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RESEARCH ARTICLE

Cardiac Toxicity in trail Comparing (Doxorubicin, Cyclophosphamide Followed by Paclitaxel, Trastuzumab) and (Trastuzumab, Weekly Paclitaxel) Carboplatin as Neoadjuvant Therapy in HER2 Positive Locally Advanced Breast Cancer

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Abstract: ***Background and purpose:*** This is a prospective study aiming to explore the efficacy and safety of anthracycline-free neoadjuvant treatment plus anti-HER2 target therapy in HER-2 positive locally advanced breast cancer. ***Patients and methods***: From January 2019 till December 2023; 172 female patients diagnosed with HER-2 positive breast cancer were recruited in the study. Eighty-three patients in Arm A (anthracycline arm) received 4 cycles of AC followed by 12 weeks of weekly paclitaxel and trastuzumab, 89 patients in arm B (anthracycline-free arm) received 6 cycles of paclitaxel and carboplatin AUC-2 day 1,8,15 every 28 days plus trastuzumab. Pertuzumab was available at NCI in the year 2020, so sub-group analysis was done for patients who received pertuzumab in both arms. Primary endpoints were pathological complete response, efficacy and toxicity profiles of both regimens. Secondary endpoint was DFS. ***Results:*** The pCR rate was 63.9% in arm A and 56.2% in arm B without statistically significant difference (P=0.35). The pCR rates in ACTH, ACTHP, TCH and TCHP were 55.6% ,73.7% 59.1% and 53.3% respectively with P=0.67. Adding pertuzumab increased the rate of conservative mastectomy significantly in arm B from 18.2% in TCH to 46.7% in TCHP with P=0. 004.The DFS of the whole study groups was 79%. The 4 years DFS was 81 % in both arms A and arm B, respectively (P=0.335). The 1-year DFS in subgroup ACTHP is significantly worse compared to other subgroups with P=0.03. Eight patients experienced a decline in EF <50% all located in arm A (P=0.002). ***Conclusion:*** Non-anthracycline regimens can be safely administered in HER2 positive breast cancer without compromising DFS or pCR. Cardiac toxicity is significantly common in the anthracycline containing arm. Further validation of larger groups of patients and longer follow-up are needed, and this may become standard care.

Keywords: HER2-positive breast cancer; neoadjuvant therapy; anthracycline-free regimen; pathological complete response.

INTRODUCTION

The phrase "locally advanced breast cancer" (LABC) includes a diverse range of conditions. This group includes stage IIB (T3N0), stage III disease, and inflammatory breast cancer (IBC). They are all characterized by widespread locoregional dissemination without obvious distant metastases [1]. About 15–25% of breast cancer subtypes are HER2-positive, prior the era of anti HER2 target therapy, this subtype was linked to a poor overall prognosis [2]. Neoadjuvant chemotherapy with dual HER2 blocking is tolerated, raises the pCR rate when compared to trastuzumab alone, and produces a pCR rate of roughly 50–70% [3]. Huober et al. [4], examined predictive markers among patients who obtained pCR following neoadjuvant therapy. They demonstrated that patients with pCR, baseline clinical nodal and tumor stage had independent correlations with DFS (HR 1.70 for nodal stage, and HR 1.61 for tumor stage). The idea of double blockade was established after results of Neosphere and Tryphanea studies. Patients who were treated with trastuzumab and docetaxel plus pertuzumab in the Neosphere study experienced the same proportion of adverse events, but their pathological CR rates were significantly greater than those of patients who received trastuzumab and docetaxel alone (45.8% versus 29%, respectively).The 5 years DFS was higher in patients who received neoadjuvant dual anti-HER2 blockade plus docetaxel compared to other groups, suggesting that achieving pCR was good indicator in HER2 early breast cancer [5].

The aim of this work was to explore the efficacy and safety of anthracycline-free neoadjuvant treatment plus anti-HER2 target therapy in HER-2 positive locally advanced breast cancer.

MATERIAL AND METHODS

This prospective study was carried out on 172 female patients, aged > 18 years old, diagnosed with HER-2 positive breast cancer eligible for neoadjuvant chemotherapy, performance status ≤ 2, with adequate laboratory tests and cardiac function. The study was done From January 2019 to December 2023 after approval from the Ethical Committee National Cancer Institute, Medical Oncology department, Cairo, Egypt. An informed written consent was obtained from the patients.

Exclusion criteria were patients with non-invasive breast cancer, metastatic breast cancer, current or past congestive heart failure, renal failure or hepatic failure, pregnancy.

The study was designed into 2 arms. Arm A (anthracycline regimens, 83 Patients): Four cycles of AC followed by 12 weeks of weekly Taxol plus Trastuzumab every 3 weeks until surgery (ACTH). Arm B (non-anthracycline regimens, 89 patients): Six cycles of weekly Taxol, carboplatin AUC2, Trastuzumab (TCH). Pertuzumab was available as anti HER2 treatment in NCI in 2020. So, the main arms (Anthracycline and non-anthracycline regimens) were sub-classified in the four subgroups.

Response and toxicity assessment scale

pCR defined as (i.e., ypT0 ypN0 in the current 9th version of AJCC staging system released in year 2023). Evaluation of cardiac toxicity was done by according to 5th version of CTCAE released in (November 2017).

Statistical analysis

Data was analyzed using IBM SPSS statistics version 22. Quantitative data was presented as mean, standard deviation (SD,) or median and range as appropriate. Qualitative data was presented as numbers and percentages. Numeric data was explored for normality using Kolmogrove- Smirnove and Shapiro-Wilk Test. Comparison between the two groups for normally distributed numeric variables was done using a student test and for non-inferiority normally distributed numeric variables, comparison between two groups was by the Whitney test. Comparison of categorical variables was done by the chi-square square test. P-value gets significant at 0.05 levels. All tests were tailed.

RESULTS AND OBSERVATIONS:

The patients' criteria of both study arms were broadly comparable Table (1). The percentage of elderly patients more than 50 were higher in arm B (P=0.02), also baseline menopausal status differed between the arms ,arm A included higher proportion of pre-menopausal women (58/83,69.9%) compared with B(45/89,50.6%) .Conversely arm B had greater proportion of post-menopausal women (44/89,49.4%) compared with arm A(25/83,30.1%). The pCR was 63.9% in arm A vs 56.2% in arm B with P=0.35 as shown in Figure 1A. The rate of pCR was higher at (ACTHP) 73.7%, 55.6% in (ACTH), 59.1% in (TCH) and 53.3% (TCHP) (p= 0.246).

Haematological toxicity and diarrhea were more seen in arm B while cardiac toxicity, vomiting and peripheral neuropathy were more in arm A as shown in table 1. Cardiac toxicity was defined as decline in EF more than 10 points linked to a decline in EF less than 53 % [6]. Baseline ECHO heart was done before the start of the first cycle of chemotherapy and was repeated every 3 cycles of anti-HER-2 target treatment to assess cardiac function.

Neoadjuvant Trastuzumab was omitted in four patients (2.3%) due to decline in EF, and they were in the anthracycline arm, 3 of them were in ACTH and 1 in ACTHP. Only 8 patients (4.6 %) in the whole study reported significant decline in EF% (below 50 %) with significant difference (p – value= 0.006) **(Table.2)**

Two of the most important trials exploring the anthracycline free regimens were TRAIN study and Tryphanea, which did not show significant difference in pCR rate between anthracycline and non-anthracycline regimens. Grade three or worse neutropenia was the most frequent cause of serious adverse events in TRAIN study, occurring in 60% of patients in the anthracycline arm and 54% in the anthracycline-free arm. The incidence of thrombocytopenia was 17% in the anthracycline group and 19% in anthracycline-free group with P=0.62 Van Ramshorst MS, et al. [7]. In Tryphanae febrile neutropenia was the most frequent SAE (Arm A: 13.9%, Arm B: 5.3%, Arm C: 14.5%).

One limitation of our study was the imbalance of menopausal status between arms. Arm A contained higher proportion of pre-menopausal women, whereas arm B had more post-menopausal women since younger and pre-menopausal patients were generally more likely to achieve pCR after neoadjuvant treatment this difference could be partly higher response rate seen in arm A.

In this study, hematological toxicity was higher in anthracycline free arm like Tryphanae study meanwhile GIT symptoms and peripheral neuropathy were higher in anthracycline arm despite the percentage of diabetic patients being fewer in the anthracycline compared to the anthracycline free arm with P=0.12.

Table 1: Demographic data, clinical, surgical criteria and toxicity of the study arms

		Arm A (N=83)	Arm B(N=89)	P
Demographic data				
Age (years)		46±9	50±12	**0.044**
Age groups	**< 50 Years**	56(67.5%)	44(49.4%)	**0.02***
	≥ 50 Years	27(32.5%)	45(50.6%)	
Diabetes mellitus	**Yes**	11(13.3%)	20(22.5%)	0.164
	No	72(86.7%)	69(77.5%)	
Cardiac	**Yes**	1(1.2%)	6(6.7%)	0.119
	No	82(98.8%)	83(93.3%)	
Hypertension	**Yes**	19(22.9%)	24(27%)	
	No	64(77.1%)	65(73%)	
Menopausal status	**Pre-menopausal**	58(69.9%)	45(50.6%)	**0.013***
	Post-menopausal	25(30.1%)	44(49.4%)	
Clinical criteria				
Clinical stage (c TNM)	**T1**	0(0%)	2(2.2%)	NA
	T2	39(47%)	38(42.7%)	
	T3	20(24.1%)	20(22.5%)	
	T4	24(28.9%)	29(32.6%)	
N stage	**N0**	14(16.9%)	26(29.2%)	0.248
	N1	52(62.7%)	51(57.3%)	
	N2	11(13.3%)	8(9%)	
	N3	6(7.2%)	4(4.5%)	
Surgical criteria				
Response	**CR**	53(63.9%)	50(56.2%)	0.35
	No-CR	30(36.1%)	39(43.8%)	
Surgery type	**MRM**	60(72.3%)	60(67.4%)	0.511
	CBS	23(27.7%)	29(32.6%)	
Post-surgical T	**T0**	57(68.7%)	63(70.8%)	0.839
	T1	19(22.9%)	20(22.5%)	
	T2	6(7.2%)	4(4.5%)	
	T3	1(1.2%)	2(2.2%)	
Post-surgical LN	**Positive**	12(14.5%)	23(25.8%)	0.087
	Negative	71(85.5)	66(74.2)	
Toxicity				
Cardio toxic	**No**	75(90.4%)	89(100%)	**0.002***
	Yes	8(9.6%)	0(0%)	
HB	**Normal**	40(48.2%)	18(20.2%)	**<0.001***
	Grade 1	30(36.1%)	52(58.4%)	
	Grade 2	13(15.7%)	16(18%)	
	Grade 3	0(0%)	3(3.4%)	
Platelets	**Normal**	81(97.6%)	81(91%)	0.101
	Grade 1	2(2.4%)	8(9%)	
Neutropenia	**Grade 1**	56(67.47%)	55(61.8%)	0.4962
	Grade 2	27(32.53%)	33(37.08%)	
	Grade 3	0(0%)	1(1.12%)	

Data are presented as mean ± SD or frequency (%). *: Statistically significant at P ≤ 0.05. NA: Not Applicable, c TNM: Clinical Tumor, Node, Metastasis Staging for Cancer, CR: Complete Response, MRM: Modified Radical Mastectomy, CBS: Conservative breast surgery, LN: Lymph Node, HB: Hemoglobin.

A meta-analysis in which 1998 patients were included from 11different studies. The rates of pCR were not significantly different (P=0.83). However, the non-anthracycline regimens showed lower cardiac toxicity rates compared with the anthracycline regimens (P=0.0001) [8]. Our study demonstrated significant association between anthracycline arm and decline in EF level. Despite more cardiac cases being presented in the anthracycline free arm. In TRAIN study, clinically left ventricular impairment were rare in both groups two (1%) Vs 0, however one patient in the anthracycline group died of pulmonary embolism. In Tryphanea study (2.7% of Arm B) experienced symptomatic left ventricular systolic dysfunction and (Arm A: (5.6%), Arm B: (5.3%), Arm C: (3.9%) had declines in left ventricular ejection fraction of ≥10% points from Baseline.The three-year DFS estimates were 87%, 88%, and 90% in groups A-C, respectively; Schneeweis et al. [9]. The three-year DFS of the TRAIN study in the anthracycline arm were 92.7% and 93.6% in

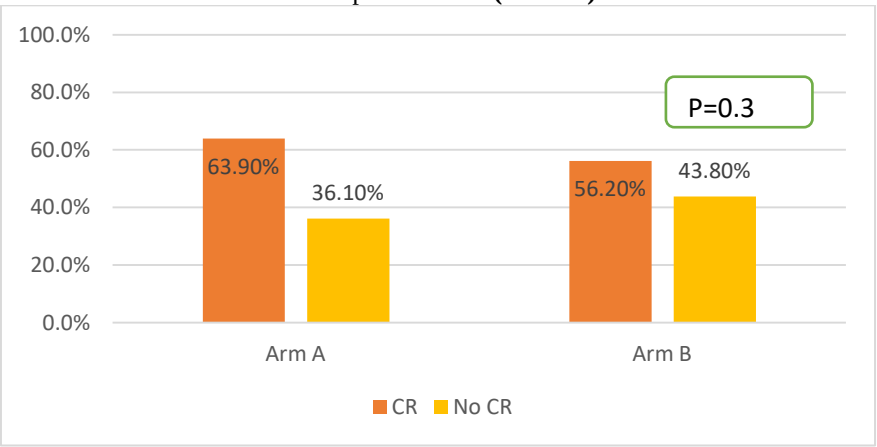
anthracycline free arm. Patients who received anthracyclines were more likely than those who did not, to experience a decrease in left ventricular ejection fraction of 10% or more from baseline to less than 50% ([7.7%] vs. [3.2%]; P=0.04). Van Ramshorst MS, et al. [7].

Table.2: Cardiotoxicity in the whole study subgroups

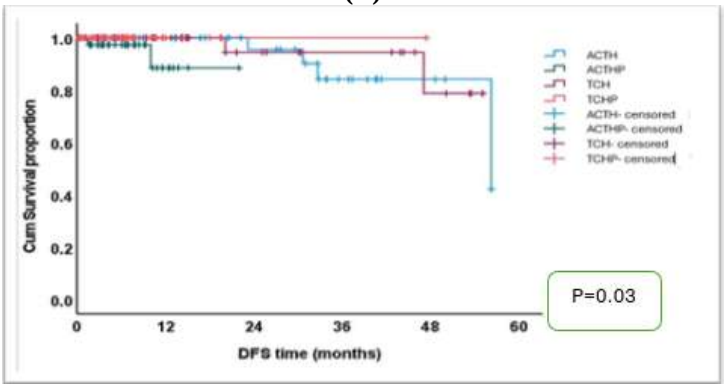
	ACTH Mean ±SD	ACTHP Mean ±SD	TCH Mean ±SD	TCHP Mean ±SD	p-value
EF (Baseline)	66 ±4	68 ±3	67 ±5	67 ±4	0.273
EF (During CTH)	66 ±6	65 ±4	66 ±4	66 ±4	0.737
Follow up EF	63 ±7	63 ±6	65 ±4	65 ±2	0.100
Cardio toxic (EF less 50 %)					
No **Yes**	42 (93.3) 3 (6.7)	33 (86.8) 5 (13.2)	44 (100) 0 (0)	45 (100) 0 (0)	0.006

The 4 years DFS was 81% in both arms A (anthracycline Based) and arm B (non-anthracycline based), respectively (P=0.335). The 1-year DFS in subgroup ACTHP was significantly worse compared to other subgroups with P=0.03 However, follow up was needed to confirm DFS in these subgroups and to assess efficiency of each regimen. There was a significant difference in DFS in cardiac patients in which median DFS was nearly half in cardiac patients compared to non-cardiac patients (23 months in cardiac patients compared to 56 months in non- cardiac patients) (P=0.02) (**Figure 1B and C).**

The independent factor that significantly affected DFS was the initial nodal stage. The Patients with initial clinical stage N3 have nearly fifty times the risk of recurrence compared to N0. **(Table.3)**



(A)



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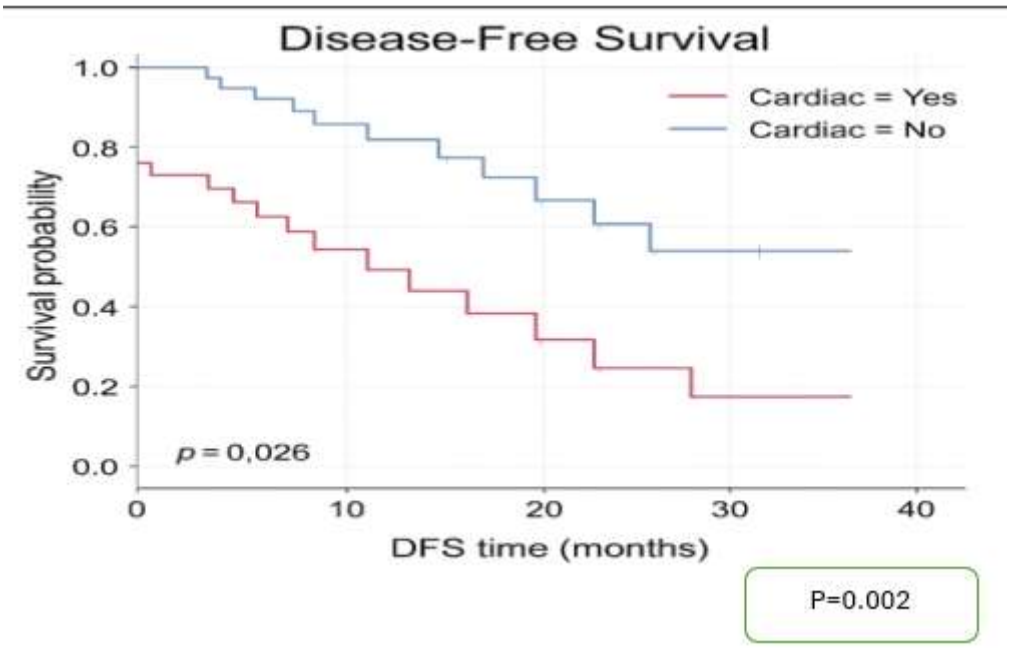
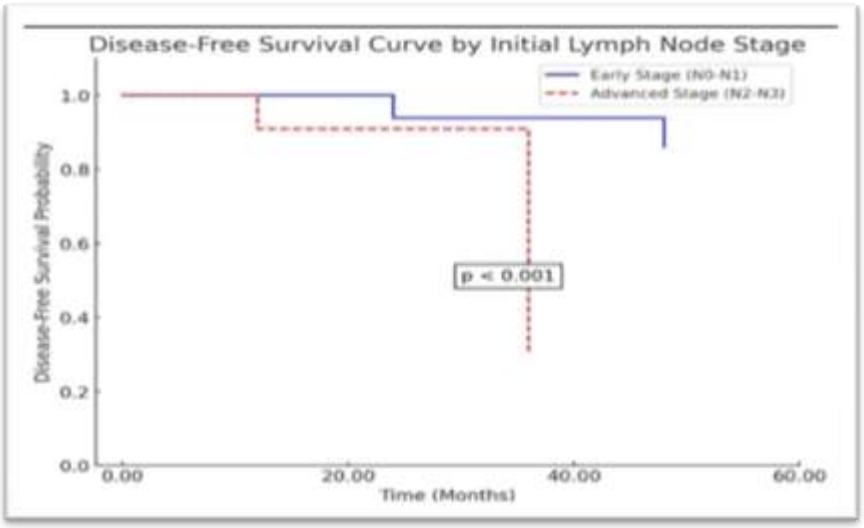


(C)



(D)

Table 3: Predictor of disease-free survival and one-year overall survival study subgroups

	B	SE	HR	95.0% CI for HR	P
N stage					**0.018***
N1 vs N0	-0.6	1.0	0.6	0.1-4.1	0.565
N2 vs N0	1.6	1.2	4.9	0.5-49.6	0.178
N3 vs N0	3.9	1.5	49.7	2.5-1007	**0.011***

*: Statistically significant at P ≤ 0.05. Kaplan-Meier Test (Log Rank (Mantel-Cox)) was used. SE: Standard Error, HR: Hazard Ratio, CI: Confidence Interval, ACTH: Adriamycin, Cyclophosphamide followed by Taxol and trastuzumab ,ACTHP: AC (Adriamycin [doxorubicin] + Cyclophosphamide) followed by T (Taxol) + H (Herceptin [trastuzumab]) + P (Pertuzumab), TCH: (Taxol), Carboplatin, and Herceptin (\(trastuzumab\)), TCHP: Taxol, Carboplatin, Trastuzumab and Pertuzumab..

DISCUSSION

Recommendations of the study included that further validation of larger groups of patients and longer follow up and this may become standard care.

CONCLUSION

Non anthracycline regimens can be safely administered in HER2 positive breast cancer without compromising cardiac function, OS, DFS or pCR.

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