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Comparative study between TCH (Paclitaxel, Carboplatin and Herceptin) and TH (Paclitaxel and Herceptin) as neoadjuvant treatment for HER-2 positive breast cancer patients

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ABSTRACT

Background: Breast cancer is considered the most commonly diagnosed cancer worldwide. Neoadjuvant chemotherapy has been shown optimal response for breast cancer with clinical significance. In addition, HER-2 overexpression or gene amplification is detected in about 20%–25% of breast cancer patients, and which shows more aggressive disease status and poor response to chemotherapy. The efficacy of trastuzumab in combination with paclitaxel and carboplatin has been revealed in many studies however, it showed frequently associated adverse event. Consequently, this study aimed at comparing the efficacy of trastuzumab in combination with paclitaxel and carboplatin with trastuzumab-paclitaxel without carboplatin.

Methodology: Our study has included 62 patients with pathologically proven breast cancer with Human Epidermal Growth Factor Receptor 2 positive , who were presented to Clinical Oncology Department Tanta University Hospital, from May 2019 to May 2021. Mammography, CT scan, ER, and PR were investigated among the studied patients.

Results: comparison between trastuzumab in combination with paclitaxel and carboplatin with trastuzumab-paclitaxel without carboplatin therapy in patients with HER-2 receptor positive revealed 64.52% pathological complete response in patients on paclitaxel-carboplatin-trastuzumab therapy in comparison to 54.84% in trastuzumab-paclitaxel without carboplatin group. Furthermore, anemia, neutropenia and asthenia were significantly higher in paclitaxel-carboplatin-trastuzumab group in comparison with trastuzumab-paclitaxel without carboplatin group (all p-value<0.05). Moreover, cardiac insufficiencies were insignificantly different between both groups.

Conclusion: paclitaxel-carboplatin-trastuzumab showed higher p(CR) than TH in patients with HER-2 receptor positive breast cancer patients but insignificant p value (p>0.05). Toxicity (anemia, neutropenia and asthenia)were significantly was higher in TCH group (p<0.05). Mortality rate was insignificantly different between TCH group and TH group (p>0.05).

Keywords: neoadjuvant chemotherapy-HER-2, positive breast cancer, TCH

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INTRODUCTION

According to GLOBOCAN 2020 report, breast cancer has become the most predominantly diagnosed cancer worldwide. Breast cancer accounts for 1 in 8 cancer diagnoses with a 2.3 million new cases in both genders together [1]. It is also among the top 25% of all cancers in females and its effects has been detected in many countries; particularly, transitioning countries [2]. Neoadjuvant chemotherapy has been shown optimal response for breast cancer with clinical significance [3]. Around 20% –25% of breast cancer patients display HER-2 overexpression or gene amplification, and which in comparison with HER-2 negative, HER-2 positive disease shows aggressive case and poor response to chemotherapy [4, 5].

In 2000s, a recombinant humanized monoclonal antibody (Trastuzumab, Herceptin®) was approved for selectively targeting the extracellular HER-2 receptor positive tumors [6]. Trastuzumab is simultaneously used with taxanes (e.g. paclitaxel) in advanced stages of HER-2 positive metastatic breast cancer [7]. One study has revealed that combination of trastuzumab with chemotherapy has demonstrated a significantly prolonged Time to Progression (TTP) and Overall Survival (OS) in comparison with chemotherapy alone in HER2-positive breast cancer patients [8].

Another has revealed that the addition of carboplatin to paclitaxel and trastuzumab showed better Objective Response Rate (ORR) and Progression Free Survival (PFS) in HER-2-overexpressing patients in comparison with paclitaxel and trustuzumab alone [9]. Nevertheless, anthracycline-free regimens have shown similar efficacy for the adjuvant therapy of HER2- positive breast cancer based on decreased toxicity and improved efficacy [10].

Pathologic Complete Response (pCR) is known as "absence of residual invasive cancer in breast and lymph nodes in surgical specimens after neoadjuvant therapy". It is crucial prognostic factor that is linked with long-term survival. pCR has been associated with the primary end point for neoadjuvant trials and reaches up to 78% in patients treated with trastuzumab [11].

Mammographic assessment of women who considered breast-conservation surgery involved the determining of size, extent, and location of the tumor within the breast. The presence of axillary nodal metastases or more distant tumors was not a contraindication to breast conservation. Tumor size was more readily determined mammographically than by physical

examination, which may overestimate tumor size because of fibrotic reaction to cancer. An accurate assessment of tumor extent was important because residual cancer may be a major reason for the failure of local treatment [2, 4].

Consequently, this study aimed at comparing the efficacy of trastuzumab in combination with paclitaxel and carboplatin with trastuzumab-paclitaxel without carboplatin.

METHODOLOGY

This prospective study was conducted on 62 patients with pathologically proven breast cancer with Human Epidermal Growth Factor Receptor 2 (HER-2/neu) positive who were presented to Clinical Oncology Department Tanta University Hospitals, from October 2019 to February 2023. All patients were subjected to informed consent according to Helsinki's declaration [12]. Ethical approval was obtained from institutional ethics committee (Approval code number: 36264).

Inclusion criteria

- Female patients with pathologically proved breast cancer.
- Adult females who were older than 18 years old at the initiation of the study.
- Performance according to ECOG less than 2.
- HER-2 overexpression.

Exclusion criteria

- HER-2 negative
- Patients with metastatic disease
- Patients with other primary cancers
- Patients who received chemotherapy before.
- Patients with inadequate kidney functions
- Patients with poor performance status

Radiological assessment

Mammogram, Chest X-ray, Ultra sound for abdomen and pelvis as well as Computerized Tomography (CT) chest and abdomen, if required were all done as routine investigation before initiating chemotherapy and, clinical assessment, and laboratory investigation before the start of each cycle. Positron Emission Tomography (PET) CT was done in advanced breast cancer stages, or to exclude distant metastasis. Bone scan was done to exclude bone metastasis in some cases.

Mammographic assessment of breast cancer

Mammograms were interpreted independently by two radiologists (the Mediolateral Oblique (MLO) view and the Craniocaudal (CC) view), for focal asymmetric density, masses, calcifications, and architectural distortion.

Margins of masses were reviewed for being circumscribed, microlobulated, indistinct, and speculated. Mammography was performed using digital radiography, Fuji Profect Plus, Fujifilm Cooperation, Tokyo, Japan.

Ultrasound by Two radiologists was performed on whole-breast for all patients. The ultrasound findings were classified as masses, low echoic area, distortions, and calcifications. Noted features, included shapes (oval, lobulated, polygonal, or irregular), patterns of internal echoes (hypoechoic, isoechoic, or hyperechoic), posterior echoes (accentuating, no change, or attenuating), and vascularity (avascular, spotty signals, hypovascular, hypervascular). Ultrasound was performed using 7.5-MHz to 13-MHz probes Toshiba nemio 2015.

All patients had mammography and ultrasound twice; initially and after chemotherapy [13].

Mammography and ultrasound features of HER-2 receptor positive breast cancer

Breast imaging-reporting and data system (BI-RADS) Classification [14]:

- Assessment incomplete
- Negative
- Benign finding
- Probably benign finding
- Suspicious abnormality
- Highly suspicious of malignancy; appropriate action should be taken.
- Known biopsy-proven malignancy, treatment pending

Pathological assessment

True cut biopsy was done before initiating chemotherapy to confirm diagnosis.

Estrogen Receptor (ER), Progesterone Receptor (PR), HER-2/neu , and KI 67 were also assessed. Post-operative pathological assessment was performed to assess response.

Laboratory assessment

Complete Blood pictures (CBC), Liver and Kidney function tests were also assessed before initiation of each chemotherapy cycle.

Treatment protocol

All the patients were subdivided into two groups; where each group had 31 Patients. Patients in group A received neoadjuvant chemotherapy of Paclitaxel-Carboplatin-Herceptin (TCH) (paclitaxel 80 mg/m^2 day 1,8,15 and Carboplatin-targeted Area Under the Curve (AUC) 5 day, repeated every 21 days, for 4-6 cycles and Herceptin dose was 8 mg/kg IV week 1 followed by 6 mg/kg IV cycled every 21 days to complete 1 year of therapy [15]. While patients in group B received the same protocol without Carboplatin (TH).

Patients who achieved clinical response after surgery and completed their neoadjuvant cycles were follow up with complete one year of Herceptin.

Patients received adjuvant Radiotherapy (RTH) after surgery to chest wall or to the breast tissue if they fulfill the criteria of indication of post-operative RTH.

Statistical analysis

Statistical analysis was done using SPSS v26 (IBM Inc., Chicago, IL, USA). Quantitative variables were presented as mean and Standard Deviation (SD) and compared between the two groups utilizing unpaired Student's t- test. Qualitative variables were presented as frequency and percentage (%) and were analyzed utilizing the Chi-square test or Fisher's exact test when appropriate. Kaplan Meier curve and Hazard ratio were used to compare survival between both groups. A two tailed P value<0.05 was considered statistically significant.

RESULTS

In this study, 86 patients were assessed for eligibility, 18 patients did not meet the criteria and 6 patients refused to participate in the study. The remaining patients were randomly allocated into two equal groups (31 patients in each). All allocated patients were followed-up and analyzed statistically (Figure 1).

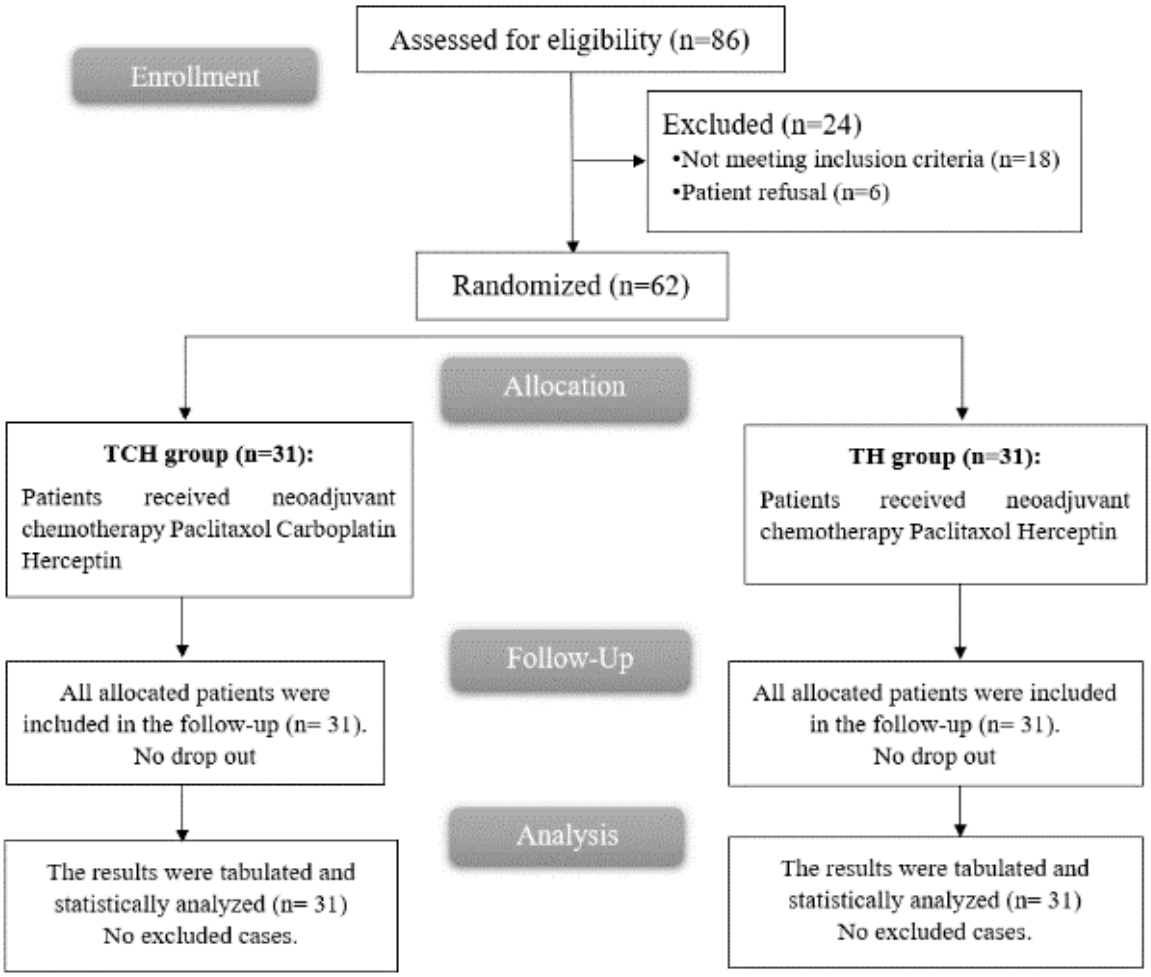

Fig. 1. CONSORT flowchart of the enrolled patients

Age, menopause status, N of TNM staging, grade and stage of breast cancer, ER, PR and Ki67 score, adjuvant chemotherapy and adjuvant RTH were insignificantly different between both groups. All cases had Invasive Ductal Carcinoma (IDC) and M0 in both groups. HER-2 status was positive in all cases in both groups. Surgery and adjuvant Herceptin were conducted in all cases in both groups (all P>0.05). as presented in (Table 1).

Tab. 1. Patient and tumors characteristics, markers and surgery and treatment of breast cancer of the studied groups

		TCH group (n=31)	TH group (n=31)	P value
Age (years)		48.5 ± 10.49	49.2 ± 9.17	0.778
Menopause status	**Perimenopause**	18 (58.06%)	15 (48.39%)	0.611
	Post menopause	13 (41.94%)	16 (51.61%)	
Pathology	**IDC**	31 (100%)	31 (100%)	--
T	**T1**	6 (19.35%)	1 (3.23%)	0.114
	T2	11 (35.48%)	17 (54.84%)	
	T3	9 (29.03%)	13 (41.94%)	
	T4	5 (16.13%)	0 (0%)	
N	**N0**	8 (25.81%)	10 (32.26%)	0.855
	N1	11 (35.48%)	10 (32.26%)	
	N2	12 (38.71%)	11 (35.48%)	
M	**M0**	31 (100%)	31 (100%)	---
Grade	**I**	3 (9.68%)	3 (9.68%)	0.285
	II	24 (77.42%)	19 (61.29%)	
	III	4 (12.9%)	9 (29.03%)	
Stage	**II**	11 (35.48%)	15 (48.39%)	0.44
	III	20 (64.52%)	16 (51.61%)	
ER	**Negative**	11 (35.48%)	8 (25.81%)	0.581
	Positive	20 (64.52%)	23 (74.19%)	
PR	**Negative**	12 (38.71%)	9 (29.03%)	0.591
	Positive	19 (61.29%)	22 (70.97%)	
Her2 status	**Negative**	0 (0%)	0 (0%)	---
	Positive	31 (100%)	31 (100%)	
Ki67 score (%)	**<15**	23 (74.19%)	28 (90.32%)	0.182
	>15	8 (25.81%)	3 (9.68%)	
Surgery		31 (100%)	31 (100%)	---
Adjuvant chemotherapy		**Yes** 11 (35.48%)	14 (45.16%)	0.604
		No 20 (64.52%)	17 (54.84%)	
Adjuvant Herceptin		31 (100%)	31 (100%)	---
Adjuvant radiotherapy		**Yes** 28 (90.32%)	26 (83.87%)	0.704
		No 3 (9.68%)	5 (16.13%)	

IDC: Invasive Ductal Carcinoma
ER: Estrogen Receptor
PR: Progesterone Receptor

According to (Table 2 and Figure 2), pCR was presented in 64.52% of patients on TCH therapy while showed 54.84% in TH group (P>0.05).

Tab. 2. pCR of the studied groups

		TCH group (n=31)	TH group (n=31)	P value
PCR	**Yes**	20 (64.52%)	17 (54.84%)	0.604
	No	11 (35.48%)	14 (45.16%)	

pCR: Pathological Complete Response.

As regards to safety of both regimens, anemia, neutropenia and asthenia were significantly higher in TCH group than TH group (all P value <0.05). LVEF decline were insignificantly different between both groups (Table 3).

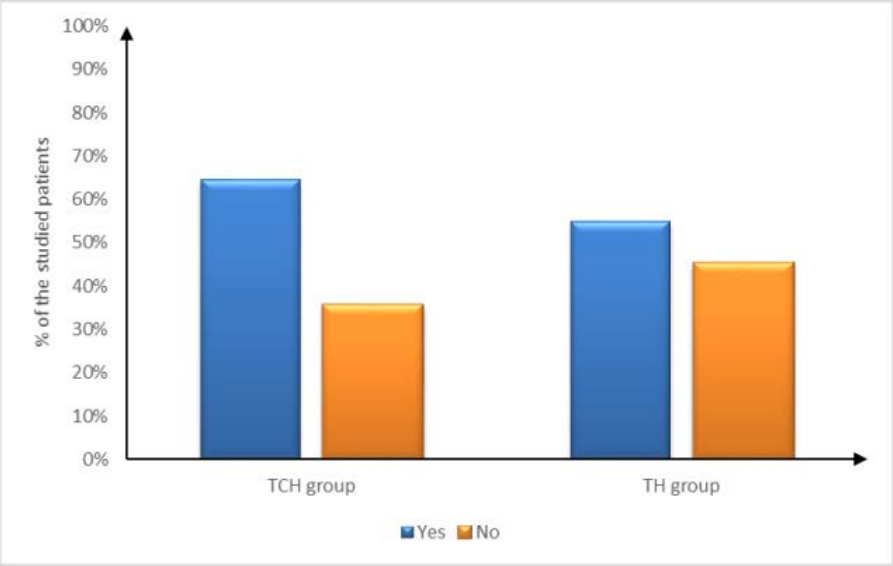

Fig. 2. pCR of the studied groups

Tab. 3. Complications after neoadjuvant chemotherapy of the studied groups

		TCH group (n=31)	TH group (n=31)	P value
Anaemia	**G1-2**	16 (51.61%)	26 (83.87%)	**0.022***
	G3	8 (25.81%)	2 (6.45%)	
	G4	7 (22.58%)	3 (9.68%)	
Neutropenia	**G1-2**	15 (48.39%)	27 (87.1%)	**0.002***
	G3	14 (45.16%)	2 (6.45%)	
	G4	2 (6.45%)	1 (3.23%)	
Asthenia	**G1-2**	18 (58.06%)	27 (87.1%)	**0.034***
	G3	8 (25.81%)	3 (9.68%)	
	G4	5 (16.13%)	1 (3.23%)	
LVEF decline	**G3**	4 (13.33%)	4 (12.5%)	0.922

LVEF: Left Ventricular Ejection Fraction.
*: significant as p value ≤ 0.05

The mean (±SE) survival was 23.4 ± 0.434 months in TCH group and 23.1±0.538 months in TH group. Mortality rate was insignificantly different between TCH group and TH group (6.67% vs 9.38% respectively, P value=0.693).

Hazard ratio of mortality in TH group was 1.42 times compared to TCH group and both were (95% CI: 0.24-8.45) higher than 90% (Table 4 and Figure 3-5).

Tab. 4. Overall survival among TCH and TH group

	Mean	SE	Mortality rate	Hazard ratio (95% CI)	P value
TCH group (month)	23.4	0.434	2(6.67)	1.42 (0.24- 8.4)	0.693
TH group (month)	23.1	0.538	3(9.38)		

SE: Standard Error
CI: Confidence Interval

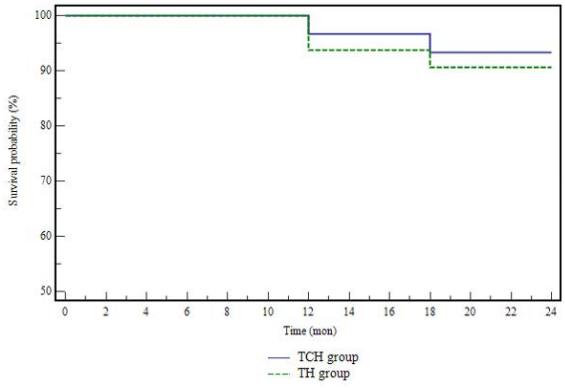

Fig. 3. Kaplan-Meier curve for overall survival in both groups

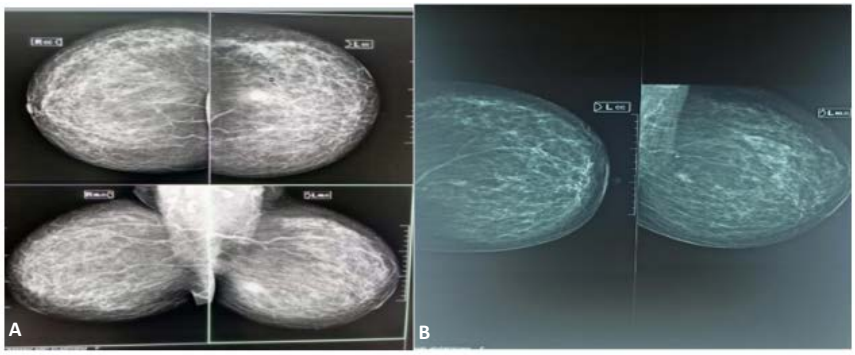

Fig. 4(A). Mammography of 42-year-old woman with left breast lower inner quadrant well defined hyperdense lesion with speculated out line BI-RADS IV, left enlarged axillary lymph nodes **Fig. 4(B).** Total resolution of the mass after receiving TH neoadjuvant therapy

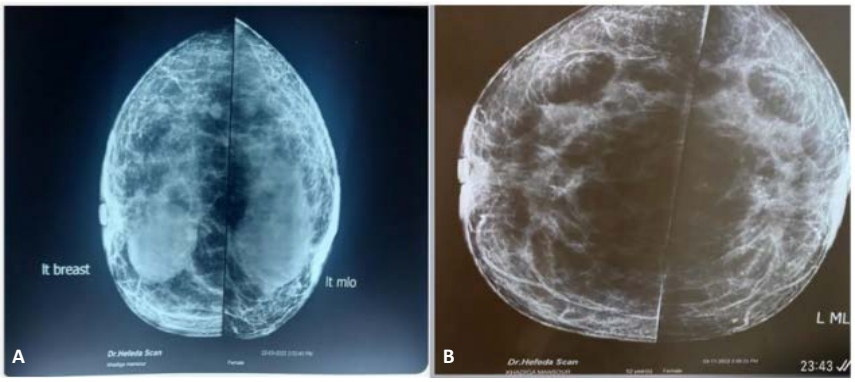

Fig 5(A). 73-year-old woman with left upper quadrant soft tissue speculated breast mass. **Fig. 5(B).** Left axillary lymph nodes complete resolution of the mass after receivingTCH neoadjuvant therapy

DISCUSSION

Although the efficacy of trastuzumab has been well established in treating patients with HER-2 receptor positive, ideal combination of neoadjuvant therapies have not been established as regards to maximizing the therapeutic benefits and reducing side effects.

In this study, comparing TCH with TH therapies in patients with HER-2 receptor positive revealed 64.52% pCR in patients on TCH therapy in comparison to 54.84% in TH group. Moreover, mortality rate was 1.42 times in TH group in comparison to TCH group (all P>0.05). The mammogram results in our study have revealed the same conclusion associated with TCH therapy. Similarly, various studies have demonstrated that the combination of TCH was considered as an effective choice for HER2-positive breast cancer patients with associated pCR rates of 40% when used in the neoadjuvant setting [16-18]. Another has demonstrated the achieved pCR after 2 cycles of TCH in HER-2 positive receptor breast cancer patients [19]. In the same line, among 8 trials with 2425 patients, carboplatin improved Disease-Free Survival (DFS) in comparison with anthracycline taxane regimens. Furthermore, the OS showed better results with carboplatin. Consequently, the pCR demonstrated a better results in carboplatin group in triple negative breast cancer patients [20]. Moreover, another study has revealed that every-3-week and weekly regimens of paclitaxel/carboplatin/trastuzumab showed better improvement in women with HER2-overexpressing [21]. In TRAIN-study, 3-year event-free survival was 88%, and the 3-year OS was 92% [22]. In the same line, comparing DFS rates for the TCH, docetaxel/epirubicin/cyclophosphamide,Xeloda/epirubicin/cyclophosphamide followed by Xeloda/docetaxel, and 5-fluorouracil/epirubicin/cyclophosphamide followed by docetaxel groups revealed; 84.6%, 62.9%, 65.7%, and 46.9% (P=0.01), respectively. In addition, 5-year OS rates for the TCH was superior to the other compared groups (P=0.069) [23].

In this study, anemia, neutropenia and asthenia were significantly higher in TCH group than TH group (all P value<0.05). LVEF decline were insignificantly different between both groups. The global reports did not reveal grade 3 or higher adverse events with TCH [24]. In the same line, one study assessing TCH side effects revealed that anemia and thrombocytopenia were higher in those patients in comparison to other regimens that did not contain carboplatin [20]. However, grade 3–4 neutropenia and febrile neutropenia were detected in 16.7 and 6.0% in another study [25]. However, no treatment-associated mortality or cardiac deficiency were detected in any of patients treated with TCH in Chen et al. study and Kolberg et al. Nevertheless, Hussain et al. showed that mild fatigue (36%) and diarrhea (49%) were the most common adverse events associated with TCH [4, 24, 26]. In the same line, the TRAIN- study has revealed that grade 3–4 adverse events were neutropenia (67%) and thrombocytopenia (43%) in TCH therapy [22].

CONCLUSION

Paclitaxel-carboplatin-trastuzumab showed higher p(CR) than TH in patients with HER-2 receptor positive breast cancer patients but insignificant p value (P>0.05). Toxicity (anemia, neutropenia and asthenia)were significantly was higher in TCH group (P<0.05). Mortality rate was insignificantly different between TCH group and TH group (P>0.05).

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ABBREVIATIONS

AUC: Area Under the Curve
BI-RADS: Breast imaging-reporting and data system
CBC: Complete Blood Corpuscles
CC: Craniocaudal
CT: Computerized Tomography
ER: Estrogen Receptor
HER-2/neu: Human Epidermal Growth Factor Receptor 2
IDC: Invasive ductal carcinoma
MLO: Mediolateral Oblique
ORR: Objective Response Rate
OS: Overall survival
PET: Positron Emission Tomography
PFS: Progression Free Survival
PR: Progesterone Receptor
RTH: Radiotherapy
TCH: Paclitaxel-Carboplatin-Herceptin
TH: Paclitaxel- Herceptin
TTP: Time to Progression

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