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Comparison of three standard neoadjuvant chemotherapy regimens based on pathological tumor response in breast cancer patients

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Abstract: We compared the efficacy of different neoadjuvant chemotherapy regimens and pathological factors related to higher pCR in localized breast cancer. This comparative retrospective study included 313 patients with breast carcinoma who received neoadjuvant therapy from January 2017 till July 31, 2019 at our institute. Patients were grouped in 3 different categories according to the treatment arms. In Arm A, patients received dose-dense AC [4 Cycles] followed by dose dense paclitaxel [4 Cycles]. In Arm B, 2 weekly dose dense AC [4 Cycles] followed-by paclitaxel every week [12 Cycles], while Arm C received 3 weekly AC [4 Cycles] and 3 weekly paclitaxel [4 Cycles]. pCR was seen in 135(43.1%) patients with the highest pCR in arm B i-e 33(55%), followed by 39(43.3%) in arm A, and 63(38.6%) in arm C. Triple-negative patients had the highest percentage of pCR 38 (65.5%). HER2 positive patients who received neoadjuvant Trastuzumab also had increased pCR rate of 21 (61.7%). ER/PR positive, HER2 negative patients had the lowest pCR 56 (33.5%). Dose dense AC [4 cycles] followed-by weekly Paclitaxel [12 cycles] is the most effective neoadjuvant therapy regimen for breast cancer patients, particularly if they were also triple negative and HER2 positive receiving Trastuzumab.

Keywords: Breast cancer, neoadjuvant therapy, trastuzumab.

INTRODUCTION

Neoadjuvant therapy (NAT) for breast cancer refers to chemotherapy administration before definitive local surgical treatment and/or radiation therapy (Gogas & Fountzilas, 2003). The aim of neo-adjuvant chemotherapy is to decrease the primary tumor size, ultimately permitting surgical intervention. NAT additionally allows an early assessment of clinical efficacy, thus at a relatively early stage modification in the applied chemotherapeutic regimen can be initiated (Rubovszky & Horváth, 2017). Multiple studies have shown that the addition of taxanes to anthracycline-based protocols in the neoadjuvant setting. result in improved pathological response rates (Evans *et al*., 2005; Rastogi *et al*., 2008).

Neo-adjuvant chemotherapy for breast cancer is one of the standard treatment options for non-metastatic invasive breast cancer. Results of randomized trials and meta analyses suggest that anthracycline, cyclophosphamide and taxane-based chemotherapy combinations are the most effective therapies for breast patients. However, it is not known as to which protocols of chemotherapy are superior. In our study, we assessed and compared the different protocol arms used in breast cancer patients and its response in terms of pathological complete response (pCR).

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Among neoadjuvant chemotherapy regimens one of the most frequently used protocol has been conventional 3 weekly AC followed by 3 weekly Paclitaxel (Gradishar *et al*., 2020). Other regimens are: DD-AC [(Dose Dense) doxorubicin and cyclophosphamide] with subsequent DD-paclitaxel and DD-AC followed by weekly paclitaxel. Trastuzumab's useful role as a part of neoadjuvant therapy for Human Epidermal Growth Factor Receptor (HER2)-positive tumors is well acknowledged, with randomized studies and meta-analyses illustrating improvements in pCR rate, EFS and OS (Event free and Overall Survival) (Cortazar *et al*., 2014).

A pCR has various definitions in the literature; however practically acceptable and appropriate definition as no residual invasive carcinoma in breast tissue as well as axillary lymph nodes in surgical specimens (Kaufmann *et al*., 2006). A pCR following neo-adjuvant therapy is related to a more encouraging outcome, compared with the patients who have residual cancer in the breast tissue and/or axilla (Carey *et al*., 2005). Due to the heterogeneity of breast cancer, different molecular subtypes of the breast cancer have shown to have a different degree of responses to chemotherapy.

The objectives of this research were to compare the efficacy of different neo-adjuvant therapy regimens in achieving pCR in breast cancer specimens of patients being treated at SKMCH & RC, Pakistan, and to determine the various patient and tumor characteristics associated with higher pCR.

MATERIALS AND METHODS

This comparative study based on retrospective data collection reviewed all breast cancer patients treated with neo-adjuvant therapy from January 2017 up till July 2019 at Shaukat Khanum Memorial Cancer Hospital and Research Center Pakistan. This study was permitted by the Institutional Review Board of the SKMCH & RC, Lahore, Pakistan.

The study population includes the patients who received neo-adjuvant therapy in the above mention period, of all ages, selected through purposive sampling. The inclusion criteria included patients with breast cancer (newly diagnosed), with the tumor size of more than 2cm (regardless of lymph node status) and no breast surgery or radiation has done previously. The exclusion criteria included patients having received neoadjuvant hormonal therapy, distant metastasis, non-operable breast tumor, and individuals who do not receive full chemotherapy regimens. Study variables included age, lymph node status, type of cancer, the menopausal status of women, ER-PR, HER2 status, targeted therapy, type of chemotherapy and pathological response. A pCR was well-defined as absence of residual tumor in the axillary lymph node and/or breast tissue surgical specimen removed after neo-adjuvant therapy.

Prior to the therapy, all breast cancer patients underwent a core needle biopsy to determine histological subtyping, Estrogen Receptors (ER), Progesterone Receptors (PR), and HER2 status. ER and PR were considered positive if a total of more than 1 per cent of tumor cell were stained. The tumor was regarded as HER2 positive if 3+ by immunohistochemistry test or positive gene amplification by in situ hybridization. Lymph nodes status was determined by physical examination and radiological imaging with or without a cytological diagnosis. The staging was established on the basis of the 8th edition of American Joint Committee on Cancer TNM staging manual.

Patients were classified into 3 groups in accordance with the standard treatment arms. Arm A: comprised of 2 weekly dose-dense AC (Doxorubicin 60mg/m^2, Cyclophosphamide 600mg/m^2) [4 Cycles] initially and then 2 weekly dose-dense Paclitaxel, 175mg/m^2 [4 Cycles]. Arm B: consisted of 2 weekly dose-dense AC [4 Cycles] succeeded by weekly Paclitaxel, 80mg/m^2 [12 Cycles] and Arm C: included conventional 3 weekly AC [4 Cycles] with subsequent 3 weekly Paclitaxel, 175mg/m^2 [4 Cycles].

STATISTICAL ANALYSIS

Statistical analysis was computed by means of SPSS software (version 23; SPSS, Chicago, IL, USA). Continuous parameters were mentioned as Mean ± SD while categorical variables were estimated as frequencies and percentages. Categorical parameters were then equated using Regression Analysis and Chi-Square test. Significance level was demarcated as a two-tailed p-value 0.05.

RESULTS

A total of 313 patients with breast carcinoma received neoadjuvant chemotherapy during the study period. The mean age and standard deviation was 39.8±8.4 years (Range 22-67 years). The majority (77.6%) of patients were premenopausal. In addition, more than half (52.1%) had right-sided breast cancer. Furthermore, (94.6%) had invasive ductal carcinoma (IDC) type. The details of the age-wise distribution of pCR are in fig.

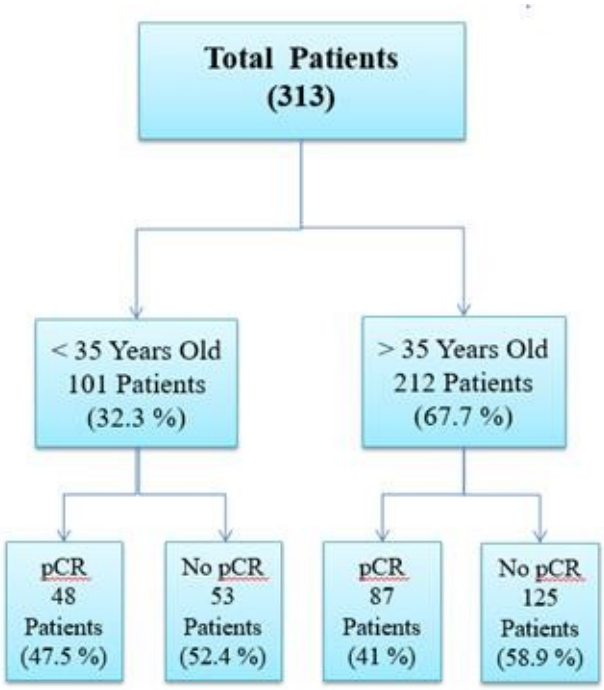

Fig. 1: Age-wise distribution of pCR

Among the patients with breast carcinoma who received neoadjuvant therapy (NAT), 90 received arm A, 60 arm B and 163 arm C. Overall, complete pathological response (pCR) was seen in 135 (43.1%) patients following NAT. The highest percentage of pCR was seen in the patients who received arm B, 55%, followed by arm A, 43.3% and arm C, 38.6%. table 1.

Lymph nodes were positive in the majority of the patients and in these patients, 104 (38.8%) had pCR. In addition, 58 patients had TNBC and out of them 38 (65.5%) patients showed pCR. Additionally, 167 (53.4%) patients were ER/PR positive/HER2 negative. In this category, only 56 (33.5%) showed pCR. In 88 tumors HER2 was over expressed but due to financial constraints, only 34

Table 1: Comparison of Neoadjuvant Chemotherapy Protocols for pCR

Variables	Patients n (%)	pCR n (%)	No pCR n (%)	p value
Protocols Arm A Arm B Arm C	 90 (28.8) 60 (19.2) 163 (52.1)	 39 (43.3) 33(55) 63 (38.6)	 51 (56.6) 27 (45) 100 (61.3)	0.092
Comparison of Individual Protocol Arms				
Protocols Arm A Arm B	 90 (28.8) 60 (19.2)	 39 (43.3) 33 (55)	 51 (56.6) 27 (45)	0.10
Arm B Arm C	60 (19.2) 163 (52.1)	33 (55) 63 (38.6)	27 (45) 100 (61.3)	0.021
Arm A Arm C	90 (28.8) 163 (52.1)	39 (43.3) 63 (38.6)	51 (56.6) 100 (61.3)	0.20

Table 2: Characteristics Influencing pCR

Variables	Patients n (%)	pCR n (%)	No pCR n (%)	p value
ER/PR Positive Negative	 216 (69.0) 97 (31.0)	 78 (36.1) 57 (58.7)	 138 (63.8) 40 (41.2)	0.001
HER2 Positive Negative	 88 (28.1) 225 (71.8)	 41 (46.5) 94 (41.7)	 47 (53.4) 131 (58.2)	0.25
Trastuzumab therapy Yes No	 34 (10.9) 54 (61.3)	 21 (61.7) 20 (37.0)	 13 (38.2) 34 (62.9)	0.017
Node status Positive Negative	 268 (85.6) 45 (14.4)	 104 (38.8) 31 (68.8)	 164 (61.1) 14 (31.1)	0.001
Receptor status Triple Negative ER+ / PR+ / HER2+ ER+ / PR+ / HER2- ER- / PR- / HER2+	 58 (18.5) 49 (15.7) 167 (53.4) 39 (12.5)	 38 (65.5) 22 (44.8) 56 (33.5) 19 (48.7)	 20 (34.4) 27 (55.1) 111 (66.4) 20 (51.2)	0.001
Comparison Triple Negative ER+ / PR+ / HER2-	 58 (18.5) 167 (53.4)	 38 (65.5) 56 (33.5)	 20 (34.4) 111 (66.4)	0.001
ER+ / PR+ / HER2+ ER- / PR- / HER2+	49 (15.7) 39 (12.5)	22 (44.8) 19 (48.7)	27 (55.1) 20 (51.2)	0.40

patients received neoadjuvant trastuzumab in addition to chemotherapy. Out of these 34 patients, 21 (61.7%) had pCR. Furthermore, 49 patients had ER+/PR+/HER2+ and 22 (44.9%) showed pCR. In this category 09 (18.4%) patients received Trastuzumab. Moreover, 39 (12.4%) patients were ER-/PR-/HER2+ and 19 (48.7%) showed pCR. In ER-/PR-/HER2+ category 25 (64.1%) patients received Trastuzumab. Additionally, ER/PR positive HER2 negative patients had a lower pCR i.e. 56 (33.5%) (table 2).

DISCUSSION

For breast cancer patients, different chemotherapy regimens are being used in neoadjuvant setting, however, there has been no comparison made between these regimens regarding pathological response achievement. Traditionally most commonly used neoadjuavnt chemotherapy protocols had anthracycline/ cyclophosphamide scheduled 3 weekly followed by a taxane 3 weekly. In a recent meta-analysis, it was found that dose dense neo-adjuvant therapy resulted in a higher pCR rate (Petrelli *et al*., 2016). Catane *et al* indicated that dose dense chemotherapy, predominantly in hormone receptor positive disease yielded a higher pathological response rate (Catane *et al*., 2005). Our study revealed that the patients who received arm B (DD-AC with subsequent weekly paclitaxel) had the highest complete pathological response followed by the patients who received arm A (DD-AC and DD-Paclitaxel).

Thus in comparison to the recent studies, our study also showed an appreciably higher complete pathological response to both the dose dense regimens compared to conventional three weekly chemotherapy. Interestingly in our study, out of the two dose dense / dose intensified regimens, paclitaxel given weekly gave superior results. One possible explanation could be that with weekly paclitaxel 12 cycles, a total higher dose of paclitaxel (960mg/m^2) is given compared to 600mg with 4 cycles of 175mg/m^2 paclitaxel.

This study also showed that TNBC and HER2 positive patients (who received trastuzumab) had higher complete response rates after neoadjuvant chemotherapy. Overall, pCR of patients in our study was 43.1%, which is significantly higher than previous reports of around 20% response rates (Sasanpour *et al*., 2018; Huober *et al*., 2010). This difference in result in might be due to higher number of younger patients, which is characteristic of breast cancer patients in Pakistan (Rufina *et al*., 2018).

Hsu-Huan Chou *et al* conducted a study on patients who had surgically resectable or locally advanced cancer treated with neo-adjuvant therapy, with age being an individual factor analyzed for pathologic complete response, it was found that younger age was a predictive factor for pCR (Chou *et al*., 2019). Untch M *et al* concluded in a study that the patients below 40 years of age had increased (57%) pCR rate. In our study age was one of the investigative factors for complete pathological response evaluation and our results also suggest that the younger patients had an increased chance of achieving pCR (Untch & von Minckwitz, 2011).

Results of our study confirmed previous observations that pathological responses to chemotherapy vary by tumor subtypes. Neo-adjuvant administration of anti-HER2 therapy along with chemotherapy has been shown to improve the survival of breast cancer patients who have HER-2 over expressing disease (Gianni *et al*., 2010).In one study adding trastuzumab to neoadjuvant chemotherapy was related with 53% pCR amongst patients with HER2+ breast cancer. Our study revealed parallel outcomes (61.7% pCR) to neoadjuvant trastuzumab administration and lower pCR (37%) in patients who did not receive trastuzumab. This major difference in pCR rates with the addition of trastuzumab demands the addition of anti HER2 therapy to all HER2 positive patients with breast cancer in neoadjuvant setting. Similarly, one recent study also showed the change of Her 2 status in pathological specimen after neoadjuvant Her 2 directed treatment in breast cancer patients (Katayama *et al*., 2021).

A meta-analysis revealed the highest pCR for triple negative and HER2 positive / hormone receptor-negative patients (Houssami *et al*., 2012). Wu *et al* showed the highest pCR rate in TNBC patients contrasted with non-TNBC patient (Wu *et al*., 2014). In another study of triple negative breast cancer, pCR was observed in 33%; Hormone positive and HER2 negative breast cancer showed a pCR of only 8% (Gianni *et al*., 2010; Chen *et al*., 2011). The results of our study were therefore parallel to prior studies with pCR rate 65.5% in TNBC and 33.5% with HER2 negative and hormone positive.

Despite the fact that triple negative breast cancer (TNBC) has a lower overall prognostic value, this subtype of carcinoma is more responsive to chemotherapy and has a greater tendency to accomplish a pCR to neoadjuvant chemotherapy compared with hormone receptor positive disease (Carey *et al*., 2007) .TNBC patients who obtain a pCR have a favourable overall survival (OS), which is analogous to patients with non TNBC who accomplish a pCR (Liedtke *et al*., 2008). One recent met analysis also confirmed the long term survival of the TNBC patients following PCR (Huang *et al*., 2020).

There were some limitations in this study. As this was a retrospective analysis, the results of this study are liable to patient and treatment selection bias. Among patients with HER-2 over expressing tumors, not all patients received trastuzumab, which could have led to even better response rates in this subtype of breast cancer.

CONCLUSION

In conclusion, results of our study suggest that for breast cancer patients receiving neoadjuvant chemotherapy highest pathological complete response may be achieved with dose dense regimens such as AC (4 cycles) followed by weekly paclitaxel (12 cycles); furthermore, increased pCR is noted for triple negative breast cancer and HER2+ patients who received trastuzumab, compared with lowest response rates for the hormone positive cancer patients.

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