068-10.123) and • pCR (p=0.028, HR = 0.354, CI95% = 0.140-0.895). AC-TH showed more cardiotoxicity (9.3% vs 3.4%). **Conclusion:** Chemotherapy regimens with or without anthracycline, when combined with trastuzumab, demonstrate similar rates of pathological complete response and recurrence-free survival. Pathological complete response and age are independent variables associated with recurrence. However, the use of anthracycline leads to increased cardiotoxicity.

Keywords: Breast Neoplasms- Genes- erbB-2- Trastuzumab- Chemotherapy

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Introduction

Breast cancer is a malignant neoplasm with a high incidence worldwide (accounting for 11.7% of all cancer cases), with 2,261,419 new cases in 2020 [1]. In Brazil, it is the most common cancer in females. In the 2020-2022 triennium, it was estimated that there would be 66,280 new cases per year, with an incidence of 61.61 cases per 100,000 women [2].

Breast neoplasia is a heterogeneous disease; the primary histology found includes non-special type carcinoma, which accounts for 70-75% of cases, and lobular carcinoma, with 10-14%, while the remainder is divided into 17 other histological types. Molecular subtypes are essential to define which treatment will be used. They can be classified according to the expression of estrogen and progesterone hormone receptors, the overexpression of the human epidermal growth factor receptor 2 (*HER2*) receptor, and the assessment of the cell proliferation marker, *Ki67* [3-5].

The expression of hormonal receptors comprises the luminal A and B subtypes (which are defined based on *Ki67* percentage and progesterone receptor expression). *HER2* overexpression or gene amplification characterizes the *HER2*-enriched subtype, and the absence of all markers defines the triple-negative subtype, regardless of *Ki67* values. Luminal subtypes account for approximately 80% of cases, followed by the *HER2*-enriched subtype, which represents about 20% of cases, and triple-negative tumors between 10-15% [3, 6]

The *HER2* protein belongs to a family of four transmembrane tyrosine kinase receptors. Its ligand is not yet known. When activated, it initiates intracellular signaling pathways that culminate in cell proliferation and

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survival. Thus, *HER2* overexpression or amplification is an independent adverse prognostic factor [7].

The development of anti-*HER2* therapies using monoclonal antibodies (such as trastuzumab and pertuzumab) has changed the natural history of the disease. Adding trastuzumab to first-line chemotherapy for metastatic disease increased the median overall survival from 20.3 months to 25.1 months [8]. Subsequently, dual anti-*HER2* blockade with trastuzumab and pertuzumab, combined with chemotherapy for metastatic disease, achieved a median overall survival of 57.1 months [9].

The use of these medications has also been evaluated in initial treatment with curative intent. In the neoadjuvant setting, incorporating trastuzumab into chemotherapy increased the pathological complete response rate, ranging in the literature from about 15-19% to 31.7-56.5% [10-12]. By adding pertuzumab to the chemotherapy and trastuzumab regimen, an increase in the rate of pathological complete response to as high as 66.2% was demonstrated [13].

We define pathological complete response as the absence of residual neoplasia in the breast (allowing for the presence of 'in situ' neoplasia) and axilla assessed after curative surgery in patients undergoing neoadjuvant therapy. It is evaluated in the surgical specimen through histopathological examination and reported as ypT0/Tis ypN0. Accumulating current data allows a correlation between pathological complete response and overall survival [14].

Thus, dual anti-*HER2* therapy becomes mandatory. However, due to the financial cost of associating pertuzumab, this medication has not become accessible for many patients in numerous healthcare systems in neoadjuvant therapy despite its proven benefit. Currently, these patients are treated with chemotherapy regimens combined only with trastuzumab. Without dual anti-*HER2* blockade, the ideal chemotherapy regimen for omitting anthracyclines without compromising treatment efficacy is still discussed in this scenario.

Anthracyclines are chemotherapeutic agents with well-documented side effects. They are cardiotoxic drugs that can induce irreversible myocardial injury, with an increased risk according to cumulative doses: 3-5% with 400mg/m² and 18-48% with 700mg/m². The specific mechanism of this adverse effect remains unexplained, but it is believed to be due to the generation of reactive oxygen species and direct damage to myocyte DNA [15].

In an attempt to omit the use of anthracyclines in the neoadjuvant treatment of *HER2*-positive breast cancer, several studies were conducted to assess the efficacy of treatment with or without this medication. In patients undergoing dual anti-*HER2* blockade with trastuzumab and pertuzumab, anthracycline-free chemotherapy is equally effective in the neoadjuvant setting [13, 16]. When pertuzumab is not used, small single-arm studies have shown variable rates of pathological complete response with anthracycline-free chemotherapy regimens, ranging from 19.4% to 45% [16-18].

Studies comparing both therapies demonstrate controversial results regarding the use or non-use of anthracyclines in neoadjuvant treatment in patients exposed to *HER2* blockade only with trastuzumab. Two retrospective studies showed a better rate of pathological complete response and recurrence-free survival with anthracycline-containing regimens, with statistical significance [19, 20]. A randomized phase II study that also compared both chemotherapy regimens showed conflicting results, with the treatment without anthracycline being superior in the pathological complete response rate [21].

The most robust data on chemotherapy with or without anthracycline associated with trastuzumab come from an adjuvant treatment study that demonstrated that both regimens, combined with trastuzumab, are similar regarding overall survival [22].

Therefore, it is known that in *HER2*-positive breast cancer patients who undergo neoadjuvant treatment with dual *HER2* blockade, the omission of anthracycline does not compromise treatment efficacy. However, in patients who do not have access to pertuzumab, the comparison between chemotherapy regimens with or without the use of anthracycline remains controversial. Phase II study data demonstrate a reasonable rate of pathological complete response, and studies in the adjuvant setting confirm equal efficacy between the therapies. However, retrospective analyses with long-term follow-up demonstrate a lower pathological complete response rate and recurrence-free survival. Hence, it is necessary to conduct studies comparing neoadjuvant treatment only with trastuzumab and chemotherapy with or without anthracycline.

Materials and Methods

Study characteristics

The study had a retrospective, quantitative, epidemiological, and analytical cohort design. It was conducted by reviewing patients' medical records at Haroldo Juaçaba Hospital- Cancer Institute of Ceará from 2017 to 2022.

Study sample and data collection

The study population consisted of the medical records of female patients treated at Haroldo Juaçaba Hospital - Cancer Institute of Ceará with *HER2*-positive breast cancer undergoing neoadjuvant therapy with trastuzumab and chemotherapy with or without anthracycline, meeting the inclusion criteria. Based on the study by GAO [21], which demonstrated that the rate of pathological complete response in breast cancer patients undergoing TCH was significantly higher than in patients treated with EC-TH, it was estimated to evaluate 258 patients to obtain a sample that represents 90% power and 95% confidence, the alternative hypothesis of this study (Fleiss method with continuity correction). Data collection was performed by evaluating medical records using a form designed by the author to standardize information regarding age, initial staging, presence of hormonal receptors, *Ki67* value determined by immunohistochemistry, chemotherapy regimen performed according to the study's inclusion criteria, and achievement of pathological complete response defined as ypT0/is ypN0 in the histopathological result obtained after surgery.

Inclusion criteria

Female patients of any age undergoing neoadjuvant chemotherapy associated with trastuzumab with confirmed *HER2*-positive breast cancer by immunohistochemistry (positive 3+) or fluorescence in situ hybridization with amplified results, in the case of immunohistochemistry with positive 2+, as defined by the American Society of Clinical Oncology/College of American Pathologists.

Chemotherapy regimens included were anthracycline-based therapy followed by taxane or vice versa (AC, EC -> TH), with trastuzumab associated during taxane use, and anthracycline-free regimens consisting of carboplatin plus a taxane, either paclitaxel or docetaxel (TCH), and patients who underwent curative surgery after completing neoadjuvant treatment.

Exclusion criteria

Patients outside the study's defined period, patients with other malignancies, those diagnosed with metastatic disease at diagnosis or during neoadjuvant treatment, those who received other chemotherapy or hormone therapy outside the inclusion criteria, those who did not undergo curative surgery, and those who did not use trastuzumab or who used pertuzumab.

Statistical design

Data were tabulated in a standard Microsoft Excel spreadsheet and exported to SPSS software for analysis with a confidence level of 95%. All variables ' absolute and percentage frequencies, means, and standard deviations were calculated and associated with the intervention group using Fisher's exact test or Pearson's chi-square test and Mann-Whitney (non-parametric data). Additionally, Kaplan-Meier curves of recurrence-free survival were constructed by calculating the difference between the recurrence date or last visit and the start date of neoadjuvant chemotherapy. The Log-Rank Mantel-Cox test and Cox regression associated the curves with the intervention group.

Ethical principles

All patient records were studied using the principles of the Declaration of Helsinki and the Nuremberg Code, respecting the Human Research Standards (Resolution CNS 196/96) of the National Health Council. Data were collected after approval from the supervisor, Haroldo Juaçaba Hospital - Cancer Institute of Ceará, the Ethics and Research Committee of Haroldo Juaçaba Hospital, and approval from the hospital's technical director. As this was a retrospective chart review, the need for a Free and Informed Consent Form (FICF) was waived by the CEP/CONEP system. It's important to note the difficulty in contacting the patients involved in the study and/or their families, as many lack updated information in the hospital's database, and many patients live in rural areas and do not regularly visit the hospital. By signing the Custodial Responsibility Form, the researcher committed to maintaining the participants' privacy in the research protocol. Moreover, the researcher ensured that the information was used solely for the execution of this project and committed to disclosing this collected information anonymously.

Results

Our cohort comprised data from 166 patients with an average age of 49.93±10.05 years; 108 underwent anthracycline-based neoadjuvant chemotherapy and 58 without anthracycline. Overall, 54% of the patients were premenopausal at diagnosis. The majority (92.2%) presented with grade II or III tumors. T3 tumors represented 44.4%, and T4 tumors 25.9% of the cases. Clinical lymph node involvement was observed in 89.2% of patients, and 33.5% did not express hormonal receptors (Table 1). Our sample mainly consisted of high-risk patients, locally advanced and high-grade (Figure 1).

The observed rate of pathological complete response in the univariate analysis was 50% in the entire population, with 50.9% for the anthracycline group and 48.3% for the non-anthracycline group (p 0.745), demonstrating similar efficacy that did not reach statistical significance between

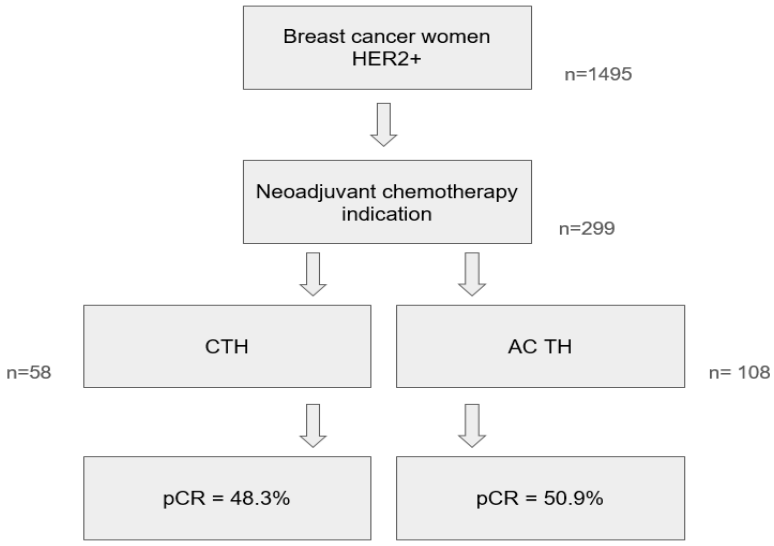

Figure 1. Flow Chart of Inclusion of Breast Cancer Women *HER2*+ and Neoadjuvant Treatment

Table 1. Clinical Profile of *HER2*-Positive Breast Cancer Patients Undergoing Neoadjuvant Chemotherapy with Trastuzumab with or without Anthracycline.

		Use of Anthracycline	
	Total (n=166)	No (n=58)	Yes (n=108)
Age at diagnosis			
Up to 50 years	83 (50.0%)	25(43.1%)	58(53.7%)
> 50 years	83 (50.0%)	33(56.9%)	50(46.3%)
Menopausal status			
Pre-menopause	91 (54.8%)	28 (48.3%)	63 (58.3%)
Post-menopause	75 (45.2%)	30 (51.7%)	45 (41.7%)
BMI			
Eutrophic	42 (25.3%)	15 (25.9%)	27 (25.0%)
Overweight	68 (41.0%)	19 (32.8%)	49 (45.4%)
Obesity	56 (33.7%)	24 (41.4%)	32 (29.6%)
T			
Tx	4 (2.5%)	-	4 (3,7%)
T1/2	48 (28.9%)	21 (36.2%)	27 (25.0%)
T3	72 (43.3%)	24 (41.4%)	48 (44.5%)
T4	42 (25.3%)	13 (22.4%)	29 (26.8%)
N			
N0	18 (10.8%)	7 (12.1%)	11 (10.2%)
N+	148 (89.2%)	51 (87.9%)	97 (89.8%)
Hormone receptors			
Positive	55 (33.1%)	22 (37.9%)	33 (30.6%)
Negative	109 (65.7%)	34 (58.7%)	75 (69.4%)
Not available	2 (1.2%)	2 (3.4%)	-
Ki67			
Up 14%	18 (11.0%)	7 (12.1%)	11 (10.2%)
> 14%	146 (89.0%)	49 (84.5%)	97 (89.8%)
Not available	2 (1.2%)	2 (3.4%)	-
Histological grade			
I	13 (7.8%)	3 (5.2%)	10 (9.3%)
II	120 (72.3%)	45 (77.6%)	75 (69.4%)
III	33 (19.9%)	10 (17.2%)	23 (21.3%)
Dose reduction			
No	152 (91.6%)	55 (94.8%)	97 (89.8%)
Yes	14 (8.4%)	3 (5.2%)	11 (10.2%)
Surgery			
Mastectomy	101 (60.8%)	36 (62.1%)	65 (60.2%)
Quadrantectomy	65 (39.2%)	22 (37.9%)	43 (39.8%)
Axillary emptying			
No	82 (49.4%)	28 (48.3%)	54 (50.0%)
Yes	84 (50.6%)	30 (51.7%)	54 (50.0%)

Data showed as frequency and percentage; BMI, body mass index.

the two treatments.

In subgroup analysis, the population with node-negative status achieved the highest rate of pathological complete response, 72.2% (p 0.04), while patients who underwent dose reduction had the lowest, 14.3% (p 0.05); no significant differences were observed in other subgroups compared to the total population.

In our multivariate analysis, the presence of node-negative status was shown to be an independent positive predictive factor for pathological complete response (HR 0.263; 95% CI 0.072-0.959; p 0.04) and non-reduction of the recommended dose (HR 0.07; 95% CI 0.007-0.667; p 0.021) (Table 2). According to the chemotherapy regimen, no regimen demonstrated superiority in any subgroup (Figure 2).

Table 2. Multivariate Analysis of Complete Pathological Response and Recurrence-Free survival in *HER2+* Breast Cancer Patients Undergoing Neoadjuvant Chemotherapy with Trastuzumab with or without Anthracycline.

	p-value	HR (IC95%)
Complete pathological response*		
Chemotherapy regimen	840	1.081 (0.505-2.315)
Age diagnosis	341	0.480 (0.106-2.173)
Histological grade	146	3.235 (0.666-15.725)
Status menopausal	542	1.361 (0.505-3.663)
T	554	1.354 (0.497-3.691)
N	43	0.263 (0.072-0.959)
RH	844	0.928 (0.438-1.963)
Ki67	518	0.681 (0.212-2.184)
Dose reduction	21	0.070 (0.007-0.667)
Recurrence-free survival**		
Chemotherapy regimen	642	1.320 (0.409-4.255)
Age diagnosis	38	3.288 (1.068-10.123)
Histological garde	315	0.594 (0.214-1.643)
Menopausal status	4	0.069 (0.011-0.428)
T	109	2.028 (0.854-4.817)
N	253	0.309 (0.041-2.316)
RH	585	1.454 (0.380-5.563)
Ki67	365	0.532 (0.136-2.080)
Dose reduction	357	0.400 (0.057-2.808)
Complete pathological response	28	0.354 (0.140-0.895)

*p<0.05, multinomial logistic regression; **Cox regression

The recurrence rate between the groups over the entire follow-up period (34.80±16.29 months in the

Table 3. Toxicity in *HER2*-Positive Breast Cancer Patients Undergoing Neoadjuvant Chemotherapy with Trastuzumab with or without Anthracycline

		Use of Anthracycline	
	Total (n=166)	No (n=58)	Yes (n=108)
Cardiotoxicity of any degree	12 (7.2%)	2 (3.4%)	10 (9.3%)
Toxicity G3/G4	16 (9.6%)	7 (12.1%)	9 (8.3%)
Anemia	3 (1.8%)	2 (3.4%)	1 (0.9%)
Diarrhea	4 (2.4%)	3 (5.2%)	1 (0.9%)
Cardiotoxicity	2 (1.2%)	0 (0.0%)	2 (1.9%)
Neutropenia	5 (3.0%)	1 (1.7%)	4 (3.7%)
Myalgia	1 (0.6%)	0 (0.0%)	1 (0.9%)
thrombocytopenia	1 (0.6%)	1 (1.7%)	0 (0.0%)

Data showed as frequency and percentage; BMI, body mass index.

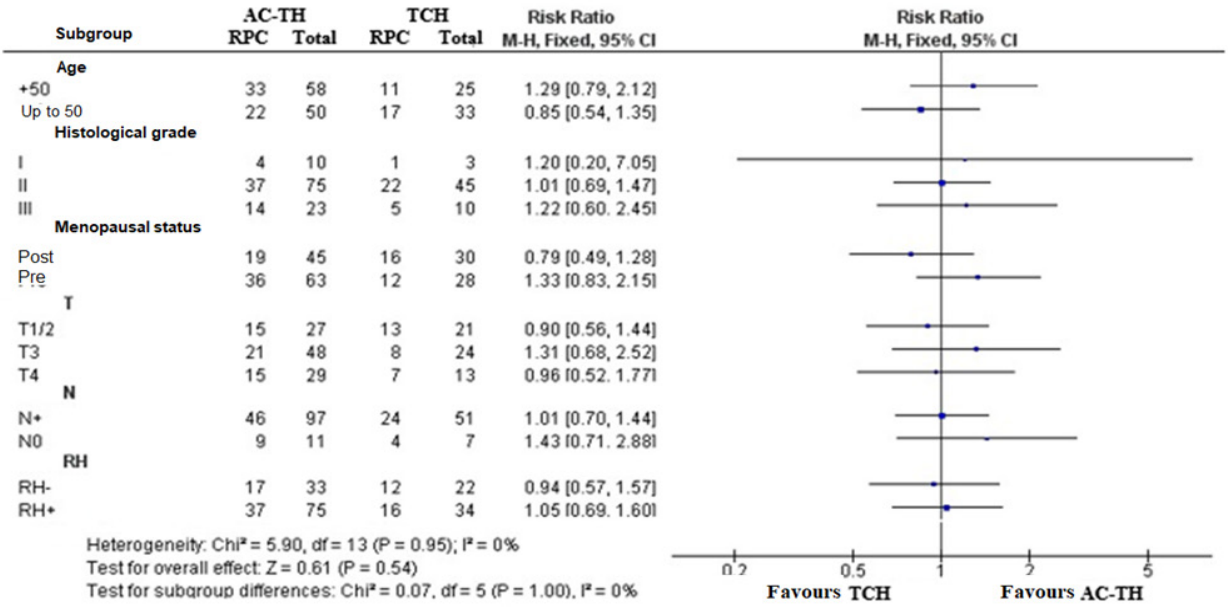

Figure 2. Forest Plot Showing the Analysis of Complete Pathological Response in Subgroups Undergoing Neoadjuvant Chemotherapy with Trastuzumab with or without Anthracycline

anthracycline group and 21.85±18.60 months in the non-anthracycline group, mean 30.27±18.16 months) was 14.8% in the anthracycline group and 8.6% in the non-anthracycline group (p 0.252), with 34.8% being locoregional recurrences. The most common distant recurrence sites were the lung, central nervous system, liver, and bones. In multivariate analysis, increasing age was shown to be an independent risk factor for recurrence

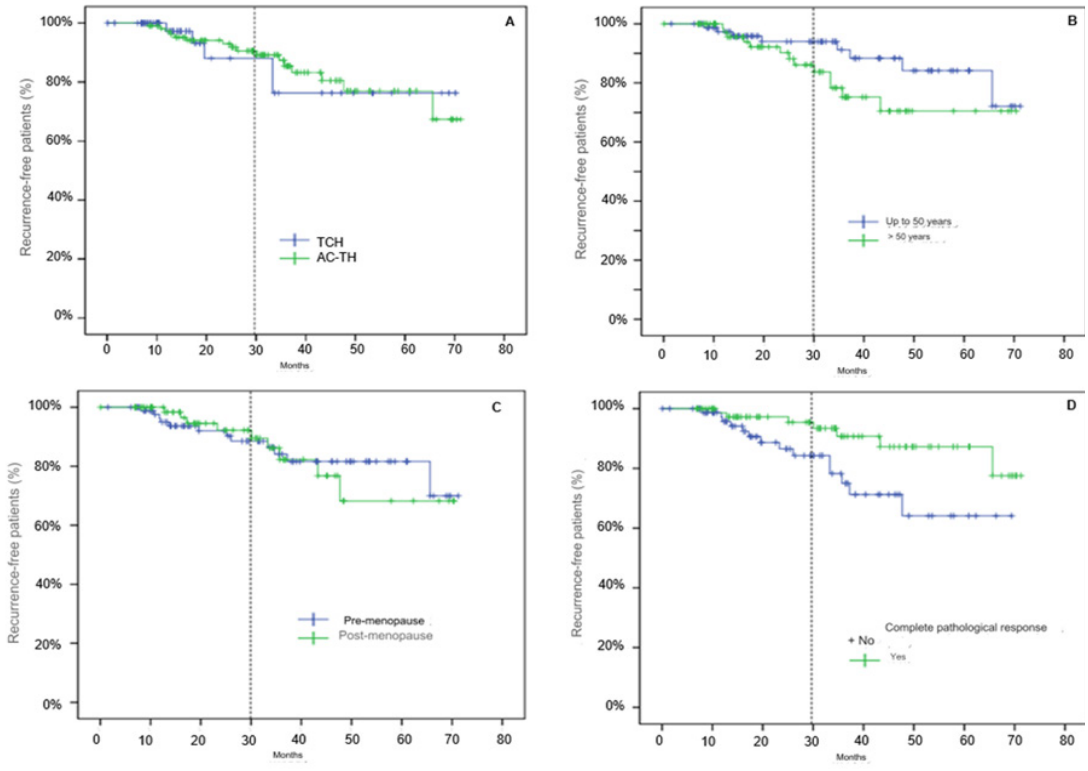

Figure 3. Recurrence-Free Survival of *HER2+* Breast Cancer Patients Undergoing Neoadjuvant Chemotherapy with Trastuzumab with or without Anthracycline. A - Recurrence-free survival at 30 months was TCH 94.8% vs. AC-TH 90.7% (p 0.546). The average recurrence-free survival time for patients who did not receive anthracycline (59.5±4.3, 95% CI 51.1-67.9 months) showed no significant difference from the group that received anthracycline (61.3±2.2, 95% CI 56.9-65.6 months) (p 0.879). B - Recurrence-free survival at 30 months was 95.2% vs. 89.2% (p 0.126) in the under-50 age group and in the over-50 age group, respectively. C - Recurrence-free survival at 30 months was 91.2% vs. 93.3% (p 0.74) in the premenopausal group and in the postmenopausal group, respectively. D - Recurrence-free survival at 30 months was 95.2% vs. 89.2% (p 0.023) in the group that achieved pathological complete response and in the group that did not achieve pathological complete response, respectively.

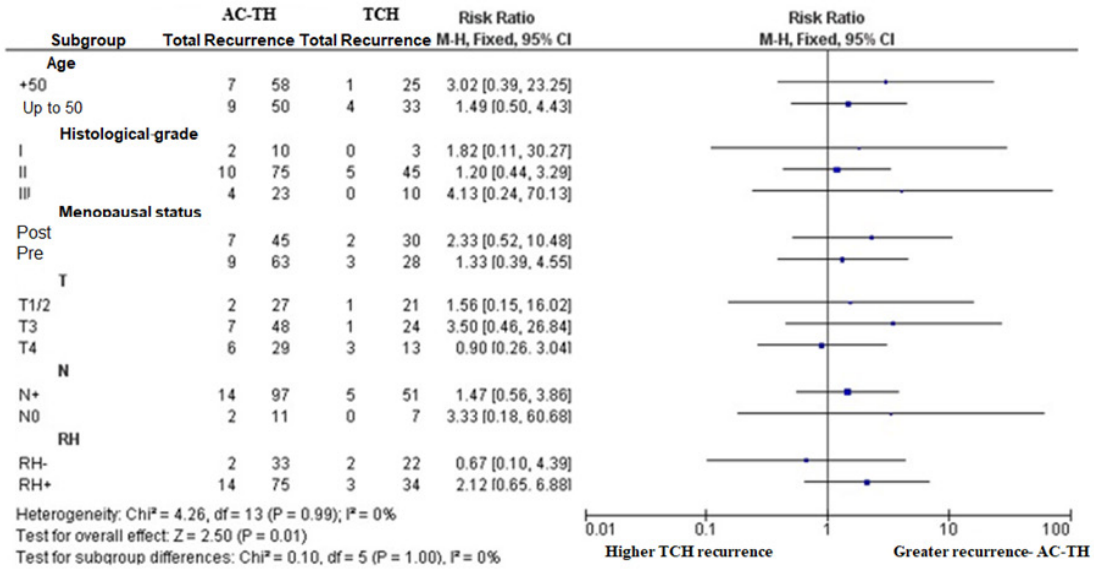

Figure 4. Forrest Plot Analyzing Recurrence in Subgroups Undergoing Neoadjuvant Chemotherapy with Trastuzumab with or without Anthracycline.

(HR 3.28; 95% CI 1.068-10.123; p 0.03), and pathological complete response also correlated with recurrence (HR 0.354; 95% CI 0.140-0.895; p 0.02) (Table 3).

Estimated recurrence-free survival at 30 months was 90.7% in the anthracycline group and 94.8% in the non-anthracycline group (p 0.54). The group that achieved pathological complete response was 95.2%, compared to 89.2% in the group that did not reach it (p 0.023) (Figure 3). Evaluating subgroups according to the chemotherapy regimen used, there was a tendency towards higher recurrence with anthracycline use in most subgroups, but without statistical significance (Figure 4).

Regarding adverse effects, any-grade cardiotoxicity was observed in 9.3% of patients who used anthracycline and 3.4% of the non-anthracycline group (p 0.168), with grade G3/G4 only in the anthracycline group in 2 patients (1.9%). All patients experienced cardiotoxicity during the adjuvant phase; none showed irreversibility, with only one patient improving upon suspension of adjuvant trastuzumab without needing beta-blockers or ACE inhibitors/ARBs. Three patients did not complete adjuvant trastuzumab doses after experiencing cardiotoxicity. Other G3/G4 toxicities were 8.3% in the anthracycline group, including febrile neutropenia (3.7%), cardiotoxicity (1.9%), anemia, myalgia, and diarrhea (<1%). The non-anthracycline group presented 12.1% of G3/G4 toxicities, with diarrhea and anemia accounting for 5.2% and 3.4%, respectively, followed by febrile neutropenia and thrombocytopenia (1.7%). No patient in our sample had treatment-related mortality (Table 3).

Discussion

Our study demonstrated a similar rate of pathological complete response for neoadjuvant chemotherapy with trastuzumab, with or without anthracycline. Currently, with the use of dual *HER2* blockade with trastuzumab and pertuzumab, omitting anthracycline in the neoadjuvant setting is considered safe [13, 23]. However, many patients do not receive pertuzumab due to the combination's high cost. The TRAIN-2 was a phase III study that demonstrated a pathological complete response rate of 67% for the anthracycline group and 68% in the non-anthracycline group; in its 3-year follow-up, it showed a progression-free survival of 93% for the anthracycline group and 94% for the non-anthracycline group, but with higher cardiotoxicity in the anthracycline group (7.7% vs. 3.2%; p 0.04), with two patients developing acute leukemia in the anthracycline group [16]. However, the safety of omitting anthracycline has not been well established for patients not using pertuzumab.

The phase II study neoCARH prospectively randomized 140 patients to undergo neoadjuvant chemotherapy with and without anthracycline associated only with trastuzumab. This study showed a pathological complete response of 37.3% and 55.9% (p 0.032) in the anthracycline and non-anthracycline groups, respectively [21]. Two retrospective studies demonstrated the superiority of the anthracycline-containing regimen; the work of HE et al. [20] showed a pathological complete response in the anthracycline group of 58.2% vs. 41.5% in the non-anthracycline group (p 0.021), BAYRAKTAR [19] demonstrated a pathological complete response rate of 60.6% vs 43.3% (p 0.016) in the anthracycline and non-anthracycline groups, respectively.

Our study demonstrated a pathological complete response rate of 50.9% and 48.3% (p 0.745). Unlike our study, neoCARH comprised patients with T1/T2 tumors, representing approximately 70% of the sample, and about 35% of these were node-negative, so it is questionable whether omitting anthracycline is safe in patients with more advanced disease, as in our sample. This study also did not report survival data, which remains the gold standard for evaluating oncology outcomes. The work of HE [20] showed a 10-year progression-free survival of 83.6% vs. 72.2% (p 0.04) in favor of the anthracycline

group; in line with these data, BAYRAKTAR [19] also demonstrated a favorable 3-year progression-free survival for the anthracycline group (93 vs. 71%, p 0.001). Our study did not observe a statistically significant difference in estimated 30-month recurrence-free survival (94.8% vs 90.7%, p 0.546; anthracycline and non-anthracycline groups, respectively).

The works of HE [20] and BAYRAKTAR [19] differ from ours and neoCARH because patients received trastuzumab concurrently with anthracycline, totaling a higher dose of trastuzumab during neoadjuvant compared to the non-anthracycline group. Data from the GeparQuattro study confirm the efficacy of trastuzumab use; patients who did not show clinical response to the initial four cycles of chemotherapy with anthracycline, considered chemotherapy-resistant, when exposed to trastuzumab achieved a pathological complete response of 16.6% [12]. A meta-analysis with 1,391 patients that evaluated the concurrent or sequential use of trastuzumab with anthracycline showed a higher rate of pathological complete response with concurrent use without apparent increased cardiotoxicity [24]. A randomized study evaluated the safety of simultaneous use, and no significant difference in cardiotoxicity was found between concurrent or sequential use [25]. Thus, the higher dose of trastuzumab during neoadjuvant may justify the higher pathological complete response and, consequently, better progression-free survival shown in these retrospective studies. However, due to the limited data proving its safety, concurrent use of trastuzumab during the anthracycline phase has not become a commonly used regimen.

Cardiotoxicity is a relevant risk associated with treatment; patients in our study showed higher cardiotoxicity in the anthracycline group but did not reach statistical significance (9.3 vs 3.4%, p 0.168). Only in this group did two patients present symptoms of congestive heart failure. In the HE [20] study, 13% of patients had cardiotoxicity vs 7.7% (p 0.352) in the anthracycline and non-anthracycline groups, respectively. In the work of BAYRAKTAR [19], there was one death from congestive heart failure in the anthracycline group, and the neoCARH study did not report a difference in the cardiotoxicity rate. These differences must be carefully evaluated, considering that patients with cardiovascular comorbidities tend to be spared anthracycline, which could be a bias for retrospective evaluations.

In our subgroup analysis, no subgroup showed better rates of pathological complete response or higher recurrence regarding the chemotherapy regimen used. Our multivariate analysis showed that clinically node-negative axilla is an independent predictive factor for achieving pathological complete response; however, this population represented only 10.8% of our sample. Dose reduction was also an independent.

In conclusion, for patients without access to dual *HER2* blockade, chemotherapy regimens with or without anthracycline associated with trastuzumab show similar rates of pathological complete response and recurrence-free survival. Pathological complete response and age are independent variables related to recurrence. The use of anthracycline leads to higher cardiotoxicity.

Author Contribution Statement

Iago Mateus Rocha: review pathological response, Alysson Bastos Lustosa: collected clinical data, Ana Beatriz Tavares Filgueira: collected clinical data, Giulianna Aparecida Barreto: performed data tabulation, Larissa Mont'Alverne: performed clinical study design, Paulo Goberlânio de Barros Silva: performed data analysis, Sérgio Ferreira Juaçaba: performed complete study design.

Acknowledgements

Compliance with ethical standards

All patient records were studied by the principles of the Declaration of Helsinki and the Nuremberg Code, respecting the National Health Council's Human Research Standards (Resolution CNS 196/96).

Ethical approval

Data were collected after approval from the supervisor, Haroldo Juaçaba Hospital-Cancer Institute of Ceará, the Ethics and Research Committee of Haroldo Juaçaba Hospital, and the hospital's technical director. As this was a retrospective chart review, the CEP/CONEP system waived the need for a Free and Informed Consent Form (FICF).

Conflict of interest

There are no conflicts of interest

References

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71:209-249. https://doi.org/10.3322/caac.21660.
2. INCA. Estimativa 2020: incidence of cancer in Brazil. Instituto Nacional de Cancer José Alencar Gomes da Silva; 2019.
3. Cardoso F, Kyriakides S, Ohno S, Penault-Llorca F, Poortmans P, Rubio IT, et al. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2019; 30:1194-220. https://doi.org/10.1016/j.annonc.2020.08.2158.
4. Harbeck N, Penault LF, Cortes J, Gnant M, Houssami N, Poortmans P, et al. Breast cancer. Nat Rev Dis Primers. 2019;5(1):1-31. https://doi.org/10.1038/s41572-019-0111-2
5. Loibl S, Poortmans P, Morrow M, Denkert C, Curigliano G. Breast cancer. The Lancet. 2021;397:1750-69. https://doi.org/10.1016/S0140-6736(21)00838-2.
6. Parise CA, Bauer KR, Brown MM, Caggiano V. Breast cancer subtypes as defined by the estrogen receptor (ER), progesterone receptor (PR), and the human epidermal growth factor receptor 2 (*HER2*) among women with invasive breast cancer in California, 1999-2004. Breast J. 2009;15:593-602. https://doi.org/10.1111/j.1524-4741.2009.00822.x.
7. Krishnamurti U, Silverman JF. *HER2* in breast cancer: a review and update. Adv Anat Pathol. 2014;21:100-7. https://doi.org/10.1097/PAP.0000000000000015.

8. Slamon DJ, Leyland-Jones B, Shak S, Fuchs H, Paton V, Bajamonde A, et al. Use of chemotherapy plus a monoclonal antibody against *HER2* for metastatic breast cancer that overexpresses *HER2*. N Engl J Med. 2001;344:783-92. https://doi.org/10.1056/NEJM200103153441101.
9. Swain SM, Miles D, Kim SB, Im YH, Im SA, Semiglazov V, et al. Pertuzumab, trastuzumab, and docetaxel for *HER2*-positive metastatic breast cancer (CLEOPATRA): end-of-study results from a double-blind, randomized, placebo-controlled, phase 3 study. Lancet Oncol. 2020;21:519-530. https://doi.org/10.1016/S1470-2045(19)30863-0.
10. Buzdar AU, Suman VJ, Meric-Bernstam F, Leitch AM, Ellis MJ, Boughey JC, et al. Fluorouracil, epirubicin, and cyclophosphamide (FEC-75) followed by paclitaxel plus trastuzumab versus paclitaxel plus trastuzumab followed by FEC-75 plus trastuzumab as neoadjuvant treatment for patients with *HER2*-positive breast cancer (Z1041): a randomized, controlled, phase 3 trial. Lancet Oncol. 2013;14:1317-25. https://doi.org/10.1016/S1470-2045(13)70502-3.
11. Gianni L, Eiermann W, Semiglazov V, Manikhas A, Lluch A, Tjulandin S, et al. Neoadjuvant chemotherapy with trastuzumab followed by adjuvant trastuzumab versus neoadjuvant chemotherapy alone, in patients with *HER2*-positive locally advanced breast cancer (the NOAH trial): a randomized controlled superiority trial with a parallel *HER2*-negative cohort. Lancet. 2010; 375:377-384. https://doi.org/10.1016/S0140-6736(09)61964-4.
12. Untch M, Rezai M, Loibl S, Fasching PA, Huober J, Tesch H, et al. Neoadjuvant treatment with trastuzumab in *HER2*-positive breast cancer: results from the GeparQuattro study. J Clin Oncol. 2010;28:2024-31. https://doi.org/10.1200/JCO.2009.23.8451.
13. Schneeweiss A, Chia A, Hickish T, Harvey V, Eniu A, Hegg R, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with *HER2*-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). Ann Oncol. 2013;24:2278-84. https://doi.org/10.1093/annonc/mdt182.
14. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014;384:164-72. https://doi.org/10.1016/S0140-6736(18)32772-7.
15. Cardinale D, Iacopo F, Cipolla CM. Cardiotoxicity of anthracyclines. Front Cardiovasc Med. 2020;7:26. https://doi.org/10.3389/fcvm.2020.00026.
16. Van Der Voort A, Van Ramshort MS, Van Werkhoven ED, Mandjes IA, Kemper I, Vulink AJ, et al. Three-year follow-up of neoadjuvant chemotherapy with or without anthracyclines in the presence of dual ERBB2 blockade in patients with ERBB2-positive breast cancer: a secondary analysis of the TRAIN-2 randomized, phase 3 trial. JAMA Oncol. 2021;7:978-984. https://doi.org/10.1001/jamaoncol.2021.
17. Chen XS, Nie XQ, Chen CM, Wu JY, Wu J, Lu JS, et al. Weekly paclitaxel plus carboplatin is an effective nonanthracycline-containing regimen as neoadjuvant chemotherapy for breast cancer. Ann Oncol. 2010;21:961-7. https://doi.org/10.1093/annonc/mdq041.
18. Coudert BP, Largillier R, Arnould L, Chollet P, Campone M, Coeffic D, et al. Multicenter Phase II Trial of Neoadjuvant Therapy With Trastuzumab, Docetaxel, and Carboplatin for Human Epidermal Growth Factor Receptor-2-Overexpressing Stage II or III Breast Cancer: Results of. J Clin Oncol. 2007; 25:2678-84. https://doi.org/10.1200/JCO.2006.09.9994.
19. Bayraktar S, Ganzalez-Ângulo AM, Lei X, Buzdar AU, Valero V, Melhem-Bertrandt A, et al. Efficacy of neoadjuvant therapy with trastuzumab concurrent with anthracycline-and nonanthracycline-based regimens for *HER2*-positive breast cancer. Cancer. 2012;118:2385-93. https://doi.org/10.1002/cncr.26555.
20. He X, Dai X, Ji J, Liu H, Shi G, Yeung SJ. Nine-Year Median Follow-up of Cardiotoxicity and Efficacy of Trastuzumab Concurrently With Anthracycline-Based and Anthracycline-Free Neoadjuvant Chemotherapy in *HER2*-Positive Breast Cancer Patients. Clin Breast Cancer. 2022;22:e80-e90. https://doi.org/10.1016/j.clbc.2021.05.008.
21. Gao HF, Wu Z, Lin Y, Song XY, Cao Y, Chen QJ, et al. Anthracycline-containing versus carboplatin-containing neoadjuvant chemotherapy in combination with trastuzumab for *HER2*-positive breast cancer: the neoCARH phase II randomized clinical trial.The Adv Med Oncol. 2021 Apr;13:17588359211009003.
22. Slamon D, Eiermann W, Robert N, Pienkowski T, Martin M, Press M, et al. Adjuvant trastuzumab in *HER2*-positive breast cancer. N Engl J Med. 2011;365:1273-83. https://doi.org/10.1056/NEJMoa0910383.
23. Van Ramshorst MS, van der Voort A, van Werkhoven ED, Mandjes IA, Kemper I, Dezentjé VO, et al. Neoadjuvant chemotherapy with or without anthracyclines in the presence of dual *HER2* blockade for *HER2*-positive breast cancer (TRAIN-2): a multicentre, open-label, randomized, phase 3 trial. Lancet Oncol. 2018;19:1630-40. https://doi.org/10.1016/S1470-2045(18)30570-9.
24. Wu YT, Xu Z, Zhang K, Wu JS, Li X, Arshad B, et al. Efficacy and cardiac safety of the concurrent use of trastuzumab and anthracycline-based neoadjuvant chemotherapy for *HER2*-positive breast cancer: a systematic review and meta-analysis. Ther Clin Risk Manag. 2018;1789-97. https://doi.org/10.2147/TCRM.S176214.
25. Shen S, Xu Y, Zhou Y, Mao F, Guan J, Sun Q. Concurrent administration of trastuzumab and anthracyclines as an adjuvant regimen for *HER2*-positive breast cancer: a randomized controlled trial. Oncotarget. 2017;8:92778. https://doi.org/10.18632/oncotarget.21579