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Original Article

Association of Various Factors in Terms of Pathological Response in Breast Cancer Patients Receiving Neoadjuvant Chemotherapy

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ABSTRACT

Objective: To analyze the association of various factors in terms of pathological response among breast cancer patients.
Study Design: Cross-sectional study.
Place and Duration of Study: Oncology Department, Combined Military Hospital, Rawalpindi Pakistan, from Jan 2019 to Jun 2020.
Methodology: This study was conducted on 82 female patients with advanced breast cancer who required neo-adjuvant chemotherapy followed by surgical tumour resection. The pathological response was classed as complete, partial, and no response based on histological findings on resected tumour sample. In addition, the age of the patient, stage of disease at presentation, intrinsic (molecular) subtypes and pathological subtype were the factors correlated with response to treatment in the target population.
Results: A total of 82 female patients were included in the final analysis. The mean age of the patients was 47.421±8.857 years. 27(32.9%) had a complete pathological response, 34(41.5%) had partial, and 21(25.6%) had no response to the neoadjuvant therapy. Intrinsic subtypes of the tumour were statistically significantly associated with pathological response to neoadjuvant therapy (p-value<0.05) in our study participants.
Conclusion: Considerable number of patients with advanced breast cancer showed pathological responses to neoadjuvant chemotherapy. In addition, intrinsic subtyping significantly predicted pathological response to therapy in our patients, with triple-negative patients having more chances of complete response to neoadjuvant chemotherapy.

Keywords: Breast cancer; Neo-adjuvant chemotherapy, Pathological response

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INTRODUCTION

Cancer has been one of the leading causes of mortality and morbidity across the globe in all age groups.[1] Breast cancer is particularly important in terms of mortality of women as early diagnosis and management may reduce the figures related to mortality and morbidity to a huge extent.[2,3] Despite awareness campaigns and education of masses, general physicians and specialist doctors; still a large number of patients have advanced disease at the time of diagnosis, which in itself is one of the important poor prognostic factors for the patients in terms of long-term management.[4] Management strategies and approach of treating team become different altogether when a patient presents with advanced disease as compared to a patient with early diagnosis of breast cancer.[5,6] Advanced disease usually requires a combination of chemotherapy and surgical resection with an aggressive approach to reducing the chances of mortality and better outcome.[7] Multiple clinical, radiological and pathological criteria have been set to assess the outcome of treatment among these patients.[8,9]

Government, non-government organizations and health care professionals in Pakistan have always emphasised prevention or early diagnosis of breast cancer. These awareness campaigns have not been very effective, and the burden of this disease is still on the rise, a lot of the patients still present at an advanced stage,[10] little work has been published locally regarding the pathological response of advanced breast cancer disease to neo-adjuvant chemotherapy and factors associated with the response. Therefore, we planned this study to analyze the association of various factors with the outcome of neoadjuvant therapy in terms of pathological subtypes among breast cancer patients.

METHODOLOGY

The cross-sectional study was conducted at the Oncology Department of Combined Military Hospital, Rawalpindi Pakistan, from January 2019 to June 2020.

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Ethical approval (Number 153/4-21) was taken from the Ethical Review Board Committee of Combined Military Hospital Rawalpindi. The sample was gathered by using the non-probability consecutive sampling technique. The sample size was calculated using the WHO sample size calculator using population proportion of complete pathological response in advanced breast cancer as 27.1%.[11]

Inclusion Criteria: All female patients aged 18 to 65 years with ECOG≤2 and normal liver and renal functions having non-metastatic newly diagnosed locally advanced carcinoma of the breast were included in the study.

Exclusion Criteria: Exclusion criteria were patients with cardiac ejection fraction less than 60% or compromised renal and liver function. Pregnant patients with a history of lumpectomy or those with Stages I and IV were also excluded from the study. Patients who refused treatment or had an allergy to standard chemotherapeutic medications were also excluded from the study. The final analysis did not include patients who were lost to follow-up or voluntarily withdrew from treatment during neoadjuvant therapy.

After written informed consent from the participants, patients presenting advanced breast cancer were included in the study. Diagnosis of locally advanced breast cancer was made by a consultant oncologist based on clinical, radiological and pathological criteria.[12] Standard neo-adjuvant chemotherapy was given to all the patients in the Oncology department under the supervision of a consultant oncologist based on their hormonal status (intrinsic subtype) accordance with the current international guidelines.[13] Standard chemotherapy was given to all the patients for six months. Then they underwent surgical resection as per the set criteria.[14] All patients received 3-weekly Inj. Doxorubicin 60mg/m^2 with Inj. Cyclophosphamide 600mg/m^2 for four cycles, followed by weekly Inj. Paclitaxel 80mg/m^2 for 12 cycles. All Her2-positive patients received single-agent antiHer2 blockade with Inj. Trastuzumab 8mg/kg loading dose, followed by 6mg/kg every three weeks. Resected tumour sample was sent to the Armed forces institute of Pathology for detailed pathological evaluation and molecular subtyping. The pathological response was classified as a complete pathological response, partial response and no response, while intrinsic subtyping was classed as ER PR positive Her2/neu negative, ER PR positive Her2/neu positive, ER PR and Her2/neu negative (triple negative), ER PR negative Her2/neu positive.[11]

All statistical analysis was performed using the Statistics Package for Social Sciences version 24.0 (SPSS-24.0). Mean and standard deviation were calculated for the age of patients. Frequency and percentages were calculated for the stage of illness at the time of diagnosis, pathological response, intrinsic subtypes and pathological subtypes. Pearson Chi-square test was applied to look for the association of the age of the patient, stage of disease at presentation, intrinsic subtype and pathological subtype with pathological response to neo-adjuvant therapy by keeping *p*-values less than or equal to 0.05 as significant.

RESULTS

After applying inclusion and exclusion criteria, eighty-two female patients were included in the final analysis. The mean age of the patients was 47.421± 8.857 years. Among them, 32(39.1%) patients were premenopausal, and 50(60.9%) were postmenopausal. 45.1% of the cases belonged to Stage II, and 54.8% had Stage III disease. In addition, 27(32.9%) cases had a complete pathological response, 34(41.5%) had partial, and 21(25.6%) had no response to the neoadjuvant chemotherapy. Most patients, 72(87.8%), had infiltrative ductal carcinoma, while 5(6.1%) had infiltrative lobular pathological subtype. Table-I summarizes the basic demographic and laboratory characteristics of the patients included in the study.

Table-I: Characteristics of Patients with Advanced Breast Cancer included in the Study (n=82)

Study Parameters	n(%)
Age (years)	
Mean±SD	47.421±8.857 years
Range (min-max)	19 years-64 years
Pathological Sub Type	
Infiltrative ductal carcinoma	72(87.8%)
Infiltrative lobular carcinoma	05(6.1%)
Others	05(6.1%)
Staging of Tumor at time of Diagnosis	
Stage-II	37(45.1%)
Stage-III	45(54.8%)
Molecular Subtypes	
ER+PR+Her-	24(29.3%)
ER+PR+Her+	18(21.9%)
ER-PR-Her-	21(25.6%)
ER-PR-Her+	19(23.2%)
Menopausal Status	
Premenopausal	32(39.1%)
Post-menopausal	50(60.9%)

It was also noted that among patients with Stage II disease, 14(51.8%) sho-wed complete response, and 13(38.3%) had partial response; however, in the Stage

III subset, 13(48.2%) showed complete and 21(61.8%) showed partial response. It was revealed that molecular subtypes of the tumour were statistically significantly associated with pathological response to neoadjuvant therapy (p-value<0.05) in our study participants. In contrast, age (p-value-0.885), stage of the tumour (p-value-0.548) and pathological subtype (p-value-0.740) had no significant association with pathological response to neoadjuvant therapy (Table-II).

Table-II: Association of Various Factors with Pathological Response to Neo-Adjuvant Therapy (n=82)

Factors	Complete response (n=27)	Partial response (n=34)	No response (n=21)	*p*-value
Age				
<50 years	12(44.4%)	15(44.1%)	08(38.1%)	0.885
>50 years	15(55.6%)	19(55.8%)	13(61.9%)	
Stage of tumor				
Stage-II	14(51.8%)	13(38.2%)	10(47.6%)	0.548
Stage-III	13(48.2%)	21(61.8%)	11(52.4%)	
Molecular sub types				
ER+PR+Her-	04(14.8%)	09(26.5%)	11(52.4%)	0.008
ER+PR+Her+	03(11.1%)	10(29.4%)	05(23.8%)	
ER-PR-Her-	12(44.4%)	08(23.5%)	01(4.7%)	
ER-PR-Her+	08(29.6%)	07(20.6%)	04(19.1%)	
Pathological sub types				
Infiltrative ductal carcinoma	22(81.4%)	31(91.2%)	19(90.5%)	0.740
Infiltrative lobular carcinoma	02(7.4%)	02(5.8%)	01(4.7%)	
Others	03(11.1%)	01(2.9%)	01(4.7%)	

DISCUSSION

We planned and conducted this study intending to analyze the association of various factors with the outcome of neo-adjuvant therapy regarding pathological subtypes among patients who have breast cancer managed in our tertiary care teaching Oncology unit at Combined Military Hospital, Rawalpindi Pakistan.

A local study done at the Institute of Nuclear Medicine and Oncology, Lahore, Pakistan, by Khokhar *et al*.[15] focused on the clinical response after neoadjuvant therapy in advanced breast carcinoma. They summarized that most of the patients had a partial response or stable disease, and this more aggressive form of therapy predicted better outcomes in these patients. Instead of the clinical response focused on pathological response, most patients had either complete or partial response. However, a considerable number of patients fell into the no-response category as well. Patel *et al*.[16] concluded that tumour necrosis and type of breast carcinoma were predictive parameters for tumour responsiveness to neoadjuvant therapy. A similar study was published by Jung *et al*.[17] concluded that a higher number of tumour infiltrating lymphocytes, absence of clear cytoplasm, low necrosis, and high histologic grade were predictors of response to therapy in patients with advanced CA breast. However, our study was diffe-rent because we recruited patients with all molecular subtypes, and out of those, the triple negative had the best pathological response. Wang *et al*.[18] concluded that neo-adjuvant chemotherapy was helpful for the patients to achieve complete or partial response, which automatically affected the prognosis and increased longevity and improved the quality of life for these patients. Our findings supported their opinion as around 75% of our patients had either complete or partial response after the neoadjuvant chemotherapy.

LIMITATIONS OF STUDY

All Her2/neu positive patients received single-agent anti-Her2 trastuzumab in combination with standard chemotherapy. Pertuzumab was not offered to these patients due to financial constraints and the policy of the institution. Use of Pertuzumab may change response in Her2/neu positive patients. In future, studies with better designs and large sample sizes may generate better results.

CONCLUSION

Many patients with advanced breast cancer showed pathological responses to neoadjuvant chemotherapy. In addition, molecular subtyping significantly predicted pathological response to therapy in our patients, with triple-negative patients having more chances of complete response to neoadjuvant therapy.

Conflict of Interest: None.

Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

AZ: Supervision, Conception, Study design, analysis and Interperitation of data, Critically reviewed manuscript & approval for the final version to be published.

RA: Co-supervision, Data entry, analysis and interpretation, manuscript writing & approval for the final version to be published.

MHB: Critically reviewed, Drafted manuscript & approval for the final version to be published.

UT & I: Data colllection, Entry and analysis of data, preparation of rough draft & approval for the final version to be published.

AB: Data collection and entry & approval for the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investi-gated and resolved.

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