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PATHOLOGICAL COMPLETE RESPONSE IN HORMONE RECEPTOR POSITIVE, HER2 NEGATIVE BREAST CANCER AFTER NEOADJUVANT CHEMOTHERAPY

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Abstract

Neoadjuvant chemotherapy (NAC) is an effective intervention in patients presenting with inoperable breast cancer. Studies have demonstrated that patients achieving pathological complete response (pCR) after receiving NAC have a better long-term outcome. This study focused to assess the efficacy of NAC in the management of hormone receptor positive, HER2 negative breast cancer, with the use of pCR as the primary end point. This prospective observational study was conducted at the Jinnah Medical Postgraduate Centre (JMPC), Karachi from January to December, 2022. Patients older than 18 years, having invasive breast carcinoma diagnosed through core needle biopsy, surgical excision (lumpectomy or mastectomy), HER2/neu negative breast cancer, hormone (i.e., ER/PR) positive breast cancer and no history of recent excision in the same breast. All patients received four cycles of NAC, which consisted of doxorubicin (60 mg/m^2 every 3 weeks), cyclophosphamide (600 mg/m^2 every 3 weeks) followed by paclitaxel (80 mg/m^2 weekly for 12 weeks). Among the total enrolled patients (n = 180), the majority (n = 169, 93.9%) were married and postmenopausal (n = 150, 83.3%). For the hormonal status, all patients were ER positive and HER2 negative. However, the PR positivity was shown by 149 (82.8%) patients. The mean and median age of the patients at diagnosis was 52.6±8.6 and 54 (range: 29-69) years, respectively. Results showed that pCR with NAC was achieved in only 07 (3.9%) patients. These results may have implications in selecting NAC regimen for the particular subtype of breast cancer.

Keywords: NCCN, TNM Staging, MRI, Mastectomy, Tumor Size.

1. INTRODUCTION

The use of neoadjuvant chemotherapy (NAC) in breast cancer not only improves the rates of breast conserving surgery (BCS) [1] but also targets any micrometastatic disease [2], thus reducing the risk for disease recurrence [3]. Studies have demonstrated that patients achieving pathological complete response (pCR) after NAC have a better long-term outcome [4].

Briefly, pCR refers to the absence of invasive and intraductal disease in the breast and the axillary lymph nodes. Consequently, enhancing the rate of pCR became the primary end point for several clinical trials that were focused on the assessment of NAC.

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It was expected that higher pCR may be translated into improved survival rates, as tumor response to NAC has been considered as a good surrogate end point for survival [5], [6]. The efficacy of NAC (as evaluated with pCR) has been associated with the pathological subtype of the breast cancer. Studies have revealed that the use of anthracyclines, taxanes, and other agents against anti–human epidermal growth factor receptor 2 (HER2) completely eradicate breast tumors at the time of surgery in around 30-40% triple-negative cases [7], [8].

It may be noted that the estrogen receptor (ER) and progesterone receptor (PR) are negative, while HER2 are not overexpressed in triple-negative cases. Long-term follow-up studies have shown a consistent correlation between pCR and low rates of relapse and mortality among patients with triple-negative breast cancer [8], [9].

Assessment of pCR after administration of NAC has been speculated as a surrogate prognostic indicator for treatment outcomes, quantified with clinical metrics such as overall survival (OS), disease-free survival (DFS) and relapse-free survival (RFS) [10]. To elaborate, NAC is being increasingly utilized in breast cancer patients towards achieving tumor downsizing [11], for elevating likelihood of tumor surgical resection [12], and potentially make a mastectomy-requiring patient eligible for BCS [13].

Despite these benefits, an inherent challenge with this approach is the inability to utilize traditional pathologic features (e.g., number of lymph nodes involved, margin status, primary tumor size, etc.) for prognostic purposes. Moreover, the relationship between RFS and pCR is primarily shaped by the clinical subtype of breast cancer and the type of NAC regimen [14]. Beyond these uncertainties, the influence of pCR on the adjuvant therapy of breast cancer is relatively unexplored.

The focus of this study was to assess the efficacy of NAC in the management of a specific subset of breast cancer patients, with the use of pCR as the primary end point. The eligible patients should express positivity for ER and PR, while negativity for HER2. Moreover, these patients received a specific regimen of NAC, which consisted of doxorubicin and cyclophosphamide followed by paclitaxel. It is expected that this study may help in designing escalation strategies in the NAC setting and may have implications for the selection of NAC drugs for the particular subtype of breast cancer.

2. MATERIALS AND METHOD

2.1 Study design

This prospective observational study was conducted at the Jinnah Medical Postgraduate Center (JMPC), Karachi from January to December, 2022. The study was assessed and approved by the Institutional Review Board (IRB) of JMPC, Karachi. Patients were briefed on the study protocol, who then signed the informed consent. All patients were authorized to withdraw their participation consent at any time point during the study.

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2.2 Inclusion and exclusion criteria

Patients older than 18 years, having invasive breast carcinoma diagnosed through core needle biopsy, surgical excision (lumpectomy or mastectomy), HER2/neu negative breast cancer, hormone (i.e., ER/PR) positive breast cancer and no history of recent excision in the same breast were eligible for enrollment in this study. All patients with non-confirmed breast cancer, who do not give consent of participation, having benign lesion of breast or recurrent breast cancer were excluded.

2.3 Data collection

The online, open-source statistical tool Select was employed for sample size calculation, with an expected proportion of pCR at 14.9% [15], confidence level of 95%, and a margin of error of 5%. A non-probability consecutive sampling technique was used to select and enroll the patients. Relevant data of the selected patients was recorded on a pre-designed questionnaire, composed of the following four main sections: demographics (i.e., age, parity, gravidity, ethnicity, menopausal status, marital status, etc.), hormone receptor status (ER, PR and HER2/neu status), pathological stage and grade and tumor type/ size. The pCR was defined as the absence of invasive and in situ cancer in the breast and axillary nodes (i.e., ypT0 ypN0) [16].

All patients enrolled in this study received four cycles of NAC, which consisted of doxorubicin (60 mg/m2 every 3 weeks), cyclophosphamide (600 mg/m2 every 3 weeks) followed by paclitaxel (80 mg/m2 weekly for 12 weeks).

2.4 Data analysis

The SPSS software was utilized for all data recording and subsequent statistical analyses. Categorical variables (e.g., stage, grade and type of breast tumor) were presented as frequency and percentages, whilst continuous variables (e.g., patient's age and tumor size) were presented and compared using mean and standard deviation. Chi square test was used to assess the association between pCR and the hormone expression status after administering four cycles of NAC. Differences in results were considered statistically significant if $p < 0.05$.

3 Results

Details of patient demographics and their relevant clinical characteristics are summarized in Table 1. For the 180 breast cancer patients enrolled in this study, the majority of enrolled patients (n = 169, 93.9%) were married.

Moreover, 60 (33.3%) patients had three children, 45 (25%) had two, while 32 (17.8%) had four children. The majority of patients (n = 150, 83.3%) presented with postmenopausal status. For the hormonal status, all patients were ER positive and HER2 negative. However, the PR positivity was shown by 149 (82.8%) patients.

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Table 1: Summary of patient's demographics (n = 180)

Demographics		Number of patients (%)
Marital Status	Married	169 (93.9)
	Unmarried	06 (6.1)
Number of children	0	18 (10.0)
	1	13 (7.2)
	2	45 (25.0)
	3	60 (33.3)
	4	32 (17.8)
	5	12 (6.7)
Hormonal status	ER positive	180 (100)
	PR positive	149 (82.8)
	HER2 negative	180 (100)
Menopausal	Premenopausal	30 (16.7)
	Postmenopausal	150 (83.3)

Figure 1 presents the age distribution of the breast cancer patients enrolled in this study. The mean (± standard deviation) and median age of the patients at diagnosis was 52.6±8.6 and 54 (range: 29-69) years, respectively. The maximum number of patients (n = 40, 22.2%) belonged to 56-60 years age bracket, followed by 32 (17.8%) between 46–50 years, 31 (17.2%) between 61–65 years and 30 (16.7%) between 51–60 years. Collectively, three-quarter of the patients (n = 133, 74%) were aged between 46-65 years. Only 03 (1.7%) patients were younger than or 30 years old.

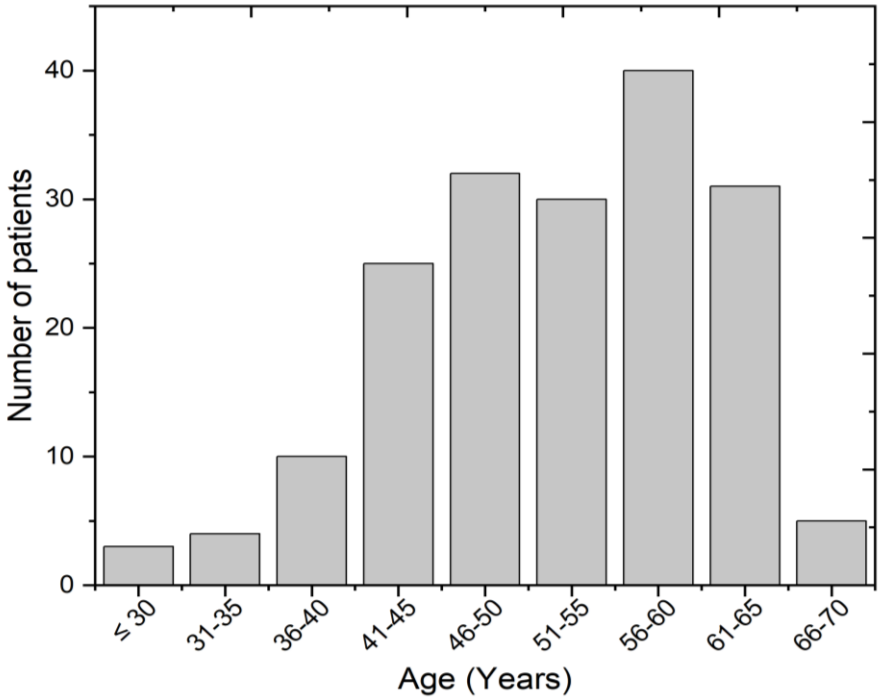

Fig 1: Age distribution of the patients (n = 180)

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All patients were administered four cycles of NAC (i.e., doxorubicin and cyclophosphamide followed by paclitaxel). Afterwards, the treatment outcomes were evaluated in all patients with the histopathology studies. Results of treatment outcomes in terms of pathological response are given in Table 2.

It is evident that pCR with NAC was achieved in only 07 (3.9%) patients. Data stratification for the patients who achieved pCR revealed a mean and median age of 52.7±10.3 and 56 (range: 34-65) years, respectively. Moreover, out of 07 patients with pCR, 06 were married while three were premenopausal.

Table 2: Assessment of complete pathological response in breast cancer patients administered with NAC (doxorubicin and cyclophosphamide followed by paclitaxel)

pCR	Number of patients (%)
Achieved	07 (3.9)
Not- achieved	173 (96.1)

Table 3 presents the tumor size distribution of the breast cancer patients and its correlation with pCR. It was observed that 18 (10%) and 36 (20%) patients presented with 2A and 3A tumors, while the number of patients for 2B, 3B and 3C were 68 (37.7%), 41 (22.8%) and 17 (9.4%), respectively.

These tumor size data were also correlated with the pCR. It is important to note that pCR with NAC was observed in 2A, 3A and 2B tumors only. Specifically, the number of patients presenting with 2A, 3A and 2B tumors who achieved pCR were 01 (0.6%), 02 (1.1%) and 04 (2.2%), respectively.

Table 3: Correlation of complete pathological response in breast cancer patients with tumor size of the disease

Tumor size	Number of patients (%)	Number of patients (%) with pCR
2A	18 (10.0)	1 (0.6)
3A	36 (20.0)	2 (1.1)
2B	68 (37.7)	4 (2.2)
3B	41 (22.8)	
3C	17 (9.4)	

4. DISCUSSION

In this study, we investigated the pCR in hormone receptor positive, HER2 negative breast cancer after administration of NAC. The NAC regimen allows direct evaluation of disease response to the treatment, as opposed to adjuvant setting where chemotherapy is given after local treatment.

It has been established that these three hormones exhibit both prognostic and predictive value for breast cancer. Moreover, these hormones have a profound impact on the clinical outcomes of patients receiving chemotherapy, including NAC.

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In this study, assessment of disease status after NAC administration was performed with the use of histopathological studies. Overall, a poor pCR was observed in breast cancer patients with ER/ PR positive and HER2 negative.

There is extensive and convincing evidence regarding the effectiveness of NAC as an adjuvant intervention in patients presenting with inoperable breast cancer. Moreover, NAC is also a treatment of choice in patients who wish to undergo BCS. These studies are inconsistent with the low pCR rate of 3.9% observed in this study. This rate of pCR was 14.9% with the use of NAC regimen composed of epirubicin and cyclophosphamide followed by docetaxel [15] It is posit that pCR is representative of short-term outcome and may not indicate long-term treatment outcomes. Importantly, pCR was adopted as a primary endpoint variable for assessment of short-term outcomes in NAC trials, presumably to enable accelerated approval of drugs [17], [18].

However, a primary concern for ER positive breast cancers is a lower rate of pCR, which do not necessarily infer poor long-term outcomes. Indeed, excellent long-term outcomes have been reported in ER positive breast cancer patients who failed to achieve pCR with NAC [19]. The present study being of short duration (only 06 months), evaluating correlation of pCR with long-term treatment outcomes was not investigated.

Since pCR to NAC has been illustrated to offer prognostic information, this study also explored if tumor staging of the patients could predict/ correlate response to NAC. Such data analyses have the potential to segregate high risk patients for locoregional recurrence following NAC. Despite enrollment of an appropriate sample size of 180 patient in this study, the number of patients who achieved pCR was not sufficient enough to be used for analyzing a meaningful correlation between pCR and TNM stage. Specifically, stratification of patients with pCR (n= 07) on the basis of TNM stage generated negligibly small number of patients in each subgroup. This hindered to establish a statistically meaningful correlation between pCR and TNG stage.

Studies have demonstrated that, in contrast to clinical response, pCR is rarely achieved in ER/ PR positive and HER2 negative tumors, as seen in this study. Moreover, a binary scale (i.e., pCR or no pCR) is utilized to quantify the treatment outcomes on the basis of pathological response. However, this binary scale seems inconsistent with the classes of clinical responses, which render lower sensitivity for exploring the predictive value of disease characteristics.

Consequently, like many other studies, the use of binary scale for evaluating pathological response of the tumor may be considered as a limitation of this study. To cope with this issue and elevate the sensitivity, a quantitative metric, called neoadjuvant response index (NRI), has been devised. Briefly, the NRI is a measure of tumor downstaging due to chemotherapy administration [20]. Residual cancer burden (RCB) index- based on tumor size, nodal status, and tumor cellularity - has also been utilized to quantify NAC response [21]–[23].

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5. CONCLUSIONS

The current study explored pCR in hormone receptor (i.e., ER/ PR) positive, HER2 negative breast cancer after NAC. Briefly, four cycles of NAC, comprising of doxorubicin and cyclophosphamide followed by paclitaxel were administered to all patients. The pCR was observed in 07/180 (3.9%) patients. However, it is speculated that pCR is a metric representative of short-term outcomes and may not necessarily infer poor long-term outcomes. Moreover, the small number of patients who achieved pCR hindered to establish a statistically meaningful correlation between pCR and TNM stage of the disease. In conclusion, it is challenging to use pCR as treatment evaluation metric in ER/ PR positive, HER2 negative breast cancer after NAC.

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