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Research Article

Pertuzumab in Combination with Trastuzumab and Docetaxel in the Neoadjuvant Treatment for HER2-Positive Breast Cancer

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ABSTRACT

Introduction: This study aims to assess safety and effectiveness of pertuzumab in combination with trastuzumab and docetaxel in the neoadjuvant treatment (NeoT) of HER2-positive breast cancer. **Methods:** Two consecutive retrospective cohorts ($n = 94$, 2012–2015 and 2015–2017) of adult women with HER2-positive breast cancer, receiving NeoT at the breast clinic in Portugal (IPO-Porto), were followed. All patients had surgery and received trastuzumab as adjuvant therapy. The 2012–2015 cohort received doxorubicin, cyclophosphamide, docetaxel plus trastuzumab, whereas the 2015–2017 cohort was treated with the same protocol plus pertuzumab. **Results:** The 2012–2015 cohort was older (median 53 years), with locally advanced tumors (48.1%), mostly hormone receptor positive (59.3%). The 2015–2017 cohort was younger (median 43 years) with 60% operable tumors. Pathologic complete response (pCR) improved in the second cohort, while maintaining a good safety profile and tolerability. Clinical staging ($p = 0.001$) and hormone receptor ($p = 0.003$) were significant predictors of pCR, but not treatment regimen ($p = 0.304$). **Conclusion:** Further research with larger samples and longer follow-up is needed to understand the clinical differences. Clinical effectiveness of treatment should also be measured through overall and progression-free survival.

Keywords: pertuzumab, trastuzumab, neoadjuvant therapy, cardiac safety, early breast cancer

INTRODUCTION

Breast cancer is the most prevalent malignant tumor in the female European population, with 2,138,117 cases in 2020, and an incidence around 531,086.[1] One in 12 women in Europe will develop breast cancer before the age of 74 years.[1] In most Western countries, prevalence has increased but mortality has recently declined, especially in younger age groups, owing to improved treatment and early detection. However, breast cancer

remains the leading cause of cancer-related death in European women.[1] In 2020, a total of 141,765 estimated deaths among European women resulted from breast cancer, accounting for 16.4% of all deaths by cancer in women.[1]

In Portugal, breast cancer represented 12% of cancer cases and was the leading cause of all cancers in women (26.4%) in 2020.[2] Advanced breast cancer comprises both locally advanced and metastatic breast cancer.[3] The histologic subtypes of breast cancer have an impact in treatment management and prognosis. Available systemic therapeutic options include chemotherapy, endocrine therapy, and anti-HER2 target therapies.[3] HER2 protein overexpression (HER2 positive) occurs in 18-20% of breast cancers as a result of the amplification of the gene encoding HER2 (part of chromosome 17).[4] This subtype is associated with worse prognosis (more recurrences and decreased overall survival [OS]) and has led to the development of an anti-HER2 monoclonal antibody, trastuzumab, that has changed the natural history of the disease. However, 20–25% of treated patients still experienced disease recurrence during follow-up, and new agents including pertuzumab, trastuzumab emtansine (T-DM1), and lapatinib were developed. [5–8]

Pertuzumab is a recombinant humanized monoclonal antibody targeting HER2 whose efficacy in the neoadjuvant treatment (NeoT) of HER2-positive breast cancer is supported by two randomized controlled trials (RCTs), NeoSphere and TRYPHAENA.[9–14] In the NeoSphere trial, patients with operable, locally advanced, or inflammatory HER2-positive breast cancer were randomly assigned to four treatment arms, two with dual-blockade alone or in combination with docetaxel and two with pertuzumab or trastuzumab with docetaxel. Breast pathologic complete response (pCR) rates, the primary endpoint of the study, were higher in the dual-blockade associated with docetaxel (45.8%).[14] The TRYPHAENA trial was a randomized, multicenter phase II trial whose primary purpose was to assess the tolerability, in particular cardiac safety, of dual-blockade NeoT. In this trial there were three arms: two with anthracyclines and taxanes, sequential or concomitant with dual-blockade, and one arm without anthracyclines. The pCR rates were similar between groups, as well as cardiotoxicity rates, which were slightly lower in the group without anthracyclines. [12]

Increased effectiveness did not result in increased toxicity, namely cardiotoxicity, which was very rare in these trials.[12–14] The results of these trials led to approval by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) of pertuzumab in combination with trastuzumab and chemotherapy for the NeoT of patients with locally advanced, inflammatory, or early HER2-positive breast cancer at high risk of relapse.

Currently pertuzumab is also approved in metastatic first-line treatment and in adjuvant treatment in early breast cancer at high risk of recurrence.[15–17] These results led to the adoption by the main international societies (European Society for Medical Oncology [ESMO], National Comprehensive Cancer Network, and others) of therapeutic schemes including pertuzumab, trastuzumab, and chemotherapy.[3,18–20] The results indicated no additional safety concerns, and both trials were essential for pertuzumab's approval by the FDA and EMA. Therapeutic indications were issued for the combination with trastuzumab and chemotherapy as the NeoT for patients with HER2-positive locally advanced or inflammatory tumors or in early stages of the disease but with high potential for relapse. However, more recent evidence suggests that a thorough risk assessment of the treatment must be performed before treatment selection. Treatment individualization must account for risk stratification; high-risk patients should be on escalated treatment strategies, and those with low risk of relapse or with a severe cardiac risk should be on a de-escalated treatment plan.[21] Differential approaches also consider the possibility of adjuvant therapy with 14 cycles of pertuzumab plus trastuzumab in high-risk patients (young, hormone receptor [HR] negative), inflammatory carcinoma). Results from the APHINITY trial also show that adding pertuzumab to existing adjuvant trastuzumab and chemotherapy improved invasive disease-free survival among HER2-positive patients with operable breast cancer.[22]

The aim of this study was to evaluate the effectiveness and safety of pertuzumab in combination with trastuzumab and docetaxel in the NeoT for HER2-positive breast cancer, based on real-world evidence. Moreover, it was also intended to characterize a historical cohort from Instituto Português de Oncologia do Porto (IPO-Porto) before the abovementioned treatment became the standard at the center.

METHODS

This research received approval from the local ethics committee of IPO-Porto, followed all national ethical standards and procedures, and was performed in accordance with the Declaration of Helsinki.

Patient informed consent was not required by the ethics committee owing to the retrospective observational nature of this study and because the data contained no unique personal identifiers.

This study follows two consecutive retrospective cohorts of women with HER2-positive breast cancer ($\geq$ 18 years old) who received NeoT between January 2012 and June 2017 in the Breast Clinic of IPO-Porto.[23] This is a public hospital in the north of Portugal, integrated in the Porto Comprehensive Cancer Centre, specialized in the treatment and management of cancer. The Breast Clinic at IPO-Porto treated 1243 cases in 2017, making it the largest breast cancer treatment center in Portugal and one of the most relevant in Europe.[24]

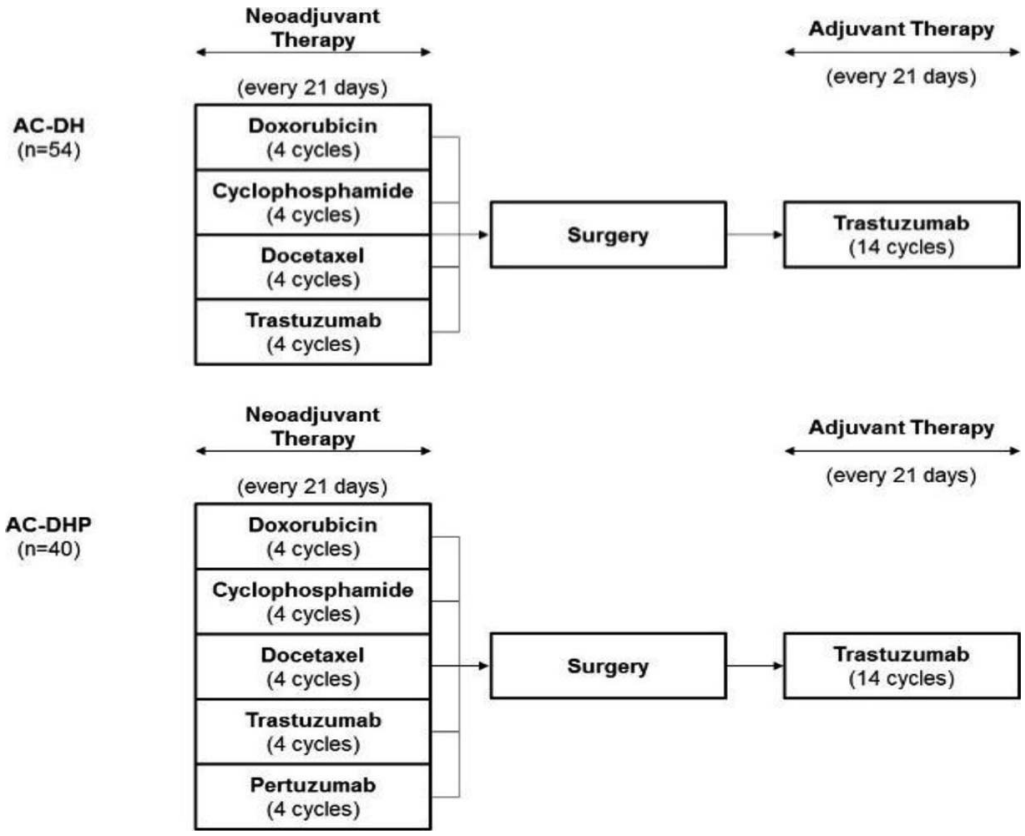

Figure 1. Representation of the treatment protocols associated with each cohort: AC-DH, 2012–2015 cohort; AC-DHP, 2015-2017 cohort. A: doxorubicin; C: cyclophosphamide; DH: docetaxel plus trastuzumab; DHP: docetaxel, trastuzumab plus pertuzumab.

The regimen adopted by IPO-Porto to treat women with HER2-positive breast cancer followed the ESMO Guidelines criteria.[25] The regimen consisted of four cycles of anthracyclines followed by four cycles of docetaxel. In the 2012–2015 cohort (AC-DH) the regimen included four cycles of trastuzumab, whereas in the 2015–2017 cohort (AC-DHP) the patients underwent four cycles of dual HER2-blockade with pertuzumab and trastuzumab as NeoT. The change of regimen followed EMA's authorization on March 4, 2013. In both cohorts, all patients also underwent surgery and received trastuzumab as adjuvant therapy (Fig. 1). All patients being treated at the center with one of these protocols between 2012 and 2017, and matching inclusion criteria, were considered. Eligible patients were female with clinically diagnosed HER2-positive breast cancer undergoing NeoT with AC-DH or AC-DHP due to having a tumor larger than 2 cm or optimal surgery not feasible (breast conservation preferred or potentially feasible after downstaging) or axillary lymph node involvement Exclusion criteria included clinical stage I or IV at diagnosis, having received another chemotherapy regimen, concomitant diagnosis of other cancer or contralateral breast cancer, formerly/currently participating in a clinical trial with anti-HER2 treatment and/or partial treatment in another institution.

Data Collection

Data on demographic and clinical characteristics and treatment were retrieved from electronic medical reports. Data collected were entered on a database devised to ensure total confidentiality and anonymization of the patients, using the least possible identifiable data. The information collected included the following: age, weight, height, diagnosis date, clinical stage/TMN, histologic grade, HRs, Eastern Cooperative Oncology Group (ECOG) performance status, left ejection ventricular function (LEVF), systemic treatment (date, type of treatment, drug, dose), surgical treatment (type of surgery, date, axillary clearance or sentinel lymph node biopsy, number of positive lymph nodes), and treatment effectiveness and safety (pCR and adverse events [AEs]). The date of diagnosis was considered as the baseline date and as the starting point for the data collection.

As for classification criteria, the clinical and pathologic stages were defined by using the American Joint Committee on Cancer (AJCC), 7th edition. HRs were considered positive if estrogen and/or progesterone receptor was $> 1\%$; HER2 was considered positive if the score was 3+ by immunohistochemistry or in case of 2+, if it was positive by fluorescence in situ hybridization.

Breast cancer at diagnosis was characterized as operable (T0-3, N-0-1, M0), locally advanced (T2-3; N2-3, M0; or T4a-c, any N, M0), or inflammatory (T4d, any N, M0).

Surgery was classified as mastectomy (modified radical mastectomy or total mastectomy) or conservative surgery. AEs were assessed according to the National Cancer Institute CTCAE (Common Terminology Criteria for Adverse Events; version 4.0). LEVF measured by echocardiography or multiple-gated acquisition was defined as an AE when below 50% or when a decrease of 10% or more from baseline was observed. The primary endpoint was pCR, which was defined as the absence of invasive neoplastic cells (ypT0/is, ypN0). Secondary endpoints included pCR in the breast, AE rate, and breast-conserving surgery rate.

Statistical Analysis

Descriptive statistics for categorical variables included tabulation of frequencies with counts and percentages.

Multivariable logistic regression models were used to quantify the relation between patient characteristics and pCR. The initial model considered all variables: age, stage of disease at diagnosis, HRs, ECOG, body mass index (BMI), and type of surgery. To obtain the optimized model retaining only significant variables, the stepwise backward elimination method was used. Regimen was forced into the optimized model to ensure proper comparison. Exponentiated coefficients (adjusted odds ratios [ORs]), *p*-value, and 95% CIs were calculated.

A p-value < 0.05 was considered statistically significant. Data were computed with STATA V.15 for Windows (StataCorp).

RESULTS

Baseline Characterization of the Cohorts

The baseline characteristics of both cohorts are depicted in Table 1, based on a total sample of 94 patients. Concerning the AC-DH cohort ($n = 54$), the average age was 50.9 years (± 9.9). Less than 25% of the cohort was younger than 45 years. At diagnosis, most patients presented with locally advanced tumors (48.1%), while operable tumors were present in 27.8% and inflammatory carcinoma, in 24.1%. A total of 32 patients (59.3%) had HR positivity, while tumor size was mostly T3 (38.9%) and T4 (37.0%). Concerning the AC-DHP cohort, the average age was 45.4 years (± 9.6). Operable tumors represented 60% of the cases ($n = 24$), followed by inflammatory carcinoma (25.0%) and locally advanced tumor (15.0%). Estrogen receptor (ER)–positive or progesterone receptor (PR)–positive tumors or both were proportionally higher (67.5%) than ER-negative and PR-negative tumors (32.5%). Lastly, tumor sizes in greater proportion were T3 (35.0%) and T2 (32.5%) (Table 1).

Clinical Effectiveness

All patients underwent surgery after systemic treatment. In the AC-DH cohort, conservative surgery was performed in 16.7% of cases, and axillary clearance was performed in 98.1% of cases. pCR was identified in 33.3% of the cases and no residual tumor was identified in 25.9%. In the AC-DHP cohort, the proportion of conservative surgery was 25.0%, axillary clearance was performed in 87.5% of cases, and pCR was identified in 45.0% of cases. No residual tumor represented a proportion of 40.0% in the histologic response. Near complete response (nCR) was 7.5%, compared to 0.0% in the AC-DH cohort.

Table 2 indicates results for pCR in the breast by HR status and by axillary lymph node status at surgery for both cohorts. The most compelling results in the AC-DH cohort concerns pCR in HR-negative cancer found in 59.1% of the cases. For the AC-DHP cohort, the results show a pCR and N– at surgery of 7.5%, and a pCR in HR-negative cancer of 76.9%.

A multivariable logistic regression model was used to quantify the relation between patients' characteristics and pCR. Breast and axilla (ypT0/isYpN0) pCR had higher probability of being observed in less advanced clinical stages and in HR-negative cases. Similar results were shown for pCR in the breast. Contrarily, regimen was not a predictor of pCR in the breast and axilla (ypT0/is ypN0) and of pCR in the breast ($p = 0.304$ and $p = 0.396$, respectively) (Table 3).

Safety and Adverse Events

This study also had a focus on safety and AEs. Figure 2 shows the most prevalent events in each cohort. Overall, anemia was the most frequent AE in the study population. Concerning the AC-DH cohort, the most frequent AEs were anemia, neutropenia, mucositis, and leukopenia. Most AEs in this cohort were grade 1–2 (92.6%), with grade 3 events representing 5.6% of cases (data not shown). In the AC-DHP cohort, the most frequent AEs were anemia, diarrhea, mucositis, and leukopenia. Grade 3 AEs represented 10% of the total, whereas grade 1–2 AEs were 87.5% in this cohort (data not shown).

Lastly, another determining factor in the safety assessment of treatment pertains to LVEF assessment. LVEF assessments were obtained at baseline, after doxorubicin plus cyclophosphamide treatment (post-AC), after NeoT (but before radiotherapy), and after adjuvant treatment. In the AC-DH cohort, 65.0% of the patients had a decline of 10% or more in LVEF post-NeoT, with 10.0% having a LVEF less than 50% (Table 4). In the AC-DHP cohort, 47.5% of the patients had LVEF declines of 10% or more from baseline post-NeoT, with only 2.5% showing a LVEF under 50% post-NeoT (Table 4).

DISCUSSION

This study presents valuable insights on the use of pertuzumab in combination with trastuzumab and docetaxel in the NeoT for HER2-positive breast cancer by using real-world data (RWD) from our institution. A greater proportion of patients showed pCR when treated

Table 1. Patient demographics and clinical characteristics at baseline

	Doxorubicin, Cyclophosphamide, Docetaxel plus Trastuzumab (*n* = 54)	**Doxorubicin, Cyclophosphamide, Docetaxel, Trastuzumab plus Pertuzumab (*n* = 40)**	***p*-value**
Age, mean ± SD, y	50.9 ± 9.9	45.4 ± 9.6	0.008
Age group, *n* (%)			
≤ 24	0 (0.0)	1 (2.5)	0.068
25–29	1 (1.9)	0 (0.0)	
30–34	1 (1.9)	2 (5.0)	
35–39	7 (13.0)	8 (20.0)	
40–44	4 (7.4)	12 (30.0)	
45–49	12 (22.2)	5 (12.5)	
50–54	7 (13.0)	5 (12.5)	
55–59	12 (22.2)	3 (7.5)	
60–64	4 (7.4)	2 (5.0)	
≥ 65	6 (11.1)	2 (5.0)	
BMI, mean ± SD, kg/m^2	27.0 ± 5.7	25.5 ± 4.7	0.168
ECOG performance status,[20] *n* (%)			
0	47 (87.0)	34 (85.0)	0.777
1	7 (13.0)	6 (15.0)	
Hormonal receptors (ER and PR), *n* (%)			
At least one positive	32 (59.3)	27 (67.5)	0.414
Both negative	22 (40.7)	13 (32.5)	
Clinical staging, *n* (%)			
IIA	2 (3.7)	4 (10.0)	0.205
IIB	8 (14.8)	8 (20.0)	
IIIA	22 (40.7)	18 (45.0)	
IIIB	17 (31.5)	10 (25.0)	
IIIC	5 (9.3)	0 (0.0)	
Histologic grade, *n* (%)			
G1	1 (1.9)	0 (0.0)	0.640
G2	19 (35.2)	11 (27.5)	
G3	32 (59.2)	28 (70.0)	
Undetermined	2 (3.7)	1 (2.5)	
At diagnosis, *n* (%)			
Operable	15 (27.8)	24 (60.0)	0.001
Locally advanced	26 (48.1)	6 (15.0)	
Inflammatory	13 (24.1)	10 (25.0)	
Lymph node status, *n* (%)			
N0	10 (18.5)	4 (10.0)	0.006
N1	18 (33.3)	27 (67.5)	
N2	21 (38.9)	9 (22.5)	
N3	5 (9.3)	0 (0.0)	
Tumor size, *n* (%)			
T0	0 (0.0)	1 (2.5)	0.420
T1	2 (3.7)	2 (5.0)	
T2	11 (20.4)	13 (32.5)	
T3	21 (38.9)	14 (35.0)	
T4	20 (37.0)	10 (25.0)	

There were no patients with ECOG PS ≥ 2. BMI: body mass index; ECOG: Eastern Cooperative Oncology Group; ER: estrogen receptor; PR: progesterone receptor; PS: performance status.

with the AC-DHP regimen with dual-blockade, which is in line with previous studies,[12,14,26,27] although it was not statistically significant.

The comparative analysis between the two cohorts would suggest a trend in which the AC-DHP cohort (2015–2017) had higher pCR after NeoT. The multivariable regression analysis also suggested higher odds of having pCR with the AC-DHP regimen, although the regimen was not a significant predictor of treatment efficacy. The differences in baseline between both groups may partially explain the results, so inferences should be made with caution. As the ongoing research efforts at our research center reach a broader sample and a longer follow-up period using RWD, clinical effectiveness, namely assessed through OS and progression-free survival (PFS), will increase the strength of the findings on the value of pertuzumab as a NeoT as shown in previous clinical trials.[14]

Owing to the importance of clinical staging and HR status, future research should match cohorts to ensure proper comparability. Also, 7.5% of patients in the dual-blockade cohort showed near pCR with a small group of

Table 2. Clinical outcomes for HER2-positive breast cancer by regimen

	AC-DH: Doxorubicin, Cyclophosphamide, Docetaxel plus Trastuzumab (*n* = 54)	**AC-DHP: Doxorubicin, Cyclophosphamide, Docetaxel, Trastuzumab plus Pertuzumab (*n* = 40)**	***p*-value**
Type of surgery			
Conservative	9 (16.7)	10 (25.0)	0.320
Mastectomy	45 (83.3)	30 (75.0)	
Lymph node surgery			
Axillary clearance	53 (98.1)	35 (87.5)	**0.037**
Biopsy of sentinel lymph node	1 (1.9)	5 (12.5)	
Positive lymph nodes at surgery			
0 nodes	26 (48.1)	24 (60.0)	0.267
1–3 nodes	15 (27.8)	12 (30.0)	
4–9 nodes	10 (18.5)	2 (5.0)	
≥ 10 nodes	3 (5.6)	2 (5.0)	
Pathological complete response (pCR)			
ypT0/is ypN0	18 (33.3)	18 (45.0)	0.250
Breast	22 (40.7)	20 (50.0)	0.372
Axilla	26 (48.1)	24 (60.0)	0.255
Histologic response			
Minimal residual disease/nCR (< 10%)	16 (29.7)	9 (22.5)	0.129
Poor response (< 50%)	4 (7.4)	4 (10.0)	
Moderate-marked response (10–50%)	12 (22.2)	4 (10.0)	
nCR with small groups of cells	0 (0.0)	3 (7.5)	
No residual tumor	14 (25.9)	16 (40.0)	
No residual tumor with DCIS	8 (14.8)	4 (10.0)	
pCR in the breast, *n*/total (%)			
pCR in the breast	22/54 (40.7)	20/40 (50.0)	0.372
pCR and N– at surgery	4/54 (7.4)	3/40 (7.5)	0.987
pCR and N+ at surgery	18/54 (33.3)	17/40 (42.5)	0.363
pCR in ER-positive or PR-positive, or both, women	9/32 (28.1)	10/27 (37.0)	0.465
pCR in ER-negative and PR-negative women	13/22 (59.1)	10/13 (76.9)	0.283

Data are number (%) unless otherwise specified. DCIS: ductal carcinoma in situ; ER: estrogen receptor; nCR: near complete response; N–: lymph-node negative; N+: lymph-node positive; PR: progesterone receptor.

cells. The frequency of pCR was also higher in patients with HR-negative cancer, which is in line with previous studies.[28–30] The dual-blockade group had a greater proportion of conservative surgery and a lower rate of axillary clearance, as expected.

Safety issues were among the objectives of this study. Treatment tolerance was similar in both cohorts, with lower adverse cardiac events observed in the treatment with dual-blockade after NeoT. Given the effect of blockage in heterodimer formation, responsible for the signaling via epidermal growth factor receptor (EGFR) and HER2, diarrhea and rash occur more frequently with pertuzumab and this was verified in this study.

This study also attempted to understand how oncologists are changing their clinical approach to treatment of breast cancer. The clinical protocol for the treatment

Table 3. Predictors of pathologic complete response

	Pathologic Complete Response ypT0/is ypN0		**Pathologic Complete Response in the Breast**	
	Adjusted OR (95% CI)	***p*-value**	**Adjusted OR (95% CI)**	***p*-value**
Regimen				
AC-DH*	1		1	
AC-DHP**	1.65 (0.63–4.30)	0.304	1.51 (0.58–3.94)	0.396
Clinical staging				
II	1		1	
III	0.14 (0.04–0.43)	0.001	0.14 (0.04–0.44)	0.001
Hormone receptor				
Both negative	1		1	
At least one positive	0.21 (0.08–0.59)	0.003	0.16 (0.06–0.43)	< 0.001

All independent variables were included in the model as categorical. The variable regimen was forced into the model.
*AC-DH: doxorubicin, cyclophosphamide, docetaxel plus trastuzumab.
**AC-DHP: doxorubicin, cyclophosphamide, docetaxel, trastuzumab plus pertuzumab.
OR: odds ratio.

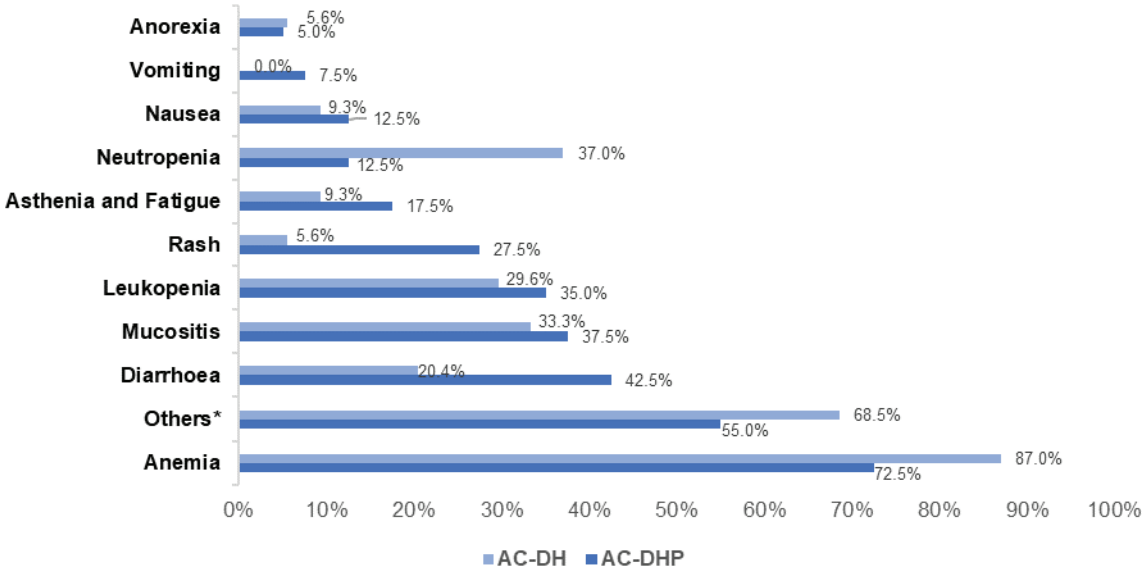

Figure 2. Summary of most common adverse events (any grade)

*Others includes arthralgias, abdominal pains, myalgias, neuropathy, and plantar-palmar erythrodysesthesia. AC-DH: doxorubicin, cyclophosphamide, docetaxel, plus trastuzumab; AC-DHP: doxorubicin, cyclphosphamide, docetaxel, trastuzumab, plus pertuzumab.

of breast cancer at IPO-Porto is perfectly defined, and the AC-DHP regimen is administered as defined in the Summary of Product Characteristics. In this study, younger and healthier women were included in the regimen with pertuzumab as a neoadjuvant. This could have led to selection bias in including younger and healthier patients owing to the known cardiotoxic effect of both trastuzumab and pertuzumab, although this study included all sequential patients who started AC-DHP in 2015–2017. Concurrently, oncologists seem to be more prone to systemic treatment earlier, which could have an impact in prognosis in this subtype of breast cancer. The AC-DHP cohort had a much greater proportion of operable tumors and lower proportion of T3 and T4 tumors, which could mean earlier diagnosis of breast cancer and increased use of NeoT, enabling the patients to be treated with dual-blockade.

Dual-blockade HER2 improved pCR and nCR, while maintaining adequate cardiac safety and tolerability, which contribute to an overall better prognosis.

Also of interest is the different approaches that can be undertaken based on clinical response. After surgery, trastuzumab is commonly used as adjuvant therapy for patients achieving pCR. This is mostly the extent of the experience with its use, namely the issues concerning the reactions of hypersensitivity to cardiotoxicity. However, for those patients not achieving pCR or with residual response, T-DM1 can be used as a postsurgical adjuvant. Results from the KATHERINE trial also show the potential of T-DM1 in adjuvant therapy for patients with residual invasive disease after NeoT, with 50% lower recurrence or death than with trastuzumab alone.[31] Still, grade $\geq$ 3 AEs were also more frequent than with trastuzumab alone. Regardless, recent results from the KRISTINE trial showed that T-DM1 plus pertuzumab as NeoT was associated with fewer grade $\geq$ 3 AEs, but with more grade $\geq$ 3 AEs, and treatment discontinuation during adjuvant therapy was similar to docetaxel, carboplatin, trastuzumab plus pertuzumab.[32,33]

Recent results obtained from the APHINITY trial corroborate the promising role of pertuzumab in combination with regular adjuvant therapy. Although this is particularly evident in operable HER2-positive breast cancer, longer follow-up periods seem to indicate that the benefits of the therapy are no longer dependent on HR status.[22]

Table 4. Patients with adverse cardiac events due to chemotherapy by regimen

	AC-DH (n = 54)			AC-DHP (n = 40)		
	Post-AC*	**Post-NeoT**	**Post-ACT**	**Post-AC**	**Post-NeoT**	**Post-ACT**
LVEF declines of 10% or more from baseline	16 (40.0)	26 (65.0)	29 (72.5)	14 (35.0)	19 (47.5)	25 (62.5)
LVEF less than 50%	3 (7.5)	4 (10.0)	1 (2.5)	1* (2.5)	1 (2.5)	1* (2.5)

Data are number (%).
Note - One patient had LVEF less than 50% at post-AC and post-ACT measurements.
*AC: doxorubicin plus cyclophosphamide.
AC-DH: doxorubicin, cyclophosphamide, docetaxel, plus trastuzumab; AC-DHP: doxorubicin, cyclophosphamide, docetaxel, trastuzumab, plus pertuzumab; ACT: adjuvant chemotherapy; LVEF: left ventricular ejection fraction; NeoT: neoadjuvant chemotherapy.

Overall, this study is relevant for more informed decision-making in breast cancer NeoT. The comprehensive approach at our cancer center, based on current trends such as patient centricity, promotes an integrated approach to treatment.[34] Implementation is difficult because this also depends on patient education and regulatory national issues, and although this is not a current practice in most institutions, this Portuguese cancer center is focused on delivering such solutions, which may also contribute to higher-quality healthcare.[35]

Limitations

Some limitations of this study should be mentioned. This is an observational cohort study with a small sample size and a retrospective analysis of nonoverlapping cohorts. There is lack of control over some key variables, but this is a limitation assumed when using RWD from a reference cancer treatment and management center in Portugal.

The two cohorts were not matched in their baseline sociodemographic and clinical characteristics, but the use of regression analysis allowed for some statistical inferences. The authors opted, based on this premise, to promote comparison between the two retrospective cohorts only as a preliminary analysis to support future work and research based on RWD, which is becoming increasingly relevant for healthcare decision-makers in the management of this disease. Although no genomic analysis was performed in this work, to date predictive accuracy of biomarkers for the pCR to NeoT for HER2-positive breast cancer remains largely unclear and future genomic analysis would add value to the analysis of these cohorts (e.g., *PIK3CA* mutations, tumor-infiltrating lymphocytes [TILs], and others).

Both cohorts have a limited number of patients; however, these represent all the patients followed up at this center who were treated with the respective regimens from 2012 to 2017, which is a strong argument in favor of this study. Moreover, more data will be available soon, which will increase these numbers and allow for more robust conclusions.

The success of the anti-HER2 therapeutics should promote screening for mutations and other genetic markers, which would give further insight concerning target patients with a higher probability of achieving pCR. Only with extended follow-up periods can conclusions be drawn concerning PFS and OS in patients with breast cancer. As recently seen in the APHINITY trial, the importance of longer follow-up periods goes beyond OS because identification of patient profiles for those who benefit from the therapy seems to broaden over time.[22] If the patient does not achieve pCR, adjuvant therapy with T-DM1 is recommended.[31] However, if the patient achieves pCR and has other associated risk factors, recommendation is for therapy of 1-year duration with pertuzumab plus trastuzumab and chemotherapy.[36] Otherwise, the recommendation still rests on trastuzumab plus docetaxel, but with consideration for HR status. In keeping with previous reports, the authors confirm that a greater proportion of patients achieved pCR when treated with the AC-DHP regimen with dual-blockade, confirming the real-world effectiveness of this combination, with better clinical outcomes such as pCR when compared to the group with monotherapy. The authors report an acceptable safety profile in a real-world setting, though there are limitations including overall lack of novelty, for example, not exploring precision medicine targets.

CONCLUSION

It is now understood that specific biomarkers can also promote better individualization of treatment and risk assessment for a complex condition, namely HER2-positive breast cancer. These individualized approaches can increase treatment response, reduce treatment-associated toxicity, namely cardiac toxicity, and improve other patient-reported outcomes, such as quality of life and work impairment, which are increasingly important in the patient-centric approach followed at IPO-Porto.

As main conclusion, this real-world evidence study showed that dual-blockade HER2 treatment tended to have better pathologic outcomes, such as pCR, than the group with monotherapy, with adequate safety profile. The results suggest this is mostly due to clinical staging and HR status at baseline. Although these data were useful for observing real-world outcomes with the regimens used in breast cancer, particularly the toxicity encountered, these results should be interpreted with caution especially because of the small sample size and differences between the groups. The NeoSphere trial was an RCT and had larger numbers of patients to achieve value comparisons between regimens.

Future research is paramount to ensure consistent results with bigger samples and longer follow-up periods. Studies are underway to increase the response rate, particularly with new molecules such as trastuzumab dexuratecan or immune checkpoint inhibitors and as adjuvant treatment, for example, with the combination of clinical kinase inhibitors with hormone therapy. This study gathered important elements to characterize the current clinical practice in Portugal.

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