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Clinicopathologic profile of breast cancer patients treated with neoadjuvant chemotherapy at HUCFF/UFRJ

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ABSTRACT

Introduction: The objective of this study is to describe the profile of patients from a public institution, submitted to neoadjuvant chemotherapy (NACT), comparing the verified pathological response with literature data. **Methods:** Observational retrospective cohort study on breast cancer patients diagnosed between September 2001 and October 2018 and treated with NACT at Hospital Universitário Clementino Fraga Filho (HUCFF/UFRJ), located in Rio de Janeiro, Brazil. The adopted neoadjuvant chemotherapy regimen was based on anthracycline and docetaxel. **Results:** A total of 133 patients were evaluated. The average age in this group was 54 years (28-86), 49 women (37%) were under 50 years old. The following distribution by molecular subtype was observed: overexpression or amplification of the human epidermal growth factor receptor 2 (HER2+) (13 women, 26.6%), Luminal (19 women, 38.8%), and Triple-negative (TN) (17 women, 34.6%). The HER2+ and TN subtypes had a higher incidence of cases between 40-49 years and 50-59 years. As for the initial staging, 34% were IIIA; 26%, IIB; and 19%, IIIB. Only one patient did not undergo surgery after NACT, 33 (24.8%) underwent conservative surgery, and 99 patients (74.4%) underwent mastectomy. Regarding the axillary approach, 41 (31%) underwent sentinel lymph node biopsy and 88 (66%) had an indication for lymphadenectomy. In the anatomopathological evaluation of the surgery, 12 (9.1%) patients obtained a pathologic complete response (pCR) and 113 (84.9%), partial or no response to chemotherapy. **Conclusion:** This research enabled the identification of clinicopathologic characteristics and outcome of patients who received neoadjuvant chemotherapy in a public university service. The predominance of advanced tumors was observed, stressing the need for public health policies for the screening of breast cancer as well as the guarantee of timely treatment for diagnosed cases. The data somewhat reflect the difficulty that the public sector encounters to carry out the most appropriate treatment. The authors expect that this article, by analyzing the profile and the adopted treatment in real-life cases and in a public university institution, can contribute to the improvement of breast cancer treatment in Brazil.

KEYWORDS: locally advanced breast cancer, neoadjuvant chemotherapy, pathological response.

INTRODUCTION

Breast cancer is the most common malignancy among women worldwide. In Brazil, 66,280 new cases of breast cancer are expected per year for the 2020-2022 triennium. This value corresponds to an estimated risk of 61.61 new cases per 100 thousand women[1].

The prognosis of breast cancer depends, among other data, on its extension (staging) and the molecular subtype. TNM (T – tumor; N – nearby lymph nodes; M – metastasis) is the international system for assessing the extent of neoplasia, whose last systematic review was carried out in January 2018 by the American Joint Committee On Cancer (AJCC); this is the 8th edition, incorporating biological factors into the anatomo-clinical data[2]. Pathological staging (pTNM) is determined after surgery or neoadjuvant treatment (ypTNM), with greater accuracy than the clinical one (cTNM).

Neoadjuvant chemotherapy (NACT) was initially adopted for locally advanced tumors aiming at cytoreduction, in order to provide conservative surgeries to patients who are candidates for mastectomy or to make it operable. However, lately, NACT has been adopted with the purpose of evaluating the response to a new protocol or medication, taking advantage of the pathological response as an intermediate outcome, identifying predictive and

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prognostic factors or indicating complementary adjuvant treatment according to the residual disease. The effectiveness of the NACT regimen can be assessed by the rate of objective clinical response, tumor reduction and operability or, preferably, by the pathologic complete response (pCR – absence of residual invasive tumor in the surgical specimen in the breast and axilla). The first studies based on anthracyclines showed rates of clinical responses (60% to 80%) and pCR (10% to 20%)[3,4]. In the early 2000s, taxanes were incorporated into neoadjuvant breast cancer treatment regimens, either alone or combined with anthracyclines, doubling the rate of clinical and pathological response[5-9]. Randomized studies on amplified HER2 (human epidermal growth factor receptor 2) patients have shown a significant increase in pCR when combining chemotherapy with anti-HER2 therapy[10-12]. pCR is the best indicator of response to neoadjuvant treatment, indicating an increase in survival (overall survival and disease-free survival), as initially demonstrated in the National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol B-18 study[13]. This correlation is especially true for triple-negative (TN) and HER2-positive[14] (HER2+) tumors.

The indications and protocols for neoadjuvant therapy in breast cancer are well established in the literature. Nevertheless, in Brazil, we find barriers, mainly in the public sector, due to the delay in diagnosis, the difficulty of infrastructure, and the incorporation of medicines. This study aims to analyze the profile and clinicopathological outcome (pathological response) of patients treated with neoadjuvant therapy, in a clinical oncology service at a university hospital in Rio de Janeiro, Brazil.

MATERIAL AND METHODS

Methodology

This is a retrospective observational cohort study, whose unit of analysis consisted in breast cancer cases diagnosed between 2001 and 2018 and treated with NACT at Hospital Universitário Clementino Fraga Filho/Universidade Federal do Rio de Janeiro (HUCFF/UFRJ), located in the city of Rio de Janeiro, state of Rio de Janeiro, Brazil. The patients included in the study were selected from the HUCFF/UFRJ hospital-based cancer registries. Clinical and pathological data were obtained by consulting physical and electronic medical records.

To assess tumor characteristics, we used the TNM Classification of the Union for International Cancer Control (UICC), 8th edition, considering the size of the tumor – T, the presence of axillary metastasis – N, and the presence of metastasis – M (locoregional or systemic), at the time of diagnosis (cTNM).

The subclassification of breast tumors by immunohistochemistry was performed based on results presented by the Pathological Anatomy of HUCFF/UFRJ based on the evaluation of hormone receptors for estrogen (ER) and progesterone (PR), overexpression of c-erb2, or amplification of the human epidermal growth factor receptor 2 (HER2), and cell proliferation index (Ki67). According to these results, three immunohistochemical subgroups were defined: Luminal subtypes (ER+ and/or PR+/- and HER2-), HER2+ (c-erb2 3+ or 2+, confirmed by FISH [Fluorescence *in situ* hybridization] amplification test), and hormone receptor-positive or negative (HR+/-) and TN or basal-like (ER-, PR-, and HER2-). There is some controversy on the evaluation of Ki67 in the literature due to the difficulty in standardizing its results in different services. The 2011 St. Gallen Consensus considers values below 14% as low or negative and values above 15% as high. However, due to lack of inputs, some patients did not perform the Ki67 evaluation, and they cannot be properly classified into Luminal A and B. Ki67 was described, when possible, to demonstrate tumor aggressiveness.

All patients underwent routine exams for staging and exclusion of metastases before primary chemotherapy. The adopted chemotherapy treatment was the PACS 01 regimen[15], which uses three cycles of FEC (5 fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2 with an interval of 21 days) followed by three cycles of docetaxel 100 mg/m^2 every 21 days. Trastuzumab, despite being incorporated into the Brazilian Unified Health System (SUS) since 2013, has not been associated with neoadjuvant chemotherapy in amplified HER2 patients due to logistical difficulties, delay in carrying out the FISH test, and unavailability of the drug to start the treatment (distribution centralized by the Brazilian Ministry of Health with delivery around three months after scheduling the patient). Trastuzumab was administered to these patients in adjuvant therapy for 12 months.

Data from surgical treatment on the breast (conservative or radical procedure) and axilla (lymphadenectomy or sentinel lymph node biopsy) were analyzed. The response to NACT was described as: pathologic complete response (pCR), in the absence of invasive neoplasia in the breast and lymph nodes, in which there may be ductal carcinoma *in situ* (DCIS) in the specimen or partial response in the existence of residual invasive tumor in the breast or lymph node.

Inclusion criteria

Female patients with infiltrating breast carcinoma treated at HUCFF/UFRJ between 2001 and 2018, with neoadjuvant chemotherapy based on anthracyclines and/or taxanes, were eligible for this study.

Exclusion criteria

Patients who abandoned chemotherapy treatment were excluded.

Statistical analysis

The results of this study are exploratory and descriptive. Analyses of quantitative variables are presented with the mean and standard

deviation; the qualitative variables are presented with their absolute and relative frequency. No statistical analysis was performed between the variables due to the small number of cases.

RESULTS

A total of 133 patients treated at HUCFF/UFRJ, diagnosed with breast cancer, and who underwent NACT followed by surgery from September 2001 to October 2018 were evaluated. The distribution of clinical characteristics according to breast cancer subtypes classified by immunohistochemistry is demonstrated in Table 1.

Regarding the age distribution at diagnosis, the average age in this group was 54 years (28–86), with no significant difference between the subgroups HER2+ 54 years old (32–86), Luminal 54 years old (28–86), and TN 52 years old (33–81). In this sample, 49 women (37%) were under 50 years old with the following distribution by molecular subtype: HER2+ (13 women, 26.6%), Luminal subtypes (19 women, 38.8%), and TN (17 women, 34.6%). The distribution by molecular subtype for 10 patients aged 70 years or older was: 5 (50%) Luminal subtypes; 4 (40%), HER2+; and 1 (10%), TN.

As for the HER2+ subgroup, 25 cases were diagnosed with 3+ in immunohistochemistry, whereas eight cases needed to perform the FISH test to confirm the diagnosis. When evaluating the Ki67 cell proliferation marker, a large percentage (69.6%) was found, which is deemed a high cell proliferation index (>14), and 10 cases did not perform the test.

In the Luminal subgroup, 52 cases were classified as HER2 negative (0 and 1+), whereas six cases were c-erbB-2 2+ and required FISH test to be performed. In the evaluation of ER and PR, the following were verified: ER+/PR+=45, ER+/PR-=10, and RPx=3.

Concerning TN, 40 cases were classified as HER2 negative (c-erbB-2 0 and 1+), whereas two cases were c-erbB-2 2+ and required FISH test to be performed. In this population, no cases of low Ki67 were found.

At the time of diagnosis, 71% of the cases had a >5-cm tumor, and in 70% of the cases the armpits were clinically compromised. Almost half of the cases (43%) were classified as staging IIIA; 26%, as IIB; and 19%, as IIIB. Fifteen patients were classified into stage I and IIA, stages in which patients are not usually submitted to neoadjuvant therapy. However, all these patients were initially evaluated by the services of mastology and clinical oncology, and opted for starting treatment with chemotherapy due to the rapid clinical evolution and structural difficulties. Subsequently, it was verified that 10 of these patients had subtypes TN and amplified HER2. See Table 1.

After receiving NACT, patients were referred to surgical evaluation, with only one patient considered inoperable. Table 2 shows that conservative surgery was an infrequent practice, and only 33 patients (25%) underwent such a procedure. Other 99 patients (74%) had an indication for radical surgery. Concerning axillary surgery, a total of 41 patients (31%) underwent sentinel lymph node biopsy (11 HER2 women, 17 Luminal, and 13 TN) and 88 patients (66%) had an indication for lymphadenectomy (21 HER2 women, 39 Luminal, and 28 TN). In this sample, seven cases (5%) did not undergo an axillary evaluation.

In the anatomopathological evaluation of post-NACT surgery, 12 patients (9%) obtained pCR (4 HER2 women, 2 Luminal, and 6 TN). In 113 (85%) patients, there was partial or no response to chemotherapy (26 HER2 women, 54 Luminal, and 33 TN).

Table 1. Distribution of clinical characteristics according to breast cancer subtypes.

	Total (%)	HER2 (%)	Luminal subtypes (%)	TN (%)
Age at diagnosis				
20–29	1 (1)	0 (0)	1 (100)	0 (0)
30–39	14 (10)	3 (21)	6 (42)	5 (37)
40–49	34 (26)	10 (30)	12 (35)	12 (35)
50–59	43 (32)	9 (21)	19 (44)	15 (35)
60–69	28 (21)	6 (21)	14 (50)	8 (29)
70–79	10 (7)	4 (40)	5 (50)	1 (10)
80–89	3 (3)	1 (33)	1 (33)	1 (33)
Tumor size				
cT1	2 (1)	1 (50)	1 (50)	0
cT2	37 (28)	12 (32)	16 (43)	9 (25)
cT3	66 (50)	15 (23)	24 (36)	27 (41)
cT4	28 (21)	5 (18)	17 (61)	6 (21)
Lymph node evaluation				
cN0	40 (30)	12 (30)	17 (42)	11 (28)
cN1	62 (47)	13 (21)	25 (40)	24 (39)
cN2	29 (22)	7 (24)	15 (52)	7 (24)
cN3	2 (1)	1 (50)	1 (50)	0 (0)
Distant metastasis				
M0	133 (97)	33 (25)	58 (43)	42 (32)
M1	0 (0)	0 (0)	0 (0)	0 (0)
Clinical Staging				
I	2 (1)	1 (50)	1 (50)	0 (0)
IIA	13 (10)	8 (62)	3 (23)	2 (15)
IIB	34 (26)	4 (12)	19 (56)	11 (32)
IIIA	57 (43)	15 (26)	17 (30)	25 (44)
IIIB	25 (19)	4 (16)	17 (68)	4 (16)
IIIC	2 (1)	1 (50)	1 (50)	0 (0)
TOTAL	133	33	58	42

HER2: human epidermal growth factor receptor 2; TN: triple-negative; cT: clinical stage of the tumor; cN: clinical stage of nearby lymph nodes; M: metastasis.

Table 2. Surgical treatment of the breast and axilla.

	Total (%)	HER2 (%)	Luminal subtypes (%)	TN (%)
Surgical treatment of the breast				
Conservative surgery	33 (25)	10 (30)	12 (36)	11 (34)
Radical surgery	99 (74)	22 (22)	46 (46)	31 (32)
Not performed	1 (1)	1 (100)	0 (0)	0 (0)
Surgical treatment of the axilla				
Sentinel lymph node biopsy	41 (31)	11 (27)	17 (41)	13 (32)
Lymphadenectomy	88 (66)	21 (24)	39 (44)	28 (32)
Not performed	4 (3)	1 (25)	2 (50)	1 (25)
Histopathology of the axilla (SL and lymphadenectomy)				
Negative lymph node	52 (39)	15 (29)	16 (31)	21 (40)
Positive lymph node	74 (56)	17 (23)	38 (51)	19 (26)
Not evaluated	7 (5)	1 (14)	4 (57)	2 (29)
TOTAL	133	33	58	42
Pathologic complete response – pCR				
Yes	12 (9)	4 (33)	2 (17)	6 (50)
No	113 (85)	26 (23)	54 (48)	33 (29)
Not evaluated	8 (6)	3 (37)	2 (26)	3 (37)
TOTAL	133	33	58	42

HER2: human epidermal growth factor receptor 2; TN: triple-negative; SL: sentinel lymph node; pCR: pathologic complete response.

DISCUSSION

Locally advanced breast cancer remains an important public health issue in Brazil. About 32% of breast cancer patients diagnosed at the National Cancer Institute have locally advanced disease[16]. This study evaluates this universe of patients, reporting their profile, adopted treatment, and obtained results.

Patients treated at HUCFF from 2001 to 2018 who underwent NACT were selected for the analysis. The patients had a mean age of 54 years (28–86) and 49 women (37%) were under 50 years old. These data are similar to those described in a Brazilian observational study that included 4,912 patients, conducted in 28 public and private healthcare centers, and described an average age of 54 years and 44.3% of patients under 50 years of age[17]. According to the guidelines of the Brazilian Ministry of Health, this population would not be subjected to screening tests[18].

At the time of diagnosis, 71% of cases had a >5-cm tumor, and 70% had a clinically compromised axilla. Almost half of the cases (43%) were classified as staging IIIA, followed by 26% IIB, and 19% IIIB, with NACT being adopted with purpose of operability and to increase conservative surgical procedures. These findings demonstrate the delay in diagnosis, probably caused by the difficulty of access to screening tests and delay in diagnosis in the public sector. These findings are similar to those described in another oncological center of national reference[19].

According to the immunohistochemical profile, a predominance of aggressive HER2+ (26.6%) and TN (34.6%) subtypes were observed, which differ from the normal distribution of the population with breast cancer described in other Brazilian series, according to which the Luminal subtypes predominate with 57.9%; overexpression of HER2 with 17.6%; and triple-negative with 24.2%[20]. This fact can be justified by the selection of locally advanced breast cancer patients.

This is a retrospective study, conducted over a long period of time (17 years). This fact could arise a methodological difficulty due to changes in the protocols considered. Nevertheless, due to the difficulty in technological incorporation, there was no major change in the adopted regimen of neoadjuvant therapy.

A 9% pCR was observed, which is well below the value currently reported in the international literature, but compatible with the report of other Brazilian series[21,22]. HER2+ tumors were not treated with neoadjuvant trastuzumab achieving a 12% response, whereas in the literature on dual inhibitor, a response of up to 60% was obtained[11,12]. Thus, these patients shall also present a lower response of overall and disease-free survival, as pCR has been confirmed as an intermediate marker capable of predicting survival[23].

Currently, the evaluation of the residual tumor according to the methodology suggested by M. D. Anderson is considered the most employed method in the literature[24]. However, considering that this is a long-term retrospective study, with difficulties in obtaining and reviewing the anatomopathological tests of the surgical specimens, the pathologic complete response was considered as the absence of an invasive tumor in the breast and lymph nodes.

Although the pCR is lower than that reported in the literature, most patients obtained a partial response and almost all patients were able to perform the surgery (99%). In 21 patients (15.7%), it was possible to perform conservative surgery and search for sentinel lymph nodes, avoiding axillary dissection. Unfortunately, the actual assessment of axillary downstaging was difficult to document, as patients did not perform histopathological or cytological analysis of the pre-NACT lymph node. Of 93 patients (69.9%) with clinically palpable axillary lymph nodes, at the beginning of the study, 52 (39%) had a negative axilla according to the histopathological examination.

HER2-positive patients (positive FISH or IHC [immunohistochemistry] 3+) have a proven benefit of combined chemotherapy treatment with anti-HER2 therapy. Studies evaluating the role of adding trastuzumab to chemotherapy have shown increased pCR and increased survival[10]. Subsequently, new inhibitors of the HER2 pathway, such as lapatinib, tyrosine kinase inhibitor

(NEO-ALTO)[11], and pertuzumab (NeoSphere)[12], were tested alone and combined with chemotherapy, and showed a pCR benefit in relation to HER2 dual inhibitor. Thus, most international guidelines recommend the use of trastuzumab and pertuzumab, preferably in an anthracycline-free regimen, to avoid cardiotoxicity[25,26] as a neoadjuvant therapy for patients with HER2-positive tumors greater than 2 cm[27].

In TN and HER2 amplified patients, NACT has been early indicated, in tumors larger than 1 cm and 2 cm respectively, or positive axilla, as these tumors are quite aggressive and have good response to chemotherapy. In addition, the adoption of NACT to these patients is intended to guide adjuvant treatment, as recent randomized and prospective studies demonstrate the benefit of survival with the use of capecitabine in TN[28] and Trastuzumab emtansine (T-DM1) in HER2[29] in patients with residual disease.

The standard treatment of neoadjuvant chemotherapy for TN patients remains anthracyclines and taxanes, with the still controversial addition of platinum, antiangiogenic therapy, poly (ADP-ribose) polymerase inhibitors (PARP), and immunotherapy[30,31].

Neoadjuvant chemotherapy based on anthracyclines and taxanes remains the standard therapy adopted in SUS. Trastuzumab was approved by SUS in 2013 for use in initial breast cancer, in adjuvant and neoadjuvant treatments. However, to date, its use has not been adequately incorporated due to difficulties in the immunohistochemistry test of HER2 or in the acquisition of the drug.

CONCLUSION

This research enabled the identification of clinicopathologic characteristics and outcome of patients who received neoadjuvant chemotherapy in a public university service. A predominance of tumors larger than 5.0 cm and positive axilla was verified, reinforcing the need for public health policies aimed at consolidating the national breast cancer screening program as well as ensuring timely treatment for diagnosed cases.

The data somewhat reflect the difficulty that the public sector encounters to perform the appropriate treatment or that recommended by international guidelines. The authors expect that this article, by analyzing the profile and the adopted treatment, in real cases and in a public university institution, can contribute to the improvement of breast cancer treatment in Brazil.

AUTHORS' CONTRIBUTION

L.C.B.A.: conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, validation, visualization, writing – original draft, writing – review & editing; M.F.D.G.: conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, validation, visualization, writing – original draft, writing – review & editing; A.H.P.C.C.: formal analysis, supervision, visualization, writing – review & editing; N.H.S.C.: formal analysis, supervision, visualization, writing – review & editing

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